Pathogenesis and Treatment in IgA Nephropathy

An International Comparison

Yasuhiko Tomino
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Preface

I have studied IgA nephropathy for more than 40 years and have obtained several findings in the fields of pathology, immunology, molecular biology, and experimental pathology—all of which have shed much light on the mechanisms of initiation, development, and progression of this disease. I have also undertaken new treatments for patients and developed animal models for IgA nephropathy. This book discusses the latest findings on the pathogeneses and treatment of IgA nephropathy. It particularly focuses on recently recognized initiation and progression factors and varying treatment strategies in different regions such as Asia, the EU, and the U.S.

Nearly 50 years have passed since Dr. Jean Berger first described primary IgA nephropathy ("Nephropathy with mesangial IgA-IgG deposits") as a new disease entity. Immunohistopathologically, IgA nephropathy is characterized by the granular deposition of IgA (polymeric IgA1) and C3 in glomerular mesangial areas with mesangial cell proliferation and the expansion of mesangial matrices. It is clear that IgA nephropathy is one of the most common types of chronic glomerulonephritis in the world. This disease may lead to end-stage kidney disease (ESKD), with its enormous economic impact on healthcare everywhere. Efforts by many investigators around the world have gradually clarified various aspects of the pathogenesis and treatment of IgA nephropathy.

It should be noted however, that there are many controversial strategies for the treatment of patients with IgA nephropathy throughout the world, and there are several limitations for treatment in each country. At present, the most important therapeutics goal for patients with IgA nephropathy is the decrease of urinary protein excretion. For example, it has been assumed that the removal of palatine tonsillar tissues might reduce the production of polymeric IgA1 and decrease the frequency of renal parenchymal injury resulting from episodes of macroscopic hematuria and proteinuria. This volume provides nephrologists everywhere with an overview and comparison of both global and regional findings in basic and clinical fields in IgA nephropathy. It covers genetic variation, aberrant IgA1

production, and classification, etiology, guidelines, and treatment goals, with each chapter written by top international researchers.

Many thanks go to Professor Emeritus Toshikazu Shirai, Juntendo University, Tokyo, Japan, who introduced me to the field of IgA nephropathy and first suggested ways in which it could be studied in the laboratory; to many other physicians who have continuously sustained me in my efforts over the years; to the technicians, dieticians, and nurses who have performed so many of the experiments or clinical tests; and to my many patients whose diseases have always provided the most important of insights.

Finally, I wish to thank all of the authors for their contributions to this volume and my family for the many hours of relaxation they provided when I was away from my work.

Overlooking the Tokyo Metropolitan Building Yasuhiko Tomino
Tokyo, Japan
August 2015

Overview

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Pathogenesis of IgA Nephropathy

IgA nephropathy is generally considered to be an immune-complex-mediated or galactose-deficient polymerized IgA (Gd IgA1)-mediated glomerulonephritis. Genetic factors are considered to be involved in the initiation and progression of IgA nephropathy. It has been hypothesized that susceptibility genes for IgA nephropathy can be detected by a genome-wide scan using a spontaneous animal model, i.e., the ddY mouse strain. The peak marker D10MIT 86 on chromosome 10 is located on a region syntenic to human 6q22-23 with *IGAN1*, which is responsible for familiar IgA nephropathy. Thus, it is important to determine the pathogenesis of Gd IgA1 production and the occurrence of sporadic IgA nephropathy.

There are several developmental and/or exacerbating factors in this disease. Factors previously reported to be associated with disease progression include the male sex, age, prolonged duration, nephrotic range proteinuria, hypertension, glomerular sclerosis, and tubulointerstitial injury in patients with IgA nephropathy. Other developmental and/or exacerbating factors for patients with IgA nephropathy are: (1) complement activation, (2) blood coagulation activity and/or its inhibition in plasma, (3) the activity of cytokines/growth factors, (4) the activity of reactive oxygen species (ROS), (5) the activation of adhesion molecules, (6) apoptosis, (7) podocyte loss (podocytopenia), and (8) the role of megalin. It is widely assumed that glomerular mesangial cell proliferation and mesangial expansion represent major pathological mechanisms in this disease using the animal models.

Treatment for IgA Nephropathy

Previous global approaches to drug therapy of IgA nephropathy have included anti-platelet drugs, anticoagulants, prednisolone (PSL), immunosuppressants, fish oil, renin angiotensin system (RAS) inhibitors (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers), and/or tonsillectomy. At present, the most

important therapeutic goal in patients with IgA nephropathy is the control of hypertension and the decrease of urinary protein excretion. Blood pressure of less than 130/80 mmHg is the therapeutic target in patients with IgA nephropathy. Patients with more or less normal renal function, with or without proteinuria or hypertension, have been preferably treated with RAS inhibitors. Several investigators reported that RAS inhibitors reduce the levels of urinary protein excretion and preserve renal function in patients with IgA nephropathy. Furthermore, RAS inhibitors are recommended on the basis of their beneficial effects on the production of cytokines and extracellular matrix (ECM) components, even when hypertension is not present. RAS inhibitors are generally considered to have cardiac and renal protective actions, and they may improve glomerular hypertension due to the dilatation of efferent arterioles in the kidneys and also suppress glomerular sclerosis. The nonspecific therapeutic approach involves a reduction in the dietary intake of protein in patients with IgA nephropathy who have developed renal failure. Long-term dietary restriction is generally considered to reduce the levels of urinary protein and ameliorate glomerular injuries in patients with IgA nephropathy.

The committees on IgA nephropathy locally and internationally have published several clinical guidelines, including the KDIGO and Japanese guidelines, for the diagnosis and treatment of patients with this disease. However, there are controversies surrounding the treatment of this disease in many societies of nephrology. One such controversy is the use of tonsillectomy, which has been applied in patients with IgA nephropathy for two reasons, especially in Japan. First, tonsillar lymphocytes from patients with IgA nephropathy have been found to produce more polymeric IgA than healthy controls. It has been assumed that the removal of tonsillar tissues might reduce the production of polymeric Gd IgA1. Second, tonsillitis is a frequent precipitating event leading to macroscopic hematuria and proteinuria, frequent glomerular crescent formation, acute tubular injury, and/or a reduction in glomerular filtration rate (GFR). Therefore, tonsillectomy may reduce the frequency of renal parenchymal damage resulting from episodes of macroscopic hematuria and proteinuria. In Japan, it is suggested that tonsillectomy with steroid pulse therapy may provide a rapid and good therapeutic outcome in IgA nephropathy patients who show high expression of TLR9 in tonsillar plasmacytoid dendritic cells. Because controversies continue to exist for the treatment of this disease, it is important to develop new treatment strategies for this disease, such as bone marrow transplantation (BMT), using spontaneous animal models and then applying it to patients.

Because the treatment of IgA nephropathy is still controversial internationally, several current topics of etiology and treatment amongst the various societies of nephrology will be discussed in this book.

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Chapter 1
Is IgA Nephropathy a Single Disease?

Chee Kay Cheung and Jonathan Barratt

Abstract IgA nephropathy (IgAN) is the commonest pattern of primary glomerular disease worldwide and a leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD). IgAN is simply defined by the presence of dominant or codominant mesangial IgA deposits on renal biopsy. Although the identification of mesangial IgA is straightforward, the consequences of this IgA deposition are highly variable. It has been recognised for some time that there is marked variability in the histopathological response to IgA deposition, and the epidemiology, clinical presentation and outcomes, pathogenesis and genetic associations are equally heterogeneous, raising the possibility that the 'disease' IgAN may in fact encompass a disparate group of endophenotypes/diseases with mesangial IgA deposition simply reflecting a final common end point. This chapter will review the evidence presented later in this book and discuss whether our traditional understanding of IgAN being a single disease, and the same disease in all parts of the world, should be challenged in the coming years.

Keywords IgA nephropathy • Pathogenesis • Histology • Glomerulonephritis

1.1 What Is a Disease?

How do we define disease? There are three main philosophical approaches to defining 'health' and 'disease' [1]. Naturalists use definitions based on scientific theory. Their definitions attempt to highlight what is biologically natural and normal for humans. Normativists believe that the use of 'health' and 'disease' reflect value judgements. Healthy states are those states we desire, and diseased states are those states we want to avoid. Hybrid theorists define 'health' and 'disease' by combining aspects of naturalism and normativism. Not surprisingly, currently used definitions range widely, are debated, and are on the whole unsatisfactory. Defining disease as the opposite of health can prove equally difficult [2]. For example, the World Health Organisation states that health is 'a state of

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complete physical, mental and social well-being, not merely the absence of disease or infirmity' [3], and the opposite of this definition encompasses a broad range of conditions.

The 'disease' IgAN was defined by Jean Berger, the Parisian pathologist who published the first description of IgAN in 1968 [4]. Our current definition of IgAN is simply based on the presence of dominant or codominant mesangial IgA deposits on renal biopsy. We now, however, recognise that mesangial IgA deposition may be seen in individuals with no overt signs of kidney disease and who would be regarded by most clinicians as 'healthy'. Whether mesangial IgA in the absence of clinically evident kidney disease can be considered as IgAN remains an unresolved issue.

A recurrent feature in this chapter is the disconnect between the pathological definition of the 'disease' IgAN – the single finding of diffuse mesangial IgA deposition – and the variations in clinical presentation and progression, variations in renal histopathology (although defined, by mesangial IgA, a wide range of glomerular and interstitial injury can ensue), variations in transplant recurrence and variations in apparent geographical incidence. This disconnect raises the issue of whether we should now move beyond a simple pathological definition for IgAN.

1.2 IgA Nephropathy: A Simple and Single Histological Diagnosis?

No single International Classification of Diseases (ICD)-10 classification for IgAN exists. The currently accepted definition, the presence of dominant or codominant mesangial IgA immune deposits, appears at first glance a reliable, reproducible and incontrovertible way to define IgAN. However, as already mentioned, mesangial IgA deposition may occur in the absence of any other histopathologic or clinical sign of disease. A number of studies have reported the prevalence of mesangial IgA deposition in apparently 'healthy' individuals. From series in Europe and Asia, 4–10 % of consecutive autopsy cases had evidence of mesangial IgA deposition [5–7]. A study from Japan found mesangial IgA deposition in 16 % of kidneys donated from individuals previously assessed and deemed fit to donate [8]. A large proportion of patients from these studies had no prior evidence of urinary abnormalities and no impairment of renal function. Whether such patients should be labelled as having a 'disease' on the basis of mesangial IgA deposition alone, in the absence of any clinically evident abnormalities, is an interesting question to consider.

When mesangial IgA deposition is associated with clinically evident 'disease', life does not become any simpler as mesangial IgA deposition is associated with a striking variety of histological patterns, which in turn translate to highly variable clinical phenotypes. The patterns of renal injury seen in IgAN include pathology that resembles minimal change disease, proliferative disease with mesangial and endocapillary hypercellularity, focal and segmental glomerulosclerosis, interstitial

fibrosis and tubular atrophy, crescentic glomerulonephritis with necrotising lesions or any combination of the above. Unlike lupus nephritis, where a similar diverse pattern of renal injury is seen, IgAN is not yet associated with serum biomarkers, such as antinuclear antibodies, that give us confidence that what we are seeing in a renal biopsy is the consequence of a single pathogenic process or 'disease'.

Variability also exists in the type and distribution of immune deposits. IgA deposition is usually mesangial, although capillary wall IgA deposits are present in a subgroup of patients, where they are associated with greater mesangial and endocapillary hypercellularity, and worse renal outcome [9–11]. IgG codeposition is highly variable and has been reported to occur in anywhere between 15 % and 85 % of renal biopsies in IgAN and has been variably reported as an independent risk factor for worse renal outcome [9, 12]. The complement component C3 is found in over 90 % of cases, and components of the alternative pathway of complement activation properdin and Factor H are often but not invariably found [9]. In a study of renal biopsies from 60 patients with IgAN, only one quarter had evidence of complement activation via the lectin pathway, with mannose-binding lectin (MBL), L-ficolin, MBL-associated serine proteases (MASP) and C4d mesangial deposition. This subgroup of cases was associated with worse histological damage and greater proteinuria [13].

It is unclear why there should be such striking differences between patients with regard to IgG and complement component codeposition if a single pathogenic pathway is activated. By comparison, in primary membranous nephropathy, where we now have a much better understanding of the disease with the discovery of M-type phospholipase A2 receptor (PLA2R) autoantibodies defining a single pathogenic pathway in the majority of patients, immunofluorescence for IgG, IgG4 and C3 is uniformly positive and evenly distributed throughout glomeruli. The variability seen in IgAN might therefore reflect activity in different pathogenic pathways, and while the final end point of these pathways is mesangial IgA deposition, these different 'disease' processes may require very different therapeutic interventions.

1.3 Is IgA Nephropathy the Same Disease in Different Parts of the World?

IgAN displays remarkable variation both regionally and globally, in terms of its prevalence, and clinical course. The reported prevalence of IgAN accounts for approximately 40 % of all native kidney biopsies performed in Japan, 25 % in Europe, 12 % in the USA, and less than 5 % in Central Africa (Fig. 1.1) [14].

Some of this variability can be attributable to differences in clinical practice and thresholds for renal biopsy. For example, in countries where screening programmes for urinary abnormalities exist, more patients will be identified, who may then proceed to having a renal biopsy. A correlation between the number of renal

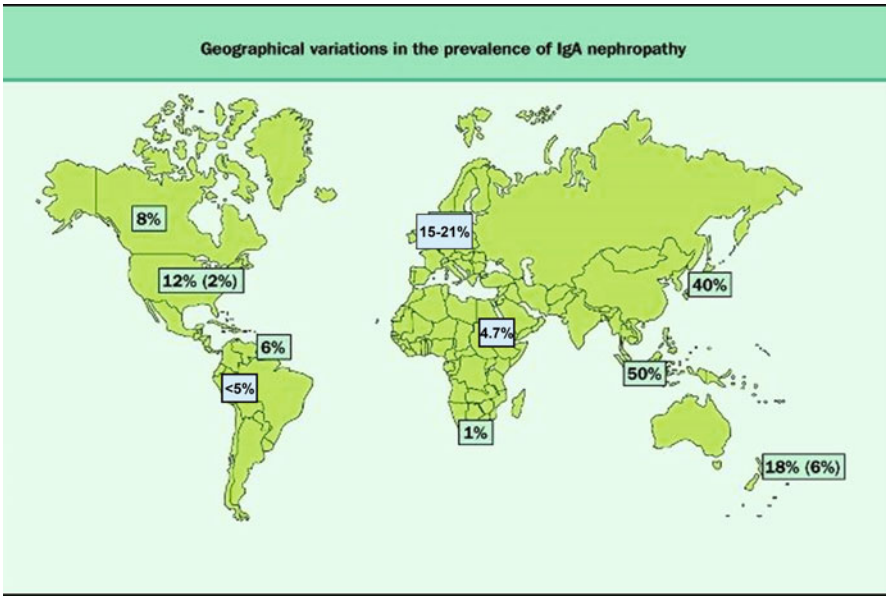

Fig. 1.1 Geographical variations in the prevalence of IgAN. Percentages represent the proportion of cases of IgAN compared to all native kidney biopsies performed. The numbers in brackets represent minority racial groups, African-Americans in the USA and Polynesians in New Zealand (From Feehally and Floege [14])

biopsies performed per country and the incidence of primary glomerulonephritis and IgAN has been observed (Fig. 1.2) [15]. The same study also showed that between two centres in Scotland, located only 100 km apart, there was a 70 % difference in the incidence of IgAN, which was associated with a marked increase in the number of renal biopsies performed per year in one of the centres [15]. This implies that increasing the range of people subjected to renal biopsy, presumable for minor urinary abnormalities, will increase the identification of IgAN.

However, data from migrant populations suggest that true variations in susceptibility exist between people of different ethnicities. In Australia, East and Southeast Asian-born patients have higher rates of IgAN accounting for ESRD compared to those born in the Middle East, Southern Europe or Australia [16]. In the USA, patients of an Asian or Pacific Island ethnicity have higher rates of IgAN than other glomerular diseases [17], whereas IgAN is much less common in African-Americans than in other ethnic groups [7].

As well as overall prevalence, marked variation in gender distribution also exists in IgAN. In North American and European cohorts, a male to female predominance is reported, with the ratio being 2–3:1, whereas in Asia this approximates 1:1 [18–20]. These differences in incidence and gender bias do suggest that the 'disease' IgAN may be behaving very differently across the globe. It is likely that both genetic and environmental factors play contributory roles in the differences

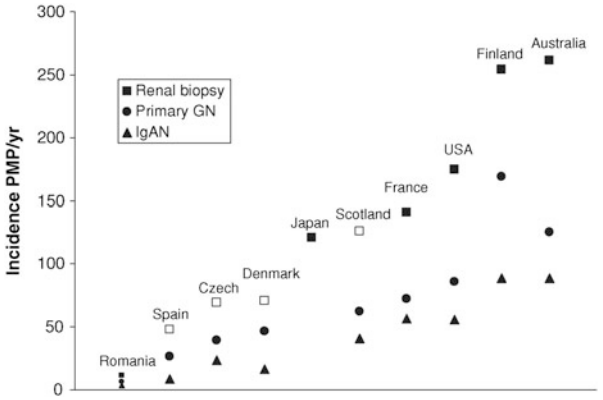

Fig. 1.2 Reported rates of biopsy incidence per million population (PMP) in published studies from national (*closed squares*) and regional (*open squares*) native renal biopsy registries. Renal biopsy incidence appears to correlate with the incidence of primary glomerulonephritis and IgAN (From McQuarrie et al. [15])

observed, although the relative importance of each is likely to vary in different populations. Emerging evidence supports an increasing gradient in currently understood risk alleles from West to East, from Africa [21]. Whether this constitutes different diseases in the West and East is open to debate.

In parallel, a number of studies have reported the importance of environmental factors in determining the prevalence of IgAN, although not all populations appear equally susceptible. Perhaps the best example of varying susceptibility to environmental antigens in IgAN is the subgroup of patients with IgAN who develop flares of nephritis, demonstrated by visible haematuria, in conjunction with stimulation of the mucosal immune system, for example, during an upper respiratory tract infection. There is also a well-described subgroup of patients where IgAN and coeliac disease overlap and where gluten avoidance leads to a reduction in severity of renal disease [22, 23]. Interestingly, a recent GWAS meta-analysis identified susceptibility loci for IgAN that are also related to inflammatory bowel disease and maintenance of the intestinal epithelial barrier [24]. On a global scale it has been suggested that an inverse relationship exists between IgAN and membranoproliferative disease, with IgAN being more prevalent in countries with a higher gross domestic product [25]. By contrast, a study from Scotland showed a higher number of renal biopsies were performed in patients from areas of socioeconomic deprivation, and of these patients, a higher proportion were diagnosed with IgAN [26]. Although most studies have reported a low prevalence of IgAN in African-Americans [14, 27], two studies conducted in specific regions of the USA found equivalent prevalence, leading some to suggest that environmental factors may have played a role [28, 29].

At present the exact role for environmental factors in IgAN has not been fully established, although there do certainly appear to be differences both across and within populations in terms of responsiveness to environmental triggers. This heterogeneity lends further support to the argument that IgAN may not be the same disease in all parts of the world. Importantly, these differences may have a direct impact on how we manage patients diagnosed with IgAN. Patients with IgAN in association with gluten-sensitive enteropathy are likely to respond to a simple

antigen exclusion diet and not require immunosuppression, whereas most patients with IgAN will gain no benefit from such a change and will require more tailored therapy.

1.4 The Clinical Presentation of IgA Nephropathy Is Highly Variable

Patients with IgAN can present with the full spectrum of nephrological presentations from asymptomatic urine abnormalities through to malignant hypertension, nephrotic syndrome or a rapidly progressive glomerulonephritis. This is perhaps not surprising given the wide variety of histopathological changes that can be seen in association with mesangial IgA deposition. In part these differences in presentation may reflect differences in an individual's willingness to access healthcare promptly, local public health screening strategies, different renal biopsy policies and differing access to specialist renal services. These factors do not, however, explain all the variation seen in patients presenting with IgAN. Within individual centres, such as our own in Leicester, UK, which has a single biopsy policy, serves a relatively homogeneous population and where there is universal primary care coverage, mesangial IgA deposition can present after detection of non-visible haematuria, with episodes of visible haematuria and normal renal function, as a rapidly progressive glomerulonephritis and as nephrotic syndrome. In each of these cases, the pattern and extent of mesangial IgA staining will be almost identical. Clearly, different pathogenic pathways are operating in these patients that require very different therapeutic interventions and have very different implications for long-term renal survival. Do these patients have the same disease?

Furthermore, accepting that there are external factors that may influence the mode of presentation of patients with IgAN, there do also appear to be global differences in the way patients with IgAN present. In a study of 711 adult patients with biopsy-proven IgAN from Glasgow, Helsinki, Sydney and Toronto, there were significant variations in age, proteinuria, mean arterial blood pressure and creatinine clearance at presentation between centres [30]. Patients from Helsinki had relatively milder disease at presentation, while patients from Glasgow and Toronto were slightly older at presentation, and there was a higher male-female ratio in Glasgow than other centres. In a separate study of 152 Asian patients from Canada and 76 Thai patients with IgAN, Thai patients were more likely to be female (63.2 vs. 44.1 %) and have less baseline proteinuria (1.2 vs. 1.7 g/day) at time of first presentation [31]. By contrast, in a study from India of 478 patients with IgAN, the mean age at presentation was 32 ($\pm$11) years, with a predominance of males (65 %) [32]. Patients presented with a much more severe clinical phenotype: nephrotic syndrome (55 %), hypertension (58 %), renal failure (serum creatinine $>$125 μmol/L in 56 %) and acute nephritis (28 %). Very few patients presented with asymptomatic urine abnormalities (5 %). The mean serum creatinine and 24 h urine protein were 205 μmol/L and 2.9 g/day, respectively.

The differences seen both within centres and across the globe in the way patients present, all of whom have almost identical patterns of mesangial IgA deposition, suggest that labelling all of these patients as having a single disease may be oversimplifying a complex group of nephrological conditions with very different natural histories.

1.5 The Clinical Course of IgA Nephropathy Varies Widely

Not only is there significant heterogeneity in the way patients with mesangial IgA deposition present to their clinician, but there is also enormous variation, both within and across populations, in the likelihood that this mesangial IgA deposition will be associated with progressive glomerular and tubulointerstitial injury and chronic kidney disease. Interestingly, clinical outcomes in IgAN do not correlate with the severity of mesangial IgA deposition, the defining feature of IgAN [33].

Spontaneous remission has been reported in a subgroup of patients with IgAN, and when a repeat biopsy has been performed, resolution of urinary abnormalities is associated with clearance of IgA immune deposits [34]. Equally most studies report that 20–30 % of patients with IgAN develop slowly progressive chronic kidney disease leading to ESRD over a period of 20 years [35]. Rates of progression have been shown to differ both within and between different ethnic groups, although accurate comparisons across populations have been difficult as most published data is retrospective and observational and may, therefore, be confounded by differences in the identification and management of patients. One additional difficulty in interpreting this type of data is the potential impact of lead-time bias (Fig. 1.3). In centres with a proactive urine screening policy, clinical presentation, renal

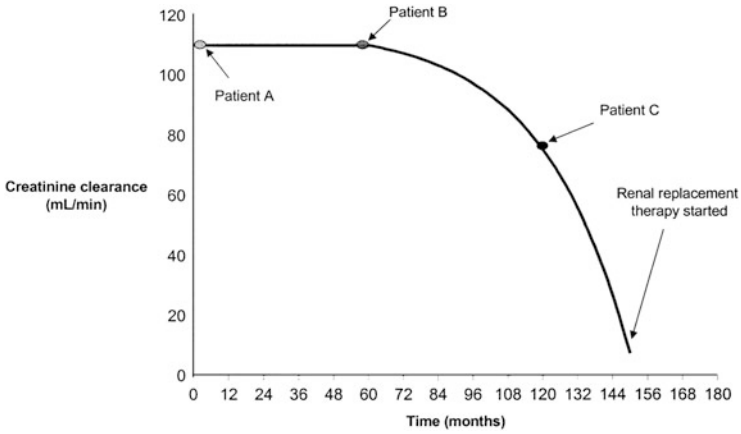

Fig. 1.3 The concept of lead-time bias. Three hypothetical patients with IgAN who have an identical clinical course are depicted. Marked differences in their prognosis are observed depending on when their disease is identified (From Geddes et al. [30])

biopsy and diagnosis are likely to be at an early stage of the disease and consequently prognosis is likely be better than that reported from a centre that only biopsies and diagnoses patients at a late stage of the disease. This is also a factor when comparing centres who have different renal biopsy policies and patient groups, who have differing access to specialist renal services.

While some studies in Asia have reported equivalent outcomes in IgAN cohorts to those in Western populations, this is not uniformly the case [19, 36]. Outcomes in 478 Indian patients from Vellore were significantly worse than those of European cohorts with a median renal survival of only 61 months from time of renal biopsy [32]. A recent study from Canada prospectively followed a multiracial cohort and, after adjusting for age, gender, eGFR, medication use, blood pressure and proteinuria, found that prognosis was worse in patients with IgAN of self-reported Pacific Asian origin compared to patients of all other backgrounds [37].

Traditionally patients with isolated non-visible haematuria, without proteinuria or renal dysfunction, are thought to have an excellent prognosis. Indeed, in a recent study from Spain, which included 141 Caucasian IgAN patients with non-visible haematuria, absent or minimal proteinuria, and no renal dysfunction, followed up for a median of 9 years, a rise in serum creatinine >50 % was observed in only 3.5 % of patients. Furthermore, 37 % of patients had complete resolution of their urinary abnormalities [38]. By contrast, in a series of 72 Chinese IgAN patients with non-visible haematuria, proteinuria <0.4 g/day and normal eGFR, 33 % developed proteinuria >1 g/day and 7 % developed impaired renal function (creatinine clearance <70 ml/min) during follow-up for up to 12 years. Only 14 % had complete resolution of their haematuria and had stable kidney function over this period [39].

If IgAN is a single disease, why do we see such varied clinical outcomes when the defining feature of mesangial IgA deposition is uniformly seen in all patients? Whether there are true global differences in clinical outcomes in IgAN is difficult to ascertain from current data due to the confounding effects of factors known to influence progression of chronic kidney disease irrespective of cause: socioeconomic status, differences in predisposing genetic backgrounds, prenatal and perinatal care and experiences, including low birth weight, inadequate diets, infectious diseases or exposure to toxins. Where it has been possible to correct as much as possible for these confounders, there does appear to be a difference both in the likelihood of spontaneous remission and the risk of developing progressive renal injury in different parts of the world. How this translates to different disease pathways in IgAN is unclear but should be the focus of future studies.

1.6 Differences in the Rates of IgA Nephropathy Recurrence in Renal Allografts

Recurrent mesangial IgA deposition in renal allografts occurs frequently, but not uniformly, in published IgAN series. Retrospective observational studies, where biopsies were performed due to allograft dysfunction, report recurrent IgA deposition in anywhere between 21 and 58 % of recipients [40]. It is clear not all patients with IgAN develop recurrent IgA deposits, and perhaps more interestingly, while recurrent IgA deposition is common, allograft failure due to recurrent disease occurs far less frequently [41]. The risk of allograft loss is greatest in younger recipients and the subgroup of patients who had an aggressive original disease course, e.g. crescentic glomerulonephritis [42]. A recent study from Japan of 29 IgAN transplant recipients with >10 years post-transplant follow-up and no urinary abnormalities showed that 11 of these patients had recurrent mesangial IgA deposition with no evidence of allograft dysfunction [43]. Compared to the 18 patients with no mesangial IgA recurrence, there were no significant differences in either histopathology or long-term allograft function between the groups.

The heterogeneity in rates of mesangial IgA deposition and translation of this deposition to allograft dysfunction reflect the varied picture we see in native kidneys. However, when reviewing the data on recurrence of IgAN post-transplant, it is impossible to remove the confounding effects of concomitant immunosuppression. Again, as in native kidneys, there appears to be little correlation between the pattern of mesangial IgA deposition in recurrent IgAN and the risk of allograft loss. It is possible, therefore, that these variations reflect underlying differences in disease processes in individual recipients and the varied susceptibility of these disease processes to the immunosuppression regimen used.

1.7 Do Differences in Treatment Responses Reflect Different Underlying Diseases?

When examining the response to pharmacological intervention in any disease, a number of factors will invariably affect the efficacy of that treatment. Drug absorption, metabolism and elimination vary and can be influenced by genetic polymorphisms (pharmacogenetics), age, body size, the use of other drugs, dietary supplements and medicinal herbs, the presence of other diseases and development of tolerance and resistance. There are also well-recognised ethnic differences in drug responses, perhaps the most well known being the differences in response between β-blockers and ACE inhibitors in hypertension [44]. Interpreting the significance of treatment effects from clinical trials in IgAN is further confounded by the different inclusion and exclusion criteria employed, the different treatment regimens used and variable endpoints chosen.

Accepting these relatively 'fixed' confounding factors, there is still marked heterogeneity in the response of patients with IgAN to a variety of immunomodulatory therapies. This variation in response could reflect underlying differences in the biochemical pathways operating in different subgroups of patients which are variably sensitive to the drug being studied. For example, the data supporting the use of corticosteroids in IgAN is mixed, and even in those studies reporting a beneficial effect of corticosteroids, the response to steroids varies greatly between trial participants, even though all met the same inclusion and exclusion criteria for the respective trial. The same is seen in trials of other immunosuppressants including azathioprine, mycophenolate mofetil (MMF) and cyclophosphamide. Perhaps more striking is the apparent variation in response to treatments in IgAN in different ethnic groups. Clinical trials of MMF suggest there is no benefit from MMF in Caucasian populations, while a beneficial effect has been observed in Chinese patients [45–48]. Tonsillectomy, a commonly used treatment in Japan, is believed to have a significant disease-modifying effect in Japanese patients; however, this is not the case in Caucasian patients [49–52].

With advances in pharmacogenetics and an improvement in clinical trial design in IgAN, it may be possible in the coming years to better understand the response to treatment in IgAN and identify subgroups of patients who may have discreet diseases and are more or less likely to respond to specific immune modulation strategies.

1.8 Does Our Knowledge of IgAN Pathogenesis Support IgA Nephropathy Being a Single Disease?

There is now convincing evidence that the production of poorly galactosylated IgA1 and O-glycan-specific IgG and IgA autoantibodies can lead to the formation of IgA-containing immune complexes and that these immune complexes deposit within the mesangium, where their consequent effects on mesangial cells, podocytes and proximal tubule cells are central to the development of IgAN [53]. Elevated levels of poorly galactosylated IgA1 and IgG and IgA autoantibodies against the IgA1 hinge region O-glycans are, however, only found in some, and not all, patients with IgAN. Elevated levels of total serum IgA, complement component C3 and other markers of alternative pathway activation may also be seen in some IgAN patients. Unlike other kidney diseases such as SLE (antinuclear antibodies), antiglomerular basement membrane (GBM) disease (anti-GBM autoantibodies), pauci-immune vasculitis (antineutrophil cytoplasmic antibodies) and primary membranous nephropathy (PLA2R autoantibodies), IgAN is not associated with a consistent serological profile. This may simply reflect the fact we have not yet made the necessary discoveries. Alternatively, it may be that we are not dealing with a simple, single disease with a predictable single serological phenotype.

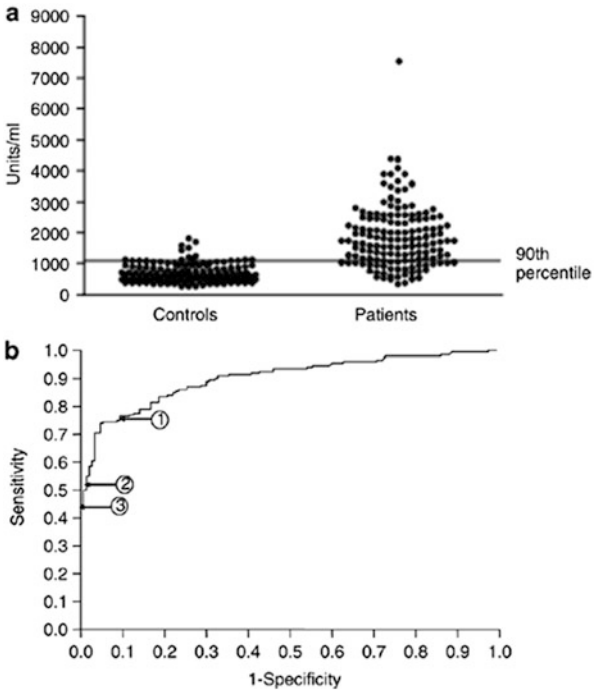

Fig. 1.4 Serum levels of galactose-deficient IgA in IgAN patients and healthy controls. Although the majority of patients display a higher serum galactose-deficient IgA level compared to the healthy controls, approximately one quarter had levels that overlapped, suggesting that other susceptibility factors play a role in the development of IgAN (From Moldoveanu et al. [54])

The most consistently reported serological abnormality in IgAN is the increase in poorly galactosylated IgA1 in IgAN [54]. However, if you look at the distribution of IgA1 O-glycoforms in any of the reported case series from across the globe, including our own, you will see marked variation in the extent of serum IgA1 O-glycosylation in IgAN, with significant overlap between patients with IgAN and healthy subjects (Fig. 1.4). This suggests that serum IgA1 O-glycosylation may be pathogenically unimportant in some cases of IgAN. In the more recent studies reporting the existence of IgG and IgA hinge region-specific autoantibodies, it is clear that these are not universally found in IgAN [55]. Alternative mechanisms for immune complex formation may therefore operate in different patient groups. It has been proposed that there is a subgroup of patients who develop IgA immune complexes as a consequence of soluble CD89 shedding from circulating myeloid cells and that in these patients CD89 is essential for mesangial cell activation by deposited IgA immune complexes [56]. We have already discussed a further subgroup of patients with gluten-sensitive enteropathy, where the pathway to mesangial IgA deposition is likely to be different again. How these different pathogenic pathways correlate with the clinical phenotype is unclear at present.

Finally, data from genetic studies is also beginning to help define potential pathogenic pathways and important disease-associated allelic variants in IgAN. While there are genetic associations common to all published studies, principally genetic variants in the HLA gene family, there is clear disparity in associations with

other genetic loci. For example, associations between IgAN and variants of the angiotensin converting enzyme, TAP1/PSMB (transporters associated with antigen processing 1/proteosomal subunit) and DEFA (α-defensin) genes have only been reported in Asian but not in Western patients [57–59]. By contrast, the familial form of IgAN has been more frequently reported in Europe than in Asia, and within Europe, familial IgAN is more evident in Southern than in Northern populations [21, 60]. These genetic observations raise the possibility of involvement of different genes in the pathogenesis of IgAN in different parts of the world. In time we may be able to use this information to redefine IgAN on the basis of clear genotypic variants rather than on the basis of a generic renal biopsy appearance.

Current concepts of the pathogenesis of IgAN are discussed extensively in this book. We would argue strongly that the data presented in the following chapters supports the existence of multiple pathogenic pathways. These pathways operate, to variable extents, in different IgAN patients, but that ultimately all of them lead to a final common end point of mesangial IgA deposition. Currently we are using the umbrella of a diagnosis of IgAN to encompass all of these patients. In the future hopefully we will be able to link each of these pathogenic pathways to a specific disease genotype/phenotype and produce a tailored treatment paradigm and thereby fully embrace the era of 'personalised medicine' in IgAN.

1.9 Conclusion

In this chapter we have been deliberately provocative in the way we have interpreted the existing literature on IgAN. No matter whether you believe IgAN is or is not a single disease, it is hard to get away from the fact that IgAN is highly heterogeneous with marked genotypic and phenotypic variation. Until we have a clear serological marker akin to antinuclear or PLA2R autoantibodies, confirming a unifying pathogenic pathway, we will be continually confronted with the argument that mesangial IgA deposition alone is a poor way to define this complex nephrological disorder.

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Ereshefsky M. Defining 'health' and 'disease'. Stud Hist Philos Biol Biomed Sci. 2009;40(3):221–7.
2. Scully JL. What is a disease? EMBO Rep. 2004;5(7):650–3.
3. World Health Organisation. Preamble to the constitution of the World Health Organization as adopted by the international health conference. New York: WHO; 1946.
4. Berger J, Hinglais N. Les depots intercapillaries d'IgA-IgG. J Urol Nephrol. 1968;74:694–5.

5. Sinniah R. Occurrence of mesangial IgA and IgM deposits in a control necropsy population. J Clin Pathol. 1983;36(3):276–9.
6. Varis J, Rantala I, Pasternack A. Immunofluorescence of immunoglobulins and complement in kidneys taken at necropsy. J Clin Pathol. 1989;42(11):1211–4.
7. Waldherr R, Rambausek M, Duncker WD, Ritz E. Frequency of mesangial IgA deposits in a non-selected autopsy series. Nephrol Dial Transplant. 1989;4(11):943–6.
8. Suzuki K, Honda K, Tanabe K, Toma H, Nihei H, Yamaguchi Y. Incidence of latent mesangial IgA deposition in renal allograft donors in Japan. Kidney Int. 2003;63(6):2286–94.
9. Roberts IS. Pathology of IgAN. Nat Rev Nephrol. 2014;10(8):445–54.
10. Yoshimura M, Kida H, Abe T, Takeda S, Katagiri M, Hattori N. Significance of IgA deposits on the glomerular capillary walls in IgAN. Am J Kidney Dis. 1987;9:404–9.
11. Bellur SS, Troyanov S, Roberts IS, Working Group of International IgAN Network and Renal Pathology Society. Immunostaining findings in IgAN: correlation with histology and clinical outcome in the Oxford classification patient cohort. Nephrol Dial Transplant. 2011; 26(8):2533–6.
12. Jennette JC, Olson JL, Schwartz MM, Silva FG. Heptinstall's pathology of the kidney, vol. 1. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2007. p. 424–87.
13. Roos A, Rastaldi MP, Calvaresi N, Oortwijn BD, Schlagwein N, van Gijlswijk-Janssen DJ, et al. Glomerular activation of the lectin pathway of complement in IgAN is associated with more severe renal disease. J Am Soc Nephrol. 2006;17(6):1724–34.
14. Feehally J, Floege J. IgAN and Henoch-Schonlein nephritis. In: Feehally J, Floege J, Johnson R, editors. Comprehensive clinical nephrology. 3rd ed. Philadelphia: Mosby Elsevier; 2007. p. 253–64.
15. McQuarrie EP, Mackinnon B, Young B, Yeoman L, Stewart G, Fleming S, Scottish Renal Biopsy Registry, et al. Centre variation in incidence, indication and diagnosis of adult native renal biopsy in Scotland. Nephrol Dial Transplant. 2009;24(5):1524–8.
16. Stewart JH, McCredie MR, McDonald SP. Incidence of end-stage renal disease in overseas-born, compared with Australian-born, non-indigenous Australians. Nephrology. 2004;9(4): 247–52.
17. Hall YN, Fuentes EF, Chertow GM, Olson JL. Race/ethnicity and disease severity in IgAN. BMC Nephrol. 2004;5:10.
18. D'Amico G, Imbasciati E, Barbiano Di Belgioioso G, Bertoli S, Fogazzi G, Ferrario F, et al. Idiopathic IgA mesangial nephropathy. Clinical and histological study of 374 patients. Medicine (Baltimore). 1985;64(1):49–60.
19. Li PK, Ho KK, Szeto CC, Yu L, Lai FM. Prognostic indicators of IgAN in the Chinese – clinical and pathological perspectives. Nephrol Dial Transplant. 2002;17(1):64–9.
20. Zeng CH, Le W, Ni Z, Zhang M, Miao L, Luo P, et al. A multicenter application and evaluation of the oxford classification of IgAN in adult chinese patients. Am J Kidney Dis. 2012; 60(5):812–20.
21. Kiryluk K, Li Y, Sanna-Cherchi S, Rohanizadegan M, Suzuki H, Eitner F, et al. Geographic differences in genetic susceptibility to IgAN: GWAS replication study and geospatial risk analysis. PLoS Genet. 2012;8(6):e1002765.
22. Woodrow G, Innes A, Boyd SM, Burden RP. A case of IgAN with coeliac disease responding to a gluten-free diet. Nephrol Dial Transplant. 1993;8(12):1382–3.
23. Koivuviita N, Tertti R, Heiro M, Metsärinne K. A case report: a patient with IgAN and coeliac disease. Complete clinical remission following gluten-free diet. NDT Plus. 2009;2(2):161–3.
24. Kiryluk K, Li Y, Scolari F, Sanna-Cherchi S, Choi M, Verbitsky M, et al. Discovery of new risk loci for IgAN implicates genes involved in immunity against intestinal pathogens. Nat Genet. 2014;46(11):1187–96.
25. Johnson RJ, Hurtado A, Merszei J, Rodriguez-Iturbe B, Feng L. Hypothesis: dysregulation of immunologic balance resulting from hygiene and socioeconomic factors may influence the epidemiology and cause of glomerulonephritis worldwide. Am J Kidney Dis. 2003;42(3): 575–81.

26. McQuarrie EP, Mackinnon B, McNeice V, Fox JG, Geddes CC. The incidence of biopsy-proven IgAN is associated with multiple socioeconomic deprivation. Kidney Int. 2014;85(1):198–203.
27. Korbet SM, Genchi RM, Borok RZ, Schwartz MM. The racial prevalence of glomerular lesions in nephrotic adults. Am J Kidney Dis. 1996;27(5):647–51.
28. Sehic AM, Gaber LW, Roy 3rd S, Miller PM, Kritchevsky SB, Wyatt RJ. Increased recognition of IgAN in African-American children. Pediatr Nephrol. 1997;11(4):435–7.
29. Wyatt RJ, Julian BA, Baehler RW, Stafford CC, McMorrow RG, Ferguson T, et al. Epidemiology of IgAN in central and eastern Kentucky for the period 1975 through 1994. Central Kentucky Region of the Southeastern United States IgAN DATABANK Project. J Am Soc Nephrol. 1998;9(5):853–8.
30. Geddes CC, Rauta V, Gronhagen-Riska C, Bartosik LP, Jardine AG, Ibels LS, et al. A tricontinental view of IgA nephropathy. Nephrol Dial Transplant. 2003;18(8):1541–8.
31. Prakash S, Kanjanabuch T, Austin PC, Croxford R, Hsu CY, Choi AI, et al. Continental variations in IgA nephropathy among Asians. Clin Nephrol. 2008;70(5):377–84.
32. Chacko B, John GT, Neelakantan N, Korula A, Balakrishnan N, Kirubakaran MG, et al. Presentation, prognosis and outcome of IgA nephropathy in Indian adults. Nephrology. 2005;10(5):496–503.
33. Working Group of the International IgAN Network, the Renal Pathology Society, Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS, Troyanov S, et al. The Oxford classification of IgAN: rationale, clinicopathological correlations, and classification. Kidney Int. 2009;76(5):534.
34. Hotta O, Furuta T, Chiba S, Tomioka S, Taguma Y. Regression of IgAN: a repeat biopsy study. Am J Kidney Dis. 2002;39(3):493–502.
35. D'Amico G. Natural history of idiopathic IgA nephropathy: role of clinical and histological prognostic factors. Am J Kidney Dis. 2000;36(2):227–37.
36. Koyama A, Igarashi M, Kobayashi M. Natural history and risk factors for immunoglobulin A nephropathy in Japan. Research Group on progressive renal diseases. Am J Kidney Dis. 1997;29(4):526–32.
37. Barbour SJ, Cattran DC, Kim SJ, Levin A, Wald R, Hladunewich MA, et al. Individuals of Pacific Asian origin with IgAN have an increased risk of progression to end-stage renal disease. Kidney Int. 2013;84(5):1017–24.
38. Gutiérrez E, Zamora I, Ballarín JA, Arce Y, Jiménez S, Quereda C, Grupo de Estudio de Enfermedades Glomerulares de la Sociedad Española de Nefrología (GLOSEN), et al. Long-term outcomes of IgAN presenting with minimal or no proteinuria. J Am Soc Nephrol. 2012;23(10):1753–60.
39. Szeto CC, Lai FM, To KF, Wong TY, Chow KM, Choi PC, et al. The natural history of immunoglobulin a nephropathy among patients with hematuria and minimal proteinuria. Am J Med. 2001;110(6):434–7.
40. Ponticelli C, Traversi L, Feliciani A, Cesana BM, Banfi G, Tarantino A. Kidney transplantation in patients with IgA mesangial glomerulonephritis. Kidney Int. 2001;60:1948–54.
41. Moroni G, Longhi S, Quaglini S, Gallelli B, Banfi G, Montagnino G, et al. The long-term outcome of renal transplantation of IgAN and the impact of recurrence on graft survival. Nephrol Dial Transplant. 2013;28(5):1305–14.
42. Ponticelli C, Glassock RJ. Post transplant recurrence of primary glomerulonephritis. Clin J Am Soc Nephrol. 2010;5:2363–72.
43. Hara S, Ichimaru N, Kyo M, Yamaguchi Y, Kojima Y, Takahara S, et al. Latent mesangial immunoglobulin A deposition in long-term functioning kidney does not correlate with disease progression and may exhibit fluctuating patterns. Transplant Proc. 2014;46(1):124–9.
44. Johnson JA. Ethnic differences in cardiovascular drug response: potential contribution of pharmacogenetics. Circulation. 2008;118(13):1383–93.
45. Tang S, Leung JC, Chan LY, Lui YH, Tang CS, Kan CH, et al. Mycophenolate mofetil alleviates persistent proteinuria in IgAN. Kidney Int. 2005;68:802–12.

46. Tang SC, Tang AW, Wong SS, Leung JC, Ho YW, Lai KN. Long-term study of mycophenolate mofetil treatment in IgAN. Kidney Int. 2010;77:543–9. doi:10.1038/ki.2009.499. Epub 2009 Dec 23.
47. Maes BD, Oyen R, Claes K, Evenepoel P, Kuypers D, Vanwalleghem J, et al. Mycophenolate mofetil in IgAN: results of a 3-year prospective placebo-controlled randomized study. Kidney Int. 2004;65:1842–9.
48. Frisch G, Lin J, Rosenstock J, Markowitz G, D'Agati V, Radhakrishnan J, et al. Mycophenolate mofetil (MMF) vs placebo in patients with moderately advanced IgAN: a double-blind randomized controlled trial. Nephrol Dial Transplant. 2005;20:2139–45.
49. Xie Y, Nishi S, Ueno M, Imai N, Sakatsume M, Narita I, et al. The efficacy of tonsillectomy on long-term renal survival in patients with IgAN. Kidney Int. 2003;63(5):1861–7.
50. Komatsu H, Fujimoto S, Hara S, Sato Y, Yamada K, Kitamura K. Effect of tonsillectomy plus steroid pulse therapy on clinical remission of IgAN: a controlled study. CJASN. 2008;3(5):1301–7.
51. Rasche FM, Schwarz A, Keller F. Tonsillectomy does not prevent a progressive course in IgAN. Clin Nephrol. 1999;51(3):147–52.
52. Piccoli A, Codognotto M, Tabbi MG, Favaro E, Rossi B. Influence of tonsillectomy on the progression of mesangioproliferative glomerulonephritis. Nephrol Dial Transplant. 2010;25(8):2583–9.
53. Suzuki H, Kiryluk K, Novak J, Moldoveanu Z, Herr AB, Renfrow MB, et al. The pathophysiology of IgA nephropathy. J Am Soc Nephrol. 2011;22(10):1795–803.
54. Moldoveanu Z, Wyatt RJ, Lee JY, Tomana M, Julian BA, Mestecky J, et al. Patients with IgA nephropathy have increased serum galactose-deficient IgA1 levels. Kidney Int. 2007;71(11):1148–54.
55. Yanagawa H, Suzuki H, Suzuki Y, Kiryluk K, Gharavi AG, Matsuoka K, et al. A panel of serum biomarkers differentiates IgA nephropathy from other renal diseases. PLoS One. 2014;9(5):e98081.
56. Launay P, Grossetête B, Arcos-Fajardo M, Gaudin E, Torres SP, Beaudoin L, et al. Fcalpha receptor (CD89) mediates the development of immunoglobulin A (IgA) nephropathy (Berger's disease). Evidence for pathogenic soluble receptor-Iga complexes in patients and CD89 transgenic mice. J Exp Med. 2000;191(11):1999–2009.
57. Schena FP, D'Altri C, Cerullo G, Manno C, Gesualdo L. ACE gene polymorphism and IgA nephropathy: an ethnically homogeneous study and a meta-analysis. Kidney Int. 2001;60(2):732–40.
58. Gharavi AG, Kiryluk K, Choi M, Li Y, Hou P, Xie J, et al. Genome-wide association study identifies susceptibility loci for IgA nephropathy. Nat Genet. 2011;43(4):321–7.
59. Yu XQ, Li M, Zhang H, Low HQ, Wei X, Wang JQ, et al. A genome-wide association study in Han Chinese identifies multiple susceptibility loci for IgA nephropathy. Nat Genet. 2011;44(2):178–82.
60. Scolari F, Amoroso A, Savoldi S, Mazzola G, Prati E, Valzorio B, et al. Familial clustering of IgA nephropathy: further evidence in an Italian population. Am J Kidney Dis. 1999;33(5):857–65.

Chapter 2
Advances in Genetics of Immunoglobulin A Nephropathy

Hong Zhang, Riccardo Magistroni, and Ali Gharavi

Abstract Familial aggregation of IgA nephropathy (IgAN) and variation in prevalence among different ethnicities indicate inherited factors contribute to disease pathogenesis. Studies have also shown that IgAN patients also have an inherited defect in O-glycosylation of IgA1. Recent genome-wide association studies (GWASs) have begun to elucidate genetic factors underlying the development of IgAN. These studies have demonstrated a strong association with *MHC* loci, highlighting an autoimmune component to disease. In addition, GWASs have identified loci involving the complement system (*CFHR1/3* and *ITGAM-ITGAX* loci), the regulation of mucosal IgA production (*TNFSF13* and *LIF/OSM* loci), innate immunity (*DEFA*, *CARD9*, *ITGAM-ITGAX*, *VAV3*, and *ST6GAL1* loci), inflammatory response (*KLF10* and *UBR5*), and epithelial cell polarization (*ACCS*). Many of the loci have been implicated in other immune-mediated and inflammatory diseases, highlighting shared pathogenesis with IgAN. The IgAN risk allele frequencies also strongly parallel the known geoepidemiology of disease and are also correlated with local pathogen diversity. These findings have helped develop a pathogenesis model and molecular candidates for disease. Analysis of larger cohorts and application of next-generation sequencing technologies are expected to identify additional genes that can further resolve pathogenesis.

Keywords Genome-wide association study • IgA glycosylation • HLA • Mucosal immunity

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2.1 Introduction

IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis, primarily affecting young adult subjects. IgAN has highly variable clinical and pathological features and causes renal failure in 20–40 % of patients in about 20 years [1, 2]. Remaining patients have persistent hematuria or proteinuria, and only a minority enters sustained clinical remission. The prognosis is also highly variable and the long-term outcome is difficult to predict in individual patients. Recurrence of the disease following kidney transplantation suggested that the primary pathogenic defect in IgAN may be of extrarenal origin, and this notion has been corroborated by the identification of altered IgA1 glycosylation and production of autoantibodies against underglycosylated IgA1 as a pathogenic determinant.

A pathogenic model for IgAN relying on a multi-hit process has been previously proposed [3]. According to this model, a series of sequential events lead to the development of the disease: the first hit consists of a deficiency in O-linked galactose in the hinge region of the IgA1 heavy chains, an abnormality that has been amply confirmed by converging experimental and clinical data [4]. Nevertheless this is not sufficient to induce the disease, and a second hit involving the production of autoantibodies directed against the undergalactosylated IgA is required [5–8]. Furthermore the formation and deposition of these immune complexes on mesangial cells constitute the third hit, and finally the inflammatory response leading to mesangial proliferation, deposition of extracellular matrix, and progression toward a fibrotic lesion is the final hit. Newer insights arising from recent genome-wide association studies (GWASs) contributed to the refinement of this model and have suggested candidate genes.

2.2 The History of Genetic Studies in IgA Nephropathy

Only few years after the first description of IgAN by Jean Berger in 1968 [9], familial aggregation was detected, arguing a genetic predisposition to this condition [10, 11]. Subsequently, multiple studies have recognized familial aggregation of IgAN and multiplex families with multiple affected individuals were reported [12–15]. In studies that performed systematic urinary analysis of family members, relatives of patients affected by IgAN also displayed a higher risk of urinary abnormalities, suggesting they are also affected [16]. Abnormalities in cytokine production among family members were also reported, suggesting an inherited dysregulation of immune response [16, 17]. Subsequent studies have also shown that relatives produce higher levels of galactose-deficient IgA1, further suggesting a shared molecular defect [18–20]. Finally, many pioneering studies described a potential link between IgAN and HLA system, an association recently confirmed in detail by GWASs [21–25].

2.2.1 Candidate Gene Studies

The candidate gene strategy is based on a priori hypotheses regarding the involvement of a specific gene or pathway, formulated from available scientific evidence about disease pathogenesis. There is an abundant literature based on this approach, with over 120 publications in IgAN research [26–148]. However, as with candidate gene studies in other fields, the replication of results has been largely disappointing [149]. Many factors contributed to the low reliability of this approach, first of all because the pathogenic mechanism of IgAN is largely unknown, complicating the formulation of a correct a priori hypothesis. Furthermore most candidate studies were underpowered, and older studies rarely sought to replicate findings in independent cohorts, contributing a high rate of false-positive (theoretically of false-negative as well, but this is partially concealed by publication bias). Additional limitations included population heterogeneity (ethnicity differences), small sample size, suboptimal matching between cases and controls. The case of the angiotensin-converting enzyme (ACE) gene insertion/deletion polymorphism illustrates these issues very well, with a large number of positive associations reported [40, 43, 50, 53, 150–153]. However, none of the unbiased GWASs conducted to date have detected a significant association at this locus.

2.2.2 Linkage Studies

Multiplex IgAN families have been described shortly after the first description of IgAN. In general, reported IgAN families are small, typically including one to three biopsy documented cases; additional family members were classified as affected based on clinical criteria if they had hematuria, proteinuria, or impaired renal function. The mode of inheritance was most consistent with autosomal dominant disease with incomplete penetrance, suggesting that genes could be mapped via linkage and positional cloning approaches. Such studies involve a genome-wide search for chromosomal segments that segregate with disease in families, followed by sequencing of positional candidates to detect mutations. This approach was extremely successful for monogenic disorders such as polycystic kidney disease but found limited success for complex traits such as IgAN. A major challenge of these studies is the high genetic heterogeneity of IgAN (i.e., different genes account for disease in different families). Nonetheless, the first application of genome-wide linkage analysis to IgAN in 30 families [154] identified the significant linkage peak on chromosome 6p22–23 under a model of autosomal dominant inheritance with genetic heterogeneity. This established genetic contribution to disease and highlighted the issue of genetic heterogeneity. In 2007 the European IgAN Consortium published their results on 22 Italian families, replicating linkage to Chr 6q22–23 and reporting additional suggestive peaks in regions 4q26–31 and 17q12–22 [155]. Subsequently another linkage study on a large Canadian

four-generation family provided another suggestive locus in the COL4A3/COL4A4 region of chromosome 2q36 [156]. Because families were small and linkage intervals were sizable, the genes were not amenable to the systematic cloning and sequencing used in traditional positional cloning approaches. Hence none of the genes underlying linkage intervals have been identified. In conclusion the linkage approach suffered from reduced power caused by genetic heterogeneity, small pedigree size, and inability to conclusively classify affected and unaffected individuals based on urinary screening alone. It is expected that the application of next-generation sequencing (whole genome or exome) could identify causal genetic variants for familial IgAN.

2.2.3 GWAS High-Density Genotyping Studies

With progress in genome-wide genotyping technology, GWAS became feasible for analysis of sporadic forms of complex traits. A GWAS is an unbiased approach that explores the association between a disease trait and a large number of single nucleotide polymorphisms (SNPs) across the entire genome. Because of the extensive linkage disequilibrium (LD) across the genome (the nonrandom association between alleles), GWAS allows detection of SNPs that are in LD with causal variants. Because SNPs for GWAS are selected to be relatively common, they pinpoint loci that are relatively common in the population. Usually 500,000–5,000,000 common SNPs are sufficient to provide adequate coverage of the genome and nowadays, ungenotyped SNPs can be imputed based on reference genome data. GWAS has successfully detected common variants associated with complex traits of common diseases such as heart disease, diabetes, autoimmune diseases, psychiatric disorders, and renal diseases (referenced in the NHGRI GWAS catalog). However, the inherent limitations of GWAS include the ability to detect only common SNPs (frequency >1–5 %), which typically exhibit relatively small effects. A consequence of their partial ability to capture all genetic information, GWAS loci tend to explain only a relatively small proportion of disease heritability [157]. Nonetheless, the GWAS data have been very informative about disease pathogenesis and disease architecture.

To date, GWAS has been successfully applied to IgAN in five large-scale studies [21–25]. Cumulatively, the 18 new and replicated GWAS loci reported in these studies explain approximately 6–8 % of the overall disease risk [24]. The first study [21] was performed in a single Caucasian cohort and readily detected association with *MHC* region, which is the strongest genetic association with IgAN and has been consistently replicated in all the studies. The subsequent studies [22, 23] performed in population of Han Chinese and European ancestry progressively expanded the size of the population analyzed. Finally, one GWAS [25] has expanded the control population of the previous study [23] to increase power and applied an imputation approach to the dataset with genotypes of 3,731,832 SNPs.

They showed novel associations at three genes: *ST6GAL1* on 3q27.3, *ACCS* on 11p11.2, and *ODF1-KLF10* on 8q22.

2.3 The New Insight of Pathogenesis in IgA Nephropathy Based on the Genetic Studies

Altogether the GWAS identified intervals implicating MHC class I and class II response (*MHC region*), the complement system (*CFHR1/3* and *ITGAM-ITGAX* loci), the regulation of mucosal IgA production (*TNFSF13* and *LIF/OSM* loci), innate immunity (*DEFA*, *CARD9*, *ITGAM-ITGAX*, *VAV3*, and *ST6GAL1* loci), inflammatory response (*KLF10* and *UBR5*), and epithelial cell polarization (*ACCS*).

2.3.1 Associations with IgA Nephropathy in the MHC *Region*

All five GWASs of IgAN identified strong signals with genome-wide significance within the *MHC* region. An association with *MHC* was reported very early with IgAN [10, 11]; however the findings were initially not reproducible because of the relatively small effect imparted by *MHC* alleles on IgAN, small sample size, and the fact that the lower resolution of classical genotyping methods could not fully capture the complex variation at *MHC* locus. The *MHC* locus is characterized by a significant amount of LD across a large region (LD extends more than 2 Mb in specific regions) [158]. Such LD poses an important obstacle in *MHC* research, making it difficult to detect functional alleles.

However, all GWASs conducted to date have identified significant associations within the *MHC*region. In addition, two studies performed detailed conditional analyses of the intervals and identified three distinct regions that implicated both class I (the *TAP1/TAP2/PSMB8/PSMB9* locus) and class II (the *HLA-DQB1*, *DQA1*, and *DRB1* loci and the *HLA-DPB2*, *DPB1*, *and DPA1* loci) immune mechanisms. Moreover, the conditional analyses also detected multiple independent alleles, indicating the presence of both risk and protective variants within each interval.

Nonetheless, by applying imputation four independent classical *HLA* alleles were associated with IgAN: two risk alleles (*DOA1*0101*, *DQB1*0301*) and two protective alleles (*DQA1*0102, DQB1*0201*) [24] that may be responsible for the association at the *HLA-DQB1*, *DQA1*, and *DRB1* loci. The identity of the functional alleles at the other *MHC* intervals is not clear, but prior data has implicated dysregulated expression of *PSMB8* in IgAN patients, suggesting that variants in this gene may be driving the association in the second *MHC* interval [159]. Systematic sequencing and fine mapping of this region in large population will identify the full spectrum of functional variants driving the association signals in this region.

2.3.2 *Associations with IgA Nephropathy in the Non-MHC Loci*

In addition to the *MHC* system, GWAS identified loci associated to the complement system, the regulation of mucosal IgA production and innate immunity against pathogens.

2.3.2.1 The Complement System

After mesangial IgA deposition, glomerular inflammation is enhanced by the activation of the complement system; this is documented by C3 glomerular staining that is a common feature of the pathology of IgAN cases [160–162] with a frequency of over 90–95 % of biopsies. Schematically, complement activation is usually grouped in three distinct pathways that converge on C3 activation: the classical, the lectin, and the alternative pathway. The presence of C3 with absence of C1q deposition in IgAN is consistent with activation of either the lectin or the alternative pathway of the complement. Lectin pathway activation is further suggested by glomerular staining for C4d that can be found in approximately 40 % of IgAN biopsies [163]. Moreover, mesangial deposition of mannose-binding lectin (MBL) is reported in 25 % of IgAN biopsies. However, the GWAS findings only provided evidence for dysregulation of the alternative complement pathway. Significant association was detected in the *CFH* locus, and this variant is in LD with a common deletion in factor H-related genes 1 and 3 (*CFHR3,1-del*). *CFHR3,1-del* is the functional allele at this interval and provides additive protection from IgAN [22, 24, 164]. Moreover, the *CFHR3,1-del* results in the absence of CFHR1 protein, which was recently shown to function as a competitive antagonist of CFH [165, 166]. Recent data suggests that *CFHR3,1-del* is associated with more effective FH-mediated inhibition of C3 and lower levels of complement activation split products. Higher FH levels are also positively associated with circulating C3 and negatively correlated with mesangial C3 deposition [167].

Interestingly, the same SNP at the *CFH* locus is protective for age-related macular degeneration, the most frequent cause of visual impairment in the elderly population. This is a common cause of retinal disease characterized by increased local activity of the alternative pathway [168]. In contrast, *CFHR3,1-del* has been associated with increased risk of systemic lupus erythematosus (SLE) and atypical hemolytic uremic syndrome [169, 170]. Finally, the same deletion is also associated to the development of autoantibodies directed against the CFH and acting as inhibitor of this complement regulator [171]. To date, anti-CFH autoantibodies in IgAN cases have not been reported. Overall the mechanisms underlying these opposed pleiotropic effects of the deletion are presently not completely understood. Interestingly, *CFHR3,1-del* is very rare in the Asian population, and therefore, this locus escaped detection in the GWAS comprised only of Han Chinese population.

2.3.2.2 The Regulation of Mucosal IgA Production

GWAS pointed to additional loci related to mucosal IgA production. For example, the *TNFSF13* locus encodes a proliferation-inducing ligand (APRIL) involved in IgA class switching. Bacteria trigger the switching by a TLR-inducible signaling program requiring APRIL [172]. The risk variant is associated with a higher serum IgA levels among IgAN cases [23, 24]. Inactivation of *Tnfsf13* in mice produces a significant decrease of serum IgA levels and reduced serum IgA antibody responses to mucosal immunization [173]. Conversely, overexpression of B cell-activating factor (BAFF), a related molecule with overlapping functions and receptors with APRIL, in a mouse model exhibits features of autoimmune disease, including B cell hyperplasia and hypergammaglobulinemia. These mice develop fatal nephritis with IgA deposits along with high circulating levels of polymeric IgA that is aberrantly glycosylated. Furthermore renal disease in BAFF-Tg mice with genetic deletion of IgA exhibited reduced pathology lesions [174].

Another GWAS hit involved the locus encoding the cytokines *LIF* and *OSM* locus on chromosome 22q12 [22]. These cytokines are members of the IL-6 family, are expressed in mucosal tissues, and have immunoregulatory properties [175–177]. The patients presenting the IgAN risk allele have higher IgA serum levels [22, 24]. LIF and OSM have been previously associated with Crohn's disease, pointing to its involvement in the regulation of intestinal inflammation [178–180]. In addition, inactivation of *Osm* in mice results in glomerulonephritis [177].

2.3.2.3 Innate Immunity Genes

Additional GWAS loci have highlighted proteins related to innate immunity: α-defensins are antimicrobial peptides mapped to chromosome 8p22–p23 in a cluster of five homologous genes (*DEFA1/3/4/5/6* genes). Together with the other family of β-defensins that maps in the same regions, the α-defensins encode for proteins with antimicrobial activity via creation of molecular pores that cause direct membrane permeabilization or by signaling to immature dendritic cells [181]. Copy number variants (CNVs) have been described for *DEFA1* and *DEFA3* and the number of copies relates to the abundance of mRNA and protein encoded [182]. The CNVs in defensins have been linked to other inflammatory conditions as Crohn's disease and psoriasis [183, 184].

Other loci related to innate immunity revealed by GWAS include *CARD9* locus. CARD9 is a pro-inflammatory adapter molecule involved in the activation of NF-κB signaling. The *CARD9* locus is implicated in the pathogenesis of inflammatory bowel disease (IBD) [180] and loss of function mutations in *CARD9* result in susceptibility invasive candidiasis. The IgAN risk allele is strongly associated with its increased expression in peripheral blood mononuclear cells. Another IgAN risk locus encompasses the *ITGAM* and *ITGAX* genes, which encode integrins αM and αX, leukocyte-specific α-integrins involved in the process of phagocytosis, and

regulation of IgA production. Intestinal dendritic cells that induce T cell-independent IgA class switch recombination express high levels of αM and αX integrins [185, 186].

2.3.3 Geoepidemiology of IgA Nephropathy

IgAN has been reported worldwide but displays a striking geographic variation. It is the most common cause of kidney failure in East Asian countries, has intermediate prevalence in European and US populations, but is rarely reported in African populations. In a geospatial analysis of 6,319 individuals representative of 85 worldwide populations, the distribution of the risk alleles was highly differentiated between ethnicities [164]. The analysis of the geographical distribution of the genetic risk score identified a west–east and a south–north gradients. The geospatial pattern of risk distribution parallels the known west-east gradient in disease prevalence. For example, the protective alleles at the *CFH* and at one of the *ITGAM*/*ITGAX* signals are virtually inexistent in East Asian populations but have a 10–25 % allele frequency in Europeans and Africans. Unexpectedly, higher resolution analysis of the European continent revealed an additional increase in the genetic risk from South to North (Fig. 2.1). To check whether this genetic finding was consistent with disease epidemiology, the authors analyzed European end-stage kidney failure registry data and confirmed the same south–north gradient in IgAN-attributable kidney failure. Similar to IgAN, other immune diseases as multiple sclerosis, type I diabetes, or IBD show a north–south geographical gradient and some susceptibility loci are shared between them [187–190], suggesting that variation in common genetic risk factors may mediate variation in prevalence of autoimmune disorders. Complex selective pressures likely underlie these gradients. Interestingly, the risk alleles with largest effects tend to have the greatest population differentiation and contribute most to the observed geo-genetic patterns. Taken together, these findings suggest that local selective pressures might have systematically increased the frequency of risk alleles in some populations through the process of multilocus adaptation. In the largest multiethnic GWAS, an analysis of different ecological variables that could potentially provide such a selective pressure was performed. Genetic risk correlated strongly with variation in local pathogen diversity, particularly helminth diversity, suggesting a possible role for host–intestinal pathogen interactions in causing the geographical distribution of genetic risk and disease prevalence [24]. Even today helminths infect nearly a quarter of the world population [191], and East Asia has the highest burden of helminth species and helminth infections with significant impact on pediatric mortality [191, 192]. It is important to point out that this model does not suggest that exposure to the helminths gives susceptibility to IgAN but rather that higher genetic risk of IgAN in Asia may represent an adverse consequence of genetic adaptation to local mucosal

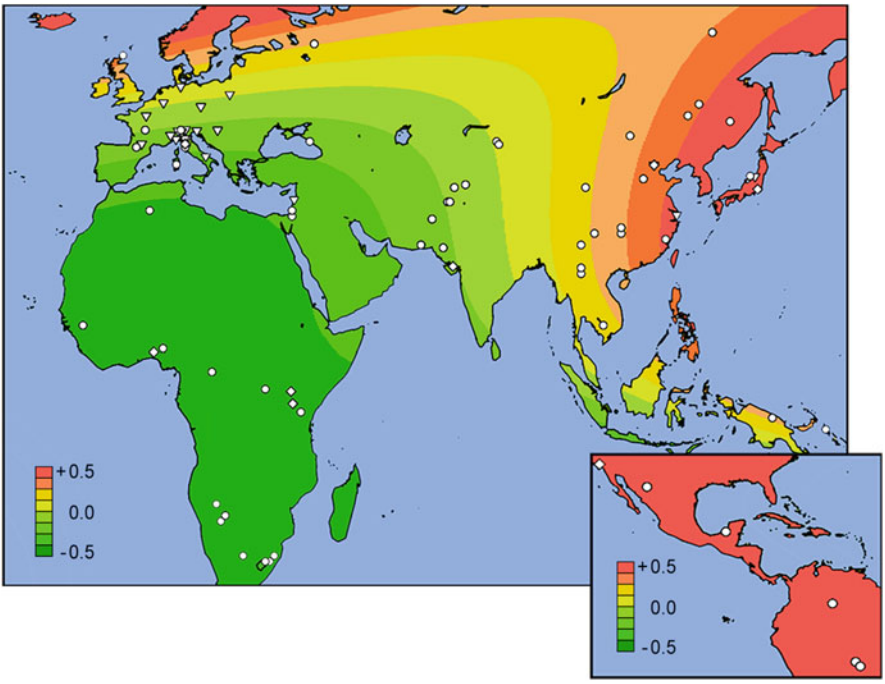

Fig. 2.1 Surface interpolation of the standardized genetic risk score over Africa and Euroasia (main) and the Americas (inset). *Symbols* represent the locations of sampled populations [164]

pathogens. The enhanced IgA response conferred by GWAS risk alleles can also explain the known association of mucosal infections as a common trigger for IgAN.

2.3.4 Shared Genetics with Inflammatory or Autoimmune Diseases

Loss of self-tolerance is fundamental to autoimmunity. A clear autoimmune component in IgAN is the development of autoantibodies directed against the undergalactosylated IgA, leading to formation of immune complexes that deposit on mesangial cell triggering an autoinflammatory cascade. The fine details of the genetic and molecular alterations that lead to this autoimmune cascade remain unknown. However the GWASs have revealed a significant number of shared loci with other autoimmune conditions. A deeper analysis of this pathway could shed light on the shared autoimmune alteration and clinical features between these heterogeneous conditions. GWASs have indicated that *HLA-DQA1*, *HLA-DQB1*, *HLA-DRB1*, and *HLA-DP* are associated with IgAN and *DQA1*0101* and *DQB1*030*1 emerged as risk alleles and *DQA1*0102* and *DQB1*0201* [22, 24]

as protective alleles after imputation analysis. A significant number of *MHC* loci identified in IgAN are shared with other autoimmune diseases such as rheumatoid arthritis [193], systemic sclerosis [194], alopecia areata [195], Graves' disease [196], type I diabetes [193], and celiac disease [197, 198]. Interestingly, a discordant effect for these loci has been found in SLE [199], multiple sclerosis [200], and ulcerative colitis [201], suggesting that some *MHC* alleles may enhance recognition of autoantigen for a specific disease but have reduced affinity for the autoantigen for another autoimmune disease and ultimately result in protection.

As mentioned above, a common deletion in *CFHR1* and *CFHR3* genes has been associated to IgAN [22]. The same deletion identified is protective in age-related macular degeneration [22, 24, 164, 168, 202] but increases risk in SLE [169] and atypical hemolytic uremic syndrome (aHUS). In aHUS, the *CFHR3,1-del* has been associated to the development of inactivating anti-FH antibodies [170] that would be the final effectors of the increased risk. Similar to *MHC*, *CFHR* loci, the IgAN risk alleles at *ITGAM*, and *ITGAX* loci have an opposite effect in SLE [203].

Significant overlap with pathways for IBD was also detected. CARD9 is a pro-inflammatory molecule which is responsible for both innate and adaptive immune responses [204]. The IgAN risk allele at the *CARD9* locus is direction consistent with associations reported on the risk of ulcerative colitis and Crohn's disease [179, 180, 205–207]. α-Defensins 5 and 6 (*DEFA5* and *DEFA6*) are constitutively produced by the intestinal Paneth cells of the intestine [208]. Deficiencies in α-defensins 5 and 6 have been previously associated with Crohn's disease [209, 210]. Finally, the *LIF/OSM* locus is also associated with IBD. Additional, suggestive associations with IBD loci were also reported and the pathway analysis revealed significant enrichment for networks involved intestinal IgA productions [24]. These shared associations between IgAN and IBD disease highlight common pathways in the pathophysiology of the inflammation of mucosal barrier and may explain co-occurrence of these two disorders [211].

TNFSF13 has not been previously related to specific autoimmune disease; however, mutations in the *TNFSF13* receptor (TACI) produce IgA deficiency or combined variable immunodeficiency, with increased propensity to mucosal infections [212]. *TNFSF13* encodes APRIL, a powerful B cell-stimulating cytokine that is induced by intestinal bacteria and promotes CD40-independent IgA class switching [213]. APRIL levels are elevated in patients with IgAN [174] and the IgAN risk allele is associated with increased IgA levels [23].

2.4 Challenges and Future Directions

The recent GWAS of IgAN demonstrated a significant association of the *LIF/OSM* and the *TNFSF13* loci with IgA levels (additive effects). In addition, the 15-SNP genetic risk score is associated with the age of presentation of disease; there was a 20-year difference in the age of presentation between individuals with the most and least number of risk alleles [24]. While the effect size is too modest to be clinically

useful, these data clearly demonstrate that genetic factors influence clinically important variables. Identification of novel loci combined with careful genotype–phenotype correlations may reveal association of individual SNPs or the genetic risk score with important variable such as proteinuria, progression, or histopathological severity. These data also suggest that detection of more common variants with GWAS or identification of rare alleles with large effect will delineate stronger clinical correlations.

Another approach is to improve phenotypic characterization. The role of undergalactosylated IgA in the pathogenesis is well established and has been the object of more than 30 years of investigation [214]. Combined measurement of galactose-deficient IgA1 and autoantibody levels may provide more refined tools for characterization of patients and relatives. The parameters are highly associated with development of disease and may enhance the resolution of genetic studies.

In addition, examination of disease mechanisms requires a strong functional assays and animal models. Cellular models to date include the production of patient-derived IgA1-producing cell lines that recapitulate defects in IgA production and allow examination of molecular defects leading to aberrant IgA1 O-glycosylation. In addition, patient-derived lymphocytes producing autoantibodies targeting undergalactosylated IgA1 have also been developed, allowing examination of pathways leading to breach in tolerance. Challenges in developing animal models include the differences in the composition and structure of IgA between rodents and humans. However, novel animal models of disease recapitulate many clinical aspects of disease and will likely prove useful for studying pathogenesis [174, 215, 216]. The recent report describing the development of IgAN in mice overexpressing BAFF [174, 217] shows convergence with detection of association of *TNFSF13* with IgAN in recent GWASs [23], indicating that these mice would be suitable for studying IgAN pathogenesis.

While GWAS represents an important advance in the evaluation of genetic component of complex diseases, it can only detect relatively frequent variants with small effect. Hence in the majority of cases, the GWAS loci explain only a fraction of the overall heritability. While fine-mapping studies may uncover additional common and rare risk alleles that together explain a larger fraction of the disease variance, there is additional "missing heritability" that may be attributable to either genetic or nongenetic factors [218–220]. In particular, the missing heritability may be due to the presence of low-frequency variants with large effect that are not detectable by GWAS methodology. For example, recent studies have also shown that CNVs with large effect contribute to many neuropsychiatric, developmental, and immune-mediated phenotypes [221–224]. In addition, next-generation sequencing (NGS) has revolutionized genomics, achieving superlative speed and accuracy in sequencing [225, 226]. Large-scale sequencing studies have now identified rare single nucleotide variants predisposing to many complex phenotypes such as autism, dyslipidemia, idiopathic pulmonary fibrosis, or ALS [227–231]. These data suggest that CNV analysis, whole genome analysis, or exome analysis of IgAN patients may similarly uncover rare genetic variants predisposing to familial and sporadic disease. Moreover these genetic studies can be combined in

clinical trials of IgAN, to detect interaction of genetic factors with progression or response to treatment.

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Schena FP. A retrospective analysis of the natural history of primary IgA nephropathy worldwide. Am J Med. 1990;89:209–15.
2. Xie J, Kiryluk K, Wang W, Wang Z, Guo S, Shen P, et al. Predicting progression of IgA nephropathy: new clinical progression risk score. PLoS ONE. 2012;7, e38904.
3. Suzuki H, Kiryluk K, Novak J, Moldoveanu Z, Herr AB, Renfrow MB, et al. The pathophysiology of IgA nephropathy. J Am Soc Nephrol. 2011;22: 1795–803.
4. Coppo R, Feehally J, Glassock RJ. IgA nephropathy at two score and one. Kidney Int. 2010; 77:181–6.
5. Yanagawa H, Suzuki H, Suzuki Y, Kiryluk K, Gharavi AG, Matsuoka K, et al. A panel of serum biomarkers differentiates IgA nephropathy from other renal diseases. PLoS ONE. 2014;9, e98081.
6. Yanagihara T, Brown R, Hall S, Moldoveanu Z, Goepfert A, Tomana M, et al. Generated immune complexes containing galactose-deficient IgA1 stimulate proliferation of mesangial cells. Results Immunol. 2012;2:166–72.
7. Berthoux F, Suzuki H, Thibaudin L, Yanagawa H, Maillard N, Mariat C, et al. Autoantibodies targeting galactose-deficient IgA1 associate with progression of IgA nephropathy. J Am Soc Nephrol. 2012;23:1579–87.
8. Suzuki H, Fan R, Zhang Z, Brown R, Hall S, Julian BA, et al. Aberrantly glycosylated IgA1 in IgA nephropathy patients is recognized by IgG antibodies with restricted heterogeneity. J Clin Invest. 2009;119:1668–77.
9. Berger J. IgA glomerular deposits in renal disease. Transplant Proc. 1969;1:939–44.
10. Sabatier JC, Genin C, Assenat H, Colon S, Ducret F, Berthoux FC. Mesangial IgA glomerulonephritis in HLA-identical brothers. Clin Nephrol. 1979;11:35–8.
11. Tolkoff-Rubin NE, Cosimi AB, Fuller T, Rublin RH, Colvin RB. IGA nephropathy in HLA-identical siblings. Transplantation. 1978;26:430–3.
12. O'Connell PJ, Ibels LS, Thomas MA, Harris M, Eckstein RP. Familial IgA nephropathy: a study of renal disease in an Australian aboriginal family. Aust N Z J Med. 1987;17:27–33.
13. Levy M. Familial cases of Berger's disease and anaphylactoid purpura: more frequent than previously thought. Am J Med. 1989;87:246–8.
14. Julian BA, Quiggins PA, Thompson JS, Woodford SY, Gleason K, Wyatt RJ. Familial IgA nephropathy. Evidence of an inherited mechanism of disease. N Engl J Med. 1985;312:202–8.
15. Scolari F, Amoroso A, Savoldi S, Mazzola G, Prati E, Valzorio B, et al. Familial clustering of IgA nephropathy: further evidence in an Italian population. Am J Kidney Dis. 1999;33:857–65.
16. Schena FP, Scivittaro V, Ranieri E, Sinico R, Benuzzi S, Di Cillo M, et al. Abnormalities of the IgA immune system in members of unrelated pedigrees from patients with IgA nephropathy. Clin Exp Immunol. 1993;92:139–44.
17. Scivittaro V, Gesualdo L, Ranieri E, Marfella C, Schewn SA, Emancipator SN, et al. Profiles of immunoregulatory cytokine production in vitro in patients with IgA nephropathy and their kindred. Clin Exp Immunol. 1994;96:311–6.
18. Gharavi AG, Moldoveanu Z, Wyatt RJ, Barker CV, Woodford SY, Lifton RP, et al. Aberrant IgA1 glycosylation is inherited in familial and sporadic IgA nephropathy. J Am Soc Nephrol. 2008;19:1008–14.

19. Kiryluk K, Moldoveanu Z, Sanders JT, Eison TM, Suzuki H, Julian BA, et al. Aberrant glycosylation of IgA1 is inherited in both pediatric IgA nephropathy and Henoch-Schonlein purpura nephritis. Kidney Int. 2011;80:79–87.
20. Lin X, Ding J, Zhu L, Shi S, Jiang L, Zhao M, et al. Aberrant galactosylation of IgA1 is involved in the genetic susceptibility of Chinese patients with IgA nephropathy. Nephrol Dial Transplant. 2009;24:3372–5.
21. Feehally J, Farrall M, Boland A, Gale DP, Gut I, Heath S, et al. HLA has strongest association with IgA nephropathy in genome-wide analysis. J Am Soc Nephrol. 2010;21:1791–7.
22. Gharavi AG, Kiryluk K, Choi M, Li Y, Hou P, Xie J, et al. Genome-wide association study identifies susceptibility loci for IgA nephropathy. Nat Genet. 2011;43:321–7.
23. Yu XQ, Li M, Zhang H, Low HQ, Wei X, Wang JQ, et al. A genome-wide association study in Han Chinese identifies multiple susceptibility loci for IgA nephropathy. Nat Genet. 2012;44:178–82.
24. Kiryluk K, Li Y, Scolari F, Sanna-Cherchi S, Choi M, Verbitsky M, et al. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. Nat Genet. 2014;46:1187–96.
25. Li M, Foo JN, Wang JQ, Low HQ, Tang XQ, Toh KY, et al. Identification of new susceptibility loci for IgA nephropathy in Han Chinese. Nat Commun. 2015;6:7270.
26. Finn JE, Li PK, Lai KN, Mathieson PW. Molecular analysis of C3 allotypes in Chinese patients with immunoglobulin A nephropathy. Am J Kidney Dis. 1994;23:543–6.
27. Li PK, Poon AS, Lai KN. Molecular genetics of MHC class II alleles in Chinese patients with IgA nephropathy. Kidney Int. 1994;46:185–90.
28. Harden PN, Rowe PA, Rodger RSC, Junor BJR, Briggs JD, Jardine AG, et al. Polymorphisms in angiotensin-converting-enzyme gene and progression of IgA nephropathy. Lancet. 1995;345:1540–2.
29. Schmidt S, Stier E, Hartung R, Stein G, Bahnisch J, Woodroffe AJ, et al. No association of converting enzyme insertion/deletion polymorphism with immunoglobulin A glomerulonephritis. Am J Kidney Dis. 1995;26:727–31.
30. Shimomura M, Yoshikawa N, Iijima K, Nakamura H, Miyazaki M, Sakai H. Polymorphism of immunoglobulin heavy chain switch region gene in children with severe IgA nephropathy. Clin Nephrol. 1995;43:211–5.
31. Yorioka T, Suehiro T, Yasuoka N, Hashimoto K, Kawada M. Polymorphism of the angiotensin converting enzyme gene and clinical aspects of IgA nephropathy. Clin Nephrol. 1995; 44:80–5.
32. Yoshida H, Mitarai T, Kawamura T, Kitajima T, Miyazaki Y, Nagasawa R, et al. Role of the deletion of polymorphism of the angiotensin converting enzyme gene in the progression and therapeutic responsiveness of IgA nephropathy. J Clin Invest. 1995;96:2162–9.
33. Fennessy M, Hitman GA, Moore RH, Metcalfe K, Medcraft J, Sinico RA, et al. HLA-DQ gene polymorphism in primary IgA nephropathy in three European populations. Kidney Int. 1996;49:477–80.
34. Hunley TE, Julian BA, Phillips JA 3rd, Summar ML, Yoshida H, Horn RG, et al. Angiotensin converting enzyme gene polymorphism: potential silencer motif and impact on progression in IgA nephropathy. Kidney Int. 1996;49:571–7.
35. Jin DK, Kohsaka T, Koo JW, Ha IS, Cheong HI, Choi Y. Complement 4 locus II gene deletion and DQA1*0301 gene: genetic risk factors for IgA nephropathy and Henoch-Schonlein nephritis. Nephron. 1996;73:390–5.
36. Burg M, Menne J, Ostendorf T, Kliem V, Floege J. Gene-polymorphisms of angiotensin converting enzyme and endothelial nitric oxide synthase in patients with primary glomerulonephritis. Clin Nephrol. 1997;48:205–11.
37. Chen X, Liu S, Ye Y, Xu Q. Association of angiotensin-converting enzyme gene insertion/deletion polymorphism with the clinico-pathological manifestations in immunoglobulin A nephropathy patients. Chin Med J (Engl). 1997;110:526–9.

38. Li PK, Poon P, Phil M, Poon AS, Szeto CC, Yu AW, et al. Association of IgA nephropathy with T-cell receptor constant alpha chain gene polymorphism. Am J Kidney Dis. 1997;30:260–4.
39. Liu ZH, Cheng ZH, Yu YS, Tang Z, Li LS. Interleukin-1 receptor antagonist allele: is it a genetic link between Henoch-Schonlein nephritis and IgA nephropathy? Kidney Int. 1997;51: 1938–42.
40. Pei Y, Scholey J, Thai K, Suzuki M, Cattran D. Association of angiotensinogen gene T235 variant with progression of immunoglobulin A nephropathy in Caucasian patients. J Clin Invest. 1997;100:814–20.
41. Tatsuma N, Tsugu H, Murakami M. HLA-DQ region and TCR gene polymorphism associated with primary IgA nephropathy in Japanese children. Nihon Jinzo Gakkai Shi. 1997;39: 734–9.
42. Amoroso A, Danek G, Vatta S, Crovella S, Berrino M, Guarrera S, et al. Polymorphisms in angiotensin-converting enzyme gene and severity of renal disease in Henoch-Schonlein patients. Italian Group of Renal Immunopathology. Nephrol Dial Transplant. 1998;13:3184–8.
43. Tanaka R, Iijima K, Murakami R, Koide M, Nakamura H, Yoshikawa N. ACE gene polymorphism in childhood IgA nephropathy: association with clinicopathologic findings. Am J Kidney Dis. 1998;31:774–9.
44. Yoshioka T, Xu Y, Yoshida H, Shiraga H, Muraki T, Ito K. Deletion polymorphism of the angiotensin converting enzyme gene predicts persistent proteinuria in Henoch-Schonlein purpura nephritis. Arch Dis Child. 1998;79: 394–9.
45. Asano T, Tatsuma N, Yoshida J, Ohashi R, Ambo K, Tsuchiya M, et al. Association of angiotensin-converting enzyme gene polymorphism and renal pathology in Japanese children with IgA nephropathy. Clin Nephrol. 1999;51:335–40.
46. Deenitchina SS, Shinozaki M, Hirano T, Ando T, Hirakata H, Kiyohara Y, et al. Association of a T-cell receptor constant alpha chain gene polymorphism with progression of IgA nephropathy in Japanese patients. Am J Kidney Dis. 1999;34:279–88.
47. Ito H, Morita T, Suehiro T, Tahara K, Ikeda Y, Nakauchi Y, et al. Neuropeptide Y Y1 receptor polymorphism as a prognostic predictor in Japanese patients with IgA nephropathy. Clin Nephrol. 1999;51:272–9.
48. Morita T, Ito H, Suehiro T, Tahara K, Matsumori A, Chikazawa H, et al. Effect of a polymorphism of endothelial nitric oxide synthase gene in Japanese patients with IgA nephropathy. Clin Nephrol. 1999;52:203–9.
49. Ong-Ajyooth S, Ong-Ajyooth L, Limmongkon A, Tiensingh A, Parichatikanon P, Nilwarangkur S. The renin – angiotensin system gene polymorphisms and clinicopathological correlations in IgA nephropathy. J Med Assoc Thai. 1999;82:681–9.
50. Stratta P, Canavese C, Ciccone G, Barolo S, Dall'Omo AM, Fasano ME, et al. Angiotensin I-converting enzyme genotype significantly affects progression of IgA glomerulonephritis in an Italian population. Am J Kidney Dis. 1999;33:1071–9.
51. Yorioka N, Nishida Y, Oda H, Watanabe T, Yamakido M. Apolipoprotein E polymorphism in IgA nephropathy. Nephron. 1999;83:246–9.
52. Dudley J, Afifi E, Gardner A, Tizard EJ, McGraw ME. Polymorphism of the ACE gene in Henoch-Schonlein purpura nephritis. Pediatr Nephrol. 2000;14:218–20.
53. Frimat L, Philippe C, Maghakian MN, Jonveaux P, Hurault de Ligny B, Guillemin F, et al. Polymorphism of angiotensin converting enzyme, angiotensinogen, and angiotensin II type 1 receptor genes and end-stage renal failure in IgA nephropathy: IGARAS–a study of 274 Men. J Am Soc Nephrol. 2000;11:2062–7.
54. Han SY, Kwon YJ, Jo SK, Shin JH, Cha DR, Cho WY, et al. ACE gene polymorphism and renal responsiveness to ACE inhibitors in IgA nephropathy patients. Korean J Intern Med. 2000;15:13–8.
55. Kim W, Kang SK, Lee DY, Koh GY, Lee KY, Park SK. Endothelial nitric oxide synthase gene polymorphism in patients with IgA nephropathy. Nephron. 2000;86:232–3.

56. Shu KH, Lee SH, Cheng CH, Wu MJ, Lian JD. Impact of interleukin-1 receptor antagonist and tumor necrosis factor-alpha gene polymorphism on IgA nephropathy. Kidney Int. 2000; 58:783–9.
57. Suzuki S, Suzuki Y, Kobayashi Y, Harada T, Kawamura T, Yoshida H, et al. Insertion/deletion polymorphism in ACE gene is not associated with renal progression in Japanese patients with IgA nephropathy. Am J Kidney Dis. 2000;35:896–903.
58. Syrjänen J, Huang XH, Mustonen J, Koivula T, Lehtimäki T, Pasternack A. Angiotensin-converting enzyme insertion/deletion polymorphism and prognosis of IgA nephropathy. Nephron. 2000;86:115–21.
59. Szelestei T, Bähring S, Kovács T, Vas T, Salamon C, Busjahn A, et al. Association of a uteroglobin polymorphism with rate of progression in patients with IgA nephropathy. Am J Kidney Dis. 2000;36:468–73.
60. Zhu X, Zhang Y, Wang Q, Wang F. Polymorphisms of TAP, LMP and HLA-DM genes in the Chinese. Chin Med J (Engl). 2000;113:372–5.
61. Gong R, Liu Z, Li L. Mannose-binding lectin gene polymorphism associated with the patterns of glomerular immune deposition in IgA nephropathy. Scand J Urol Nephrol. 2001;35: 228–32.
62. Kim YS, Kang D, Kwon DY, Park WY, Kim H, Lee DS, et al. Uteroglobin gene polymorphisms affect the progression of immunoglobulin A nephropathy by modulating the level of uteroglobin expression. Pharmacogenetics. 2001;11:299–305.
63. Lee EY, Yang DH, Hwang KY, Hong SY. Is tumor necrosis factor genotype (TNFA2/TNFA2)a genetic prognostic factor of an unfavorable outcome in IgA nephropathy? J Korean Med Sci. 2001;16:751–5.
64. Maruyama K, Yoshida M, Nishio H, Shirakawa T, Kawamura T, Tanaka R, et al. Polymorphisms of renin-angiotensin system genes in childhood IgA nephropathy. Pediatr Nephrol. 2001;16:350–5.
65. Narita I, Goto S, Saito N, Sakatsume M, Jin S, Omori K, et al. Genetic polymorphisms in the promoter and 5' UTR region of the Fc alpha receptor (CD89) are not associated with a risk of IgA nephropathy. J Hum Genet. 2001;46: 694–8.
66. Narita I, Kondo D, Goto S, Saito N, Watanabe Y, Yamazaki H, et al. Association of gene polymorphism of polymeric immunoglobulin receptor and IgA nephropathy. Intern Med. 2001;40:867–72.
67. Pirulli D, Boniotto M, Vatta L, Crovella S, Spano A, Morgutti M, et al. Polymorphisms in the promoter region and at codon 54 of the MBL2 gene are not associated with IgA nephropathy. Nephrol Dial Transplant. 2001;16:759–64.
68. Tsuge T, Shimokawa T, Horikoshi S, Tomino Y, Ra C. Polymorphism in promoter region of Fc alpha receptor gene in patients with IgA nephropathy. Hum Genet. 2001;108:128–33.
69. Akiyama F, Tanaka T, Yamada R, Ohnishi Y, Tsunoda T, Maeda S, et al. Single-nucleotide polymorphisms in the class II region of the major histocompatibility complex in Japanese patients with immunoglobulin A nephropathy. J Hum Genet. 2002;47:532–8.
70. Drouet M, Aupetit C, Denizot Y, Bois M, Bridoux F, Aldigier JC, et al. Analysis of three genetic markers in IgA nephropathy patients from a single region. Clin Nephrol. 2002;57:253–60.
71. Gong R, Liu Z, Chen Z, Li L. Genetic variation of mannose-binding protein associated with glomerular immune deposition in IgA nephropathy. Chin Med J (Engl). 2002;115:192–6.
72. Goto S, Narita I, Saito N, Watanabe Y, Yamazaki H, Sakatsume M, et al. A(-20)C polymorphism of the angiotensinogen gene and progression of IgA nephropathy. Kidney Int. 2002;62:980–5.
73. Lau YK, Woo KT, Choong HL, Zhao Y, Tan HB, Cheung W, et al. ACE gene polymorphism and disease progression of IgA nephropathy in Asians in Singapore. Nephron. 2002;91:499–503.
74. Lim CS, Zheng S, Kim YS, Ahn C, Han JS, Kim S, et al. The – 174 G to C polymorphism of interleukin-6 gene is very rare in Koreans. Cytokine. 2002;19:52–4.

75. Matsunaga A, Numakura C, Kawakami T, Itoh Y, Kawabata I, Masakane I, et al. Association of the uteroglobin gene polymorphism with IgA nephropathy. Am J Kidney Dis. 2002;39:36–41.
76. Menegatti E, Nardacchione A, Alpa M, Agnes C, Rossi D, Chiara M, et al. Polymorphism of the uteroglobin gene in systemic lupus erythematosus and IgA nephropathy. Lab Invest. 2002;82:543–6.
77. Merta M, Reiterova J, Tesar V, Stekrova J, Viklicky O. Influence of the endothelial nitric oxide synthase polymorphism on the progression of autosomal dominant polycystic kidney disease and IgA nephropathy. Ren Fail. 2002;24:585–93.
78. Narita I, Saito N, Goto S, Jin S, Omori K, Sakatsume M, et al. Role of uteroglobin G38A polymorphism in the progression of IgA nephropathy in Japanese patients. Kidney Int. 2002;61:1853–8.
79. Narita I, Saito N, Goto S, Shirasaki A, Morioka Y, Jin S, et al. Role of genetic polymorphism in the SA gene on the blood pressure and prognosis of renal function in patients with immunoglobulin A nephropathy. Hypertens Res. 2002;25:831–6.
80. Santos NM, Ault BH, Gharavi AG, Kritchevsky SB, Quasney MW, Jackson EC, et al. Angiotensin-converting enzyme genotype and outcome in pediatric IgA nephropathy. Pediatr Nephrol. 2002;17:496–502.
81. Syrjanen J, Hurme M, Lehtimaki T, Mustonen J, Pasternack A. Polymorphism of the cytokine genes and IgA nephropathy. Kidney Int. 2002;61:1079–85.
82. Takei T, Iida A, Nitta K, Tanaka T, Ohnishi Y, Yamada R, et al. Association between single-nucleotide polymorphisms in selectin genes and immunoglobulin A nephropathy. Am J Hum Genet. 2002;70:781–6.
83. Watanabe M, Iwano M, Akai Y, Kurioka H, Nishitani Y, Harada K, et al. Association of interleukin-1 receptor antagonist gene polymorphism with IgA nephropathy. Nephron. 2002;91:744–6.
84. Wolf G, Panzer U, Harendza S, Wenzel U, Stahl RA. No association between a genetic variant of the p22(phox) component of NAD(P)H oxidase and the incidence and progression of IgA nephropathy. Nephrol Dial Transplant. 2002;17:1509–12.
85. Yoon HJ, Kim H, Kim HL, Lee SG, Zheng SH, Shin JH, et al. Interdependent effect of angiotensin-converting enzyme and platelet-activating factor acetylhydrolase gene polymorphisms on the progression of immunoglobulin A nephropathy. Clin Genet. 2002;62:128–34.
86. Masutani K, Miyake K, Nakashima H, Hirano T, Kubo M, Hirakawa M, et al. Impact of interferon-gamma and interleukin-4 gene polymorphisms on development and progression of IgA nephropathy in Japanese patients. Am J Kidney Dis. 2003;41:371–9.
87. Narita I, Goto S, Saito N, Song J, Ajiro J, Sato F, et al. Interaction between ACE and ADD1 gene polymorphisms in the progression of IgA nephropathy in Japanese patients. Hypertension. 2003;42:304–9.
88. Narita I, Goto S, Saito N, Song J, Kondo D, Omori K, et al. Genetic polymorphism of NPHS1 modifies the clinical manifestations of Ig A nephropathy. Lab Invest. 2003;83:1193–200.
89. Narita I, Goto S, Saito N, Song J, Omori K, Kondo D, et al. Renoprotective efficacy of renin-angiotensin inhibitors in IgA nephropathy is influenced by ACE A2350G polymorphism. J Med Genet. 2003;40, e130.
90. Narita I, Goto S, Saito N, Song J, Omori K, Kondo D, et al. Angiotensinogen gene variation and renoprotective efficacy of renin-angiotensin system blockade in IgA nephropathy. Kidney Int. 2003;64:1050–8.
91. Obara W, Iida A, Suzuki Y, Tanaka T, Akiyama F, Maeda S, et al. Association of single-nucleotide polymorphisms in the polymeric immunoglobulin receptor gene with immunoglobulin A nephropathy (IgAN) in Japanese patients. J Hum Genet. 2003;48:293–9.
92. Song J, Narita I, Goto S, Saito N, Omori K, Sato F, et al. Gender specific association of aldosterone synthase gene polymorphism with renal survival in patients with IgA nephropathy. J Med Genet. 2003;40:372–6.

93. Song J, Sakatsume M, Narita I, Goto S, Omori K, Takada T, et al. Peroxisome proliferator-activated receptor gamma C161T polymorphisms and survival of Japanese patients with immunoglobulin A nephropathy. Clin Genet. 2003;64: 398–403.
94. Tuglular S, Berthoux P, Berthoux F. Polymorphisms of the tumour necrosis factor alpha gene at position -308 and TNFd microsatellite in primary IgA nephropathy. Nephrol Dial Transplant. 2003;18:724–31.
95. Yoon HJ, Shin JH, Yang SH, Chae DW, Kim H, Lee DS, et al. Association of the CD14 gene -159C polymorphism with progression of IgA nephropathy. J Med Genet. 2003;40:104–8.
96. Bantis C, Heering PJ, Aker S, Klein-Vehne N, Grabensee B, Ivens K. Association of interleukin-10 gene G-1082A polymorphism with the progression of primary glomerulonephritis. Kidney Int. 2004;66:288–94.
97. Bantis C, Ivens K, Kreusser W, Koch M, Klein-Vehne N, Grabensee B, et al. Influence of genetic polymorphisms of the renin-angiotensin system on IgA nephropathy. Am J Nephrol. 2004;24:258–67.
98. Carturan S, Roccatello D, Menegatti E, Di Simone D, Davit A, Piazza A, et al. Association between transforming growth factor beta1 gene polymorphisms and IgA nephropathy. J Nephrol. 2004;17:786–93.
99. Lau YK, Woo KT, Choong HL, Zhao Y, Tan HB, Chong SM, et al. Renin-angiotensin system gene polymorphisms: its impact on IgAN and its progression to end-stage renal failure among Chinese in Singapore. Nephron Physiol. 2004; 97:p1–8.
100. Li YJ, Du Y, Li CX, Guo H, Leung JC, Lam MF, et al. Family-based association study showing that immunoglobulin A nephropathy is associated with the polymorphisms 2093C and 2180T in the 3′ untranslated region of the Megsin gene. J Am Soc Nephrol. 2004;15:1739–43.
101. Nakanishi K, Sako M, Yata N, Aoyagi N, Nozu K, Tanaka R, et al. A-20C angiotensinogen gene polymorphism and proteinuria in childhood IgA nephropathy. Pediatr Nephrol. 2004;19:144–7.
102. Sato F, Narita I, Goto S, Kondo D, Saito N, Ajiro J, et al. Transforming growth factor-beta1 gene polymorphism modifies the histological and clinical manifestations in Japanese patients with IgA nephropathy. Tissue Antigens. 2004;64:35–42.
103. Steinmetz OM, Panzer U, Harendza S, Mertens PR, Ostendorf T, Floege J, et al. No association of the -2518 MCP-1 A/G promoter polymorphism with incidence and clinical course of IgA nephropathy. Nephrol Dial Transplant. 2004;19: 596–601.
104. Suzuki H, Sakuma Y, Kanesaki Y, Eiro M, Asahi K, Sanada H, et al. Close relationship of plasminogen activator inhibitor-1 4G/5G polymorphism and progression of IgA nephropathy. Clin Nephrol. 2004;62:173–9.
105. Thibaudin L, Berthoux P, Thibaudin D, Mariat C, Berthoux F. G protein beta3 subunit C825T polymorphism in primary IgA nephropathy. Kidney Int. 2004;66:322–8.
106. Woo KT, Lau YK, Choong LH, Zhao Y, Tan HB, Fook-Chong S, et al. Polymorphism of renin-angiotensin system genes in IgA nephropathy. Nephrology (Carlton). 2004;9:304–9.
107. Bantis C, Heering PJ, Aker S, Kuhr N, Grabensee B, Ivens K. Influence of beta3 integrin gene Leu/Pro33 polymorphism on primary glomerulonephritis. Nephron Exp Nephrol. 2005;99: e33–7.
108. Chin HJ, Na KY, Kim SJ, Oh KH, Kim YS, Lim CS, et al. Interleukin-10 promoter polymorphism is associated with the predisposition to the development of IgA nephropathy and focal segmental glomerulosclerosis in Korea. J Korean Med Sci. 2005;20:989–93.
109. Lim CS, Kim YS, Chae DW, Ahn C, Han JS, Kim S, et al. Association of C-509T and T869C polymorphisms of transforming growth factor-beta1 gene with susceptibility to and progression of IgA nephropathy. Clin Nephrol. 2005;63:61–7.
110. Mori H, Kaneko Y, Narita I, Goto S, Saito N, Kondo D, et al. Monocyte chemoattractant protein-1 A-2518G gene polymorphism and renal survival of Japanese patients with immunoglobulin A nephropathy. Clin Exp Nephrol. 2005; 9:297–303.
111. Ohtsubo S, Iida A, Nitta K, Tanaka T, Yamada R, Ohnishi Y, et al. Association of a single-nucleotide polymorphism in the immunoglobulin mu-binding protein 2 gene with immunoglobulin A nephropathy. J Hum Genet. 2005;50: 30–5.

112. Tanaka Y, Suzuki Y, Tsuge T, Kanamaru Y, Horikoshi S, Monteiro RC, et al. FcgammaRIIa-131R allele and FcgammaRIIIa-176V/V genotype are risk factors for progression of IgA nephropathy. Nephrol Dial Transplant. 2005;20:2439–45.
113. Berthoux FC, Berthoux P, Mariat C, Thibaudin L, Afiani A, Linossier MT. CC-chemokine receptor five gene polymorphism in primary IgA nephropathy: the 32 bp deletion allele is associated with late progression to end-stage renal failure with dialysis. Kidney Int. 2006;69:565–72.
114. Chow KM, Szeto CC, Lai FM, Poon P, Wong TY, Li PK. Genetic polymorphism of vascular endothelial growth factor: impact on progression of IgA nephropathy. Ren Fail. 2006;28:15–20.
115. Di Duca M, Oleggini R, Sanna-Cherchi S, Pasquali L, Di Donato A, Parodi S, et al. Cis and trans regulatory elements in NPHS2 promoter: implications in proteinuria and progression of renal diseases. Kidney Int. 2006;70:1332–41.
116. Eisenstein EM, Choi M. Analysis of a uteroglobin gene polymorphism in childhood Henoch-Schonlein purpura. Pediatr Nephrol. 2006;21:782–4.
117. Kovács TJ, Harris S, Vas TK, Seres I, Short CD, Wittmann IK, et al. Paraoxonase gene polymorphism and serum activity in progressive IgA nephropathy. J Nephrol. 2006;19:732–8.
118. Li G, Zhang H, Lv J, Hou P, Wang H. Tandem repeats polymorphism of MUC20 is an independent factor for the progression of immunoglobulin A nephropathy. Am J Nephrol. 2006;26:43–9.
119. Schena FP, Cerullo G, Torres DD, Scolari F, Foramitti M, Amoroso A. Role of interferon-gamma gene polymorphisms in susceptibility to IgA nephropathy: a family-based association study. Eur J Hum Genet. 2006;14:488–96.
120. Watanabe Y, Inoue T, Okada H, Kotaki S, Kanno Y, Kikuta T, et al. Impact of selectin gene polymorphisms on rapid progression to end-stage renal disease in patients with IgA nephropathy. Intern Med. 2006;45:947–51.
121. Xia YF, Huang S, Li X, Yang N, Huang J, Xue C, et al. A family-based association study of megsin A23167G polymorphism with susceptibility and progression of IgA nephropathy in a Chinese population. Clin Nephrol. 2006;65:153–9.
122. Bicanski B, Wenderdel M, Mertens PR, Senderek J, Panzer U, Steinmetz O, et al. PDGF-B gene single-nucleotide polymorphisms are not predictive for disease onset or progression of IgA nephropathy. Clin Nephrol. 2007;67:65–72.
123. Chacko B, Raghuraman S, Neelakantan N, John GT, Jacob CK. Impact of ACE gene polymorphisms on the progression of IgA nephropathy in India. Ren Fail. 2007;29:647–8.
124. Coppo R, Amore A, Chiesa M, Lombardo F, Cirina P, Andrulli S, et al. Serological and genetic factors in early recurrence of IgA nephropathy after renal transplantation. Clin Transplant. 2007;21:728–37.
125. Li GS, Zhang H, Lv JC, Shen Y, Wang HY. Variants of C1GALT1 gene are associated with the genetic susceptibility to IgA nephropathy. Kidney Int. 2007;71:448–53.
126. Li GS, Zhu L, Zhang H, Lv JC, Ding JX, Zhao MH, et al. Variants of the ST6GALNAC2 promoter influence transcriptional activity and contribute to genetic susceptibility to IgA nephropathy. Hum Mutat. 2007;28:950–7.
127. Lim CS, Kim SM, Oh YK, Kim YS, Chae DW, Han JS, Kim S, Lee JS, Yoon HJ, et al. Association between the clara cell secretory protein (CC16) G38A polymorphism and the progression of IgA nephropathy. Clin Nephrol. 2007;67:73–80.
128. Maixnerová D, Merta M, Reiterová J, Stekrová J, Rysavá R, Obeidová H, et al. The influence of three endothelin-1 polymorphisms on the progression of IgA nephropathy. Folia Biol (Praha). 2007;53:27–32.
129. Mao J, DU L, Gu W, Dai Y, Liu A, Xia Y, et al. Lack of association between NPHS2 gene polymorphisms and sporadic IgA nephropathy. Nephrology (Carlton). 2007;12:371–5.

130. Reiterová J, Merta M, Stekrová J, Maixnerová D, Obeidová H, Kebrdlová V, et al. The influence of endothelin-A receptor gene polymorphism on the progression of autosomal dominant polycystic kidney disease and IgA nephropathy. Folia Biol (Praha). 2007;53:134–7.
131. Woo KT, Lau YK, Zhao Y, Liu FE, Tan HB, Tan EK, et al. Disease progression, response to ACEI/ATRA therapy and influence of ACE gene in IgA nephritis. Cell Mol Immunol. 2007;4:227–32.
132. Xu G, He Q, Shou Z, Wang H, Zhang X, Wang Y, et al. NA1/NA2 heterozygote of Fcgr3b is a risk factor for progression of IgA nephropathy in Chinese. J Clin Lab Anal. 2007;21:298–302.
133. Bantis C, Heering P, Aker S, Kuhr N, Grabensee B, Ivens K. Influence of cytokine gene polymorphisms on IgA nephropathy. Ren Fail. 2008;30:135–40.
134. Bantis C, Heering PJ, Aker S, Schwandt C, Grabensee B, Ivens K. Influence of interleukin-10 gene G-1082A polymorphism on recurrent IgA nephropathy. J Nephrol. 2008;21:941–6.
135. Courtney AE, McNamee PT, Heggarty S, Middleton D, Maxwell AP. Association of functional haem oxygenase-1 gene promoter polymorphism with polycystic kidney disease and IgA nephropathy. Nephrol Dial Transplant. 2008;23:608–11.
136. Draman CR, Kong NC, Gafor AH, Rahman AF, Zainuddin S, Mustaffa WM, et al. The effects of angiotensin-converting enzyme gene polymorphism on the progression of immunoglobulin A nephropathy in Malaysian patients. Singap Med J. 2008; 49:924–9.
137. Lim CS, Kim SM, Oh YK, Joo KW, Kim YS, Han JS, et al. Megsin 2093T-2180C haplotype at the 3' untranslated region is associated with poor renal survival in Korean IgA nephropathy patients. Clin Nephrol. 2008;70:101–9.
138. Liu XQ, Paterson AD, He N, St George-Hyslop P, Rauta V, Gronhagen-Riska C, et al. IL5RA and TNFRSF6B gene variants are associated with sporadic IgA nephropathy. J Am Soc Nephrol. 2008;19:1025–33.
139. Maixnerová D, Merta M, Reiterová J, Stekrová J, Rysavá R, Viklický O, et al. The influence of two megsin polymorphisms on the progression of IgA nephropathy. Folia Biol (Praha). 2008;54:40–5.
140. Qin W, Zhong X, Fan JM, Zhang YJ, Liu XR, Ma XY. External suppression causes the low expression of the Cosmc gene in IgA nephropathy. Nephrol Dial Transplant. 2008;23:1608–14.
141. Suzuki H, Suzuki Y, Narita I, Aizawa M, Kihara M, Yamanaka T, et al. Toll-like receptor 9 affects severity of IgA nephropathy. J Am Soc Nephrol. 2008;19:2384–95.
142. Woo KT, Lau YK, Chan CM, Wong KS. Angiotensin-converting enzyme inhibitor versus angiotensin 2 receptor antagonist therapy and the influence of angiotensin-converting enzyme gene polymorphism in IgA nephritis. Ann Acad Med Singap. 2008;37:372–6.
143. Chin HJ, Cho HJ, Lee TW, Na KY, Yoon HJ, Chae DW, et al. The heme oxygenase-1 genotype is a risk factor to renal impairment of IgA nephropathy at diagnosis, which is a strong predictor of mortality. J Korean Med Sci. 2009;24(Suppl):S30–7.
144. Edey M, Strain L, Ward R, Ahmed S, Thomas T, Goodship TH. Is complement factor H a susceptibility factor for IgA nephropathy? Mol Immunol. 2009;46:1405–8.
145. Li R, Xue C, Li C, Lou T, Tao Y, Li Y, et al. TRAC variants associate with IgA nephropathy. J Am Soc Nephrol. 2009;20: 1359–67.
146. Malycha F, Eggermann T, Hristov M, Schena FP, Mertens PR, Zerres K, et al. No evidence for a role of cosmc-chaperone mutations in European IgA nephropathy patients. Nephrol Dial Transplant. 2009;24:321–4.
147. Pirulli D, Crovella S, Ulivi S, Zadro C, Bertok S, Rendine S, et al. Genetic variant of C1GalT1 contributes to the susceptibility to IgA nephropathy. J Nephrol. 2009;22:152–9.
148. Yoon HJ, Chin HJ, Na KY, Chae DW, Kim S, Jeon US, et al. Association of angiotensin II type 2 receptor gene A1818T polymorphism with progression of immunoglobulin A nephropathy in Korean patients. J Korean Med Sci. 2009;24(Suppl):S38–43.
149. Ioannidis JP, Ntzani EE, Trikalinos TA, Contopoulos-Ioannidis DG. Replication validity of genetic association studies. Nat Genet. 2001;29:306–9.

150. Tiret L, Rigat B, Visvikis S, Breda C, Corvol P, Cambien F, et al. Evidence, from combined segregation and linkage analysis, that a variant of the angiotensin I-converting enzyme (ACE) gene controls plasma ACE levels. Am J Hum Genet. 1992;51:197–205.
151. Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J Clin Invest. 1990;86:1343–6.
152. Schena FP, D'Altri C, Cerullo G, Manno C, Gesualdo L. ACE gene polymorphism and IgA nephropathy: an ethnically homogeneous study and a meta-analysis. Kidney Int. 2001;60: 732–40.
153. Yong D, Qing WQ, Hua L, Kan JJ, Xi CJ, Jin QQ, et al. Association of angiotensin I-converting enzyme gene insertion/deletion polymorphism and IgA nephropathy: a meta-analysis. Am J Nephrol. 2006;26:511–8.
154. Gharavi AG, Yan Y, Scolari F, Schena FP, Frasca GM, Ghiggeri GM, et al. IgA nephropathy, the most common cause of glomerulonephritis, is linked to 6q22-23. Nat Genet. 2000;26:354–7.
155. Bisceglia L, Cerullo G, Forabosco P, Torres DD, Scolari F, Di Perna M, et al. Genetic heterogeneity in Italian families with IgA nephropathy: suggestive linkage for two novel IgA nephropathy loci. Am J Hum Genet. 2006;79:1130–4.
156. Paterson AD, Liu XQ, Wang K, Magistroni R, Song X, Kappel J, et al. Genome-wide linkage scan of a large family with IgA nephropathy localizes a novel susceptibility locus to chromosome 2q36. J Am Soc Nephrol. 2007;18: 2408–15.
157. Maher B. Personal genomes: the case of the missing heritability. Nature. 2008;456:18–21.
158. Fernando MM, Stevens CR, Walsh EC, De Jager PL, Goyette P, Plenge RM, et al. Defining the role of the MHC in autoimmunity: a review and pooled analysis. PLoS Genet. 2008;4, e1000024.
159. Coppo R, Camilla R, Alfarano A, Balegno S, Mancuso D, Peruzzi L, et al. Upregulation of the immunoproteasome in peripheral blood mononuclear cells of patients with IgA nephropathy. Kidney Int. 2009;75:536–41.
160. Jennette JC. The immunohistology of IgA nephropathy. Am J Kidney Dis. 1988;12:348–52.
161. Roberts IS. Pathology of IgA nephropathy. Nat Rev Nephrol. 2014;10:445–54.
162. Haas M. IgA nephropathy and Henoch-Schonlein purpura nephritis. In: Jennette JC, D'Agait VD, Olson JL, Silva FG, editors. Heptinstall's pathology of the kidney. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2015. p. 475–524.
163. Espinosa M, Ortega R, Sánchez M, Segarra A, Salcedo MT, González F, et al. Association of C4d deposition with clinical outcomes in IgA nephropathy. Clin J Am Soc Nephrol. 2014;9:897–904.
164. Kiryluk K, Li Y, Sanna-Cherchi S, Rohanizadegan M, Suzuki H, Eitner F, et al. Geographic differences in genetic susceptibility to IgA nephropathy: GWAS replication study and geospatial risk analysis. PLoS Genet. 2012;8, e1002765.
165. Goicoechea de Jorge E, Caesar JJ, Malik TH, Patel M, Colledge M, Johnson S, et al. Dimerization of complement factor H-related proteins modulates complement activation in vivo. Proc Natl Acad Sci U S A. 2013;110:4685–90.
166. Tortajada A, Yébenes H, Abarrategui-Garrido C, Anter J, García-Fernández JM, Martínez-Barricarte R, et al. C3 glomerulopathy-associated CFHR1 mutation alters FHR oligomerization and complement regulation. J Clin Invest. 2013;123:2434–46.
167. Zhu L, Zhai YL, Wang FM, Hou P, Lv JC, Xu DM, et al. Variants in complement factor H and complement factor H-related protein genes, CFHR3 and CFHR1, affect complement activation in IgA nephropathy. J Am Soc Nephrol. 2015;26:1195–204.
168. Hughes AE, Orr N, Esfandiary H, Diaz-Torres M, Goodship T, Chakravarthy U. A common CFH haplotype, with deletion of CFHR1 and CFHR3, is associated with lower risk of age-related macular degeneration. Nat Genet. 2006;38:1173–7.

169. Zhao J, Wu H, Khosravi M, Cui H, Qian X, Kelly JA, et al. Association of genetic variants in complement factor H and factor H-related genes with systemic lupus erythematosus susceptibility. PLoS Genet. 2011;7, e1002079.
170. Zipfel PF, Edey M, Heinen S, Józsi M, Richter H, Misselwitz J, et al. Deletion of complement factor H-related genes CFHR1 and CFHR3 is associated with atypical hemolytic uremic syndrome. PLoS Genet. 2007;3, e41.
171. Loirat C, Fremeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis. 2011;6:60.
172. He B, Xu W, Santini PA, Polydorides AD, Chiu A, Estrella J, et al. Intestinal bacteria trigger T cell-independent immunoglobulin A(2) class switching by inducing epithelial-cell secretion of the cytokine APRIL. Immunity. 2007;26: 812–26.
173. Castigli E, Scott S, Dedeoglu F, Bryce P, Jabara H, Bhan AK, et al. Impaired IgA class switching in APRIL-deficient mice. Proc Natl Acad Sci U S A. 2004;101:3903–8.
174. McCarthy DD, Kujawa J, Wilson C, Papandile A, Poreci U, Porfilio EA, et al. Mice overexpressing BAFF develop a commensal flora-dependent. IgA-associated nephropathy. J Clin Invest. 2011;121:3991–4002.
175. Rockman SP, Demmler K, Roczo N, Cosgriff A, Phillips WA, Thomas RJ, et al. Expression of interleukin-6, leukemia inhibitory factor and their receptors by colonic epithelium and pericryptal fibroblasts. J Gastroenterol Hepatol. 2001;16: 991–1000.
176. Guimbaud R, Abitbol V, Bertrand V, Quartier G, Chauvelot-Moachon L, Giroud J, et al. Leukemia inhibitory factor involvement in human ulcerative colitis and its potential role in malignant course. Eur Cytokine Netw. 1998;9:607–12.
177. Esashi E, Ito H, Minehata K, Saito S, Morikawa Y, Miyajima A. Oncostatin M deficiency leads to thymic hypoplasia, accumulation of apoptotic thymocytes and glomerulonephritis. Eur J Immunol. 2009;39:1664–70.
178. Imielinski M, Baldassano RN, Griffiths A, Russell RK, Annese V, Dubinsky M, et al. Common variants at five new loci associated with early-onset inflammatory bowel disease. Nat Genet. 2009;41:1335–40.
179. Franke A, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. Nat Genet. 2010;42:1118–25.
180. Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern DP, Hui KY, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature. 2012;491:119–24.
181. Oppenheim JJ, Yang D. Alarmins: chemotactic activators of immune responses. Curr Opin Immunol. 2005;17:359–65.
182. Linzmeier RM, Ganz T. Human defensin gene copy number polymorphisms: comprehensive analysis of independent variation in alpha- and beta-defensin regions at 8p22-p23. Genomics. 2005;86:423–30.
183. Hollox EJ. Copy number variation of beta-defensins and relevance to disease. Cytogenet Genome Res. 2008;123:148–55.
184. Hollox EJ, Huffmeier U, Zeeuwen PL, Palla R, Lascorz J, Rodijk-Olthuis D, et al. Psoriasis is associated with increased beta-defensin genomic copy number. Nat Genet. 2008;40:23–5.
185. Fujimoto K, Karuppuchamy T, Takemura N, Shimohigoshi M, Machida T, Haseda Y, et al. A new subset of CD103+CD8alpha+ dendritic cells in the small intestine expresses TLR3, TLR7, and TLR9 and induces Th1 response and CTL activity. J Immunol. 2011;186:6287–95.
186. Uematsu S, Fujimoto K, Jang MH, Yang BG, Jung YJ, Nishiyama M, et al. Regulation of humoral and cellular gut immunity by lamina propria dendritic cells expressing Toll-like receptor 5. Nat Immunol. 2008;9:769–76.
187. Shapira Y, Agmon-Levin N, Shoenfeld Y. Defining and analyzing geoepidemiology and human autoimmunity. J Autoimmun. 2010;34:J168–77.

188. Borchers AT, Uibo R, Gershwin ME. The geoepidemiology of type 1 diabetes. Autoimmun Rev. 2010;9:A355–65.
189. Milo R, Kahana E. Multiple sclerosis: geoepidemiology, genetics and the environment. Autoimmun Rev. 2010;9:A387–94.
190. Handel AE, Handunnetthi L, Giovannoni G, Ebers GC, Ramagopalan SV. Genetic and environmental factors and the distribution of multiple sclerosis in Europe. Eur J Neurol. 2010;17:1210–4.
191. Pullan RL, Smith JL, Jasrasaria R, Brooker SJ. Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. Parasit Vectors. 2014;7:37.
192. Barry MA, Simon GG, Mistry N, Hotez PJ. Global trends in neglected tropical disease control and elimination: impact on child health. Arch Dis Child. 2013;98:635–41.
193. Wellcome Trust Case Control, C. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007;447:661–78.
194. Radstake TR, Gorlova O, Rueda B, Martin JE, Alizadeh BZ, Palomino-Morales R, et al. Genome-wide association study of systemic sclerosis identifies CD247 as a new susceptibility locus. Nat Genet. 2010;42:426–9.
195. Petukhova L, Duvic M, Hordinsky M, Norris D, Price V, Shimomura Y, et al. Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. Nature. 2010;466:113–7.
196. Chu X, Pan CM, Zhao SX, Liang J, Gao GQ, Zhang XM, et al. A genome-wide association study identifies two new risk loci for Graves' disease. Nat Genet. 2011;43:897–901.
197. van Heel DA, Franke L, Hunt KA, Gwilliam R, Zhernakova A, Inouye M, et al. A genome-wide association study for celiac disease identifies risk variants in the region harboring IL2 and IL21. Nat Genet. 2007;39:827–9.
198. Dubois PC, Trynka G, Franke L, Hunt KA, Romanos J, Curtotti A, et al. Multiple common variants for celiac disease influencing immune gene expression. Nat Genet. 2010;42:295–302.
199. Yang W, Tang H, Zhang Y, Tang X, Zhang J, Sun L, et al. Meta-analysis followed by replication identifies loci in or near CDKN1B, TET3, CD80, DRAM1, and ARID5B as associated with systemic lupus erythematosus in Asians. Am J Hum Genet. 2013;92:41–51.
200. International Multiple Sclerosis Genetics Consortium, Hafler DA, Compston A, Sawcer S, Lander ES, Daly MJ, et al. Risk alleles for multiple sclerosis identified by a genomewide study. N Engl J Med. 2007;357:851–62.
201. Okada Y, Yamazaki K, Umeno J, Takahashi A, Kumasaka N, Ashikawa K, et al. HLA-Cw*1202-B*5201-DRB1*1502 haplotype increases risk for ulcerative colitis but reduces risk for Crohn's disease. Gastroenterology. 2011;141(864–871):e1–5.
202. Raychaudhuri S, Ripke S, Li M, Neale BM, Fagerness J, Reynolds R, et al. Associations of CFHR1-CFHR3 deletion and a CFH SNP to age-related macular degeneration are not independent. Nat Genet. 2010;42:553–5; author reply 555–6.
203. Hom G, Graham RR, Modrek B, Taylor KE, Ortmann W, Garnier S, et al. Association of systemic lupus erythematosus with C8orf13-BLK and ITGAM-ITGAX. N Engl J Med. 2008;358:900–9.
204. Bertin J, Guo Y, Wang L, Srinivasula SM, Jacobson MD, Poyet JL, et al. CARD9 is a novel caspase recruitment domain-containing protein that interacts with BCL10/CLAP and activates NF-kappa B. J Biol Chem. 2000;275:41082–6.
205. McGovern DP, Gardet A, Törkvist L, Goyette P, Essers J, Taylor KD, et al. Genome-wide association identifies multiple ulcerative colitis susceptibility loci. Nat Genet. 2010;42:332–7.
206. Prunotto M, Carnevali ML, Candiano G, Murtas C, Bruschi M, Corradini E, et al. Autoimmunity in membranous nephropathy targets aldose reductase and SOD2. J Am Soc Nephrol. 2010;21:507–19.

207. Rivas MA, Beaudoin M, Gardet A, Stevens C, Sharma Y, Zhang CK, et al. Deep resequencing of GWAS loci identifies independent rare variants associated with inflammatory bowel disease. Nat Genet. 2011;43:1066–73.
208. Chu H, Pazgier M, Jung G, Nuccio SP, Castillo PA, de Jong MF, et al. Human alpha-defensin 6 promotes mucosal innate immunity through self-assembled peptide nanonets. Science. 2012;337:477–81.
209. Bevins CL, Salzman NH. Paneth cells, antimicrobial peptides and maintenance of intestinal homeostasis. Nat Rev Microbiol. 2011;9:356–68.
210. Wehkamp J, Salzman NH, Porter E, Nuding S, Weichenthal M, Petras RE, et al. Reduced Paneth cell alpha-defensins in ileal Crohn's disease. Proc Natl Acad Sci U S A. 2005;102:18129–34.
211. Velciov S, Gluhovschi G, Sporea I, Trandafirescu V, Petrica L, Bozdog G, et al. Asymptomatic urinary anomalies, hematuria and proteinuria, in patients with inflammatory bowel disease. Preliminary study. Rom J Intern Med. 2011;49:113–20.
212. Castigli E, Wilson SA, Garibyan L, Rachid R, Bonilla F, Schneider L, et al. TACI is mutant in common variable immunodeficiency and IgA deficiency. Nat Genet. 2005;37:829–34.
213. Litinskiy MB, Nardelli B, Hilbert DM, He B, Schaffer A, Casali P, et al. DCs induce CD40-independent immunoglobulin class switching through BLyS and APRIL. Nat Immunol. 2002;3:822–9.
214. Coppo R, Basolo B, Martina G, Rollino C, De Marchi M, Giacchino F, et al. Circulating immune complexes containing IgA. IgG and IgM in patients with primary IgA nephropathy and with Henoch-Schonlein nephritis. Correlation with clinical and histologic signs of activity. Clin Nephrol. 1982;18:230–9.
215. van der Boog PJ, De Fijter JW, Van Kooten C, Van Der Holst R, Van Seggelen A, Van Es LA, et al. Complexes of IgA with FcalphaRI/CD89 are not specific for primary IgA nephropathy. Kidney Int. 2003;63:514–21.
216. Marquina R, Díez MA, López-Hoyos M, Buelta L, Kuroki A, Kikuchi S, et al. Inhibition of B cell death causes the development of an IgA nephropathy in (New Zealand white x C57BL/6) F(1)-bcl-2 transgenic mice. J Immunol. 2004;172:7177–85.
217. McCarthy DD, Chiu S, Gao Y, Summers-deLuca LE, Gommerman JL. BAFF induces a hyper-IgA syndrome in the intestinal lamina propria concomitant with IgA deposition in the kidney independent of LIGHT. Cell Immunol. 2006;241:85–94.
218. Visscher PM, Brown MA, McCarthy MI, Yang J. Five years of GWAS discovery. Am J Hum Genet. 2012;90:7–24.
219. Visscher PM, Hill WG, Wray NR. Heritability in the genomics era – concepts and misconceptions. Nat Rev Genet. 2008;9:255–66.
220. Tenesa A, Haley CS. The heritability of human disease: estimation, uses and abuses. Nat Rev Genet. 2013;14:139–49.
221. Stefansson H, Rujescu D, Cichon S, Pietiläinen OP, Ingason A, Steinberg S, et al. Large recurrent microdeletions associated with schizophrenia. Nature. 2008;455:232–6.
222. Weiss LA, Shen Y, Korn JM, Arking DE, Miller DT, Fossdal R, et al. Association between microdeletion and microduplication at 16p11.2 and autism. N Engl J Med. 2008;358:667–75.
223. Xu B, Roos JL, Levy S, van Rensburg EJ, Gogos JA, Karayiorgou M. Strong association of de novo copy number mutations with sporadic schizophrenia. Nat Genet. 2008;40:880–5.
224. McCarroll SA. Extending genome-wide association studies to copy-number variation. Hum Mol Genet. 2008;17:R135–42.
225. Mardis ER. Next-generation sequencing platforms. Annu Rev Anal Chem (Palo Alto, Calif). 2013;6:287–303.
226. Metzker ML. Sequencing technologies – the next generation. Nat Rev Genet. 2010;11:31–46.
227. Li B, Liu DJ, Leal SM. Identifying rare variants associated with complex traits via sequencing. Curr Protoc Hum Genet. 2013; Chapter 1: Unit 1.26.
228. Goldstein DB, Allen A, Keebler J, Margulies EH, Petrou S, Petrovski S, et al. Sequencing studies in human genetics: design and interpretation. Nat Rev Genet. 2013;14:460–70.

229. Sanders SJ, Murtha MT, Gupta AR, Murdoch JD, Raubeson MJ, Willsey AJ, et al. De novo mutations revealed by whole-exome sequencing are strongly associated with autism. Nature. 2012;485:237–41.
230. Emond MJ, Louie T, Emerson J, Zhao W, Mathias RA, Knowles MR, et al. Exome sequencing of extreme phenotypes identifies DCTN4 as a modifier of chronic Pseudomonas aeruginosa infection in cystic fibrosis. Nat Genet. 2012;44:886–9.
231. Chesi A, Staahl BT, Jovičić A, Couthouis J, Fasolino M, Raphael AR, et al. Exome sequencing to identify de novo mutations in sporadic ALS trios. Nat Neurosci. 2013;16:851–5.

Chapter 3
Is IgA Nephropathy (IgAN) a Familial or Sporadic Disease?

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Abstract There have been several lines of evidences for familial aggregation of IgA nephropathy (IgAN), as well as mesangial deposition of IgA, suggesting that the susceptibility to this disease is genetically controlled. In our institute, family histories of hematuria, end-stage kidney disease, and glomerulonephritis are observed in about 10 % of cases with IgAN, even in those without any significant hereditary nephritis or kidney diseases. Recent large-scale genome-wide association studies (GWAS) of sporadic IgAN have identified multiple susceptibility loci, providing an insight into the genetic architecture of this disease, although each of their individual impact to the development of the disease is still not enough. It has been recognized that most of these loci are either directly associated with risk of inflammatory bowel disease (IBD) or maintenance of the intestinal epithelial barrier and response to mucosal pathogens. Further elucidation of the role of genetic variants underlying IgAN, and hologenetic views of gene variants and environmental factors, would be necessary to understand the precise pathogenic mechanism of IgAN in more detail.

Keywords Familial IgAN • GWAS • Exome sequencing

3.1 Introduction

IgA nephropathy (IgAN) is the most common form of glomerulonephritis [1], which accounts for up to 40 % of primary glomerulonephritis in Asia [2, 3], and is also highly prevalent among Native Americans and Australian aborigines. On the other hand, it has been reported to be uncommon in populations originating from Africa and the Indian subcontinent [4, 5], whereas more recent data from Kentucky

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and Tennessee contrarily showed that population-based incidence rates of IgAN were similar in African American and white populations, suggesting that the differences in the incidence of IgAN might be partially explained by differences in the policy of kidney biopsy [6, 7].

Although it is still controversial, a recent large-scale genome-wide association study has confirmed that the incidence of end-stage renal disease due to IgAN is geographically different and that was obviously in accordance with the distribution of several risk alleles [8]. The possible existence of ethnic and racial difference in the incidence of this disease may support the contribution of genetic backgrounds in the pathogenesis of IgAN.

Furthermore, familial mesangial deposition of IgA has been reported to have a prevalence of up to 30 % or more regarding the family members of donor of kidney transplantation for end-stage renal disease (ESRD) patients due to IgAN [9–11], which is much higher than that in a general population; the prevalence has been reported as 16 % in autopsy studies.

On the other hand, evidence of concomitant mesangial proliferative glomerulonephritis is present in less than 2 % of individuals surveyed [12]. Variations in manifestations of this disease, such as the severities in both clinical and histopathological findings or the prognosis of renal outcome, may indicate that IgAN includes multiple disease subsets that cannot be distinguished by the standard methods based on renal pathology or clinical characteristics.

The evidence indicating the contribution of a genetic effect in IgAN might be given from reports of familial aggregation of the disease.

In this chapter, the evidences for familial aggregation of this disease will be discussed, and in addition, I would like to overview on the genetic studies for both sporadic and familial IgAN to identify the responsible genes that determine susceptibility to this disease.

3.2 Familial Aggregation of IgA Nephropathy

The majority of cases with IgAN are clinically found to be sporadic, whereas familial clustering is also not uncommonly observed [13]. Because of the requirement of renal biopsy for definite diagnosis, and the intermittent nature of urinary abnormalities, no systematic data has been available about the prevalence of familial IgAN or sibling recurrence risk, which would allow the genetic contribution to the disease to be formally quantified. Karnib et al. identified a large Lebanese-Druze kindred ascertained via an index case with biopsy-proven IgAN and performed systematic screening of 38 family members [14]. In general, the proportion of patients with glomerulonephritis who had familial disease was higher than expected, and the family history is an important point to consider in the examination of patients with glomerulonephritis. Among 101 patients of glomerulonephritis with positive family history screened from 860 patients, 17.8 % had familial IgA glomerulonephritis [15]. Twenty-six of 185 patients (14 %) with IgAN

Table 3.1 Family history observed in cases with IgA nephropathy in Niigata University Hospital

Family history	1992–2000	2001–2010
With GN	95/908 (10.5 %)	77/822 (9.5 %)
With dialysis	42/908 (4.6 %)	58/822 (7.1 %)

Number of positive case/total number (%)

investigated in Brescia, Italy, were related to at least one other patient with the disease [16]. In Japan, Wakai et al. have reported that a family history of chronic nephritis was an independent risk factor for the development of IgAN, with an odds ratio of 4.8 (95 % CI, 1.69–13.6) for those with glomerulonephritis within second-degree relatives [17]. Table 3.1 summarizes the frequencies of patients with biopsy-proven IgAN and those with family history of any glomerulonephritis, which was defined by urinary abnormalities or any history of nephritis, or ESRD, based on a survey undertaken in Niigata University Hospital, Niigata, Japan, from 1992 to 2000 and those from 2001 to 2010. These findings in concert indicated that family histories of hematuria, end-stage kidney disease, and glomerulonephritis are observed in about 10 % of cases with IgAN, even in those without any significant hereditary nephritis or kidney diseases.

Clinical phenotype of familial IgAN is generally similar to that of sporadic IgAN. There have been some reports of families clustering with Henoch-Schonlein purpura or thin basement membrane disease [18, 19], whereas clinical and pathological findings specific to familial IgAN have not been described.

3.3 Genetic Studies for the Pathogenesis of IgA Nephropathy

From decades ago, genetic analysis in sporadic IgAN had been performed. Initially, the majority of them were case-control association studies by using classical techniques, such as restriction fragment length polymorphism (RFLP) to measure allele frequencies of one or a few genetic polymorphisms of functional candidate [20–26]. Although these studies may have contributed to our better understanding of the mechanisms of the initiation, as well as progression of the disease, not all the results had been confirmed by replication studies, and majority of them were not convincing enough to influence the clinical diagnosis and practice of this disease.

Recently, using microarray DNA analysis methods, genome-wide association studies (GWAS) of sporadic IgAN have been performed using large cohorts of more than thousands of cases with IgAN and controls. These studies have identified multiple susceptibility loci, providing an insight into the genetic architecture of this disease [27–29]. They demonstrated strong associations of the major histocompatibility (MHC) locus and four non-HLA loci, including chromosome 1q32, a common deletion of the complement factor H-related *CFHR3* and *CFHR1* genes (*CFHR3*,*1-delta*); 8p23, the α-defensin (*DEFA*) gene cluster; 17p23 (including *TNFSF13*); and 22q12 (including *HORMAD2* and several other genes).

More recently, by international collaboration, the largest GWAS has been performed in 2,747 biopsy-confirmed cases and 3,952 controls as the discovery cohorts (stage I), and subsequently, top signals, defined by $P < 5 \times 10^{-5}$, were genotyped in an additional 4,911 cases and 9,002 controls (stage II), followed by meta-analysis to identify genome-wide significant signals across the combined cohorts of 20,612 individuals. This two-stage design was adequately powered to detect ORs as small as 1.15–1.25. This study has identified six novel genome-wide significant associations including genes as follows: four in *ITGAM-ITGAX* (encoding leukocyte-specific integrin αX, a component of complement receptor 4 (CR4)), *VAV3* (encoding a guanine nucleotide exchange factor for Rho GTPases that is important for B and T lymphocyte development and antigen presentation), and *CARD9* (encoding caspase recruitment domain-containing protein 9, an adapter protein that promotes activation of NF-κB in macrophages) and two new independent signals at *HLA-DQB1* and *DEFA*, replicating the nine previously reported signals, including known SNPs in the *HLA-DQB1* and *DEFA* loci (Table 3.2). The cumulative burden of risk alleles was strongly associated with age at disease onset. Interestingly, most loci are either directly associated with risk of inflammatory bowel disease (IBD) or maintenance of the intestinal epithelial barrier and response to mucosal pathogens. The geospatial distribution of risk alleles is highly suggestive of multi-locus adaptation, and genetic risk correlates strongly with variation in local pathogens, particularly helminth diversity, suggesting a possible role for host-intestinal pathogen interactions in shaping the genetic landscape of IgAN [8, 28, 30].

An additional GWAS of IgAN in Han Chinese, which was comprising 8,313 cases and 19,680 controls, has most recently been reported [31]. The authors identified novel associations at *ST6GAL1* and *ACCS*, and their risk variants were strongly associated with mRNA expression levels in blood cells. Many studies described aberrant glycosylation of IgA1 in sporadic IgAN, and in also familial IgAN, that defect was reported to be inherited [32]. The associations of *ST6GAL1* elucidated by GWAS might explain the genetic basis of defect of glycosylation in IgAN.

Indeed, it is obvious that recent genome-wide association studies have identified hundreds of genetic variants associated with complex human diseases and traits including IgAN and that these studies have provided valuable insights into their genetic architecture. However in general, most reported variants confer relatively small increments in risk and explain only a small proportion of familial clustering, leading many to question how the remaining, "missing" heritability can be explained. The underlying rationale for GWAS is the "common disease, common variant" hypothesis, positing that common diseases are attributable in part to allelic variants present in more than 1–5 % of the population. It has been suggested that low-frequency variants of intermediate effect might also contribute to explaining missing heritability that should be tractable through large meta-analyses and/or imputation of genome-wide association data to illuminate the genetics of complex diseases and enhance its potential to enable effective disease prevention or treatment (Fig. 3.1) [33].

Table 3.2 GWAS loci reported to be associated with IgAN

						Nat Genet 2014;46:1187–96 [30]
CHR	SNP	Type of SNP	Risk allele	Locus	OR	Function
1	rs17019602	Intronic	G	VAV3	1.17	Chemokine signaling pathway
1	rs6677604	Intronic	G	CFHR3,1-delta	1.35	Innate immunity system (alternative pathway)
6	rs7763262	Intergenic	C	HLA-DR/DQ	1.41	Antigen presentation
6	rs9275224	Intergenic	G	HLA-DR/DQ	1.36	
6	rs2856717	Intergenic	G	HLA-DR/DQ	1.27	
6	rs9275596	Intergenic	T	HLA-DR/DQ	1.44	
6	rs9357155	Intronic	G	TAP2/PSMB9	1.13	Antigen digestion and processing
6	rs1883414	ncRNA	G	HLA-DP	1.22	Antigen presentation
8	rs2738048	Intergenic	A	DEFA	1.10	Innate immunity system (antimicrobial)
8	rs10086568	Intergenic	A	DEFA	1.16	
9	rs4077515	Missense	T	CARD9	1.16	Innate immune system
16	rs11150612	Intergenic	A	ITGAM-ITGAX	1.18	Cell adhesion molecules
16	rs11574637	Intronic	T	ITGAM-ITGAX	1.32	
17	rs3803800	Intronic	A	TNFSF13	1.12	Mucosal immunity and immunoglobulin class switching
22	rs2412971	Intronic	G	HORMAD2	1.20	Mucosal immunity and inflammation

3.4 Genome-Wide Linkage and Whole Exome Sequencing Analysis of Familial IgAN

Apart from sporadic IgAN, researchers have intensely searched for causative genes for familial IgAN by positional cloning approach, as the other Mendelian diseases achieved success by that analysis. Gharavi et al. reported in 2000 a genome-wide analysis of linkage in 30 multiplex IgAN kindreds, demonstrating the remarkable linkage of IgAN to 6q22-23 under a dominant model of transmission with incomplete penetrance, with a LOD score of 5.6 and 60 % of kindreds linked. These findings for the first time indicated the existence of a locus with large effect on development of IgAN and identify the chromosomal location of this disease gene [34]. However, even by these expensive methods including positional cloning techniques as "genome-wide" microsatellite markers, the genes responsible for

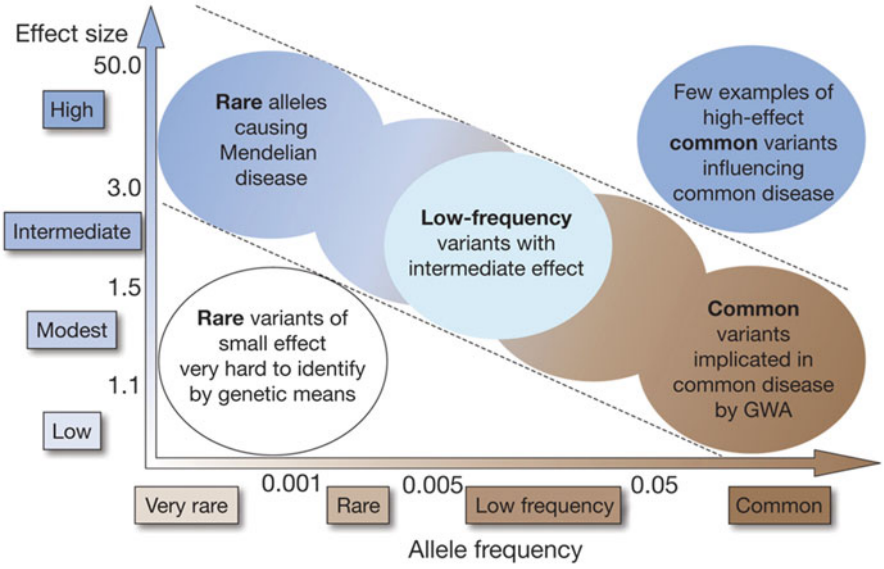

Fig. 3.1 Feasibility of identifying genetic variants by risk allele frequency and strength of genetic effect (From Ref. [33])

susceptibility to IgAN have not yet been identified. After that, two more genome-wide linkage analyses described other candidate loci for the development of familial IgAN [35, 36]. Until now, four loci have been reported, and locus heterogeneity is considered to exist in the genetic backgrounds of even in familial IgAN, which is one of the causes of difficulty in identifying the genes for IgAN.

With next-generation sequencing technology, whole exome sequencing has emerged as a powerful and cost-effective strategy for dissecting the genetic basis of diseases, and numerous causative genes for rare diseases have been identified so far. As described above, from the point of view of genetic heterogeneity of familial IgAN, an oligo-/polygenic and multiple susceptibility gene model for the disease has been proposed. Therefore, in order to identify the genetic causality of familial IgAN, sequencing analysis of each family would be necessary. Workflow of exome analysis is described in the following: (1) the whole exomes of affected and unaffected individuals were captured and subjected to massive parallel sequencing. (2) Variants identified by exome sequencing were filtered on the basis of variant annotation, functional expectation, and allele frequency. (3) The variants shared by the affected individuals in the family were selected and compared with public genetic variation database. Finally, causative gene variants must fulfill the following requirements: allele frequency of rare mutation, co-segregation in the family members, and demonstration of functional significance of the variants.

Recently, Italian researchers reported a genetic study of Sicilian family where IgAN segregates with an autosomal dominant pattern [37]. The exome and bioinformatic analysis identified p.Arg119Trp variant in the *SPRY2* gene, and functional

analysis of this variant demonstrated the inhibition of the MAPK/ERK1/2 pathway demonstrated only in the affected individuals. They suggested that downregulation of the MAPK/ERK1/2 pathway represents a common mechanism leading to IgAN. In other paper [38], Chinese researchers analyzed ten IgA families and described six deleterious variants in four genes co-segregated in the families. They mentioned causal relationships between the variants and IgAN; however, functional significance of these variants has not been demonstrated.

Rare variants and/or mutation for familial IgAN are considered as key genetic factors with moderate to strong effects. In the near future, identification of them would provide novel insights for the pathophysiology in the developments of IgAN.

3.5 Conclusion

Progress in technologies of genomic science has been uncovering the genetic diversity in patients with IgAN. From these studies, basic framework of pathogenesis of IgAN has been revealed. We speculate that the effects of genetic variants in each gene might influence the inheritance pattern of disease, sporadic or familial. To understand the precise pathogenic mechanism of IgAN in more detail, further elucidation of the role of genetic variants underlying IgAN, and hologenetic views of gene variants and environmental factors, would be necessary in the future.

Conflict of Interest The authors declare that they have no conflict of interest.

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References

1. Donadio JV, Grande JP. IgA nephropathy. N Engl J Med. 2002;347:738–48.
2. Glassock RJ, Kurokawa K, Yoshida M, Sakai O, Okada M, Shigematsu H, et al. IgA nephropathy in Japan. Am J Nephrol. 1985;5:127–37.
3. Sugiyama H, Yokoyama H, Sato H, Saito T, Kohda Y, Nishi S, et al. Japan Renal Biopsy Registry and Japan Kidney Disease Registry: Committee report for 2009 and 2010. Clin Exp Nephrol. 2013;17:155–73.
4. D'Amico G. The commonest glomerulonephritis in the world: IgA nephropathy. Q J Med. 1987;64:709–27.
5. Levy M, Berger J. Worldwide perspective of IgA nephropathy. Am J Kidney Dis. 1988;12:340–7.
6. Wyatt RJ, Julian BA, Baehler RW, Stafford CC, McMorrow RG, Ferguson T, et al. Epidemiology of IgA nephropathy in central and eastern Kentucky for the period 1975 through 1994. Central Kentucky Region of the Southeastern United States IgA Nephropathy DATABANK Project. J Am Soc Nephrol. 1998;9:853–8.

7. Sehic AM, Gaber LW, Roy 3rd S, Miller PM, Kritchevsky SB, Wyatt RJ. Increased recognition of IgA nephropathy in African-American children. Pediatr Nephrol. 1997;11:435–7.
8. Kiryluk K, Li Y, Sanna-Cherchi S, Rohanizadegan M, Suzuki H, Eitner F, et al. Geographic differences in genetic susceptibility to IgA nephropathy: GWAS replication study and geospatial risk analysis. PLoS Genet. 2012;8, e1002765.
9. Suzuki K, Honda K, Tanabe K, Toma H, Nihei H, Yamaguchi Y. Incidence of latent mesangial IgA deposition in renal allograft donors in Japan. Kidney Int. 2003;63:2286–94.
10. Cosyns JP, Malaise J, Hanique G, Mourad M, Baldi A, Goebbels RM, et al. Lesions in donor kidneys: nature, incidence, and influence on graft function. Transpl Int. 1998;11:22–7.
11. Rosenberg HG, Martinez PS, Vaccarezza AS, Martinez LV. Morphological findings in 70 kidneys of living donors for renal transplant. Pathol Res Pract. 1990;186:619–24.
12. Waldherr R, Rambausek M, Duncker WD, Ritz E. Frequency of mesangial IgA deposits in a non-selected autopsy series. Nephrol Dial Transplant. 1989;4:943–6.
13. Beerman I, Novak J, Wyatt RJ, Julian BA, Gharavi AG. The genetics of IgA nephropathy. Nat Clin Pract Nephrol. 2007;3:325–38.
14. Karnib HH, Sanna-Cherchi S, Zalloua PA, Medawar W, D'Agati VD, Lifton RP, et al. Characterization of a large Lebanese family segregating IgA nephropathy. Nephrol Dial Transpl. 2007;22:772–7.
15. Rambausek M, Hartz G, Waldherr R, Andrassy K, Ritz E. Familial glomerulonephritis. Pediatr Nephrol. 1987;1:416–8.
16. Scolari F, Amoroso A, Savoldi S, Mazzola G, Prati E, Valzorio B, et al. Familial clustering of IgA nephropathy: further evidence in an Italian population. Am J Kidney Dis. 1999;33:857–65.
17. Wakai K, Kawamura T, Matsuo S, Hotta N, Ohno Y. Risk factors for IgA nephropathy: a case-control study in Japan. Am J Kidney Dis. 1999;33:738–45.
18. Miyagawa S, Dohi K, Hanatani M, Yamanaka F, Okuchi T, Sakamoto K, et al. Anaphylactoid purpura and familial IgA nephropathy. Am J Med. 1989;86:340–2.
19. Frasca GM, Soverini L, Gharavi AG, Lifton RP, Canova C, Preda P, et al. Thin basement membrane disease in patients with familial IgA nephropathy. J Nephrol. 2004;17:778–85.
20. Suzuki S, Suzuki Y, Kobayashi Y, Harada T, Kawamura T, Yoshida H, et al. Insertion/deletion polymorphism in ACE gene is not associated with renal progression in Japanese patients with IgA nephropathy. Am J Kidney Dis. 2000;35:896–903.
21. Schena FP, D'Altri C, Cerullo G, Manno C, Gesualdo L. ACE gene polymorphism and IgA nephropathy: an ethnically homogeneous study and a meta-analysis. Kidney Int. 2001;60:732–40.
22. Goto S, Narita I, Saito N, Watanabe Y, Yamazaki H, Sakatsume M, et al. A(-20)C polymorphism of the angiotensinogen gene and progression of IgA nephropathy. Kidney Int. 2002;62:980–5.
23. Narita I, Goto S, Saito N, Song J, Omori K, Kondo D, et al. Angiotensinogen gene variation and renoprotective efficacy of renin-angiotensin system blockade in IgA nephropathy. Kidney Int. 2003;64:1050–8.
24. Narita I, Goto S, Saito N, Song J, Ajiro J, Sato F, et al. Interaction between ACE and ADD1 gene polymorphisms in the progression of IgA nephropathy in Japanese patients. Hypertension. 2003;42:304–9.
25. Song J, Narita I, Goto S, Saito N, Omori K, Sato F, et al. Gender specific association of aldosterone synthase gene polymorphism with renal survival in patients with IgA nephropathy. J Med Genet. 2003;40:372–6.
26. Sato F, Narita I, Goto S, Kondo D, Saito N, Ajiro J, et al. Transforming growth factor-beta1 gene polymorphism modifies the histological and clinical manifestations in Japanese patients with IgA nephropathy. Tissue Antigens. 2004;64:35–42.
27. Feehally J, Farrall M, Boland A, Gale DP, Gut I, Heath S, et al. HLA has strongest association with IgA nephropathy in genome-wide analysis. J Am Soc Nephrol. 2010;21:1791–7.

28. Gharavi AG, Kiryluk K, Choi M, Li Y, Hou P, Xie J, et al. Genome-wide association study identifies susceptibility loci for IgA nephropathy. Nat Genet. 2011;43:321–7.
29. Yu XQ, Li M, Zhang H, Low HQ, Wei X, Wang JQ, et al. A genome-wide association study in Han Chinese identifies multiple susceptibility loci for IgA nephropathy. Nat Genet. 2012;44:178–82.
30. Kiryluk K, Li Y, Scolari F, Sanna-Cherchi S, Choi M, Verbitsky M, et al. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. Nat Genet. 2014;46:1187–96.
31. Li M, Foo JN, Wang JQ, Low HQ, Tang XQ, Toh KY, et al. Identification of new susceptibility loci for IgA nephropathy in Han Chinese. Nat Commun. 2015;6:7270.
32. Gharavi AG, Moldoveanu Z, Wyatt RJ, Barker CV, Woodford SY, Lifton RP, et al. Aberrant IgA1 glycosylation is inherited in familial and sporadic IgA nephropathy. J Am Soc Nephrol. 2008;19:1008–14.
33. Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, et al. Finding the missing heritability of complex diseases. Nature. 2009;461:747–53.
34. Gharavi AG, Yan Y, Scolari F, Schena FP, Frasca GM, Ghiggeri GM, et al. IgA nephropathy, the most common cause of glomerulonephritis, is linked to 6q22-23. Nat Genet. 2000;26:354–7.
35. Bisceglia L, Cerullo G, Forabosco P, Torres DD, Scolari F, Di Perna M, et al. Genetic heterogeneity in Italian families with IgA nephropathy: suggestive linkage for two novel IgA nephropathy loci. Am J Human Genet. 2006;79:1130–4.
36. Paterson AD, Liu XQ, Wang K, Magistroni R, Song X, Kappel J, et al. Genome-wide linkage scan of a large family with IgA nephropathy localizes a novel susceptibility locus to chromosome 2q36. J Am Soc Nephrol. 2007;18:2408–15.
37. Milillo A, La Carpia F, Costanzi S, D'Urbano V, Martini M, Lanuti P, et al. A SPRY2 mutation leading to MAPK/ERK pathway inhibition is associated with an autosomal dominant form of IgA nephropathy. Eur J Hum Genet*:* EJHG. 2015
38. Liu R, Hu B, Li Q, Jing X, Zhong C, Chang Y et al. Novel genes and variants associated with IgA nephropathy by co-segregating with the disease phenotypes in 10 IgAN families. Gene 2015.

Chapter 4
Heterogeneity of Aberrant *O*-Glycosylation of IgA1 in IgA Nephropathy

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Abstract IgA nephropathy (IgAN), a frequent cause of end-stage renal disease, is an autoimmune disease wherein immune complexes consisting of IgA1 with galactose-deficient *O*-glycans (Gd-IgA1; autoantigen) and anti-glycan autoantibodies deposit in the glomeruli and induce renal injury. Serum IgA1 has three to six clustered *O*-glycans, some of which may be deficient in galactose and thus expose terminal or sialylated *N*-acetylgalactosamine. Patients with IgAN usually have elevated serum levels of Gd-IgA1. The mechanisms involved in production of Gd-IgA1 are not fully understood.

Using IgA1-producing cell lines, we have analyzed the heterogeneity of IgA1 *O*-glycosylation and the corresponding biosynthetic pathways. IgA1 secreted by

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cells from IgAN patients vs. healthy controls had more galactose-deficient sites and overall more *O*-glycans. These changes were associated with differential expression/activity of key glycosyltransferases in cells from patients with IgAN vs. controls, elevated for an initiating enzyme *N*-acetylgalactosaminyl (GalNAc)-transferase 14 and for GalNAc-specific sialyltransferase (ST6GalNAc-II) and, conversely, decreased for the galactosyltransferase (C1GalT1) and C1GalT1-associated chaperone Cosmc. Involvement of the key enzymes in the production of Gd-IgA1 was confirmed by siRNA knockdown and biochemical approaches. Moreover, expression of these enzymes is affected by some cytokines that further enhance the enzyme imbalance to increase Gd-IgA1 production.

In summary, the production of Gd-IgA1, the key autoantigen in IgAN, by IgA1-secreting cells results from dysregulation of key glycosyltransferases and is augmented by certain cytokines. These findings provide insight into possible approaches for future disease-specific therapy.

Keywords IgA1 • *O*-glycosylation • Galactose deficiency • Autoantigen

4.1 Introduction

IgA nephropathy (IgAN) was described for the first time by Berger and Hinglais in 1968 based on the observation of "intercapillary deposits of IgA-IgG" using fluorochrome-conjugated antibodies for immunofluorescence examination of renal biopsy specimens from patients with recurrent hematuria [1]. IgAN was later recognized as the most common glomerulonephritis worldwide [2, 3] and an important cause of end-stage kidney disease [4]. The disease incidence varies greatly by geographical location [5]. For example, IgAN is found in up to 40 % of native-kidney biopsies in eastern Asia but in less than 5 % of such biopsies in central Africa [5–9]. Some of this variability may be due to local differences with regard to which patients are selected to undergo renal biopsy, but genetically determined influences on the pathogenesis of the disease are thought to play a significant role in disease incidence [8, 10–12].

4.1.1 Clinical Presentation and Diagnosis

IgAN is commonly manifested in adolescents and young adults. Asymptomatic proteinuria and hematuria are common clinical presentations [13]. Painless macroscopic hematuria is frequent in children and adolescents and often coincides with mucosal infections, particularly those of the upper respiratory tract and/or digestive system. IgAN more commonly affects males than females (2–3:1) in Caucasians but affects both genders equally in eastern Asia. This disease is diagnosed based on pathological evaluation of renal biopsy specimens, with the typical feature of

glomerular immunodeposits containing predominant or codominant IgA1 [14]. These IgA1 deposits are enriched for molecules with some galactose-deficient *O*-glycans [15, 16]. Light microscopy typically shows mesangial proliferation and expansion of extracellular matrix [14]. Glomerular sclerosis and interstitial fibrosis are associated with progressive disease that leads to renal insufficiency. Several different histopathologic classification schemes have been developed, including the Haas, Lee, and Oxford classification systems (for details, see [5, 17–21]). Notably, there is no disease-specific treatment for IgAN [5, 22].

4.1.2 Pathogenesis of IgA Nephropathy

Research during the past 15 years has defined IgAN as an autoimmune disease with a postulated multi-hit mechanism [23] (Fig. 4.1). Molecules of IgA1 with some *O*-glycans deficient in galactose (galactose-deficient IgA1; Gd-IgA1) are produced in amounts sufficient to increase their blood levels (hit 1). These molecules are recognized by unique circulating anti-glycan autoantibodies (hit 2). This process leads to formation of immune complexes (hit 3), some of which reach the

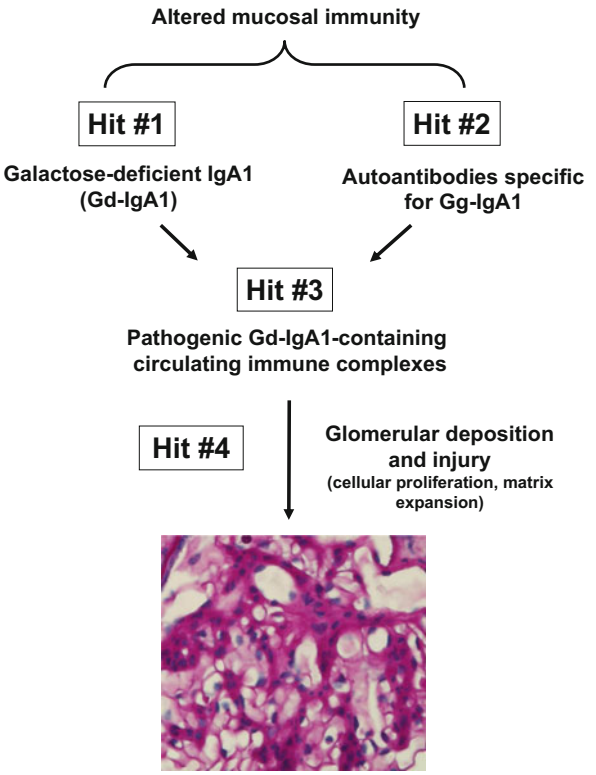


Fig. 4.1 A proposed multi-hit pathogenesis of IgAN. IgA1 with some *O*-glycans deficient in galactose (galactose-deficient IgA1; Gd-IgA1) is produced in increased amounts, leading to increased levels in the circulation (hit 1) and such molecules are recognized by unique circulating anti-glycan autoantibodies (hit 2). This process leads to formation of pathogenic immune complexes (hit 3), some of which reach the glomerular circulation and deposit in the mesangium and induce renal injury (hit 4). Moreover, there are likely upstream factors involved in abnormal mucosal immune responses characteristic for patients with IgAN

glomerular circulation and deposit in the mesangium and induce renal injury (hit 4). It is to be noted that activation of mesangial cells in vitro by Gd-IgA1 requires that the molecule be contained in an immune complex; uncomplexed Gd-IgA1 does not stimulate proliferation of mesangial cells [23–32]. The basis for the accentuated synthesis of Gd-IgA1 remains uncertain, but abnormalities in mucosal immunity have been implicated [33–36].

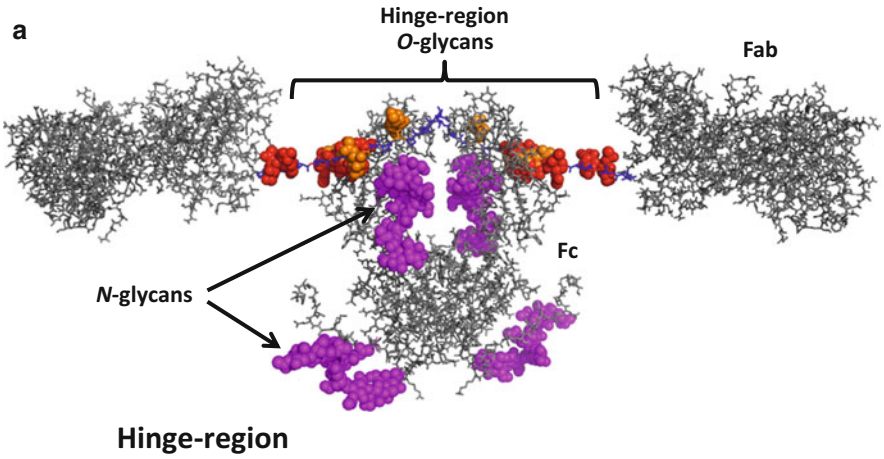
4.2 Structure of IgA1

Monomeric human IgA1 has two heavy chains and two light chains connected by disulfidic bridges [37]. Each heavy chain has three constant (C_α) domains and one variable (V) domain; each light chain has one C and one V domain (Fig. 4.2a). Unlike IgA2, the other IgA subclass in humans, IgA1 has a unique hinge region between $C_\alpha1$ and $C_\alpha2$ that consists of two octapeptide repeats (TPPTPSPS) and is the site of attachment of *O*-glycans [38]. On circulatory IgA1, usually three to six of the nine potential *O*-glycosylation sites are glycosylated (Fig. 4.2a) [39–42]. There are also two *N*-glycosylation sites on each heavy chain containing complex glycans [43–47]. Monomers of IgA1 can be covalently associated during their production in plasma cells with a ~15-kDa J-chain [48–50] and thus the immunoglobulin can be present as dimers and higher oligomers, termed polymeric IgA1. In the circulation, most of IgA1 is monomeric [51, 52].

O-glycans of serum IgA1 of healthy individuals are usually core 1 glycans, i.e., disaccharides consisting of Ser/Thr-linked *N*-acetylgalactosamine with a β1,3-linked galactose (Fig. 4.2b). The disaccharide may be sialylated on either sugar or on both sugars [45, 53]. Sialic acid (in humans, *N*-acetylneuraminic acid) is attached to *N*-acetylgalactosamine of IgA1 by an alpha2,6-linkage and to galactose by an alpha2,3-linkage. Lectins (proteins that bind to particular carbohydrates) serve as useful tools to determine presence of terminal *N*-acetylgalactosamine or the disaccharide consisting of *N*-acetylgalactosamine with β1,3-linked galactose (Fig. 4.2b), but careful assessment of lectin specificities should always be performed using well-characterized IgA proteins [40–42, 54–57].

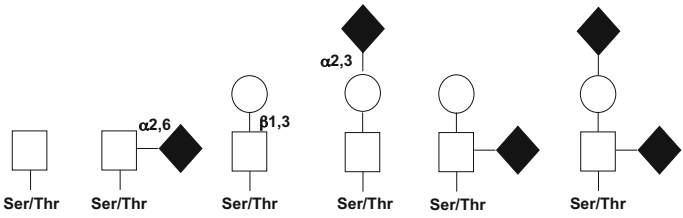
4.3 Biosynthesis of IgA1 *O*-Glycans

O-glycosylation of IgA1 is a stepwise process beginning with attachment of *N*-acetylgalactosamine to Ser/Thr residues of the hinge region; it is mediated by *N*-acetylgalactosaminyl-transferase 2 (GalNAc-T2) [58, 59], but other GalNAc-Ts, including GalNAc-T1, GalNAc-T11, and GalNAc-T14, may contribute to the process [60, 61]. The *O*-glycan chain can be then extended by attachment of galactose to the *N*-acetylgalactosamine residue (Fig. 4.3); this process is mediated by core 1 beta1,3-galactosyltransferase (C1GalT1) [62]. The stability of this



b

O-glycan



Lectin reactivity

Helix aspersa	+	-	-	-	-	-
Helix aspersa (+sialidase)	+	+	-	-	-	-
Jacalin (+/-sialidase)	-	-	+	+	+	+

Fig. 4.2 Structure and *O*-glycosylation of human circulatory IgA1. (**a**) Modeled structure of glycosylated monomeric IgA1 based on PDB ID: 1IGA (*top*) and hinge-region amino-acid sequence with attachment sites of six *O*-glycans [125]. Modeled *O*- and *N*- glycans are depicted as spheres for clarity and are based on observed glycoforms: *red* for Gal-GalNAc; *orange* for GalNAc; and *magenta* for *N*-glycan $(NeuAc)_2(Gal)_2(GlcNAc)_2+(Fuc)_1(Man)_3(GlcNAc)_2$ [40, 46]. Hinge-region non-glycosylated amino-acid residues are in blue. There are up to six sites of *O*-glycosylation in the IgA1 hinge region – at T225, T228, S230, S232, T233, and T236 (marked by *stars*) [40]. (**b**) *O*-glycans of circulatory IgA1 and their lectin reactivities. Core 1 glycans consists of *N*-acetylgalactosamine and galactose, with or without sialic acid. Lectin from *Helix aspersa* recognizes terminal *N*-acetylgalactosamine whereas jacalin binds to the disaccharide composed of *N*-acetylgalactosamine and galactose

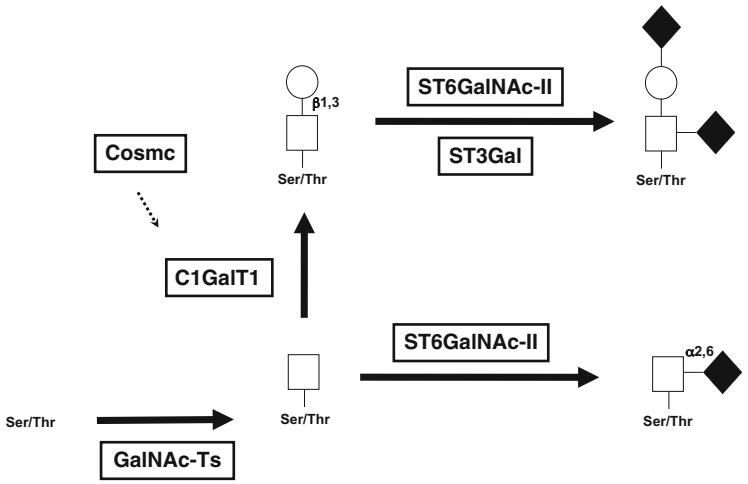


Fig. 4.3 Biosynthesis of *O*-glycans of IgA1. *O*-glycans are synthesized in a stepwise manner, starting with attachment of *N*-acetylgalactosamine to an oxygen molecule of serine or threonine (catalyzed by GalNAc-transferases), followed by addition of galactose (catalyzed by C1GalT1). Sialic acid can be added to each glycan by different enzymes, ST3Gal for attachment to galactose or ST6GalNAC-II for attachment to GalNAc. Sialylation of GalNAc prevents subsequent addition of galactose

enzyme during biosynthesis depends on interaction with its chaperone (Cosmc) for assistance with protein folding. Without this association with Cosmc, the C1GalT1 nascent protein is rapidly degraded [63–65]. The core 1 structures of IgA1 may be further modified by sialyltransferases that attach sialic acid to the galactose residues (mediated by an ST3Gal enzyme) and/or *N*-acetylgalactosamine residues (mediated by ST6GalNAc-II, as the usual ST6GalNAc-I is not expressed in IgA-producing cells) [61, 66, 67].

4.4 Aberrant Glycosylation of IgA1 in IgA Nephropathy

Serum IgA1 of healthy individuals had been thought to contain few or no galactose-deficient *O*-glycans [45], but it has been shown that galactose-deficient *O*-glycans may be present at some sites in the IgA1 hinge region [40]. Glycosylation studies have revealed aberrancies in the *O*-glycans of IgA1 in the circulation of patients with IgAN. Specifically, most patients with IgAN have elevated serum levels of IgA1 with some *O*-glycans deficient in galactose [68–73]. Thus, a fraction of circulatory IgA1 molecules has some hinge-region *O*-glycans without galactose, i.e., consisting of terminal *N*-acetylgalactosamine or sialylated *N*-acetylgalactosamine (Fig. 4.2). This galactosylation defect appears to be specific for IgA1, as other *O*-glycosylated serum proteins such as C1 inhibitor and IgD do not exhibit galactose deficiency [40, 41, 56, 57, 74].

4.4.1 Synthesis of IgA and Possible Origin of Gd-IgA1

Humans produce approximately 70 mg of IgA per kg of body weight daily [75]. Most IgA is produced in mucosal tissues, e.g., in the gut, as polymeric IgA that is then selectively transported by a receptor-mediated pathway into the external secretions (secretory IgA); only a small percentage of polymeric IgA enters the circulation [52, 76, 77]. IgA in the circulation, predominantly of IgA1 subclass, is produced mainly in the bone marrow and to a lesser extent in the spleen and lymph nodes. A contribution of tonsillar IgA-producing cells to serum IgA has been considered to play a role in pathogenesis of IgAN [33, 34, 78–83]. IgA is rapidly catabolized; the half-life of IgA in the circulation is about 5 days. Circulatory IgA is catabolized predominantly in the liver by hepatocytes [84–92].

Genetic influences on development and expression of IgAN have been recognized and risk alleles of multiple genomic loci have been recently identified (for review, see [5, 7, 9, 93, 94]). Notably, serum levels of Gd-IgA1 are genetically determined and may be predictive of disease progression [95–98]. Thus, it is clinically relevant to determine the nature of aberrant *O*-glycosylation of IgA1 in IgAN at a molecular level.

Assessment of IgA1 *O*-glycosylation in general and in IgAN in particular initially utilized *O*-glycan-specific lectins and monosaccharide compositional analysis [15, 68–70, 72, 99, 100]. Lectin-based assays, using carefully selected lectins specific for particular sugars [54], evolved into a quantitative lectin ELISA [71]. This unique test has been used for analyses of serum IgA1 from multiple cohorts and the accumulated data show that most adult and pediatric patients with IgAN have elevated serum levels of Gd-IgA1 [54, 71, 73, 98, 101–105]. Moreover, the lectin-based assay was instrumental in establishing that serum levels of Gd-IgA1 are heritable in familial as well as sporadic IgAN [95].

To characterize *O*-glycosylation of IgA1 at a molecular level, mass spectrometric analyses have been used in addition to monosaccharide compositional analyses [16, 55, 69, 72, 106–111]. Importantly, a new approach for direct localization of *O*-glycan attachment sites on IgA1 has been developed by combining a technique to fragment hinge-region glycopeptides (electron-capture or electron-transfer dissociation) with high-resolution mass spectrometry, a process termed tandem mass spectrometry [40–42, 56, 57, 112]. In this approach, the individual glycoforms are identified by their molecular masses and the sites of *O*-glycan attachment are determined by fragmentation. These protocols revealed *O*-glycoform isomers, i.e., hinge-region glycopeptides with the same number of glycans but with some attached at different sites [40, 113–116]. It remains to be determined whether this microheterogeneity affects the expression or prognosis of IgAN.

4.5 Studies with IgA1-Producing Cells

Development of immortalized IgA1-secreting cells derived from cells in the circulation of patients with IgAN and healthy and disease controls provided a new tool for studies of normal and aberrant *O*-glycosylation of IgA1 [103]. IgA1 secreted by the cells from patients with IgAN had higher degrees of galactose deficiency of the *O*-glycans than that from cells of healthy controls. Notably, the relative degree of galactose deficiency of the IgA1 secreted by IgA1-producing cells correlates with that of serum IgA1 from the corresponding donor [103]. Thus, these cells served as an excellent model system to study enzymatic pathways and the actual *O*-glycosylation of secreted IgA1. Initial studies showed that the polymeric IgA1 form is the most affected by galactose deficiency. Furthermore, this phenotype is related to decreased expression and activity of C1GalT1 and elevated expression and activity of ST6GalNAc-II [103]. Moreover, the expression of C1GalT1-specific chaperone Cosmc [63, 64], that is necessary for stability of the nascent C1GalT1 protein, is decreased [103]. More recently, the roles of C1GalT1 and ST6GalNAc-II in production of Gd-IgA1 have been confirmed, using siRNA knockdown and biochemical approaches [67, 117, 118].

IgA1 secreted by our established cell lines was isolated and its *O*-glycosylation characterized by using high-resolution mass spectrometry. The IgA1 secreted by cells from patients with IgAN has more galactose-deficient *O*-glycans, consisting of terminal or sialylated *N*-acetylgalactosamine, compared to IgA1 from the cells from healthy controls [119]. Moreover, IgA1 from patients with IgAN also had more *O*-glycans per heavy chain. Together, these data revealed another type of glycosylation abnormality, an elevated number of *O*-glycans on IgA1 from patients with IgAN. This finding implicated a central role for an *O*-glycosylation-initiating enzyme, a GalNAc-T, in production of Gd-IgA1.

Several GalNAc-Ts are abundantly expressed in IgA1-producing cells [61, 120], including GalNAc-T2 [103]. Of this family of enzymes, only GalNAc-T14, the closest structural relative of GalNAc-T2, was expressed at several-fold greater levels in the cells from patients with IgAN compared to cells from healthy controls [120]. Conversely, the expression of GalNAc-T2 and other GalNAc-Ts did not differ between patients and healthy controls [103]. These findings thus indicate that overexpression of GalNAc-T14 may contribute to enhanced *O*-glycosylation of IgA1 in IgAN [9, 61].

Notably, the dysregulated expression and activities of several key glycosyltransferases are further enhanced by some cytokines, including IL-6 [117]. The signaling process through the IL-6 receptor/gp130 complex is mediated by STAT3 [121, 122] and increases activity of ST6GalNAc-II and decreases activity of C1GalT1 (Fig. 4.4) [117]. This process leads to greater production of Gd-IgA1 [117]. Another type of signal involved in cellular differentiation and survival that may be relevant to Gd-IgA1-producing cells includes B-cell activating factor (BAFF) [122]. Notably, overexpression of human BAFF in mice leads to overproduction of IgA and development of IgA glomerular deposits [123].

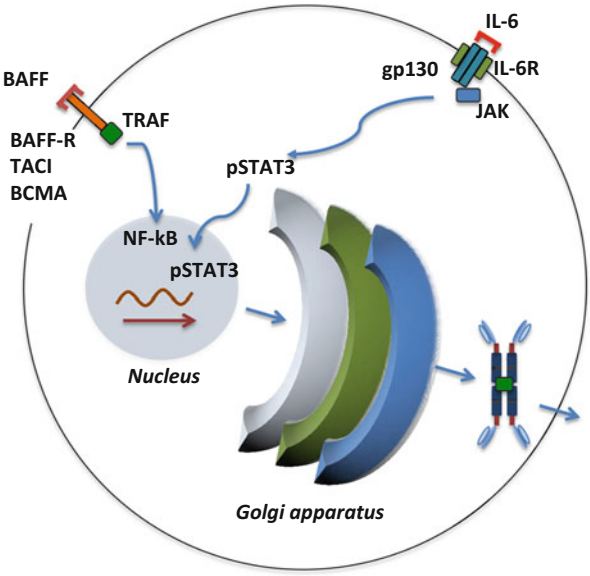


Fig. 4.4 Examples of two signaling pathways involved in cell survival and differentiation of IgA1-producing cells. BAFF is a growth/differentiation factor for plasma cells and its overproduction may enhance survival or differentiation of cells involved in production of autoantigen, Gd-IgA1. IL-6 can increase production of Gd-IgA1 in IgA1-secreting cells of patients with IgAN

These observations may together explain why the clinical onset or a flare in the activity of IgAN often coincides with an active mucosal infection of the upper respiratory tract and/or digestive system. It can be speculated that such environmental factors exert their activity through cytokines (e.g., IL-6) and growth factors (e.g., BAFF, APRIL) (Fig. 4.4) to upregulate cellular production of Gd-IgA1 and/or cell survival in susceptible individuals [9, 94, 122].

4.6 Summary and Implications for Diagnosis, Prognosis, and Treatment of IgA Nephropathy

Multiple lines of evidence allow us to characterize IgAN as an autoimmune disease in which Gd-IgA1, produced in increased amounts and leading to increased levels in the blood, is bound by unique autoantibodies. This sequence of events leads to formation of pathogenic circulating Gd-IgA1-containing immune complexes. Some of these complexes deposit in the kidney and induce a mesangioproliferative glomerular injury [124]. Elevated serum levels of Gd-IgA1 are genetically codetermined and can be further increased by some cytokines. Moreover, serum levels of Gd-IgA1 may be predictive of disease progression. Gd-IgA1 is produced by IgA1-secreting cells of patients with IgAN due to dysregulation of several key glycosylation enzymes. A combination of approaches with use of IgA1-producing cell lines and high-resolution mass spectrometry will likely provide a better understanding at cellular and molecular levels of the heterogeneity of Gd-IgA1 in patients with IgAN. We believe that through a detailed understanding of the disease

processes, biomarkers specific for IgAN can be identified and developed into clinical assays to aid in the diagnosis, assessment of prognosis, and monitoring of the disease progression. Moreover, characterization of specific pathogenetic pathways, such as those involved in Gd-IgA1 production, will identify targets for future disease-specific therapies.

Conflict of Interest The authors declare that they have no conflict of interest.

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References

1. Berger J, Hinglais N. Les dépôts intercapillaires d'IgA-IgG (intercapillary deposits of IgA-IgG). J Urol Nephrol. 1968;74:694–5.
2. D'Amico G, Colasanti G, Barbiano di Belgioioso G, Fellin G, Ragni A, Egidi F, et al. Long-term follow-up of IgA mesangial nephropathy: clinico-histological study in 374 patients. Semin Nephrol. 1987;7(4):355–8.
3. Julian BA, Waldo FB, Rifai A, Mestecky J. IgA nephropathy, the most common glomerulonephritis worldwide. A neglected disease in the United States? Am J Med. 1988;84:129–32.
4. D'Amico G. Natural history of idiopathic IgA nephropathy and factors predictive of disease outcome. Semin Nephrol. 2004;24(3):179–96.
5. Wyatt RJ, Julian BA. IgA nephropathy. N Engl J Med. 2013;368(25):2402–14.
6. Beerman I, Novak J, Wyatt RJ, Julian BA, Gharavi AG. Genetics of IgA nephropathy. Nat Clin Pract Nephrol. 2007;3:325–38.
7. Kiryluk K, Julian BA, Wyatt RJ, Scolari F, Zhang H, Novak J, et al. Genetic studies of IgA nephropathy: past, present, and future. Pediatr Nephrol. 2010;25(11):2257–68.
8. Kiryluk K, Li Y, Sanna-Cherchi S, Rohanizadegan M, Suzuki H, Eitner F, et al. Geographic differences in genetic susceptibility to IgA nephropathy: GWAS replication study and geospatial risk analysis. PLoS Genet. 2012;8(6):e1002765.
9. Kiryluk K, Novak J. The genetics and immunobiology of IgA nephropathy. J Clin Invest. 2014;124(6):2325–32.
10. Julian BA, Quiggins PA, Thompson JS, Woodford SY, Gleason K, Wyatt RJ. Familial IgA nephropathy. Evidence of an inherited mechanism of disease. N Engl J Med. 1985;312:202–8.
11. Gharavi AG, Kiryluk K, Choi M, Li Y, Hou P, Xie J, et al. Genome-wide association study identifies susceptibility loci for IgA nephropathy. Nat Genet. 2011;43:321–7.
12. Kiryluk K, Li Y, Scolari F, Sanna-Cherchi S, Choi M, Verbitsky M, et al. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. Nat Genet. 2014;46(11):1187–96.
13. Julian BA, Suzuki H, Suzuki Y, Tomino Y, Spasovski G, Novak J. Sources of urinary proteins and their analysis by urinary proteomics for the detection of biomarkers of disease. Proteomics Clin Appl. 2009;3(9):1029–43.
14. Jennette JC. The immunohistology of IgA nephropathy. Am J Kidney Dis. 1988;12(5):348–52.

15. Allen AC, Bailey EM, Brenchley PEC, Buck KS, Barratt J, Feehally J. Mesangial IgA1 in IgA nephropathy exhibits aberrant *O*-glycosylation: observations in three patients. Kidney Int. 2001;60:969–73.
16. Hiki Y, Odani H, Takahashi M, Yasuda Y, Nishimoto A, Iwase H, et al. Mass spectrometry proves under-*O*-glycosylation of glomerular IgA1 in IgA nephropathy. Kidney Int. 2001;59:1077–85.
17. Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS, Troyanov S, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney Int. 2009;76(5):534–45.
18. Coppo R, Troyanov S, Camilla R, Hogg RJ, Cattran DC, Cook HT, et al. The Oxford IgA nephropathy clinicopathological classification is valid for children as well as adults. Kidney Int. 2010;77(10):921–7.
19. Haas M. Histologic subclassification of IgA nephropathy: a clinicopathologic study of 244 cases. Am J Kidney Dis. 1997;29:829–42.
20. Haas M. IgA nephropathy and Henoch-Schoenlein purpura nephritis. In: Jennette JC, Olsen JL, Scwartz MM, Silva FG, editors. Heptinstall's pathology of the kidney. 6th ed. Philadelphia: Lippincott, Williams and Wilkins; 2007. p. 423–86.
21. Haas M, Reich HN. Morphologic markers of progressive immunoglobulin A nephropathy. Adv Chronic Kidney Dis. 2012;19(2):107–13.
22. Floege J, Eitner F. Current therapy for IgA nephropathy. J Am Soc Nephrol. 2011;22 (10):1785–94.
23. Suzuki H, Kiryluk K, Novak J, Moldoveanu Z, Herr AB, Renfrow MB, et al. The pathophysiology of IgA nephropathy. J Am Soc Nephrol. 2011;22:1795–803.
24. Moura IC, Arcos-Fajardo M, Sadaka C, Leroy V, Benhamou M, Novak J, et al. Glycosylation and size of IgA1 are essential for interaction with mesangial transferrin receptor in IgA nephropathy. J Am Soc Nephrol. 2004;15:622–34.
25. Novak J, Cook WJ, Julian BA, Mestecky J, Tomana M. IgA nephropathy (IgAN): a similarity in the mechanism of IgA1 deposition in the kidney in humans and mice. J Am Soc Nephrol. 2000;11:478–9A.
26. Novak J, Moldoveanu Z, Julian BA, Raska M, Wyatt RJ, Suzuki Y, et al. Aberrant glycosylation of IgA1 and anti-glycan antibodies in IgA nephropathy: role of mucosal immune system. Adv Otorhinolaryngol. 2011;72:60–3.
27. Novak J, Raskova Kafkova L, Suzuki H, Tomana M, Matousovic K, Brown R, et al. IgA1 immune complexes from pediatric patients with IgA nephropathy activate cultured mesangial cells. Nephrol Dial Transplant. 2011;26:3451–7.
28. Novak J, Tomana M, Matousovic K, Brown R, Hall S, Novak L, et al. IgA1-containing immune complexes in IgA nephropathy differentially affect proliferation of mesangial cells. Kidney Int. 2005;67:504–13.
29. Novak J, Vu HL, Novak L, Julian BA, Mestecky J, Tomana M. Interactions of human mesangial cells with IgA and IgA-containing circulating immune complexes. Kidney Int. 2002;62:465–75.
30. Tamouza H, Chemouny J, Raskova Kafkova L, Berthelot L, Flamant M, Demion M, et al. IgA1 immune complex-mediated activation of MAPK/ERK kinase pathway in mesangial cells is associated with glomerular damage in IgA nephropathy. Kidney Int. 2012;82:1284–96.
31. Tomana M, Novak J, Julian BA, Matousovic K, Konecny K, Mestecky J. Circulating immune complexes in IgA nephropathy consist of IgA1 with galactose-deficient hinge region and antiglycan antibodies. J Clin Invest. 1999;104:73–81.
32. Yanagihara T, Brown R, Hall S, Moldoveanu Z, Goepfert A, Julian BA, et al. In vitro-formed immune complexes containing galactose-deficient IgA1 stimulate proliferation of mesangial cells. Results Immunol. 2012;2:166–72.
33. Bene MC, Faure GC. Mesangial IgA in IgA nephropathy arises from the mucosa. Am J Kidney Dis. 1988;12:406–9.

34. Bene MC, Hurault De Ligny B, Kessler M, Faure GC. Confirmation of tonsillar anomalies in IgA nephropathy: a multicenter study. Nephron. 1991;58(4):425–8.
35. Boyd JK, Cheung CK, Molyneux K, Feehally J, Barratt J. An update on the pathogenesis and treatment of IgA nephropathy. Kidney Int. 2012;81(9):833–43.
36. Smith AC, Molyneux K, Feehally J, Barratt J. *O*-glycosylation of serum IgA1 antibodies against mucosal and systemic antigens in IgA nephropathy. J Am Soc Nephrol. 2006;17 (12):3520–8.
37. Putnam FW. Structure of the human IgA subclasses and allotypes. Protides Biol Fluids. 1989;36:27–37.
38. Frangione B, Wolfenstein-Todel C. Partial duplication in the "hinge" region of IgA1 myeloma proteins. Proc Natl Acad Sci U S A. 1972;69:3673–6.
39. Tarelli E, Smith AC, Hendry BM, Challacombe SJ, Pouria S. Human serum IgA1 is substituted with up to six *O*-glycans as shown by matrix assisted laser desorption ionisation time-of-flight mass spectrometry. Carbohydr Res. 2004;339(13):2329–35.
40. Takahashi K, Smith AD, Poulsen K, Kilian M, Julian BA, Mestecky J, et al. Identification of structural isomers in IgA1 hinge-region *O*-glycosylation using high-resolution mass spectrometry. J Proteome Res. 2012;11:692–702.
41. Takahashi K, Wall SB, Suzuki H, Smith AD, Hall S, Poulsen K, et al. Clustered *O*-glycans of IgA1: defining macro- and micro-heterogeneity by use of electron capture/transfer dissociation. Mol Cell Proteomics. 2010;9:2545–57.
42. Franc V, Rehulka P, Raus M, Stulik J, Novak J, Renfrow MB, et al. Elucidating heterogeneity of IgA1 hinge-region *O*-glycosylation by use of MALDI-TOF/TOF mass spectrometry: role of cysteine alkylation during sample processing. J Proteomics. 2013;92:299–312.
43. Tomana M, Niedermeier W, Mestecky J, Hammack WJ. The carbohydrate composition of human myeloma IgA. Immunochemistry. 1972;9:933–40.
44. Tomana M, Niedermeier W, Mestecky J, Skvaril F. The differences in carbohydrate composition between the subclasses of IgA immunoglobulins. Immunochemistry. 1976;13:325–8.
45. Mattu TS, Pleass RJ, Willis AC, Kilian M, Wormald MR, Lellouch AC, et al. The glycosylation and structure of human serum IgA1, Fab, and Fc regions and the role of *N*-glycosylation on Fcα receptor interactions. J Biol Chem. 1998;273:2260–72.
46. Gomes MM, Wall SB, Takahashi K, Novak J, Renfrow MB, Herr AB. Analysis of IgA1 *N*-glycosylation and its contribution to Fc Renfrow MB, Herr AB. Analysis of IgA1. A1 sylati
47. Field MC, Amatayakul-Chantler S, Rademacher TW, Rudd PM, Dwek RA. Structural analysis of the *N*-glycans from human immunoglobulin A1: comparison of normal human serum immunoglobulin A1 with that isolated from patients with rheumatoid arthritis. Biochem J. 1994;299(Pt 1):261–75.
48. Niedermeier W, Tomana M, Mestecky J. The carbohydrate composition of J chain from human serum and secretory IgA. Biochim Biophys Acta. 1972;257(2):527–30.
49. Mestecky J, Schrohenloher RE, Kulhavy R, Wright GP, Tomana M. Site of J chain attachment to human polymeric IgA. Proc Natl Acad Sci U S A. 1974;71(2):544–8.
50. Zikan J, Mestecky J, Kulhavy R, Bennett JC. The stoichiometry of J chain in human secretory dimeric IgA. Mol Immunol. 1986;23(5):541–4.
51. Novak J, Mestecky J. IgA immune-complex. In: Lai KN, editor. Recent advances in IgA nephropathy. Hong Kong: Imperial College Press/The World Scientific Publisher; 2009. p. 177–91.
52. Mestecky J, Moro I, Kerr MA, Woof JM. Mucosal immunoglobulins. In: Mestecky J, Bienenstock J, Lamm ME, Mayer L, McGhee JR, Strober W, editors. Mucosal immunology. 3rd ed. Amsterdam: Elsevier Academic Press; 2005. p. 153–81.
53. Field MC, Dwek RA, Edge CJ, Rademacher TW. *O*-linked oligosaccharides from human serum immunoglobulin A1. Biochem Soc Trans. 1989;17:1034–5.
54. Moore JS, Kulhavy R, Tomana M, Moldoveanu Z, Suzuki H, Brown R, et al. Reactivities of *N*-acetylgalactosamine-specific lectins with human IgA1 proteins. Mol Immunol. 2007;44:2598–604.

55. Novak J, Tomana M, Kilian M, Coward L, Kulhavy R, Barnes S, et al. Heterogeneity of *O*-glycosylation in the hinge region of human IgA1. Mol Immunol. 2000;37:1047–56.
56. Renfrow MB, Cooper HJ, Tomana M, Kulhavy R, Hiki Y, Toma K, et al. Determination of aberrant *O*-glycosylation in the IgA1 hinge region by electron capture dissociation Fourier transform-ion cyclotron resonance mass spectrometry. J Biol Chem. 2005;280:19136–45.
57. Renfrow MB, MacKay CL, Chalmers MJ, Julian BA, Mestecky J, Kilian M, et al. Analysis of *O*-glycan heterogeneity in IgA1 myeloma proteins by fourier transform ion cyclotron resonance mass spectrometry: implications for IgA nephropathy. Anal Bioanal Chem. 2007;389:1397–407.
58. Iwasaki H, Zhang Y, Tachibana K, Gotoh M, Kikuchi N, Kwon YD, et al. Initiation of *O*-glycan synthesis in IgA1 hinge region is determined by a single enzyme, UDP-*N*-acetyl-α-D-galactosamine: polypeptide *N*-acetylgalactosaminyltransferase 2. J Biol Chem. 2003;278 (8):5613–21.
59. Horynova M, Takahashi K, Hall S, Renfrow MB, Novak J, Raska M. Production of *N*-acetylgalactosaminyl-transferase 2 (GalNAc-T2) fused with secretory signal Igκ in insect cells. Protein Expr Purif. 2012;81(2):175–80.
60. Wandall HH, Irazoqui F, Tarp MA, Bennett EP, Mandel U, Takeuchi H, et al. The lectin domains of polypeptide GalNAc-transferases exhibit carbohydrate-binding specificity for GalNAc: lectin binding to GalNAc-glycopeptide substrates is required for high density GalNAc-*O*-glycosylation. Glycobiology. 2007;17(4):374–87.
61. Stuchlova Horynova M, Raska M, Clausen H, Novak J. Aberrant *O*-glycosylation and anti-glycan antibodies in an autoimmune disease IgA nephropathy and breast adenocarcinoma. Cell Mol Life Sci. 2013;70:829–39.
62. Ju T, Brewer K, D'Souza A, Cummings RD, Canfield WM. Cloning and expression of human core 1 β1,3-galactosyltransferase. J Biol Chem. 2002;277(1):178–86.
63. Ju T, Cummings RD. A unique molecular chaperone Cosmc required for activity of the mammalian core 1 β3-galactosyltransferase. Proc Natl Acad Sci U S A. 2002;99 (26):16613–8.
64. Ju T, Cummings RD. Protein glycosylation: chaperone mutation in Tn syndrome. Nature. 2005;437(7063):1252.
65. Ju T, Otto VI, Cummings RD. The Tn antigen-structural simplicity and biological complexity. Angew Chem Int Ed Engl. 2011;50(8):1770–91.
66. Raska M, Moldoveanu Z, Suzuki H, Brown R, Kulhavy R, Hall S, et al. Identification and characterization of CMP-NeuAc: GalNAc-IgA1 α2,6-sialyltransferase in IgA1-producing cells. J Mol Biol. 2007;369:69–78.
67. Stuchlova Horynova M, Vrablikova A, Stewart TJ, Takahashi K, Czernekova L, Yamada K, et al. *N*-Acetylgalactosaminide α2,6-sialyltransferase II is a candidate enzyme for sialylation of galactose-deficient IgA1, the key autoantigen in IgA nephropathy. Nephrol Dial Transplant. 2015;30(2):234–8.
68. Andre PM, Le Pogamp P, Chevet D. Impairment of jacalin binding to serum IgA in IgA nephropathy. J Clin Lab Anal. 1990;4:115–9.
69. Mestecky J, Tomana M, Crowley-Nowick PA, Moldoveanu Z, Julian BA, Jackson S. Defective galactosylation and clearance of IgA1 molecules as a possible etiopathogenic factor in IgA nephropathy. Contrib Nephrol. 1993;104:172–82.
70. Allen AC, Harper SJ, Feehally J. Galactosylation of *N*- and *O*-linked carbohydrate moieties of IgA1 and IgG in IgA nephropathy. Clin Exp Immunol. 1995;100:470–4.
71. Moldoveanu Z, Wyatt RJ, Lee J, Tomana M, Julian BA, Mestecky J, et al. Patients with IgA nephropathy have increased serum galactose-deficient IgA1 levels. Kidney Int. 2007;71:1148–54.
72. Tomana M, Matousovic K, Julian BA, Radl J, Konecny K, Mestecky J. Galactose-deficient IgA1 in sera of IgA nephropathy patients is present in complexes with IgG. Kidney Int. 1997;52:509–16.

73. Shimozato S, Hiki Y, Odani H, Takahashi K, Yamamoto K, Sugiyama S. Serum under-galactosylated IgA1 is increased in Japanese patients with IgA nephropathy. Nephrol Dial Transplant. 2008;23:1931–9.
74. Wada Y, Tajiri M, Ohshima S. Quantitation of saccharide compositions of *O*-glycans by mass spectrometry of glycopeptides and its application to rheumatoid arthritis. J Proteome Res. 2010;9(3):1367–73.
75. Conley ME, Delacroix DL. Intravascular and mucosal immunoglobulin A: two separate but related systems of immune defence? Ann Intern Med. 1987;106:892–9.
76. Mestecky J, Russell MW, Jackson S, Brown TA. The human IgA system: a reassessment. Clin Immunol Immunopathol. 1986;40(1):105–14.
77. Mestecky J, Lue C, Tarkowski A, Ladjeva I, Peterman JH, Moldoveanu Z, et al. Comparative studies of the biological properties of human IgA subclasses. Protides Biol Fluids. 1989;36:173–82.
78. Bene MC, de Ligny BH, Kessler M, Foliguet B, Faure GC. Tonsils in IgA nephropathy. Contrib Nephrol. 1993;104:153–61.
79. Harper SJ, Allen AC, Bene MC, Pringle JH, Faure G, Lauder I, et al. Increased dimeric IgA-producing B cells in tonsils in IgA nephropathy determined by in situ hybridization for J chain mRNA. Clin Exp Immunol. 1995;101(3):442–8.
80. Horie A, Hiki Y, Odani H, Yasuda Y, Takahashi M, Kato M, et al. IgA1 molecules produced by tonsillar lymphocytes are under-*O*-glycosylated in IgA nephropathy. Am J Kidney Dis. 2003;42(3):486–96.
81. Itoh A, Iwase H, Takatani T, Nakamura I, Hayashi M, Oba K, et al. Tonsillar IgA1 as a possible source of hypoglycosylated IgA1 in the serum of IgA nephropathy patients. Nephrol Dial Transplant. 2003;18(6):1108–14.
82. Miura N, Imai H, Kikuchi S, Hayashi S, Endoh M, Kawamura T, et al. Tonsillectomy and steroid pulse (TSP) therapy for patients with IgA nephropathy: a nationwide survey of TSP therapy in Japan and an analysis of the predictive factors for resistance to TSP therapy. Clin Exp Nephrol. 2009;13(5):460–6.
83. Nakata J, Suzuki Y, Suzuki H, Sato D, Kano T, Yanagawa H, et al. Changes in nephritogenic serum galactose-deficient IgA1 in IgA nephropathy following tonsillectomy and steroid therapy. PLoS One. 2014;9(2):e89707.
84. Baenziger JU, Fiete D. Galactose and *N*-acetylgalactosamine-specific endocytosis of glycopeptides by isolated rat hepatocytes. Cell. 1980;22:611–20.
85. Baenziger JU, Maynard Y. Human hepatic lectin. Physicochemical properties and specificity. J Biol Chem. 1980;255:4607–13.
86. Baenziger JU, Fiete D. Recycling of hepatocyte asialoglycoprotein receptor does not require delivery of ligand to lysosomes. J Biol Chem. 1982;257:6007–9.
87. Moldoveanu Z, Epps JM, Thorpe SR, Mestecky J. The sites of catabolism of murine monomeric IgA. J Immunol. 1988;141:208–13.
88. Moldoveanu Z, Moro I, Radl J, Thorpe SR, Komiyama K, Mestecky J. Site of catabolism of autologous and heterologous IgA in non-human primates. Scand J Immunol. 1990;32:577–83.
89. Phillips JO, Russell MW, Brown TA, Mestecky J. Selective hepatobiliary transport of human polymeric IgA in mice. Mol Immunol. 1984;21:907–14.
90. Phillips JO, Komiyama K, Epps JM, Russell MW, Mestecky J. Role of hepatocytes in the uptake of IgA and IgA-containing immune complexes in mice. Mol Immunol. 1988;25:873–9.
91. Tomana M, Phillips JO, Kulhavy R, Mestecky J. Carbohydrate-mediated clearance of secretory IgA from the circulation. Mol Immunol. 1985;22:887–92.
92. Tomana M, Kulhavy R, Mestecky J. Receptor-mediated binding and uptake of immunoglobulin A by human liver. Gastroenterology. 1988;94:887–92.
93. Kiryluk K, Gharavi AG, Izzi C, Scolari F. IgA nephropathy – the case for a genetic basis becomes stronger. Nephrol Dial Transplant. 2010;25(2):336–8.

94. Kiryluk K, Novak J, Gharavi AG. Pathogenesis of immunoglobulin a nephropathy: recent insight from genetic studies. Annu Rev Med. 2013;64:339–56.
95. Gharavi AG, Moldoveanu Z, Wyatt RJ, Barker CV, Woodford SY, Lifton RP, et al. Aberrant IgA1 glycosylation is inherited in familial and sporadic IgA nephropathy. J Am Soc Nephrol. 2008;19(5):1008–14.
96. Hastings MC, Moldoveanu Z, Julian BA, Novak J, Sanders JT, McGlothan KR, et al. Galactose-deficient IgA1 in African Americans with IgA nephropathy: serum levels and heritability. Clin J Am Soc Nephrol. 2010;5(11):2069–74.
97. Kiryluk K, Moldoveanu Z, Sanders JT, Eison TM, Suzuki H, Julian BA, et al. Aberrant glycosylation of IgA1 is inherited in both pediatric IgA nephropathy and Henoch-Schönlein purpura nephritis. Kidney Int. 2011;80:79–87.
98. Zhao N, Hou P, Lv J, Moldoveanu Z, Li Y, Kiryluk K, et al. The level of galactose-deficient IgA1 in the sera of patients with IgA nephropathy is associated with disease progression. Kidney Int. 2012;82(7):790–6.
99. Mestecky J, Hashim OH, Tomana M. Alterations in the IgA carbohydrate chains influence the cellular distribution of IgA1. Contrib Nephrol. 1995;111:66–72.
100. Mestecky J, Tomana M, Czerkinsky C, Tarkowski A, Matsuda S, Waldo FB, et al. IgA-associated renal diseases: immunochemical studies of IgA1 proteins, circulating immune complexes, and cellular interactions. Semin Nephrol. 1987;7:332–5.
101. Lau KK, Gaber LW, Delos Santos NM, Fisher KA, Grimes SJ, Wyatt RJ. Pediatric IgA nephropathy: clinical features at presentation and outcome for African-Americans and Caucasians. Clin Nephrol. 2004;62(3):167–72.
102. Leung JCK, Poon PYK, Lai KN. Increased sialylation of polymeric immunoglobulin A1: mechanism of selective glomerular deposition in immunoglobulin A nephropathy? J Lab Clin Med. 1999;133:152–60.
103. Suzuki H, Moldoveanu Z, Hall S, Brown R, Vu HL, Novak L, et al. IgA1-secreting cell lines from patients with IgA nephropathy produce aberrantly glycosylated IgA1. J Clin Invest. 2008;118:629–39.
104. Berthoux F, Suzuki H, Thibaudin L, Yanagawa H, Maillard N, Mariat C, et al. Autoantibodies targeting galactose-deficient IgA1 associate with progression of IgA nephropathy. J Am Soc Nephrol. 2012;23:1579–87.
105. Camilla R, Suzuki H, Dapra V, Loiacono E, Peruzzi L, Amore A, et al. Oxidative stress and galactose-deficient IgA1 as markers of progression in IgA nephropathy. Clin J Am Soc Nephrol. 2011;6(8):1903–11.
106. Hiki Y, Horii A, Iwase H, Tanaka A, Toda Y, Hotta K, et al. *O*-linked oligosaccharide on IgA1 hinge region in IgA nephropathy. Fundamental study for precise structure and possible role. Contrib Nephrol. 1995;111:73–84.
107. Iwase H, Tanaka A, Hiki Y, Kokubo T, Ishii-Karakasa I, Nishikido J, et al. Application of matrix-assisted laser desorption ionization time-of-flight mass spectrometry to the analysis of glycopeptide-containing multiple *O*-linked oligosaccharides. J Chromatogr Biomed Sci Appl. 1998;709(1):145–9.
108. Iwase H, Tanaka A, Hiki Y, Kokubo T, Karakasa-Ishii I, Kobayashi Y, et al. Estimation of the number of *O*-linked oligosaccharides per heavy chain of human IgA1 by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOFMS) analysis of the hinge glycopeptide. J Biochem. 1996;120:393–7.
109. Odani H, Hiki Y, Takahashi M, Nishimoto A, Yasuda Y, Iwase H, et al. Direct evidence for decreased sialylation and galactosylation of human serum IgA1 Fc *O*-glycosylated hinge peptides in IgA nephropathy by mass spectrometry. Biochem Biophys Res Commun. 2000;271:268–74.
110. Odani H, Yamamoto K, Iwayama S, Iwase H, Takasaki A, Takahashi K, et al. Evaluation of the specific structures of IgA1 hinge glycopeptide in 30 IgA nephropathy patients by mass spectrometry. J Nephrol. 2010;23(1):70–6.

111. Takahashi K, Hiki Y, Odani H, Shimozato S, Iwase H, Sugiyama S, et al. Structural analyses of *O*-glycan sugar chains on IgA1 hinge region using SELDI-TOFMS with various lectins. Biochem Biophys Res Commun. 2006;350(3):580–7.
112. Wada Y, Dell A, Haslam SM, Tissot B, Canis K, Azadi P, et al. Comparison of methods for profiling *O*-glycosylation: human proteome organisation human disease glycomics/proteome initiative multi-institutional study of IgA1. Mol Cell Proteomics. 2010;9(4):719–27.
113. Hastings MC, Moldoveanu Z, Suzuki H, Berthoux F, Julian BA, Sanders JT, et al. Biomarkers in IgA nephropathy: relationship to pathogenetic hits. Expert Opin Med Diagn. 2013;7(6):615–27.
114. Mestecky J, Raska M, Julian BA, Gharavi AG, Renfrow MB, Moldoveanu Z, et al. IgA nephropathy: molecular mechanisms of the disease. Annu Rev Pathol. 2013;8:217–40.
115. Mestecky J, Tomana M, Moldoveanu Z, Julian BA, Suzuki H, Matousovic K, et al. The role of aberrant glycosylation of IgA1 molecules in the pathogenesis of IgA nephropathy. Kidney Blood Press Res. 2008;31:29–37.
116. Novak J, Julian BA, Mestecky J, Renfrow MB. Glycosylation of IgA1 and pathogenesis of IgA nephropathy. Semin Immunopathol. 2012;34(3):365–82.
117. Suzuki H, Raska M, Yamada K, Moldoveanu Z, Julian BA, Wyatt RJ, et al. Cytokines alter IgA1 *O*-glycosylation by dysregulating C1GalT1 and ST6GalNAc-II enzymes. J Biol Chem. 2014;289(8):5330–9.
118. Takahashi K, Raska M, Stuchlova Horynova M, Hall SD, Poulsen K, Kilian M, et al. Enzymatic sialylation of IgA1 O-glycans: implications for studies of IgA nephropathy. PLoS One. 2014;9(2):e99026.
119. Takahashi K, Suzuki H, Yamada K, Hall S, Moldoveanu Z, Poulsen K, et al. Molecular characterization of IgA1 secreted by IgA1-producing cell lines from patients with IgA nephropathy. J Am Soc Nephrol. 2012;23:853A.
120. Raska M, Yamada K, Horynova M, Takahashi K, Suzuki H, Moldoveanu Z, et al. Role of GalNAc-transferases in the synthesis of aberrant IgA1 *O*-glycans in IgA nephropathy. J Am Soc Nephrol. 2011;22:625A.
121. Yamada K, Huang ZQ, Suzuki H, Raska M, Moldoveanu Z, Suzuki Y, et al. IL-6 increases production of galactose-deficient IgA1 by IgA1-secreting cells from IgA nephropathy patients through STAT3 signaling pathways. J Am Soc Nephrol. 2012;23:389A.
122. Reily C, Ueda H, Huang ZQ, Mestecky J, Julian BA, Willey CD, et al. Cellular signaling and production of galactose-deficient IgA1 in IgA nephropathy, an autoimmune disease. J Immunol Res. 2014;2014:197548.
123. McCarthy DD, Kujawa J, Wilson C, Papandile A, Poreci U, Porfilio EA, et al. Mice overexpressing BAFF develop a commensal flora-dependent, IgA-associated nephropathy. J Clin Invest. 2011;121(10):3991–4002.
124. Maillard N, Wyatt RJ, Julian BA, Kiryluk K, Gharavi A, Fremeaux-Bacchi V et al. Current understanding of the role of complement in IgA nephropathy. J Am Soc Nephrol. 2015;26 (7):1503–12.
125. Boehm MK, Woof JM, Kerr MA, Perkins SJ. The Fab and Fc fragments of IgA1 exhibit a different arrangement from that in IgG: a study by X-ray and neutron solution scattering and homology modelling. J Mol Biol. 1999;286(5):1421–47.

Chapter 5
Differences of Histological Classification Between the Japanese Histological Grade Classification and the Oxford Classification

Kensuke Joh and Keely May McNamara

Abstract Two evidence-based histological classifications, the Oxford and Japanese histological grade classification (JHGC), have been recently developed. However, they differ on a number of points both in the methodological approach to developing the classification schemes, classification system (split or lumped), and in the predictive pathological parameters. As these two classification systems coexist in Japan, there has been a great deal of motivation to compare the two in order to try and determine which approach may produce the most informative information for the sake of clinicians and ultimately for the benefit of the patients. Even though JHGC was not produced with the same rigor as the Oxford classification, its utility can be evaluated by the clinical information that it provides. For the aim to overcome the task of histological classification, JHGC may not be inferior to Oxford classification.

Keywords IgA nephropathy • Histological classification • Split system • Lumped system • Natural history

5.1 Introduction

IgA nephropathy (IgAN) is a serious disease with a wide range of clinical outcomes. The quantitative assessment of the active and chronic histological lesions present in renal tissues has been shown to be a useful predictor of patient's outcome and responsiveness to certain therapies [1]. However, as pathological classification can be considered by some to be subject to a degree of subjectivity and in addition needs highly trained and skilled pathologists, of whom there is a worldwide shortage, various approaches to developing classification schemes using quantifiable variables have been developed. Because of this histologic diversity of IgAN, a number of histologic classification systems were devised and tested for their value

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in predicting clinical outcomes [1]. Of these, the two most widely used were those of Lee et al. [2, 3] and of Haas [4]. However, these classifications were both expert's opinion-based classifications without accurate definitions of each lesion. Therefore, there were minimal validation studies of these approaches and neither gained widespread acceptance among renal pathologists.

In response to the need for adoptable and standardized classification methods, evidence-based histological classifications have been pursued for the classification of IgAN. The underlying logic of using evidence-based methods is that classification systems whose origins lie in evidenced-based methods are more rigorous, less biased, and more transferable between institutional settings and individuals than their expert opinion-based counterparts. Of the published evidence-based classification schemes, this chapter is going to concern itself with describing and comparing two methodologically divergent approaches; these are the Oxford Classification and the Japanese Histological Grade Classification [5–7]. Additionally, beyond the description and comparison of these two evidence-based classification schemes, we also will attempt to address the benefits and pitfalls of both evidence-based and expert opinion-based classification of IgAN.

5.2 Histological Classification

As touched on above, the role of histological classification is the clear communication of histological information between pathologists and clinicians. The utility of classification schemes is that by typifying an individual case with all its inherent individual variability to a subclass within a classification, pathologists can provide both easily digestible information concerning prognosis and guidance for therapeutic decisions. In addition, classification schemes can aid in the development of new therapeutic strategies by allowing the comparison of lesions across unrelated clinical trials and patient cohorts, although this latter objective has been yet less of a focus in the current published approaches.

Currently, the most commonly used international classification scheme is that of the Oxford classification. This is based on a multicenter case-control study on IgA nephropathy (IgAN). This was the first evidence-based study conducted to develop an evidence-based clinicopathological classification of IgAN [5, 6]. Within Japan, an alternate system has been developed through the IgAN Study Group of the Progressive Renal Diseases Study Committee organized by the Ministry of Health, Labor and Welfare. This approach to classification began in 2004 with the goal to develop an evidence-based clinicopathological classification of IgAN, a time line comparable with that of the Oxford classification, and subsequently published an updated evidence-based histological classification in 2013, which is called the Japanese Histological Grade Classification (JHGC) [7]. These two classifications systems (Oxford and JHGC) differ concerning the classification system (split or

Table 5.1 Comparison between JHGC and Oxford classification

1. *Oxford classification: split system*				
M	Mesangial hypercellularity	≤0.5 (M0) or ≥0.5 (M1)		
E	Endocapillary hypercellularity	Absent (E0) or present (E1)		
S	Segmental sclerosis	Absent (S0) or present (S1)		
T	Tubular atrophy/interstitial fibrosis	<25 % (T0), 26-50 % (T1), or >50 % (T2)		
2. *Japanese histological grading classification: lumped system*				
Histological grade	No of lesions*/total no. of glomeruli	Active lesions only	Active lesion + chronic lesion	Chronic lesion only
H-Grade I	0–24.9 %	A	A/C	C
H-Grade II	25–49.9 %	A	A/C	C
H-Grade III	50–74.9 %	A	A/C	C
H-Grade IV	75 %	A	A/C	C

*Lesions
Active lesion (A): Cellular crescent, Fibrocellular crescent
Chronic lesion (C): Global sclerosis, Segmental sclerosis, Fibrous crescent

Table 5.2 Pathological parameters of Oxford and JHGC

		Oxford	JHGC
Active glomerular lesions	Mesangial hypercellularity	○	×
	Endocapillary hypercellularity	○	×
	Cellular or fibrocellular crescent	×	○ (late progressor)
Chronic glomerular lesions	Global sclerosis	×	○ (early and late progressor)
	Segmental sclerosis	×	○ (early progressor)
	Segmental sclerosis or adhesion	○	×
	Fibrous crescent	×	○ (early progressor)
	Adhesion	×	×
Tubulointerstitium	Tubular atrophy/interstitial fibrosis	○	×
Vascular lesions	Interlobular artery	×	×
	Afferent artery	×	×

○ adopted
× not adopted

lumped) and the parameters involved in the classification (Tables 5.1 and 5.2). In Japan, we are currently examining the problem of how to use this double standard of classification and hence are motivated to compare these classifications in terms of their clinicopathological utility.

5.2.1 Oxford Classification

5.2.1.1 Development

An international committee of pathologists and nephrologists from four continents were first convened in 2004 for the purpose of developing a new, evidence-based, international consensus histologic classification for IgAN. The 265 cases were assembled including biopsies from 206 adults and 59 children and were from 17 different centers based in eight countries and four continents.

The following rigorous procedure was taken to develop the evidence-based classification (Fig. 5.1). First, the histological parameters which are necessary to take in the lesions of IgAN were discussed and determined. Using these selected lesions, a score sheet was produced to quantify these selected histological parameters consisting of glomerular, tubulointerstitial, and vascular lesions. Second, on the basis of data-using score sheets, reproducibility was tested by the Intraclass Correlation Coefficient (ICC), and the parameters with poor reproducibility were excluded for further analysis. Third, the histological parameters with reasonable reproducibility were assessed by linear regression analysis and Cox regression analysis to determine if they were independent predictors for the renal functional outcome for a minimum of 3 years and/or until an end point of end-stage renal disease (ESRD) or $\geq$50 % decline in estimated glomerular filtration rate (eGFR).

As a consequence, three histologic parameters were selected as independent predictors within this classification (M: mesangial hypercellularity, S: segmental sclerosis, and T: tubular atrophy/interstitial fibrosis (TA/IF)). One additional histologic parameter—endocapillary hypercellularity (E) in >= 1 glomerulus—was not significantly correlated with the above outcomes by multivariate analysis but

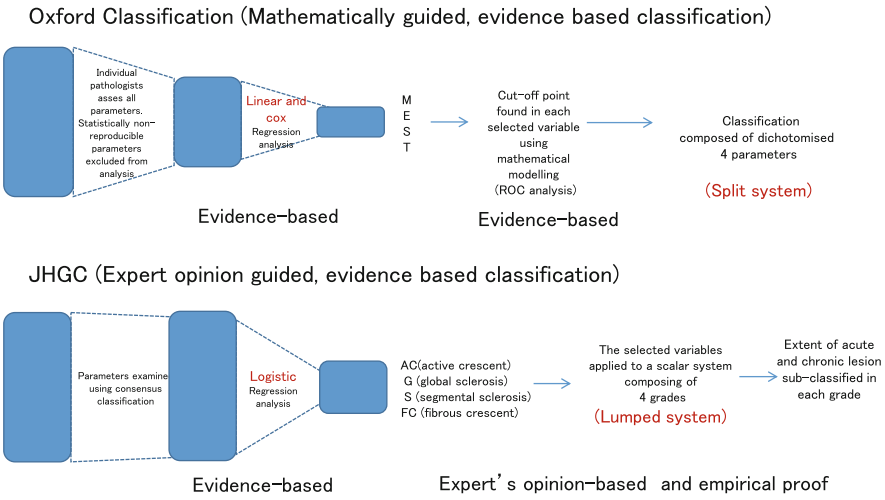

Fig. 5.1 Comparison of the producing procedure between Oxford and JHGC

was strongly correlated with response to immunosuppressive therapy and hence this additional parameter was included in the classification. Finally, in order to dichotomize each of the selected parameters to produce a split classification system, cutoff points were determined by ROC (Receiver Operating Characteristic) analysis. Thus, the recommendation of the classification with IgAN includes four independently reported histologic parameters (M, E, S, and T): M0 or M1, indicating mesangial hypercellularity in $\leq$50 % versus >50 % of glomeruli; E0 or E1, indicating endocapillary hypercellularity in 0 versus $\geq$1 glomeruli; S0 or S1, indicating segmental sclerosis in 0 versus $\geq$1 glomeruli; and T0, T1, or T2, indicating TA/IF in $\leq$25 %, 26–50 %, or >50 % of renal cortex, respectively. They produced a four-parameter dichotomous scoring system to describe IgAN lesions.

5.2.1.2 Validation Studies of Oxford Classification

The Oxford Histologic Classification has gained a significant level of worldwide acceptance and has been the subject of several single-center or multicenter validation studies. Validating the classification in a diverse range of cohorts treated in different ways is important to confirm that the classification can be widely applied. Among validation studies, the selected independent predictors for renal functional outcome by multivariate analysis were M, S, and T [8] in one, M and S in one, 2 [9], S and T in two [10–12], M and T in two [13, 14], E and T in one, [15], only T in three, [16–18], only CT in one [11], and none in one study [19], respectively (Fig. 5.2).

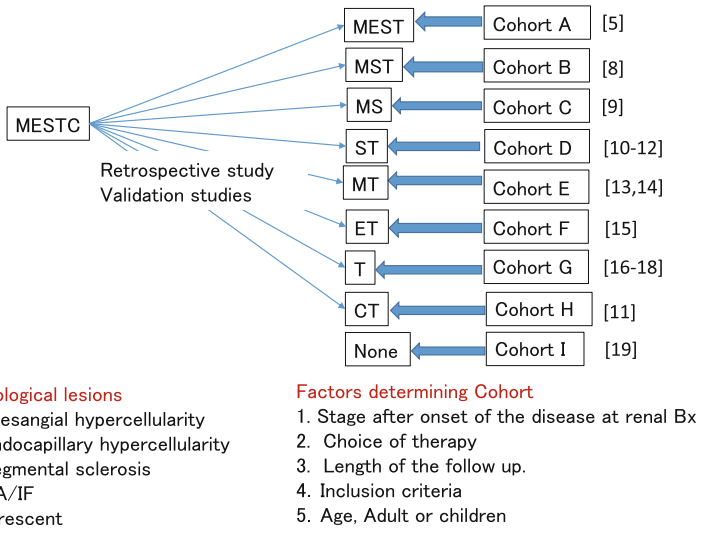

Fig. 5.2 Evidence-based Oxford classification (Split system)

Confirmatory Studies

Coppo et al. compared the applicability of the Oxford classification to predict renal outcomes in 59 children as compared with the 206 adults included in the original Oxford study cohort. M1 vs. M0 and S1 vs. S0 were associated with an increased rate of renal functional decline. In contrast, E1 vs. E0 was not. These findings are similar to those reported in the entire Oxford cohort and suggested that selected parameters were not influenced by the patient age. However, the effects of the T variable were not directly examined because there were too few children with tubulointerstitial lesions to draw conclusions [9]. European validation study of the Oxford classification of IgA (VALIGA) also confirmed the results from the original Oxford classification study using 1,147 patients from 13 European countries. Over a median follow-up of 4.7 years, M, S, and T lesions independently predicted the loss of eGFR and a lower renal survival. In individuals with eGFR less than 30 ml/min per 1.73 m^2, the M and T lesions independently predicted a poor survival [8].

Using a cohort of 187 adults and children with IgAN from 4 North American centers, S and T scores were confirmed as independent predictors of renal functional decline, and this study also confirmed that endocapillary proliferation (E1) was associated with an increased rate of renal functional decline in patients not treated with immunosuppression but not in patients receiving immunosuppression, similar to findings in the original Oxford cohort. M score was not an independent predictor of renal functional decline in the study [10]. Katafuchi et al. studied 702 Japanese adults and children by multivariate analysis and found that S and T lesions were associated with ESRD. M1 showed a trend toward high risk of ESRD compared with M0. E score showed no significant association with the development of ESRD. When crescent (C) was added to the multivariate analysis, C and T, but not S, were significantly associated with the development of ESRD. They documented also that an association of crescent with ESRD was not observed in patients who met the inclusion criteria of Oxford cohort but was evident in those who did not [11].

Shi et al. evaluated 410 Chinese patients and found that S and T scores were independent predictors of ESRD. Furthermore, patients having >25 % of glomeruli with endocapillary proliferation (termed E25), crescents, and M1 were more likely to be treated with immunosuppressive agents, but none of these parameters were independent predictors of prognosis [12]. Zeng et al. found that only M1 and T scores were associated with an increased rate of eGFR decline or reduced renal survival from a combined event by multivariate analysis using 1,026 adult IgAN patients from 18 centers in China [13]. Shima et al. defined as a decline in eGFR to <60 ml/min per 1.73 m^2 in 161 consecutive Japanese IgAN children (<20 years old) and found that M and T scores (but not S) and crescents in >30 % of glomeruli (but not in ≥1 glomerulus) were significant predictors of renal outcome in multivariate analyses [14]. Lee et al. reported on 69 adult patients followed for >36 months and found that E1 and T1/T2 lesions independently predicted a

≥50 % decline in eGFR or ESRD, even though patients with E1 lesions received more immunosuppression than those with E0 [15].

Divergent Studies (One or Less Parameters)

Four studies found only one of the Oxford M, S, and T scores, most often the T score, to be independently predictive of clinical outcome. El Karoui et al. studied 128 adult patients and found only T score predicted rate of eGFR decline, and only M score was associated with doubling of serum creatinine or ESRD by multivariate analysis [16]. In the study by Kang et al. using 197 Korean adult patients, they showed that only T lesions predicted a 50 % reduction in eGFR or ESRD. Lee et al. reported on 69 adult patients followed for >36 months. E1 and T1/T2 lesions independently predicted a ≥50 % decline in eGFR or ESRD, even though patients with E1 lesions received more immunosuppression than those with E0 [17]. Le et al., in a study of 218 Chinese children, found that only T1/2 was an independent predictor of poor outcome in multivariate analysis [18]. Finally, Alamartine et al. studied 183 French adults including very mild and very severe forms of the disease for an average of 77 months; only baseline eGFR was predictive of reaching this end point by multivariate analysis [19].

As shown above, the Oxford classification offers a simple approach for predicting renal outcome by describing the presence or absence of active (M, E) and chronic lesions (S, T). It is also the only current glomerular disease classification that was developed in a truly evidenced-based manner.

5.2.2 Japanese Histological Grade Classification (JHGC)

5.2.2.1 Development

As mentioned in the introduction, within Japan, an alternate classification system has been developed. This came from the work of the IgAN Study Group of the Progressive Renal Diseases Study Committee under the auspices of the Ministry of Health, Labor and Welfare. A multicenter case-control study on IgAN was conducted to develop an evidence-based clinicopathological classification for predicting long-term renal outcome.

This working group consisted of 16 centers. The cohort was drawn from patients seen in Japanese hospitals. Lesions were assessed independently by two pathologists, and if they did not agree, lesions were reviewed by both pathologists until a consensus was reached. The initial panel of histological parameters examined was very similar to that of the Oxford classification. During a median follow-up of 9.3 years after biopsy, 49 out of 287 patients (19 %) progressed to ESRD. The associations between pathological variables and the need for chronic dialysis were examined by multivariate logistic regression analysis separately in patients who

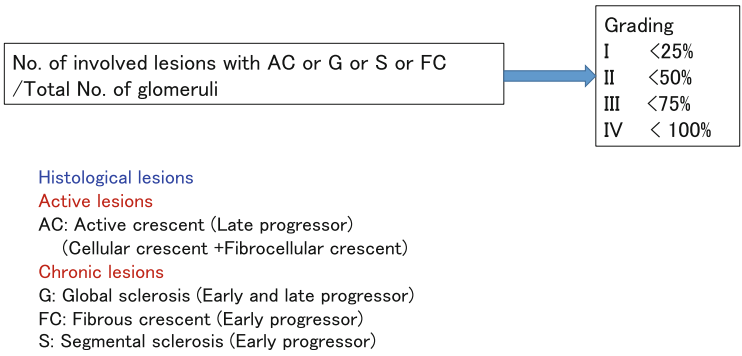

Fig. 5.3 Japanese Histological Grading Classification (Lumped system)

required dialysis earlier than 5 years (early progressors) and those who required dialysis within 5–10 years (late progressors) after biopsy. Independent pathological variables predicting progression to ESRD were global sclerosis, segmental sclerosis, and fibrous crescents for early progressors and global sclerosis and cellular/fibrocellular crescents for late progressors (Fig. 5.3). Four histological grades (HGs), such as HG 1, HG 2, HG 3, and HG 4, were established corresponding to <25 %, 25–49 %, 50–74 %, and ≥ 75 % of glomeruli, exhibiting cellular or fibrocellular crescents, global sclerosis, segmental sclerosis, or fibrous crescents. Eleven (7 %) patients in HG 1, 12 (16 %) in HG 2, 13 (31 %) in HG 3, and 13 (68 %) in HG 4 progressed to ESRD. Multivariate logistic analysis revealed that the risk of progression to ESRD was significantly higher in HG 2, 3, and 4 than in HG 1 (odds ratio, 2.4, 5.7, and 27.6 vs. 1.0). Age, mean arterial pressure, and urinary protein excretion were higher, while eGFR was lower in higher grades, suggesting that our histological grading agrees with the prognostic clinical features of IgAN at the time of diagnosis. The risk of progression to ESRD and the rate of GFR decline were significantly greater in higher grades, indicating that the grading can identify the magnitude of the risk of progression to ESRD as well as the deterioration rate of renal function [7]. In addition to the grading system, this classification allowed for active (A) chronic lesions (C) and mixed (A/C) to be produced as a subgroup of each grade which allows identification of a balance between activity and chronicity.

5.2.2.2 Validation Studies

Compared to the Oxford classification scheme, a limited number of validation studies have been conducted, and these have been confined to Japanese cohorts. Sato et al. validated the JHGC in a Japanese single-center cohort [20]. This was a retrospective study in 198 Japanese adult patients with IgAN. Clinical parameters including blood pressure, urinary protein, eGFR, and outcomes were evaluated in these patients. The glomerular lesion percentage score (GLPS) [number of glomeruli with cellular crescents, fibrocellular crescents, global sclerosis, segmental

sclerosis, or fibrous crescents per number of total obtained glomeruli] was assessed in each patient and categorized into histologic grades of HG1 (<25 %), HG2 (25–49 %), and HG3/4 (≥50 %). Associations of GLPS (or HG) with disease progression (50 % eGFR decline or ESRD-requiring dialysis) within 10 years after biopsy and the rate of annual eGFR decline were examined. During a median follow-up period of 12.0 years after biopsy, disease progression occurred in 12.8 % (12/94) of HG1 patients, 32.3 % (21/65) of HG2 patients, and 46.2 % (18/39) of HG3/4 patients. The risk of disease progression was significantly higher in the HG2 and HG3/4 groups than in the HG1 group (odds ratios: 3.3 and 5.9 vs.1). A higher GLPS was significantly associated with a higher risk of disease progression and a greater annual eGFR decline. JHGC based on GLPS (or HG) was well correlated with long-term prognosis in the cohort of Japanese adult patients with IgAN [20].

5.3 Comparison Between Oxford Classification and Japanese Histological Grade Classification

Despite similar objective (the communication of complex pathological information using a simplified scoring system), the Oxford and Japanese histological grade classification schemes differ on a number of points, both in the methodological approach to developing the classification schemes and in the predictive pathological parameters suggested by each classification scheme. As these two classification systems coexist in Japan, there has been a great deal of motivation to compare the two in order to try and determine which approach may produce the most informative information for the sake of clinicians and ultimately for the benefit of the patients. In order to provide background to our subsequent discussion of the two classification schemes, the differences in their development and methodology are detailed below.

5.3.1 Differences in Development of Classification Schemes

5.3.1.1 Inclusion Criteria

The cohorts used in the studies were different between JHGC study and the Oxford classification study. The differences were influenced mainly by the inclusion criteria. The Oxford classification excluded patients with proteinuria less than 0.5 g/day and those with an initial eGFR of <30 ml/min per 1.73 m^2, whereas in the JHGC study, there was no limitation for the cohort. This is a relevant variation as a significant fraction of Japanese patients had asymptomatic proteinuria with microhematuria or isolated microhematuria in their initial clinical presentation and were detected owing to the health-screening programs of Japan, whereas these patients would have been excluded from analysis within the Oxford cohort. This

means that despite the overall Japanese cohort presenting with less severe IgAN lesions, it also included those with severe lesions, providing a wider range of IgAN lesions from which to develop its classification.

5.3.1.2 Baseline Differences Between Cohorts Used in the Studies (Table 5.3)

When comparing baseline characteristic between the two cohorts, the majority of parameters were different, possibly due to a combination of the differences in inclusion criteria as mentioned above and other factors. These differences are summarized in Table 5.3. The difference between the cohorts included the proportion of pediatric and female patients, follow-up period, degree of proteinuria, and the eGFR slope. The mean rate of renal function decline was 3.5 ± 8.4 ml/min per 1.73 m^2 per year (-3.7 ± 6.6 in adults and -2.7 ± 1.05 in children,) in Oxford, whereas eGFR decline was -2.9 ± 3.8 in JHGC. Considering the lower degree of proteinuria and lower eGFR slope in the JHGC study, overall this cohort consists of earlier stage of the disease process of IgAN. This speculation is supported by the evidence that correlation efficient between endocapillary hypercellularity and mesangial hypercellularity is 0.5 in JHGC and 0.3 in Oxford, whereas correlation efficient between endocapillary hypercellularity and crescent was 0.2 in JHGC and 0.4 in Oxford, respectively (data not shown) [6, 7] . Since crescent became an independent predictor between 5 and 10 years (late progressor) in JHGC study and mean follow-up period is 69 months (5.8 years) in Oxford study, crescent may not be selected in Oxford study due to the shorter follow-up time [5–7].

Table 5.3 Clinical profile of the cohort

Clinical profile at time of biopsy	Oxford study	Japanese retrospective study
Cohort	265	287
Median age (yrs)	32 (4–73)	35 (18–70)
Female	28 %	49 %
Pediatric at time of biopsy (<18 yrs)	**22 %**	**9.1 %**
Ethnicity Caucasian/African/Asian/Other)	66, 3, 27, 4 %	Japanese
MAP (mmHg)	98 ± 18	94 ± 14
eGFR (ml/min/1.73 m^2)	83 ± 36	78 ± 25
Proteinuria(g/day)	**1.7 (0.5–18.5)**	**0.8 (0.0–7.6)**
Period of follow-up (Months)	**69(12–268)**	**110 (17–602)**
Treated with RAS blockade (ACEi, ARB)	74 % (68 %, 22 %)	77 %
Steroid	29 %	37 %
eGFR slope (ml/min/1.73 m^2/y)	$\mathbf{-3.5 \pm 8.4}$	$\mathbf{-2.9 \pm 3.8}$

5.3.1.3 Statistical Methodology Involved

The mathematical and statistical approaches to parameter selection differed between the two approaches. Of the two, the Oxford classification can be said to be the most rigorously developed as it is the product of a blinded analysis by multiple pathologists, it tested the reproducibility of each parameter, and it excluded those showing poor reproducibility. It then subjected parameters that passed this initial criterion of good interobserver reproducibility to regression analysis in both univariate and multivariate linear and Cox regression models in order to find those parameters which modeled both renal functional decline (through eGFR slope) and outcomes (measured by survival from 50 % reduction in renal function or ESRD). In contrast, the JHGC used a consensus-based approach to parameters without a quantitative estimation of the reproducibility of each parameter. The parameters assessed in this manner were then tested by multivariate logistic regression analysis in order to determine which parameter most closely followed lesion for progression in early progressors (dialysis <5 years after biopsy) or late progressors (dialysis 5–10 years after biopsy) (Fig. 5.1).

Hence, despite similarities (retrospective cohorts, evidence-based modeling), the Oxford classification has the more rigorous mathematical approach to reproducibility by only including highly reproducible histological features as examined by multiple pathologists. In contrast, the JHGC still relies on a degree of expertise by the examining pathologist in classifying the lesions examined. When comparing the effectiveness of the models used, linear and Cox regression models are preferable to assess the renal functional outcome in middle observation time of 5.8 years in Oxford study. On the other hand, in logistic analysis used in the JHGC study, a number of events attaining the hard end point become more in the longer observation period. So the observation period in this study was divided into early phase (within 5 years) and late phase (between 5 and 10 years), allowing the parameters assessed to encompass a greater spectrum of the natural history of IgAN.

5.3.1.4 Differences in the Predictive Pathological Parameters Obtained from Both Classification Schemes

While having similar objectives and approaches, the Oxford classification and the JHGC obtained different pathological parameters as key components in their model of the best way to quantify IgAN lesions, despite both models starting with a similar panel of pathological characteristics. The only overlap between the two scoring systems was the adoption of segmental sclerosis as a component of the overall score in both the Oxford classification and the JHGC.

In the Oxford classification, the additional parameters selected on their basis of predicting renal function and outcome were tubular atrophy/interstitial fibrosis (T) and mesangial hypercellularity (M), while in the JHGC, the parameters were global sclerosis, cellular crescent, fibrocellular crescent, and fibrous crescents.

Within these, there are probably parallels as global sclerosis and TA/IF showed a high degree of correlation in the JHGC study ($R = 0.741$ and $p < 0.001$ by Spearman's rank correlation). While the reproducibility of TA/IF was high in the Oxford study (ICC, 0.78/0.79) and this reproducibility was one of the reasons for its selection, IF/TA was estimated by semiquantitative methods (eyeball estimation) in both studies and hence may only be reliable only in an expert's estimation. From this point of view, global sclerosis showed outstanding reproducibility in the Oxford classification (ICC;0.90), as well as being a more quantitative variable so hence was adopted in preference to IF/TA as predictors in the JHGC. Despite its utility in traditional expert's opinion classification, vascular lesion was not adopted in either classification because reproducibility of quantification for vascular lesions was considered to be insufficient in both studies. One additional histologic parameter—endocapillary hypercellularity was not significantly correlated with the above outcomes by multivariate analysis but was strongly correlated with response to immunosuppressive therapy—could be a predictor for poor prognosis in the patients without immunosuppressive therapy in the Oxford study, but a similar analysis was not performed in the JHGC.

Of note, despite its clinical utility, crescent (C) was not found to be significant predictors of clinical outcomes in the Oxford study but was included in the JHGC. A possible explanation behind this is that the rapidly progressing patients (progression to ESRD within 12 months of biopsy and/or those with an initial eGFR of <30 ml/min per 1.73 m^2) were excluded from the Oxford study, but included in the Japanese study. Given that crescent is a parameter associated with rapidly progressive disease, it is possible that the cohort selection predisposed the models to preselect different characteristics [11]. Thus, this may explain the lack of selection of crescents in the Oxford classification.

5.3.1.5 Treatment and Outcome Differences Between Cohorts Used in the Studies

Immunosuppressive therapy is a common treatment approach used in IgAN. Twenty-nine percent of the patients enrolled (47 % of children and 23 % of adults) received immunosuppressive therapy in the Oxford study, whereas 37 % of the patients received variable dosages of corticosteroids with additional immunosuppressive agents in the JHGC. The difference in rates of therapy between these two groupings may be explained by their inclusion criteria and differences in the nature and natural history of IgAN lesions. While dealt with in more detail below, IgAN lesions can be subclassified into active and chronic lesions. The former responds to immunosuppressive therapy, while the latter does not. In traditional expert's opinion-based pathology, active lesions can be characterized by the presence of various pathological parameters (mesangial hypercellularity, endocapillary hypercellularity, and cellular crescents) and thus in these retrospective cohort were most probably recognized and more likely to be treated by immunosuppressive therapy. As the Oxford cohort limited the inclusion of early stage lesions by its

inclusion criteria while the cohort of JHGC consists of earlier stage cases, it is unsurprising that there may be differences in the rates of treatment. Additionally, this difference in cohort composition may have biased the models selection of significant outcomes, as if in the Japanese cohort, a higher proportion of early lesions was included and treated parameters that are reversible upon steroid treatment (such as those mentioned above) would not be independent predictors for renal outcome in contrast to the Oxford study. Interestingly, fibrous crescents, which are traditionally interpreted as a marker of lesions that will not respond to steroid therapy, were selected as early progressor in the JHGC [7], which is in line with the idea that these lesions are non-responsive to treatment. Such an assessment was not made in the Oxford cohort as the quantification of fibrous crescents failed the initial selection step of interindividual reproducibility [5, 6].

5.4 The Relative Advantages of a Lumped System of Classification Compared to a Split System of Classification

The purpose of the histological classification is principally to identify the risk of progression of renal disease, enabling us to improve individual patient prognostication, to identify the potential for response to immunosuppression or other specific treatments, and to refine recruitment to clinical trials. With these aims in mind, it is important to look at the function of both the Oxford and JHG classification schemes in meeting these needs. Before doing so, however, it is important to review the natural history of IgAN in order to better understand the clinical implications of various histological aspects of the disease, because renal biopsy to diagnose IgAN is undertaken before therapy and is one of the main parameters used in classifying disease course and subsequent treatment.

One important aspect of IgAN is that they can have very different disease courses. A diagrammatic overview of the natural history of IgAN is shown in Fig. 5.4. There are three types of disease courses expected by the clinician; rapidly progressive, slowly progressive with acute exacerbation, and slowly progressive type without acute exacerbation. These disease types are important as they have an impact on the patient's progression and guide clinicians in regards to treatment and overall prognosis. In the early phase, active lesions are prominent and chronic lesions are rare. Active lesions, which affect renal function, are characterized by crescents. The frequency and/or severity of these lesions has traditionally guided pathologists and clinicians in choosing immunosuppressant therapy for an individual patient. In addition to crescents within the acute lesions, mesangial hypercellularity and endocapillary hypercellularity predict for lesions that will respond well to immunosuppressant therapy and hence will not develop into chronic lesions characterized by a greater degree of structural alteration. In contrast, glomerular tuft necrosis can develop into cellular crescents and finally into more permanent

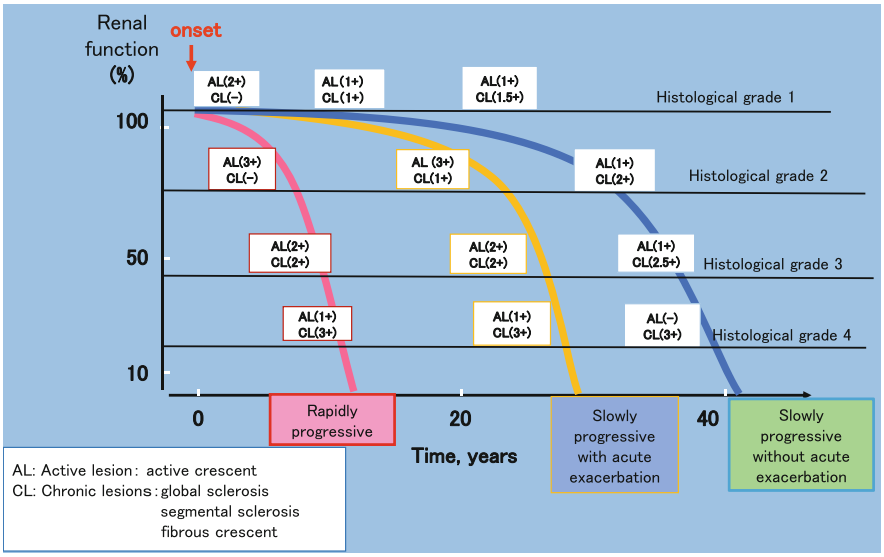

Fig. 5.4 Natural history of IgAN

structural alterations such as fibrocellular and fibrous crescent together with adhesion and segmental sclerosis. Global sclerosis and TA/IF are terminal lesions of fibrous crescent and segmental sclerosis and thus indicate more chronic disease. In the majority of individual cases, the lesions of IgAN stand on the balance of acute and chronic lesions. As renal biopsy is performed before a diagnosis and treatment is made and is a static measure (i.e., may be performed at any point on the disease course depending on how quickly the initial diagnosis was made), assessment of a number of the factors above may be important in differentiating the three possible disease processes present and the most appropriate choice of therapy.

With this aim, we would argue that the lumped system as used by the JHGC is a more favorable procedure than that of split system used by the Oxford classification system. The reason for this is that the Oxford classification system reduced the complexity and diversity of the histology observed in the biopsy into a series of dichotomous values (present/absent), thus potentially losing valuable information on the pathology within the lesion. This is especially true when trying to assign an individual to one of the three disease courses mentioned above. In addition, the current Oxford system reports four independent parameters without any information of how varied combinations of these parameters will interact. This means that the utility that this classification scheme provides to clinicians, in terms of identifying the disease course in patients, still relies on interpretation of the various values from the pathology report.

In contrast, the JHGC utilizes a lumped system consisting of markers for both chronic and active lesions and utilizes a scalar system in order to grade each component (Fig. 5.3). In this system, four histological grades, HG 1, HG 2, HG

3, and HG 4, are assigned corresponding to <25 %, 25–49 %, 50–74 %, and ≥75 % of glomeruli, exhibiting cellular or fibrocellular crescents, global sclerosis, segmental sclerosis, or fibrous crescents. In addition, the JHCG then combines these parameters to produce a singular lumped value incorporating all elements of the classification. By this systemic scoring, the histology of the patients from early phase of the disease to advanced phase can be graded, which correlates well with grade of the renal functional deterioration (Fig. 5.4). The reproducibility of the JHGC is 0.85 in ICC in a multicenter case-control prospective study in the IgAN Study Group of the Progressive Renal Diseases Study Committee organized by the Ministry of Health, Labor and Welfare (preliminary data), suggesting recognition of glomerular lesion either cellular and fibrocellular crescent, global sclerosis, segmental sclerosis, or fibrous crescent, and quantitative scoring of the summation of the number of the constituting lesions can be a reproducible procedure. While this approach needs further validation studies across a greater range of cohorts, we believe that the greater overview of the lesion it provides makes it a better tool for communication between pathologists and physicians as to the full nature of the lesions observed in IgAN biopsies (Fig. 5.4). Indeed, the potential utility of a lumped rather than split classification system has been highlighted by the suggestion that the Oxford classification system could be improved by developing and validating it in this manner.

5.5 Is Evidence-Based Classification Superior to Expert's Opinion-Based Classification?

As mentioned in the introduction, there is a continuing discussion of the merits of evidence-based classification as opposed to expert opinion-based classification. In this article, we have described two separate evidence-based classification systems for IgAN lesions. The Oxford Classification of IgAN is the only classification of glomerular disease that is rigorously evidence-based through the nature of its development. In choosing the parameters to be included in the system, priority was given to those that were statistically reproducible between individual pathologists, and only when histological characteristics were shown to be such were they then tested for their ability to describe the disease course. Values that then predicted outcome in the specific cohort selected for the development of this system were subsequently dichotomized in order to produce the Oxford MEST classification (Fig. 5.1). However, the limitation of such a purely evidence-based method may be its ability to be generalized to a wide range of cohorts whose clinical parameters do not match those used to develop the method. This could potentially be attributed to its complete reliance on mathematical development without combining mathematical testing with understanding of the natural history and contributing histopathology of the disease. This potential weakness is evident in the fact that none of the validation studies of the Oxford classification described above completely

confirmed the results from the original Oxford cohort regarding the predictive value of M, S, and T scores.

One possible approach to overcoming this apparent limitation of an evidence-based classification would be subclassification within any cohort in order to standardize patient background or treatment as shown in Fig. 5.2. For example, this could be performed by classifying on a number of different parameters including the aforementioned three different disease courses: early phase vs. advanced phase of disease course; immunosuppressant therapy vs. without immunosuppressant therapy; child vs. adults, mild proteinuria vs. severe proteinuria, and long-term follow-up vs. short-term follow-up; and so on. By standardizing the clinical subtypes of cohorts before generating evidence-based histological classification, possible variation limiting the generalizability of any individual classification scheme may be avoided. However, even in this instance, the clinical utility of such approaches may be limited by the necessity of making an initial expert-driven decision as to which cohort a patient belongs to before applying the relevant criteria.

As opposed to evidence-based classification systems, expert's opinion-based classifications are inherently more subjective and yet have for many years proved of extreme utility in communication between pathologists and clinicians. Expert's opinion-based classification, including the characterization of histological features decided among experts as applicable to clinical decision-making (e.g., lupus nephritis [21], antineutrophil cytoplasmic autoantibody-associated glomerulonephritis [22], focal segmental glomerulosclerosis [23], and diabetic glomerulosclerosis [24]) however have not been tested in the development process as to their reproducibility or effectiveness in the same way that evidence-based medicine approaches have been. Even lesions selected in a systematic manner, such as those mentioned previously that are recognized by panels of experts as being important in the analysis of IgAN, are currently grouped into descriptive classes within expert's opinion classifications rather than semiquantitative grades. Hence, as with the evidenced-based approach, the expert's opinion-based approach to describing IgAN lesions needs further testing and refinement before being sure that they are the most applicable means of classification. Ideally, this validation would take the form of retrospective studies firstly to test the reliability and reproducibility of expert's production of classification without quantitative evidence and secondly to test if this classification adequately captures the disease spectrum.

Between these two approaches, that of purely mathematical evidence-based classification and purely descriptive expert opinion-based classification, there is a middle road. Such an approach was taken by the JHGC in the hope that this could combine the strengths while minimizing the disadvantages of the two approaches above. In this manner, the JHGC was developed using evidence-based means but was guided in its development by expert opinion's understanding of the physiopathology of these lesions. As shown in Table 5.1, each grade consists of a subgroup including A, A/C, and C, which are proposal from expert's opinion for clinical use. In this approach, the selection of pathological parameters can be weighted on the basis of our understanding of their role in disease development rather than in an

entirely blind fashion. While this limits the claim to rigor in method development, it may mean that parameters that are known to be generalizable across a wide disease spectrum can be selected in preference to parameters that may be strongly recognized and unique or specific in the one cohort. This middle road has been used with success in other diseases, and until other approaches are validated with a greater degree of rigor, this approach may be the best means to classify and hence communicate the pathology of IgAN between health-care professionals.

The final goal of any classification system will be an ability to typify an individual case with morphological diversity into a simple category of histological classification, and doing this enables the pathology observed in the lesion to give the appropriate information about the outcome and responsiveness and guide an appropriate and effective therapy for any individual case. At present, none of the classification systems described meets these ideal criteria. However, as a current compromise, the JHGC incorporates some of the lesions diversity captured by the expert opinion approach to grading while also incorporating some of the reproducibility and evidence-based values associated with the Oxford classification.

5.6 Conclusion

The two classifications, Oxford classification and JHGC, were compared concerning classification system (split or lumped) and adopted parameters. Even though JHGC was not produced with the same rigor as the Oxford classification, its utility can be evaluated by the clinical information that it provides. A prospective study from the work of the IgAN Study Group of the Progressive Renal Diseases Study Committee under the auspices of the Ministry of Health, Labor and Welfare is ongoing to show that the evidences that JHGC is reproducible and can predict renal outcome in different cohorts with different follow-up periods, different stages of the disease, and different therapies. In addition to this, the lumped system employed by the JHGC more accurately captures the diversity of IgAN lesions, allowing different courses of the disease to be distinguished from each other. Thus, for the task of effective communication of lesion histology between pathologist and clinician by a reproducible scoring system, the approach taken by the JHGC may prove superior to the four-parameter Oxford classification. In this way, starting with a subjective measure, such as expert option, that is subjected to and refined by empirical validation may prove a more satisfactory approach to the development of a classification system for IgAN. In this way, decades of sound knowledge regarding the physiopathology of IgAN, even if acquired historically by trial and error, can be incorporated into an empirically validated classification. Hence, in addressing the aim to overcome the task of histological classification, lumped system and/or expert's opinion-based classification that has been developed and validated in a number of studies may not be inferior to purely evidence-based Oxford classification.

Conflict of Interest The authors declare that they have no conflict of interest.

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References

1. Haas M, Rastaldi MP, Fervenza FC. Histologic classification of glomerular diseases: clinicopathologic correlations, limitations exposed by validation studies, and suggestions for modification. Kidney Int. 2014;85:779–93. doi: 10.1038/ki.2013.375. Epub 2013 Oct 2. Lee SM, Rao VM, Franklin WA, Schiffer MS, Aronson AJ, Spargo BH, Katz AI. IgA nephropathy: morphologic predictors of progressive renal disease. Hum Pathol. 1982;13:314–22.
2. Lee SM, Rao VM, Franklin WA, Schiffer MS, Aronson AJ, Spargo BH, et al. IgA nephropathy: morphologic predictors of progressive renal disease. Hum Pathol. 1982;13:314–22.
3. Lee HS, Lee MS, Lee SM, Lee SY, Lee ES, Lee EY, et al. Histological grading of IgA nephropathy predicting renal outcome: revisiting H.S. Lee's glomerular grading system. Nephrol Dial Transplant. 2005;20:342–8. Epub 2004 Dec 23.
4. Haas M. Histologic subclassification of IgA nephropathy: a clinicopathologic study of 244 cases. Am J Kidney Dis. 1997;29:829–42.
5. Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS, Troyanov S, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney Int. 2009;76:534–45. doi:10.1038/ki.2009.243. Epub 2009 Jul 1.
6. Roberts IS, Cook HT, Troyanov S, Alpers CE, Amore A, Barratt J, et al. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. Kidney Int. 2009;76:546–56. doi:10.1038/ki.2009.168. Epub 2009 Jul 1.
7. Kawamura T, Joh K, Okonogi H, Koike K, Utsunomiya Y, Miyazaki Y, et al. A histologic classification of IgA nephropathy for predicting long-term prognosis: emphasis on end-stage renal disease. J Nephrol. 2013;26:350–7. doi:10.5301/jn.5000151. Epub 2012 Jun 7.
8. Coppo R, Troyanov S, Bellur S, Cattran D, Cook HT, Feehally J, et al. Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments. Kidney Int. 2014;86:828–36. doi:10.1038/ki.2014.63. Epub 2014 Apr 2.
9. Coppo R, Troyanov S, Camilla R, Hogg RJ, Cattran DC, Cook HT, et al. The Oxford IgA nephropathy clinicopathological classification is valid for children as well as adults. Kidney Int. 2010;77:921–7. doi:10.1038/ki.2010.43. Epub 2010 Mar 3.
10. Herzenberg AM, Fogo AB, Reich HN, Troyanov S, Bavbek N, Massat AE, et al. Validation of the Oxford classification of IgA nephropathy. Kidney Int. 2011;80:310–7. doi:10.1038/ki.2011.126.Epub2011May.
11. Katafuchi R, Ninomiya T, Nagata M, Mitsuiki K, Hirakata H. Validation study of oxford classification of IgA nephropathy: the significance of extracapillary proliferation. Clin J Am Soc Nephrol. 2011;6:2806–13. doi:10.2215/CJN.02890311.
12. Shi SF, Wang SX, Jiang L, Lv JC, Liu LJ, Chen YQ, et al. Pathologic predictors of renal outcome and therapeutic efficacy in IgA nephropathy: validation of the oxford classification. Clin J Am Soc Nephrol. 2011;6:2175–84. doi:10.2215/CJN.11521210. Epub 2011 Aug 18.
13. Zeng CH, Le W, Ni Z, Zhang M, Miao L, Luo P, et al. A multicenter application and evaluation of the oxford classification of IgA nephropathy in adult Chinese patients. Am J Kidney Dis. 2012;60:812–20. doi:10.1053/j.ajkd.2012.06.011. Epub 2012 Jul 20.

14. Shima Y, Nakanishi K, Hama T, Mukaiyama H, Togawa H, Hashimura Y, et al. Validity of the Oxford classification of IgA nephropathy in children. Pediatr Nephrol. 2012;27:783–92. doi:10.1007/s00467-011-2061-0. Epub 2011 Dec 2.
15. Lee H, Yi SH, Seo MS, Hyun JN, Jeon JS, Noh H, et al. Validation of the Oxford classification of IgA nephropathy: a single-center study in Korean adults. Korean J Intern Med. 2012;27:293–300. Epub 2012 Sep 1.
16. El Karoui K, Hill GS, Karras A, Jacquot C, Moulonguet L, Kourilsky O, et al. A clinicopathologic study of thrombotic microangiopathy in IgA nephropathy. J Am Soc Nephrol. 2012;23:137–48. doi:10.1681/ASN.2010111130. Epub 2011 Nov 3.
17. Le W, Zeng CH, Liu Z, Liu D, Yang Q, Lin RX, et al. Validation of the Oxford classification of IgA nephropathy for pediatric patients from China. BMC Nephrol. 2012;13:158. doi:10.1186/1471-2369-13-158.
18. Kang SH, Choi SR, Park HS, Lee JY, Sun IO, Hwang HS, et al. The Oxford classification as a predictor of prognosis in patients with IgA nephropathy. Nephrol Dial Transplant. 2012;27:252–8. doi:10.1093/ndt/gfr295. Epub 2011May 23.
19. Alamartine E, Sauron C, Laurent B, Sury A, Seffert A, Mariat C. The use of the Oxford classification of IgA nephropathy to predict renalsurvival. Clin J Am Soc Nephrol. 2011;6:2384–8. doi:10.2215/CJN.01170211. Epub 2011 Sep 1.
20. Sato R, Joh K, Komatsuda A, Ohtani H, Okuyama S, Togashi M, et al. Validation of the Japanese histologic classification 2013 of immunoglobulin A nephropathy for prediction of long-term prognosis in a Japanese single-center cohort. Clin Exp Nephrol. 2014 Jul 8. [Epub ahead of print].
21. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int. 2004;65:521–30.
22. Berden AE, Ferrario F, Hagen EC, Jayne DR, Jennette JC, Joh K, et al. Histopathologic classification of ANCA-associated glomerulonephritis. J Am Soc Nephrol. 2010;21:1628–36. doi:10.1681/ASN.2010050477. Epub 2010 Jul 8.
23. D'Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. Am J Kidney Dis. 2004;43:368–82.
24. Tervaert TW, Mooyaart AL, Amann K, Cohen AH, Cook HT, Drachenberg CB, et al. Pathologic classification of diabetic nephropathy. J Am Soc Nephrol. 2010;21:556–63. doi:10.1681/ASN.2010010010. Epub 2010 Feb 18.

Chapter 6
Podocyte Injury and Significance of Urinary Podocalyxin and Megalin

Katsuhiko Asanuma

Abstract Several factors cause podocyte injury in IgA nephropathy (IgAN), which leads to podocyte loss and progressive glomerulosclerosis. A new type of noninvasive biomarker is needed to aid in the interpretation of the histological results of IgAN patients. Podocalyxin (PCX), located on the apical cell membrane of podocytes, is shed into urine from injured podocytes. High levels of urinary PCX were detected in IgAN patients with acute extracapillary abnormalities. Megalin is highly expressed at the apical membranes of proximal tubular epithelial cells. High levels of urinary megalin were detected in IgAN patients with chronic extracapillary abnormalities. Reliable urinary biomarkers could help us better interpret the histological results of renal biopsies, which would greatly aid in the design of a therapeutic plan for each IgAN patient.

Keywords Podocyte • Podocyte injury • Podocalyxin • Megalin

6.1 Introduction

IgA nephropathy (IgAN) is the most common pattern for primary chronic glomerulonephritis, and a diagnosis of IgAN always requires renal biopsy [1]. An often insidious progression to end-stage kidney disease is found in 25–40 % of cases and is accompanied by the development of glomerulosclerosis [2]. The histological characteristics of IgAN are mesangial cell proliferation, mesangial matrix expansion, and mesangial IgA deposition [3, 4]. Activate mesangial cells secrete various proinflammatory and profibrotic mediators of renal injury. These mediators cause podocyte injury and PTEC activation, which drives tubulointerstitial abnormalities [5, 6]. Continued immune complex deposition and mesangial cell activation lead to progressive glomerulosclerosis through irreversible podocyte loss [7]. Lemley

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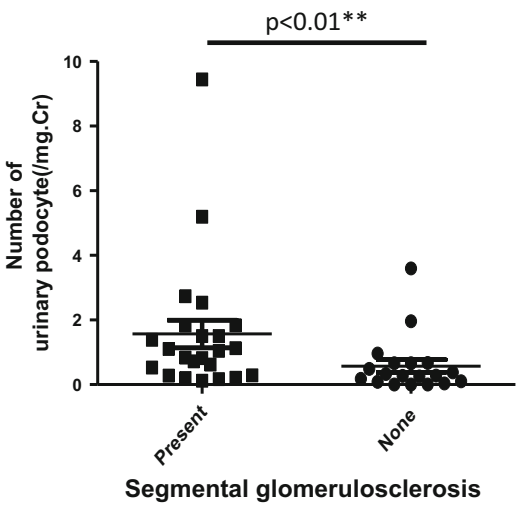


Fig. 6.1 The number of urinary podocytes in patients with IgAN with segmental sclerosis was higher than those in patients without (Modified from Ref. [12])

et al. reported that podocyte loss is associated with increased disease severity in IgAN [8, 9]. Ongoing studies in many research groups are focused on understanding podocytes under physiological and pathological conditions. Such studies will potentially translate into better treatment and prevention of proteinuria and progressive glomerular diseases.

Research by Hara et al. provided evidence that detached podocytes in the urine indicate podocyte injury in glomerulonephritis [10]. They also revealed a potential causative role for prolonged urinary loss of podocytes in disease progression in children with IgAN [11]. We showed that the number of urinary podocytes in adult IgAN patients with segmental sclerosis in the Oxford classification was significantly higher than that in patients without segmental sclerosis (Fig. 6.1) [12].

To more easily interpret the current histological results of patients suspected of having IgAN, it is necessary to develop new noninvasive biomarkers.

6.2 Urinary Podocalyxin

Podocalyxin (PCX) is a sialomucin that is most closely related to CD34 and endoglycan and is expressed by podocytes, hematopoietic progenitors, vascular endothelia, and a subset of neurons [13]. PCX is usually located on the apical cell membrane of podocytes and is shed into urine from injured podocytes [14]. Human urinary PCX (u-PCX) originates not from podocyte exosomes but from the tip vesiculation of glomerular podocyte microvilli [15]. Kanno et al. measured the levels of u-PCX in children with glomerular diseases such as IgAN and concluded that u-PCX was a useful biomarker for estimating the severity of active glomerular injury and could serve as a urinary index of acute extracapillary abnormalities in children [16]. Levels of u-PCX in adults with various forms of active

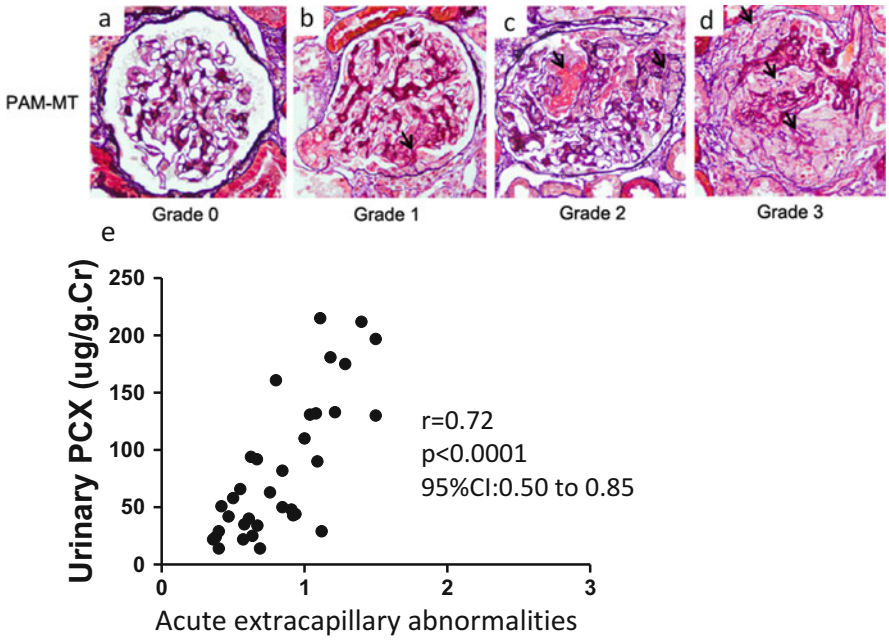


Fig. 6.2 Representative histological findings of acute extracapillary abnormalities stained with periodic acid methenamine silver-Masson trichrome. (**a**) In grade 0, no acute extracapillary abnormality was observed. (**b**) In grade 1, a small cellular crescent formation was observed (*arrow*). (**c**) In grade 2, exudates that had escaped into the urinary space and a cellular crescent were observed (*arrows*). (**d**) In grade 3, three cellular crescents were observed (*arrows*). (**e**) Urinary podocalyxin was significantly correlated with the severity of acute extracapillary abnormalities in adult patients with IgAN (Modified from Ref. [12])

glomerulonephritis were reported to be significantly higher than those in patients with chronic glomerulonephritis in long-term remission [17]. We used the Shigematsu classification to determine acute and chronic extracapillary abnormalities [18]. We found a positive correlation between levels of u-PCX and acute extracapillary abnormalities in adults with IgAN (Fig. 6.2) [12]. Conversely, levels of urinary protein excretion did not correlate with acute glomerular abnormalities. Acute extracapillary abnormalities can be followed by the detachment of podocytes and glomerular basement membrane (GBM) denudation, which are the initial steps in the development of glomerulosclerosis [19]. Possibly, u-PCX reflects acute extracapillary abnormalities and is an index of ongoing podocyte injury leading to glomerulosclerosis.

Several studies have shown that corticosteroid treatment decreases the levels of urinary protein excretion and improves renal outcomes in patients with IgAN [20–22]. Shoji et al. reported that early corticosteroid treatment for active and proliferative IgAN in adults was effective for reducing renal injury [23]. Immunosuppressive treatment, including corticosteroids, is recommended for crescentic IgAN with active glomerular inflammation [24]. These results suggest that the measurement of

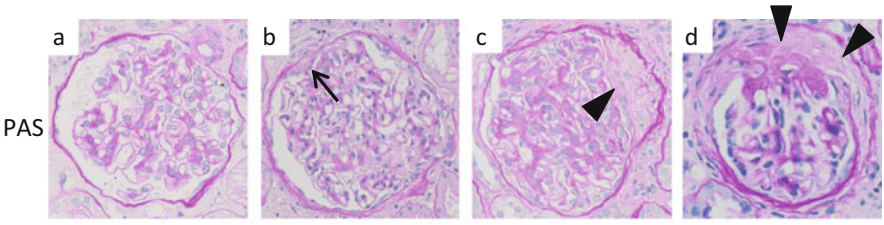
u-PCX may be a useful biomarker to determine the effectiveness of corticosteroid treatment.

6.3 Urinary Megalin (uMegalin)

Megalin is a large (600 kDa) glycoprotein that is a member of the low-density lipoprotein receptor family [25, 26]. It is highly expressed at the apical membranes of proximal tubular epithelial cells (PTECs) [27]. Megalin plays a central role in the endocytotic functions of PTECs [27]. Low-molecular-weight protein markers of PTEC injury, such as α1-microglobulin (α1-MG) and β2-microglobulin (β2-MG), are filtered by glomeruli and reabsorbed by PTECs via megalin [28, 29]. Megalin is detected in human urine, and increases in urinary megalin (uMegalin) excretion appear in microalbuminuric patients with type 1 diabetes [30–33]. The levels of uMegalin have been linked to the severity of diabetic nephropathy in type 2 diabetes [34].

To understand the relationship between the levels of uMegalin and renal histological findings in adult IgAN patients, we focused on uMegalin. The levels of uMegalin, α1-MG, β2-MG, and N-acetyl-β-D-glucosaminidase (NAG) are not correlated with tubular atrophy and interstitial fibrosis in the Oxford classification. Surprisingly, however, the levels of uMegalin are correlated with chronic extracapillary abnormalities, showing a distinctive significance compared to preexisting urinary biomarkers (β2-MG, α1-MG, NAG, and urinary total protein) (Fig. 6.3). In addition, the levels of uMegalin are correlated with mesangial hypercellularity in the Oxford classification. Megalin is localized in the brush border of proximal tubules, but not in the glomerulus in the human kidney [35, 36]. There are two proposed mechanisms for uMegalin levels that reflect glomerular abnormalities. The first theory is that glomerular abnormalities trigger PTEC dysfunction, leading to the excretion of megalin in the urine. Although it remains unclear how glomerular abnormalities lead to tubulointerstitial injury in IgAN, a possible pathogenetic mechanism is glomerulopodocytic-tubular communication [37]. The second theory involves the possibility that PTEC dysfunction aggravates chronic glomerular abnormalities. Selective PTEC injury reportedly drives the formation of interstitial fibrosis and potentially glomerulosclerosis [38]. The progression of PTEC injury may aggravate chronic extracapillary abnormalities and lead to glomerulosclerosis.

Supportive therapy with the cautious use of either angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) should be continued with IgAN patients in order to slow the process, although an eGFR that is persistently less than 30 mL/min/1.73 m^2 poses a substantial risk of progression to end-stage renal disease (ESRD) [39]. ACEI or ARB is effective for long-term renal survival of advanced IgAN patients whose histological findings contain chronic glomerular abnormalities [40]. In future studies, we aim to clarify whether uMegalin is a useful biomarker to determine the effectiveness of ACEI or ARB



e

variables	chronic extracapillary abnormalities	
	IgAN patients (N=59)	
	β	*p* value
C-megalin(pmole/g.Cr)	0.33	0.008
β_2-MG (μg/g.Cr)	0.21	0.075
α_1-MG (mg/g.Cr)	-	-
NAG(IU/g.Cr)	-	-
Urinary total protein(g/g.Cr)	-	-

Fig. 6.3 Representative histological findings of chronic extracapillary abnormalities stained with periodic acid-Schiff (PAS). (**a**) In grade 0, no chronic extracapillary abnormalities were observed. (**b**) In grade 1, a small adhesion with Bowman's capsule was observed (*arrow*). **c** In grade 2, a moderate fibrous crescent was observed (*arrowhead*). (**d**) In grade 3, a severe fibrous crescent was observed (*arrowheads*). (**e**) There was a significant correlation between the levels of urinary megalin and the severity of chronic extracapillary abnormalities (Modified from Ref. [35])

treatment. We also must examine the levels of uMegalin before and after the treatment of IgAN patients.

In our study, levels of uMegalin were associated with dialysis that required risk levels from the Clinical Guidelines for IgAN in Japan, third version [35, 41] (Fig. 6.4). The Oxford classification of IgAN identifies four pathologic abnormalities that independently determine the risk of developing progressive renal disease: mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis, and tubular atrophy/interstitial fibrosis [7, 42]. Levels of uMegalin were correlated with only mesangial hypercellularity, according to the Oxford classification. Although levels of urinary β2-MG were correlated with segmental glomerulosclerosis, its urinary excretion offered no advantage over proteinuria to predict the prognosis in IgAN patients [43]. Thus, there is a possibility that uMegalin is an independent predictor of disease progression with IgAN. In future studies, it will be necessary to perform a longitudinal study to follow up with IgAN patients to determine whether uMegalin is a predictor.

The number of glomeruli obtained by renal biopsy was sometimes insufficient in order to evaluate the severity of glomerular changes. However, because u-PCX and uMegalin originate primarily from all nephrons in the kidney, the urinary biomarkers seem to reflect the histological findings of all nephrons. Urinary biomarkers might help us to speculate on the histological results of renal biopsy.

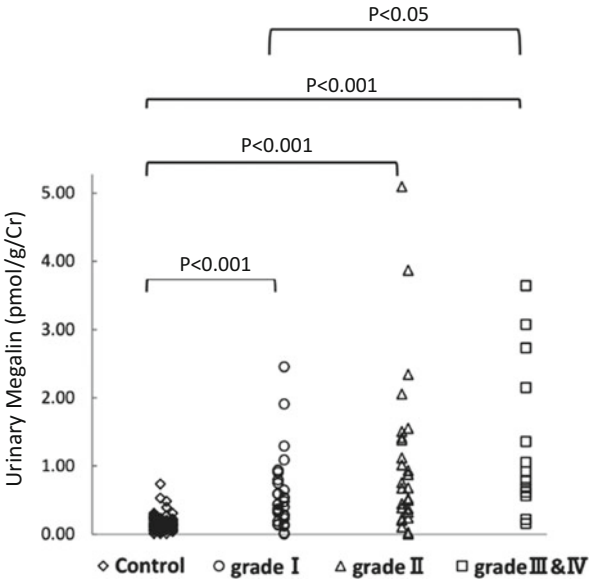


Fig. 6.4 Relationship of risk levels requiring dialysis to levels of urinary megalin. *I*, low-risk group; *II*, medium-risk group; and, *III* and *IV*, high- and superhigh-risk groups (Modified from Ref. [35])

In conclusion, the biomarkers u-PCX and uMegalin have a potential role as an adjunct to the diagnosis of renal histology in IgAN patients.

Conflict of Interest The author declares that he has no conflict of interest.

References

1. Barratt J, Feehally J. Primary IgA nephropathy: new insights into pathogenesis. Semin Nephrol. 2011;31(4):349–60.
2. Rychlik I, Andrassy K, Waldherr R, Zuna I, Tesar V, Jancova E, et al. Clinical features and natural history of IgA nephropathy. Ann Med Interne. 1999;150(2):117–26.
3. Berger J, Hinglais N. Intercapillary deposits of IgA-IgG. J Urol Nephrol. 1968;74(9):694–5.
4. Haas M. Histologic subclassification of IgA nephropathy: a clinicopathologic study of 244 cases. Am J Kidney Dis. 1997;29(6):829–42.
5. Lai KN, Leung JC, Chan LY, Saleem MA, Mathieson PW, Tam KY, et al. Podocyte injury induced by mesangial-derived cytokines in IgA nephropathy. Nephrol Dial Transplant. 2009;24(1):62–72.
6. Chan LY, Leung JC, Tsang AW, Tang SC, Lai KN. Activation of tubular epithelial cells by mesangial-derived TNF-alpha: glomerulotubular communication in IgA nephropathy. Kidney Int. 2005;67(2):602–12.
7. Boyd JK, Cheung CK, Molyneux K, Feehally J, Barratt J. An update on the pathogenesis and treatment of IgA nephropathy. Kidney Int. 2012;81(9):833–43.
8. Lemley KV, Lafayette RA, Safai M, Derby G, Blouch K, Squarer A, et al. Podocytopenia and disease severity in IgA nephropathy. Kidney Int. 2002;61(4):1475–85.

9. Hishiki T, Shirato I, Takahashi Y, Funabiki K, Horikoshi S, Tomino Y. Podocyte injury predicts prognosis in patients with iga nephropathy using a small amount of renal biopsy tissue. Kidney Blood Press Res. 2001;24(2):99–104.
10. Hara M, Yanagihara T, Takada T, Itoh M, Matsuno M, Yamamoto T, et al. Urinary excretion of podocytes reflects disease activity in children with glomerulonephritis. Am J Nephrol. 1998;18(1):35–41.
11. Hara M, Yanagihara T, Kihara I. Cumulative excretion of urinary podocytes reflects disease progression in IgA nephropathy and Schonlein-Henoch purpura nephritis. Clin J Am Soc Nephrol. 2007;2(2):231–8.
12. Asao R, Asanuma K, Kodama F, Akiba-Takagi M, Nagai-Hosoe Y, Seki T, et al. Relationships between levels of urinary podocalyxin, number of urinary podocytes, and histologic injury in adult patients with IgA nephropathy. Clin J Am Soc Nephrol. 2012;7(9):1385–93.
13. Nielsen JS, McNagny KM. The role of podocalyxin in health and disease. J Am Soc Nephrol. 2009;20(8):1669–76.
14. Hara M, Yanagihara T, Kihara I, Higashi K, Fujimoto K, Kajita T. Apical cell membranes are shed into urine from injured podocytes: a novel phenomenon of podocyte injury. J Am Soc Nephrol. 2005;16(2):408–16.
15. Hara M, Yanagihara T, Hirayama Y, Ogasawara S, Kurosawa H, Sekine S, et al. Podocyte membrane vesicles in urine originate from tip vesiculation of podocyte microvilli. Hum Pathol. 2010;41(9):1265–75.
16. Kanno K, Kawachi H, Uchida Y, Hara M, Shimizu F, Uchiyama M. Urinary sediment podocalyxin in children with glomerular diseases. Nephron Clin Pract. 2003;95(3):c91–9.
17. Habara P, Mareckova H, Sopkova Z, Malickova K, Zivorova D, Zima T, et al. A novel method for the estimation of podocyte injury: podocalyxin-positive elements in urine. Folia Biol. 2008;54(5):162–7.
18. Shigematsu H. Histological grading and staging of IgA nephropathy. Pathol Int. 1997;47 (4):194–202.
19. Schwartz MM, Lewis EJ. Focal segmental glomerular sclerosis: the cellular lesion. Kidney Int. 1985;28(6):968–74.
20. Pozzi C, Andrulli S, Del Vecchio L, Melis P, Fogazzi GB, Altieri P, et al. Corticosteroid effectiveness in IgA nephropathy: long-term results of a randomized, controlled trial. J Am Soc Nephrol. 2004;15(1):157–63.
21. Pozzi C, Bolasco PG, Fogazzi GB, Andrulli S, Altieri P, Ponticelli C, et al. Corticosteroids in IgA nephropathy: a randomised controlled trial. Lancet. 1999;353(9156):883–7.
22. Samuels JA, Strippoli GF, Craig JC, Schena FP, Molony DA. Immunosuppressive treatments for immunoglobulin A nephropathy: a meta-analysis of randomized controlled trials. Nephrology. 2004;9(4):177–85.
23. Shoji T, Nakanishi I, Suzuki A, Hayashi T, Togawa M, Okada N, et al. Early treatment with corticosteroids ameliorates proteinuria, proliferative lesions, and mesangial phenotypic modulation in adult diffuse proliferative IgA nephropathy. Am J Kidney Dis. 2000;35(2):194–201.
24. Barratt J, Feehally J. Treatment of IgA nephropathy. Kidney Int. 2006;69(11):1934–8.
25. Saito A, Pietromonaco S, Loo AK, Farquhar MG. Complete cloning and sequencing of rat gp330/"megalin," a distinctive member of the low density lipoprotein receptor gene family. Proc Natl Acad Sci U S A. 1994;91(21):9725–9.
26. Hjalm G, Murray E, Crumley G, Harazim W, Lundgren S, Onyango I, et al. Cloning and sequencing of human gp330, a Ca(2+)-binding receptor with potential intracellular signaling properties. Eur J Biochem FEBS. 1996;239(1):132–7.
27. Saito A, Sato H, Iino N, Takeda T. Molecular mechanisms of receptor-mediated endocytosis in the renal proximal tubular epithelium. J Biomed Biotechnol. 2010;2010:403272.
28. Leheste JR, Rolinski B, Vorum H, Hilpert J, Nykjaer A, Jacobsen C, et al. Megalin knockout mice as an animal model of low molecular weight proteinuria. Am J Pathol. 1999;155 (4):1361–70.

29. Saito A, Kazama JJ, Iino N, Cho K, Sato N, Yamazaki H, et al. Bioengineered implantation of megalin-expressing cells: a potential intracorporeal therapeutic model for uremic toxin protein clearance in renal failure. J Am Soc Nephrol. 2003;14(8):2025–32.
30. Birk HW, Piberhofer S, Schutterle G, Haase W, Kotting J, Koepsell H. Analysis of Na+-D-glucose cotransporter and other renal brush border proteins in human urine. Kidney Int. 1991;40(5):823–37.
31. Bachinsky DR, Zheng G, Niles JL, McLaughlin M, Abbate M, Andres G, et al. Detection of two forms of GP330. Their role in Heymann nephritis. Am J Pathol. 1993;143(2):598–611.
32. Kounnas MZ, Chappell DA, Strickland DK, Argraves WS. Glycoprotein 330, a member of the low density lipoprotein receptor family, binds lipoprotein lipase in vitro. J Biol Chem. 1993;268(19):14176–81.
33. Thrailkill KM, Nimmo T, Bunn RC, Cockrell GE, Moreau CS, Mackintosh S, et al. Microalbuminuria in type 1 diabetes is associated with enhanced excretion of the endocytic multiligand receptors megalin and cubilin. Diabetes Care. 2009;32(7):1266–8.
34. Ogasawara S, Hosojima M, Kaseda R, Kabasawa H, Yamamoto-Kabasawa K, Kurosawa H, et al. Significance of urinary full-length and ectodomain forms of megalin in patients with type 2 diabetes. Diabetes Care. 2012;35(5):1112–8.
35. Seki T, Asanuma K, Asao R, Nonaka K, Sasaki Y, Oliva Trejo JA, et al. Significance of urinary full-length megalin in patients with IgA nephropathy. PLoS One. 2014;9(12):e114400.
36. Kerjaschki D, Horvat R, Binder S, Susani M, Dekan G, Ojha PP, et al. Identification of a 400-kd protein in the brush borders of human kidney tubules that is similar to gp330, the nephritogenic antigen of rat Heymann nephritis. Am J Pathol. 1987;129(1):183–91.
37. Lai KN, Tang SC, Leung JC. Recent advances in IgA nephropathy – the glomerulopodocytic-tubular communication. Adv Otorhinolaryngol. 2011;72:40–4.
38. Grgic I, Campanholle G, Bijol V, Wang C, Sabbisetti VS, Ichimura T, et al. Targeted proximal tubule injury triggers interstitial fibrosis and glomerulosclerosis. Kidney Int. 2012;82 (2):172–83.
39. Wyatt RJ, Julian BA. IgA nephropathy. N Engl J Med. 2013;368(25):2402–14.
40. Moriyama T, Amamiya N, Ochi A, Tsuruta Y, Shimizu A, Kojima C, et al. Long-term beneficial effects of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker therapy for patients with advanced immunoglobulin A nephropathy and impaired renal function. Clin Exp Nephrol. 2011;15(5):700–7.
41. Kawamura T, Joh K, Okonogi H, Koike K, Utsunomiya Y, Miyazaki Y, et al. A histologic classification of IgA nephropathy for predicting long-term prognosis: emphasis on end-stage renal disease. J Nephrol. 2013;26(2):350–7.
42. Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS, Troyanov S, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney Int. 2009;76(5):534–45.
43. Peters HP, van den Brand JA, Wetzels JF. Urinary excretion of low-molecular-weight proteins as prognostic markers in IgA nephropathy. Neth J Med. 2009;67(2):54–61.

Chapter 7
Complement Activation

Isao Ohsawa

Abstract The complement system has devastating effects on several forms of glomerulonephritis. Although the pathogenesis of IgA nephropathy (IgAN) has heterogeneity, ample studies have clearly demonstrated that the alternative and lectin pathways act as an enhancer of glomerular damage. However, certain ligands of starter molecules in these two pathways are not yet identified. On the other hand, the clinical progress of IgAN is often more than a decade, with the patients' nutritional status fluctuating. An excess of nutrition might exacerbate the natural course of IgAN. Actually, serum levels of C3 fluctuate with not only disease activity but also metabolic parameters. Concomitant with recent genetic analysis, we can deduce that the gene mutations of complement components and regulatory proteins affect disease progression. Mannose-binding lectin (MBL) deficiency is very common in a normal population, but conversely, patients with sufficient MBL have a risk for a worse prognosis of IgAN. This review documents contemporary information concerning the possible role of the complement system in the pathogenesis of IgAN.

Keywords Alternative pathway • Factor H • Complement factor H-related (CFHR) proteins • Lectin pathway • Mannose-binding lectin (MBL)

7.1 Introduction

A basic knowledge of the complement system seems to have become important, and recent progress in complement research has unraveled a close relationship between the complement system and the pathogenesis of many types of glomerulonephritis. In patients with IgA nephropathy (IgAN), glomerular deposition of C3 is highly detected in glomeruli, and the detection rate is found in more than 90 % of patients [1]. Other complement molecules, such as properdin, C5, and the C5b-9 complex, are co-localized in the glomerular mesangial areas, but C1q is absent and there is an increase of C3 breakdown products in the serum of patients with IgAN. As already mentioned, we have recognized that alternative pathway (AP) activation

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is involved in the pathogenesis of IgAN, whereas the classical pathway (CP) is dissociated from IgAN [2]. However, there is accumulating evidence of lectin pathway (LP) activation in the pathogenesis of IgAN. Furthermore, other topics, such as the gene mutations of complement components and regulatory proteins and the application of the anti-C5 antibody, have arisen.

7.2 Complement System

7.2.1 Three Activation Pathways

The complement system contains more than 30 plasma and membrane-bound proteins, which originated from several gene duplications during human evolution [3]. Activation through CP, AP, or LP merges at the proteolytic activation of C3 and activates the complement late component, C5b-9 (membrane attack complex, MAC). In our body, complement activation is a double-edged sword. On one hand, it is vital for host defense (innate immunity), and on the other its resultant inflammation can play a role in the pathogenesis of human diseases.

The trigger molecules are different in each of the three pathways (Fig. 7.1). CP activation can start with C1q which is a part of C1qr2s2 complex and recognize IgM- or IgG-binding immune complex (IC). C1q leads to the activation of its C1r and C1s serine protease units, and C1s activates C4 and C2, resulting in the formation of the C4b2a complex (C3 convertase). C3 convertase can cleave C3 to C3a and C3b and initiate an amplification loop. C3 has few ligands and forms C3(H_2O), which depends on spontaneous hydrolysis, the so-called tick-over. C3(H_2O) exposes a factor B (fB) binding site. Subsequent proteolysis with factor D (fD) forms C3(H_2O)Bb (C3 convertase) [4]. AP is spontaneously and constantly activated on the biological surface. Recently, a properdin-directed pathway (PDP) was proposed, in which properdin is a starter molecule and can recognize pathogen-associated molecular patterns such as glycosaminoglycan on the surface directly [5]. Properdin also binds to either C3(H_2O) or C3b. In the presence of fB and fD, assembled C3bBb is stabilized with properdin (C3bBbP) and also initiates an amplification loop. C3b covalently attaches with the target surface via amine and carbohydrates and opsonizes them. LP can start with mannose-binding lectin (MBL) and ficolins, which recognize carbohydrates on the surface. MBL-associated serine protease (MASP) is functionally similar to C1s and cleaves C4. The following cascade is the same as CP [6]. C3b binds with C3 convertase and forms C5 convertase (C4b2a3b or C3bBb3b), as well as the subsequent cleavage of C5 into C5a and C5b. The above three pathways converge with the late components of the complement system. C5b assembles with C6, C7, C8, and C9 and results in forming MAC. MAC inserts into cell membranes, culminating in cell lysis.

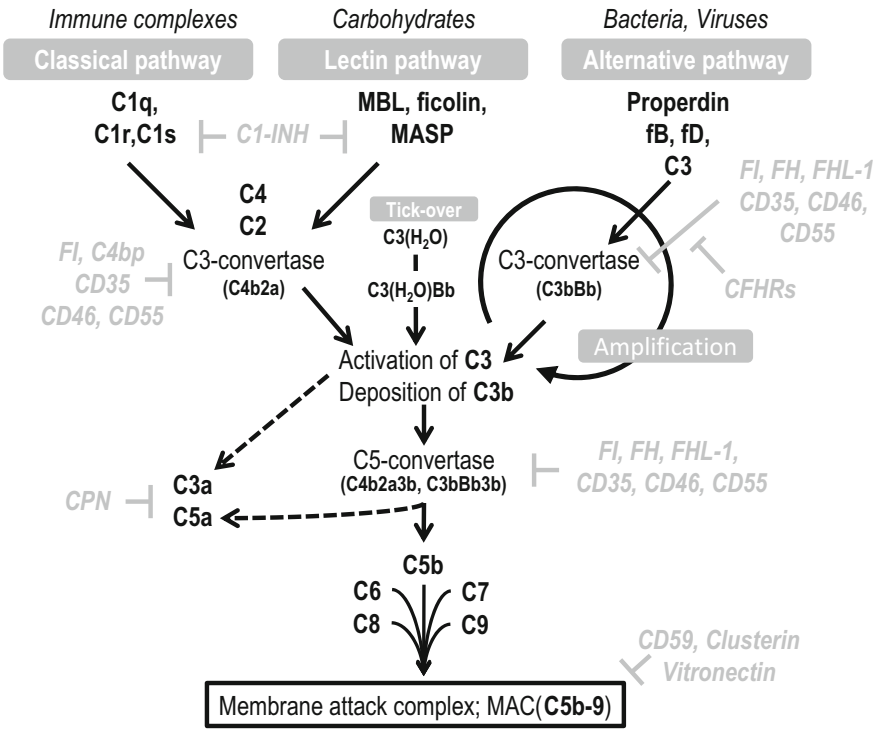

Fig. 7.1 Complement activation and regulation system. The complement system consists of more than 30 molecules and forms three major pathways: the classical pathway (CP), alternative pathway (AP), and lectin pathway (LP). *Italic* characters mean complement regulatory proteins. *C1-INH* C1 inhibitor, *MBL* mannose-binding lectin, *MASP* MBL-associated serine protease, *fB* factor B, *fD* factor D, *fI* factor I, *fH* factor H, *FHL-1* fH-like protein-1, *CFHR proteins* complement FH-related proteins

7.2.2 Regulation Mechanism

The complement system is controlled by soluble and cell-bound regulators. The C1 inhibitor (C1-INH), which belongs to the serpin family, is only one strong inhibitor in circulation for early components such as C1r, C1s, and MASP (Fig. 7.2) [7, 8]. AP is controlled by two types of inhibition mechanisms, termed decay-accelerating activity and cofactor-mediated cleavage. Decay-accelerating activity dissociates C3 and C5 convertases. Cofactor activity cleaves C3b into iC3b (inactivated form) and C3f with factor I. Plasma factor H (fH) and its truncated form factor H-like protein-1 (FHL-1), plasma C4-binding protein (C4bp), cell-bound complement receptor 1 (CR1, CD35), decay-accelerating factor (DAF, CD55), and membrane cofactor protein (MCP, CD46) belong to regulators of the complement activation family [9]. Cell-bound regulators, CD59, soluble clusterin, and vitronectin, prevent MAC formation. Carboxypeptidase N (CPN) is a soluble

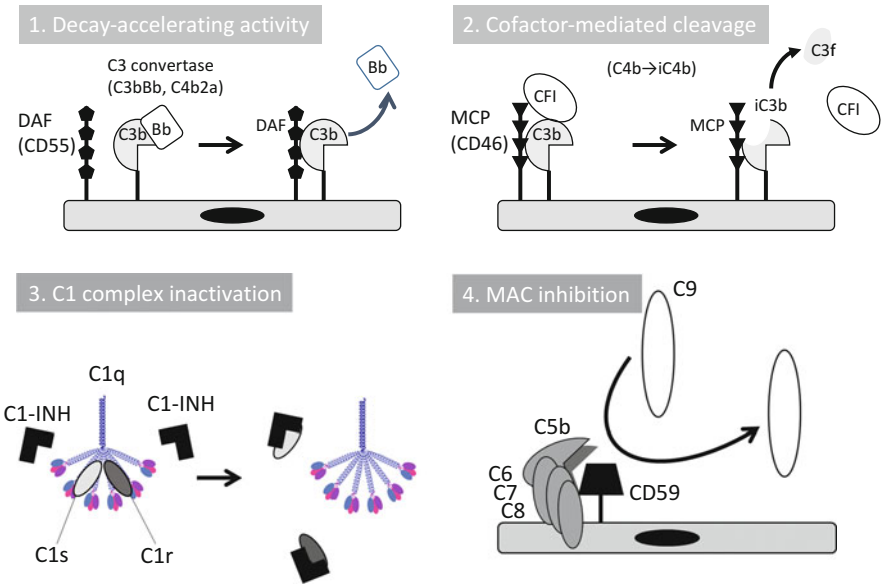

Fig. 7.2 Complement regulation mechanisms. Complement activation cascades are regulated by humoral and cell membrane-bound molecules. *DAF* decay-accelerating factor, *Bb* activated split form of factor B, *MCP* membrane cofactor protein, *CFI* complement factor I, *C1-INH* C1 inhibitor (The figure was modified from Kavanagh et al. [38])

protease that digests anaphylatoxin, C3a, and C5a and inactivates them into C3a desArg and C5a desArg, respectively [4, 8].

7.2.3 Complement Production and Consumption

A detailed analysis of the role of the complement system in the pathogenesis of glomerulonephritis would discriminate a subpopulation of patients from others. It is emphasized that we need to have concern about the production, consumption, and deficiencies of complement components. Complement deficiencies are common genetic disorders. In most cases, heterozygotes produce one-half of the normal plasma level of a specific complement protein. The frequency of deficiency of C1-INH, MBL, C4, and C9 is approximately 1:50,000, 1:10, 1:3 (including partial deletion), and 1:1000 (in Japanese healthy blood donors), respectively [10, 11]. In an analysis of a patient with low CH50, we were first concerned with the possibility of complement deficiencies. Next, we should take notice of overproduction of complement components. The liver is the main source of these components. Because the complement components belong to the acute reactive proteins, like C-reactive protein, infections and chronic inflammation enhance the production of complement components by hepatocytes [12]. Intriguingly, the target organ can

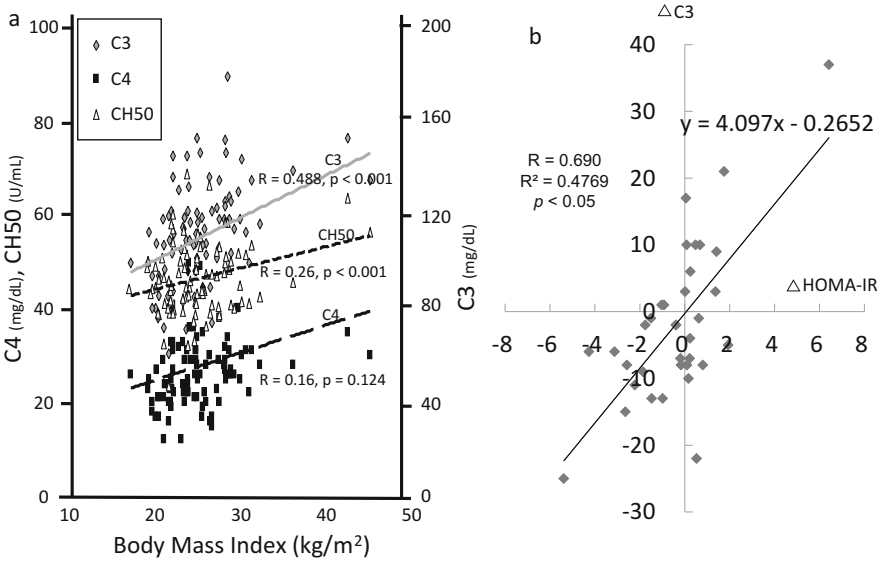

Fig. 7.3 Metabolic impact on the serum levels of C3 in hypertensive and/or chronic kidney disease patients. (**a**) Correlations between serum levels of complement parameters and body mass index. The serum levels of C3 presented the most significant positive correlation with body mass index. (**b**) Fluctuations of serum levels of C3 and insulin resistance. Scatter plots of follow-up differences in 35 subjects who were free of dietary restrictions at two time points in the following 6 months. The plots of 24 subjects (69.9 %) were located in the first quadrant or third quadrant and showed a significant positive relationship. Insulin resistance was assessed using the homeostasis model assessment (HOMA-IR) (The figure was modified from Ohsawa et al. [17])

also produce the components in situ [13, 14]. For example, C3 is synthesized by kidney resident cells and a single donor kidney is able to produce 5 % of circulating C3 [13, 15]. Actually, we can see the fluctuations of complement levels in the context of many clinical situations. The breakdown product of C3, C3a desArg or, in another term, "acylation-stimulating protein (ASP)," is recognized as one type of adipocytokine. Adipocytes also produce C3, fB, and fD, which are spontaneously activated by the nearby adipocytes themselves. CPN splits C3a into C3a desArg and arginine. C3a desArg has been recognized as an inactivated form of C3a, but energetic studies identified it as a potent stimulator of glucose transport and triglyceride synthesis in adipocytes [16, 17]. Then, the level of C3 increases in an overnutrition state, such as metabolic syndrome, diabetes, or obesity (Fig. 7.3a, b). Body mass index (BMI) and serum complement parameters such as C3, C4, and CH50 have a positive correlation. Especially, the serum level of C3 has a strong correlation with BMI and can fluctuate with insulin resistance. Cryoglobulin-containing serum easily activates CP in test tubes (the so-called cold activation), with the results of the serum level of components and the titer of CH50 being overestimated [18]. Generally, in autoimmune diseases, such as lupus nephritis (LN) and IgG4-related tubulointerstitial nephritis, IC activates CP. In these

diseases, IC leads to the consumption of early components of CP in the fluid phase, and laboratory data presents a low serum level of C4 and a low titer of CH50 [19]. Simultaneously, renal depositions of early components of CP, C1q, and C4 were observed. On the other hand, in the cases of post-streptococcal acute glomerulonephritis (PSAGN), most patients presented a low serum level of C3, a low titer of CH50, and glomerular depositions of C3. Thus, it is recognized that AP is the main route of complement activation in PSAGN. From the viewpoint of excess of AP activation, a newly defined clinical entity "C3 glomerulopathy," which comprises of glomerular lesions with predominant C3 staining, was proposed. Although this category contains cases of membranoproliferative glomerulonephritis (MPGN) and dense deposit disease, many pathogenic abnormalities, such as fH mutations, C3 gene variants, nephritic factors, anti-complement regulatory proteins, were reported [20]. The histological damage of these cases was deduced due to uncontrolled AP activation.

7.3 The Role of Complements in IgA Nephropathy: Fluid Phase

Because serum levels of C3 and C4 fluctuate within the normal range, complement activation in the fluid phase has not been focused on in clinical practice. However, the ratio of the serum level of IgA and C3 (IgA/C3 ratio, more than 3.01) has become a candidate biomarker for the diagnosis of IgAN [21, 22]. In this clinical parameter, a low serum level of C3 contributes to the increase of the IgA/C3 ratio. A cross-sectional study has also indicated that serum C3 levels do not increase despite the elevated levels of other complement components in IgAN at the time of biopsy (Table 7.1). These evidences suggest the possibility that the consumption of serum C3 and MBL via AP and LP might be increased compared with hepatic production of C3 and MBL [23]. Aggregated IgA, polymeric IgA, and chemically deglycosylated IgA1 can activate directly with AP; however, the molecular basis for this difference is not fully understood [24, 25]. To the best of our knowledge, galactose-deficient IgA1 itself is able to activate C3 directly in fluid phase [26].

There is accumulating evidence to support a hypothesis of the occurrence of LP activation in the pathogenesis of IgAN. Under-*O*-glycosylated IgA leads to the polymerization of IgA [27], and purified polymeric IgA from patients with IgAN can activate LP [28]. On the other hand, prominent ligands for MBL are mannose and N-acetylglucosamine (GlcNAc), and ligands for ficolins are GlcNAc. Although such an under-*O*-glycosylated IgA1 (N-acetylgalactosamine, GalNAc) from patients with IgAN could potentially interact with plant lectins [29], GalNAc residues cannot be recognized by MBL and ficolins. So far, certain ligands of MBL and ficolin are yet to be defined. Secretory IgA (SIgA) is the first line of defense in protecting the respiratory and intestinal tract and is a credible candidate.

Table 7.1 Serum levels of complement components in patients with IgA nephropathy

	N	CH50 (U/ml)	C1q (mg/dl)	C4 (mg/dl)	C3 (mg/dl)	C5 (%)	B (%)	P (μg/ml)	MBL (mg/ml)
IgA nephropathy	50	44.0 ± 8.1[a]	13.4 ± 2.8	28 ± 11[a]	101 ± 26	122 ± 28	114 ± 32[a]	32.6 ± 27.0[a]	1.8 ± 1.8
Healthy controls	50	33.5 ± 5.4	12.6 ± 1.7	21 ± 5	106 ± 17	112 ± 17	95 ± 18	21.0 ± 24.0	2.1 ± 1.8

%, expressed as a percentage of pooled normal human serum

[a] $p < 0.01$ IgA nephropathy vs. healthy controls

Since the N-glycans on the heavy chains of both IgA1 and SIgA2 present terminal GlcNAc and mannose residues, they could be recognized by MBL and ficolins [30].

7.3.1 *Fluctuation of Serum Level of C3 and MBL Deficiency*

Because IgAN is a chronic glomerular disease and progresses gradually over the long term, additional factors may have a lot of influence on the prognosis. We reported on the fluctuations of the serum level of C3 over a long-term observation (mean observation period, 6.7 ± 2.1 years) in 122 patients with IgAN. In the patients whose renal symptoms, including hematuria, proteinuria, and estimated glomerular filtration rate (eGFR), were improved, the serum level of C3 was significantly elevated (Fig. 7.4) [31]. A subsequent analysis showed that body mass index has a positive correlation with the serum levels of C3 and C4 (Table 7.2) [32]. Thus, the levels and fluctuations of serum C3 and/or C4 might reflect the disease activity and simultaneously, metabolic alteration in patients with IgAN, leading us to believe that we have to pay attention when evaluating the serum levels of complement components.

Functional MBL deficiency is involved in 10–20 % of the healthy population. It is characterized by low levels of functional multimers due to a number of genetic polymorphisms within the coding (codon 54 of exon 1 is the most common in humans and it determines serum concentration and carbohydrate recognition

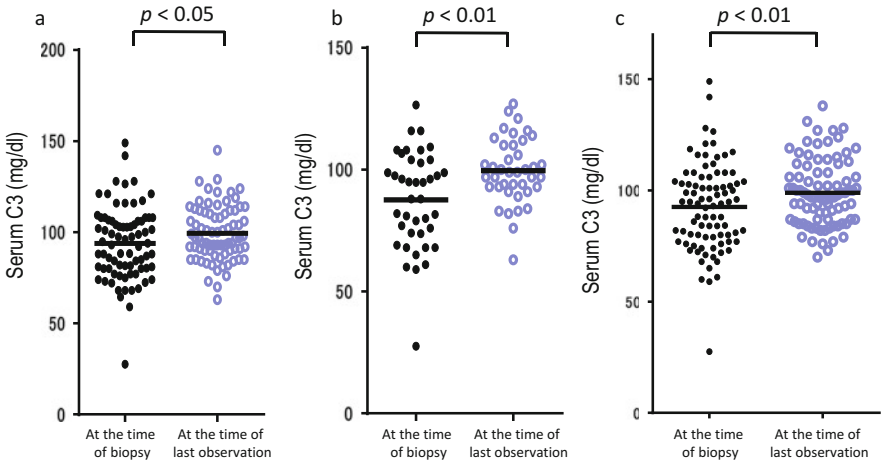

Fig. 7.4 Fluctuations of serum levels of C3 in IgA nephropathy. Serum C3 levels of the 122 patients at the time of biopsy and last observation were collected. The patients whose hematuria (**a**) and proteinuria (**b**) had disappeared presented significantly increased serum levels of C3. Also the patients whose estimated glomerular filtration rate (eGFR) had been maintained presented significantly increased serum levels of C3 (**c**) (The figure was modified from Suzuki et al. [31])

Table 7.2 Relationship of body mass index and clinical data by linear regression models in patients with IgA nephropathy

		R	*p*
Uric acid	(mg/dL)	0.4427	<0.0001
Triglyceride	(mg/dL)	0.4231	<0.0001
C4	(mg/dL)	0.4179	<0.0001
Hemoglobin	(mg/dL)	0.3540	<0.0001
C3	(mg/dL)	0.3575	<0.0001
HDL cholesterol	(mg/dL)	−0.3480	<0.0001
Creatinine	(mg/dL)	0.3416	<0.0001
Systolic blood pressure	(mmHg)	0.3311	<0.0001
Diastolic blood pressure	(mmHg)	0.3052	<0.0001
		($n = 193$)	

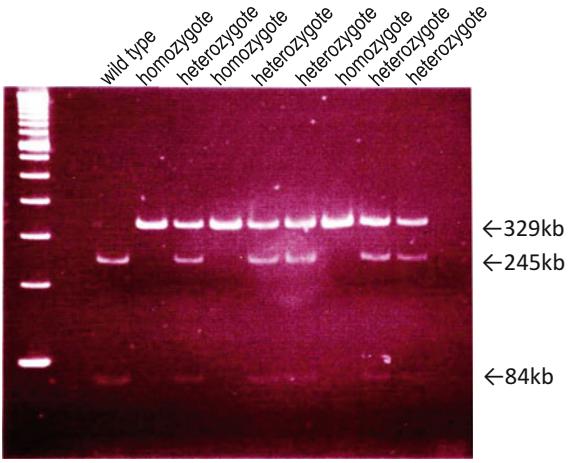

Fig. 7.5 *Mbl-2* gene polymorphism of eight of mannose-binding lectin (MBL)-deficient patients. Codon 54 wild-type allele showed two bands (245 bp and 84 bp), the heterozygote allele showed three bands (329 bp, 245 bp, and 84 bp), and the homozygote allele only one band (329 bp) (The figure was modified from Ishii et al. [34])

ability) and the promoter regions of the *MBL2* gene (Fig. 7.5) [33, 34]. We previously compared the clinical backgrounds between MBL-sufficient patients of IgAN and MBL-deficient patients of IgAN (Table 7.3) [35]. The mean urinary protein and eGFR levels in MBL-deficient subjects were better than in MBL-sufficient subjects. Pirulli et al. reported a similar distribution of polymorphism frequency between healthy volunteers and IgAN patients [36]. Of great interest is whether a difference can be found between MBL deficiency and MBL sufficiency at the onset and progression of IgAN.

7.3.2 Mutation of CFHR Proteins

fH, a strong regulator of C3 convertase formation via the binding of C3b, has binding sites to self-cell surface via glycosaminoglycan and thus is a biphasic

Table 7.3 Clinical background compared with MBL-sufficient and MBL-deficient patients with IgA nephropathy

	MBL sufficient	MBL deficient
n	55	6
Gender (M/F)	22:33	3:3
Age (y)	30.6 ± 8.7	26.5 ± 6.7
Serum creatinine (mg/dL)	0.83 ± 0.30	0.71 ± 0.14
Estimated GFR (mL/min/1.73 m^2)	85.3 ± 30.9	98.4 ± 13.8
Urinary protein (g/g·creatinine)	1.45 ± 1.58	0.69 ± 0.97
History of macrohematuria (%)	27.3	33.3
IgA (mg/dL)	316.9 ± 112.9	265.2 ± 69.6
C3 (mg/dL)	97.8 ± 15.8	93.2 ± 2.6
C4 (mg/dL)	21.9 ± 6.1	19.8 ± 6.6
CH50 (unit/mL)	40.1 ± 6.7	34.4 ± 3.4

regulator of AP, namely, in the fluid phase and on the cell surface [37]. Complement factor H-related (CFHR) proteins (CFHR1, CHFR2, CFHR3, CFHR4, and CFHR5) are not able to bind any complement components, but inhibit binding activity between fH and C3b [38]. The *complement factor H (CFH)* gene and *CFHR1–CFHR5* encoding five CFHR proteins are located in tandem in the regulators of complement activation cluster at chromosome 1q32 [39]. Gharavi et al. identified the gene deletion of *CFHR3* and *CFHR1* within the *CFH* locus by genome-wide association study (GWAS) [40]. This CFHR3–CFHR1 homozygous deletion is protective in the pathogenesis of IgAN, C3 glomerulopathy, and age-related macular degeneration [41, 42]. Recently, advanced data was reported, and minor allele A of rs6677604, which is a noncoding single nucleotide polymorphism in intron 11 of the *CFHR* gene, highly tagged *CFHR3–CFHR1* deletion [43].

7.4 The Role of Complements in IgA Nephropathy: Local Tissue

Tomino et al. deduced that the polymeric form of IgA1 is predominantly eluted from the renal tissues of IgAN patients [44]. Tomino and Conley et al. also confirmed the predominantly glomerular deposition of IgA1, rather than that of IgA2 [45, 46]. A subsequent report showed that patients with mesangial deposits of IgA1 and C3c showed no deposits of C4, MBL, and MASP-1. AP is certainly activated in glomerulus [47]. Endo et al. first demonstrated that the glomerular deposition of MBL/MASP-1 occurred in 25 % of cases of IgAN and that this was not observed in the normal kidney and that the frequency was higher than that found in the other forms of glomerulonephritis [48]. Patients with glomerular deposits of MBL/MASP-1 were young, and the duration of the disease prior to renal biopsy was short compared with that in patients without MBL/MASP-1 deposition. Therefore,

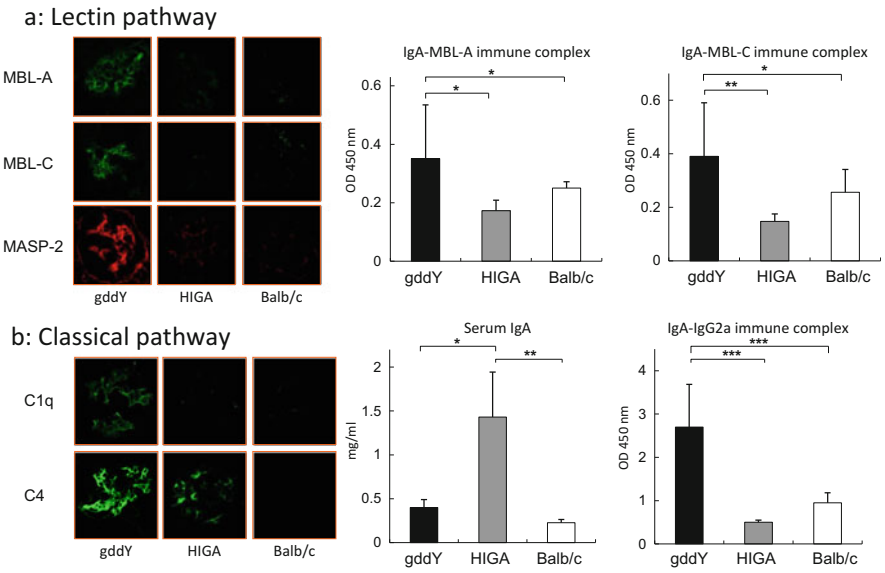

Fig. 7.6 Pathological role of lectin pathway and classical pathway in mouse model. (**a**) Mannose-binding lectin (MBL) and MBL-associated serine protease (MASP)-2 were positive in glomerulus obtained from grouped ddY (gddY) mice and negative in control mice (HIGA and Balb/c mice). Serum levels of IgA–MBL-A immune complex (*IC*) and IgA–MBL-C IC were significantly higher in gddY mice than those of HIGA and Balb/c mice. $*p = 0.01$, $**p = 0.001$. (**b**) The positive area of glomerular C1q and C4 staining in gddY mice was stronger than that in HIGA mice. *A*: The serum level of IgA was significantly higher in HIGA mice than in those of gddY and Balb/c mice. However, the serum level of IgA–IgG2a IC was significantly higher in gddY mice than those of HIGA and Balb/c mice (The figure was modified from Hashimoto et al. [50])

Roos et al. concluded that the glomerular activation of LP was associated with more severe renal damage, as demonstrated by proteinuria, decreased renal function, and more severe histological findings, such as mesangial proliferation, crescent formation, glomerular sclerosis, and interstitial fibrosis [26]. Because a recent cohort study also confirmed the significance of MBL deposition in IgAN, the glomerular deposition of MBL is a prognostic marker of IgAN [49].

In an experimental model, Hashimoto et al. analyzed the grouped ddY mouse, which presents spontaneous IgAN [50]. They found that the complement components belonging to LP and CP were deposited in glomeruli; furthermore, the serum level of IgA–MBL complex and IgA–IgG2a complex was significantly higher (Fig. 7.6). Further analysis of this model might unravel the pathogenic obscurities between complement activation and IgAN.

7.4.1 Ligands for MBL

Hisano et al. reported that patients with mesangial deposits of IgA1 alone showed no deposition of C4, MBL, and MASP-1, and patients with deposits of both of IgA1 and IgA2 showed depositions of C4, MBL, and MASP-1. They concluded that AP activation occurs as a result of the mesangial deposition of IgA1 and that LP activation is associated with mesangial deposition of IgA2 [47]. On the other hand, Oortwijn et al. focused on SIgA and clearly demonstrated glomerular staining of SIgA with MBL and C4d in the patients with IgAN [30].

Generally, the protease-damaged surface of glomerular resident cells or apoptotic cells can be recognized by MBL. In regard to patients of lupus nephritis (LN), we recently proposed that positive glomerular staining for annexin V would be seen in the majority of patients who had confirmed glomerular deposits of MBL, L-ficolin, and properdin [51]. Further examinations will also be necessary to elucidate the initial activator of LP in situ.

7.4.2 Other Histological Significances of Complement Deposition

Two recent studies focused on the glomerular deposition of C4d and revealed that renal survival was significantly more ameliorated in patients of C4d-negative IgAN than in those of C4d positive [52, 53]. The 3-year renal survival rate was 39 % in C4d-positive patients and 66 % in C4d-negative patients, and the 20-year renal survival rate was 28 % in C4d-positive patients and 85 % in C4d-negative patients. In these studies, C4d-positive IgAN also presented higher blood pressure, urinary protein, and findings of segmental sclerosis and tubular damage than in those of C4d-negative IgAN. It is deeply interesting that these factors are the same as previously recognized independent worsening factors in IgAN. Thus, the presence of mesangial deposits of C4d may help us to identify patients with a worse prognosis.

Mesangial C3 deposition is highly observed in more than 90 % of renal specimens in IgAN [1, 54]. Although we also encounter the extraglomerular deposition of C3 (ex-C3) in the results of a routine histological study (Fig. 7.7), these findings have received less attention in the pathogenesis of IgAN. We analyzed 170 patients who were diagnosed with IgAN [55]. 79 cases presented C3 deposition in glomeruli without other ex-C3 deposits, and 91 cases presented C3 deposition with ex-C3 deposition located in Bowman's capsules and/or afferent and efferent arterial walls. Valenzuela et al. suggested that passive diffusion probably does not explain ex-C3 deposition, and a drainage pathway of IC, which connects from the intraglomerulus to extraglomerulus, is assumed. Because the intraglomerular mesangial matrix is continuous to the extraglomerular mesangial matrix in the juxtaglomerular region, as shown in several tracer injection studies, arteriolar C3 deposits might be derived

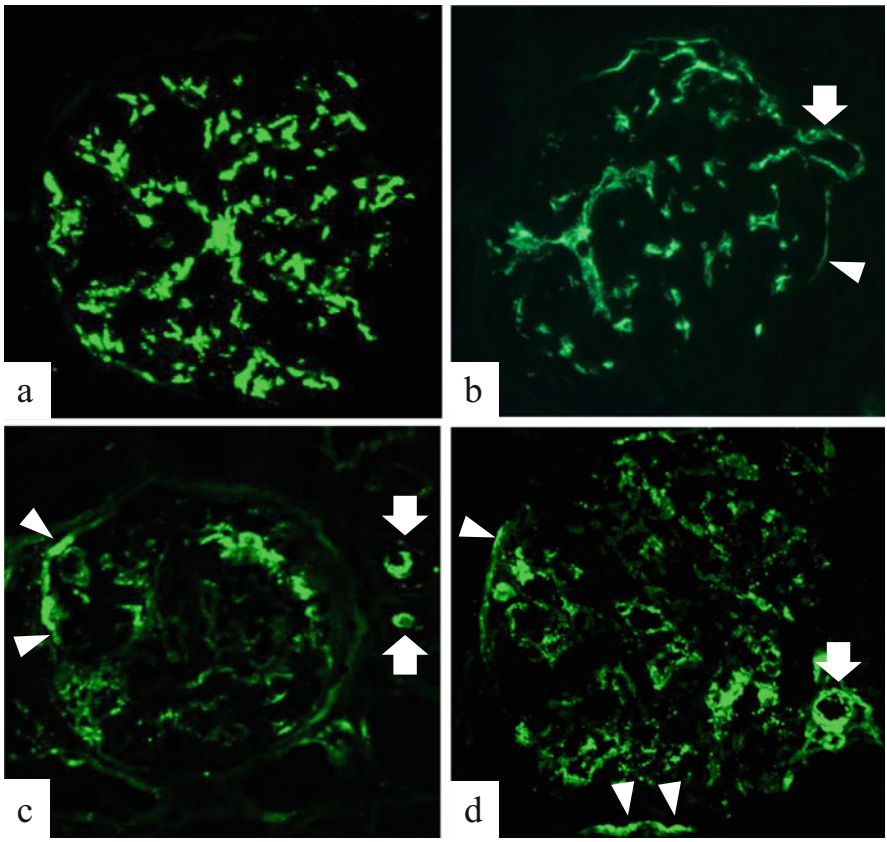

Fig. 7.7 Staining pattern of C3 deposition of IgA nephropathy (×200). Representative immunofluorescence photograph of IgA nephropathy. (**a**) C3 deposits in mesangial area. (**b–d**) These glomeruli have mesangial and extraglomerular deposits of C3 (*arrow*, afferent and/or efferent arteriolar deposition; *arrow head*, Bowman's capsule deposition) (The figure was modified from Ohsawa et al. [55])

from paramesangial areas [56–58]. We also speculated that an IC that consists of C3 is able to translocate from the paramesangial region to Bowman's capsule through the adhesive lesion between the glomerular capillaries and Bowman's capsules. In our study, the cases of ex-C3 deposits presented distinct clinical characteristics, such as hypertension and dyslipidemia at the time of renal biopsy. Especially, in the cases of ex-C3 deposits with obeity, the conventional symptomatic therapy resulted in their worse prognosis. Thus, we need to highlight the metabolic impacts on the progression of IgAN patients who have ex-C3 deposit.

7.5 New Insights

Several pathogenic viral and bacterial antigens have been proposed as being responsible for the formation of mesangial deposits of IgA, and infection might trigger the onset and progression of IgAN [59, 60]. Gong et al. described the association of the MBL polymorphism of codon 54 and infection in patients with IgAN [61]. In that report, patients carrying the variant allele (GAC) had episodes of upper respiratory or gastrointestinal infections prior to onset, or exacerbation of IgAN, which are absent in wild homozygotes (GGC/GGC).

In other types of glomerular disease, such as membranous nephropathy and LN, patient's urine contains complement regulatory proteins and MAC, amounts of which fluctuate with disease activity [62–64]. We found strong associations between the urinary level of fH and that of MAC along with the disease progression of IgAN [65]. Also, urinary levels of fH and MAC were positively correlated with serum creatinine, urinary N-acetyl-ß-D-glucosaminidase, urinary ß2-microglobulin, urinary protein, the degree of interstitial fibrosis, and the percentage of global glomerular sclerosis. Recently, Liu et al. showed that urinary MBL and C3 are candidates for predicting biomarkers for IgAN [66]. Especially, in urinary MBL, the concentration of MBL was significantly elevated along with histological damage, estimated GFR, and proteinuria.

Looking at recent progress, the pathological importance of LP activation and properdin are in focus for kidney diseases. In the case of LN, LP and PDP might be activated via the recognition of surface molecules of glomerular resident cells, which are usually hidden in the cell membrane [51, 67]. On the other hand, properdin can directly bind to proximal tubular epithelial cells (PTEC) and accelerate PTEC damage via AP activation by surpassing fH regulation [67]. The pathophysiological significance of PDP will be mandatory in the search for renal damage mechanisms.

To elucidate the participations of complement system paves to develop the new therapeutic strategies. The anti-C5 monoclonal antibody eculizumab® achieves therapeutic success in atypical hemolytic uremic syndrome and C3 glomerulopathy [68]. A constant region of eculizumab consists of IgG4 that lacks the ability to bind to the Fc receptor and to activate complements via CP. The following case report is interesting: a 16-year-old male presented rapidly progressive glomerulonephritis with heavy proteinuria, and his histological diagnosis was IgAN [69]. In spite of aggressive immunosuppressive treatment, his renal function had been worsening. The induction of eculizumab for 3 months was able to rescue renal function, and discontinuation of eculizumab resulted in deterioration of renal function. We have to explore the application of eculizumab and develop new complement-directed drugs.

7.6 Conclusion

A deeper understanding of the mechanism of complement activation may help to elucidate the pathogenesis of IgAN. This chapter summarizes the current knowledge of the role of the complement system in the pathogenesis of IgAN. Because traces of LP activation in the fluid phase and local glomerular tissues have accumulated, it appears that the activations of AP and LP are very much involved in the pathogenesis of IgAN.

Conflict of Interest The author declares that he has no conflict of interest.

References

1. Haas M. Histologic subclassification of IgA nephropathy: a clinicopathologic study of 244 cases. Am J Kidney Dis. 1997;29:829–42.
2. Wyatt RJ, Julian BA. Activation of complement in IgA nephropathy. Am J Kidney Dis. 1988;12:437–42.
3. Ermini L, Wilson I, Goodship T, Sheerin N. Complement polymorphisms: geographical distribution and relevance to disease. Immunobiology. 2012;217:265–71.
4. Ricklin D, Hajishengallis G, Yang K, Lambris JD. Complement: a key system for immune surveillance and homeostasis. Nat Immunol. 2010;11:785–97.
5. Kemper C, Atkinson JP, Hourcade DE. Properdin: emerging roles of a pattern-recognition molecule. Annu Rev Immunol. 2009;28:131–55.
6. Chen M, Daha MR, Kallenberg CG. The complement system in systemic autoimmune disease. J Autoimmun. 2010;34:J276–86.
7. Zipfel PF, Skerka C. Complement regulators and inhibitory proteins. Nat Rev Immunol. 2009;9:729–40.
8. Noris M, Remuzzi G. Overview of complement activation and regulation. Semin Nephrol. 2013;33:479–92.
9. Nilsson B, Ekdahl KN. Complement diagnostics: concepts, indications, and practical guidelines. Clin Dev Immunol. 2012. doi:10.1155/2012/962702.
10. Hauptmann G, Goetz J, Uring-Lambert B, Grosshans E. Component deficiencies: 2. Fourth Component. 1986;39:232–49.
11. Pettigrew HD, Teuber SS, Gershwin ME. Clinical significance of complement deficiencies. Ann N Y Acad Sci. 2009;1173:108–23.
12. Dean M, Minchinton R, Heatley S, Eisen D. Mannose binding lectin acute phase activity in patients with severe infection. J Clin Immunol. 2005;25:346–52.
13. Ohsawa I, Ohi H, Endo M, Fujita T, Kanmatsuse K, Nonaka M. Novel estimation of histologic activity in human glomerulonephritis by detection of complement component C3 messenger RNA. Clin Exp Nephrol. 1998;2:50–7.
14. Sheerin NS, Risley P, Abe K, Tang Z, Wong W, Lin T, et al. Synthesis of complement protein C3 in the kidney is an important mediator of local tissue injury. FASEB J. 2008;22:1065–72.
15. Tang S, Zhou W, Sheerin NS, Vaughan RW, Sacks SH. Contribution of renal secreted complement C3 to the circulating pool in humans. J Immunol. 1999;162:4336–41.
16. Cianflone K, Xia Z, Chen LY. Critical review of acylation-stimulating protein physiology in humans and rodents. Biochim Biophys Acta (BBA) Biomembr. 2003;1609:127–43.
17. Ohsawa I, Inoshita H, Ishii M, Kusaba G, Sato N, Mano S, et al. Metabolic impact on serum levels of complement component 3 in Japanese patients. J Clin Lab Anal. 2010;24:113–8.

18. Sargur R, White P, Egner W. Cryoglobulin evaluation: best practice? Ann Clin Biochem. 2010;47(Pt 1):8–16.
19. Nagamachi S, Ohsawa I, Sato N, Ishii M, Kusaba G, Kobayashi T, et al. Immune complex-mediated complement activation in a patient with IgG4-related tubulointerstitial nephritis. Case Rep Nephrol Urol. 2011;1:7–14.
20. Pickering MC, D'Agati VD, Nester CM, Smith RJ, Haas M, Appel GB, et al. C3 glomerulopathy: consensus report. Kidney Int. 2013;84:1079–89.
21. Tomino Y, Suzuki S, Imai H, Saito T, Kawamura T, Yorioka N, et al. Measurement of serum IgA and C3 may predict the diagnosis of patients with IgA nephropathy prior to renal biopsy. J Clin Lab Anal. 2000;14:220–3.
22. Nakayama K, Ohsawa I, Maeda-Ohtani A, Murakoshi M, Horikoshi S, Tomino Y. Prediction of diagnosis of immunoglobulin A nephropathy prior to renal biopsy and correlation with urinary sediment findings and prognostic grading. J Clin Lab Anal. 2008;22:114–8.
23. Onda K, Ohi H, Tamano M, Ohsawa I, Wakabayashi M, Horikoshi S, et al. Hypercomplementemia in adult patients with IgA nephropathy. J Clin Lab Anal. 2007;21:77–84.
24. Hiemstra PS, Gorter A, Stuurman ME, Van Es LA, Daha MR. Activation of the alternative pathway of complement by human serum IgA. Eur J Immunol. 1987;17:321–6.
25. Nikolova EB, Tomana M, Russell MW. The role of the carbohydrate chains in complement (C3) fixation by solid-phase-bound human IgA. Immunology. 1994;82:321–7.
26. Roos A, Rastaldi MP, Calvaresi N, Oortwijn BD, Schlagwein N, van Gijlswijk-Janssen DJ, et al. Glomerular activation of the lectin pathway of complement in IgA nephropathy is associated with more severe renal disease. J Am Soc Nephrol. 2006;17:1724–34.
27. Kokubo T, Hiki Y, Iwase H, Tanaka A, Toma K, Hotta K, et al. Protective role of IgA1 glycans against IgA1 self-aggregation and adhesion to extracellular matrix proteins. J Am Soc Nephrol. 1998;9:2048–54.
28. Roos A, Bouwman LH, van Gijlswijk-Janssen DJ, Faber-Krol MC, Stahl GL, Daha MR. Human IgA activates the complement system via the mannan-binding lectin pathway. J Immunol. 2001;167:2861–8.
29. Coppo R, Amore A. Aberrant glycosylation in IgA nephropathy (IgAN). Kidney Int. 2004;65:1544–7.
30. Oortwijn BD, Rastaldi MP, Roos A, Mattinzoli D, Daha MR, van Kooten C. Demonstration of secretory IgA in kidneys of patients with IgA nephropathy. Nephrol Dial Transplant. 2007;22:3191–5.
31. Suzuki H, Ohsawa I, Kodama F, Nakayama K, Ohtani A, Onda K, et al. Fluctuation of serum C3 levels reflects disease activity and metabolic background in patients with IgA nephropathy. J Nephrol. 2013;26:708–15.
32. Shimamoto M, Ohsawa I, Suzuki H, Hisada A, Nagamachi S, Honda D, et al. Impact of body mass index on progression of IgA nephropathy among Japanese patients. J Clin Lab Anal. 2014. doi:10.1002/jcla.21778.
33. Garred P, Larsen F, Seyfarth J, Fujita R, Madsen H. Mannose-binding lectin and its genetic variants. Genes Immun. 2006;7:85–94.
34. Ishii M, Ohsawa I, Inoshita H, Kusaba G, Onda K, Wakabayashi M, et al. Serum concentration of complement components of the lectin pathway in maintenance hemodialysis patients, and relatively higher levels of L-ficolin and MASP-2 in mannose-binding lectin deficiency. Ther Apher Dial. 2011;15:441–7.
35. Ohsawa I, Ishii M, Ohi H, Tomino Y. Pathological scenario with the mannose-binding lectin in patients with IgA nephropathy. J Biomed Biotechnol. 2012. doi:10.1155/2012/476739.
36. Pirulli D, Boniotto M, Vatta L, Crovella S, Spano A, Morgutti M, et al. Polymorphisms in the promoter region and at codon 54 of the MBL2 gene are not associated with IgA nephropathy. Nephrol Dial Transplant. 2001;16:759–64.
37. Barbour TD, Pickering MC, Cook HT. Dense deposit disease and C3 glomerulopathy. Semin Nephrol. 2013;33:493–507.

38. Kavanagh D, Goodship TH, Richards A. Atypical hemolytic uremic syndrome. Semin Nephrol. 2013;33:508–30.
39. Díaz-Guillén MA, Rodríguez de Córdoba S, Heine-Suñer D. A radiation hybrid map of complement factor H and factor H-related genes. Immunogenetics. 1999;49:549–52.
40. Gharavi AG, Kiryluk K, Choi M, Li Y, Hou P, Xie J, et al. Genome-wide association study identifies susceptibility loci for IgA nephropathy. Nat Genet. 2011;43:321–7.
41. Malik TH, Lavin PJ, de Goicoechea JE, Vernon KA, Rose KL, Patel MP, et al. A hybrid CFHR3-1 gene causes familial C3 glomerulopathy. J Am Soc Nephrol. 2012;23:1155–60.
42. Raychaudhuri S, Ripke S, Li M, Neale BM, Fagerness J, Reynolds R, et al. Associations of CFHR1-CFHR3 deletion and a CFH SNP to age-related macular degeneration are not independent. Nat Genet. 2010;42:553–5.
43. Zhu L, Zhai YL, Wang FM, Hou P, Lv JC, Xu DM, et al. Variants in complement factor H and complement factor H-related protein genes, CFHR3 and CFHR1, affect complement activation in IgA nephropathy. J Am Soc Nephrol 2014; pii: ASN.2014010096
44. Tomino Y, Endoh M, Nomoto Y, Sakai H. Immunoglobulin A1 and IgA nephropathy. N Engl J Med. 1981;305:1159–60.
45. Conley ME, Cooper MD, Michael AF. Selective deposition of immunoglobulin A1 in immunoglobulin A nephropathy, anaphylactoid purpura nephritis, and systemic lupus erythematosus. J Clin Invest. 1980;66:1432–6.
46. Tomino Y, Sakai H, Miura M, Endoh M, Nomoto Y. Detection of polymeric IgA in glomeruli from patients with IgA nephropathy. Clin Exp Immunol. 1982;49:419–25.
47. Hisano S, Matsushita M, Fujita T, Endo Y, Takebayashi S. Mesangial IgA2 deposits and lectin pathway-mediated complement activation in IgA glomerulonephritis. Am J Kidney Dis. 2001;38:1082–8.
48. Endo M, Ohi H, Ohsawa I, Fujita T, Matsushita M, Fujita T. Glomerular deposition of mannose-binding lectin (MBL) indicates a novel mechanism of complement activation in IgA nephropathy. Nephrol Dial Transplant. 1998;13:1984–90.
49. Liu L, Liu N, Chen Y, Wang L, Jiang Y, Wang J, et al. Glomerular mannose-binding lectin deposition is a useful prognostic predictor in immunoglobulin A nephropathy. Clin Exp Immunol. 2013;174:152–60.
50. Hashimoto A, Suzuki Y, Suzuki H, Ohsawa I, Brown R, Hall S, et al. Determination of severity of murine IgA nephropathy by glomerular complement activation by aberrantly glycosylated IgA and immune complexes. Am J Pathol. 2012;181:1338–47.
51. Sato N, Ohsawa I, Nagamachi S, Ishii M, Kusaba G, Inoshita H, et al. Significance of glomerular activation of the alternative pathway and lectin pathway in lupus nephritis. Lupus. 2011;20:1378–86.
52. Espinosa M, Ortega R, Sanchez M, Segarra A, Salcedo MT, Gonzalez F, et al. Association of C4d deposition with clinical outcomes in IgA nephropathy. Clin J Am Soc Nephrol. 2014;9:897–904.
53. Sahin OZ, Yavas H, Taslı F, Gibyeli DG, Ersoy R, Uzum A, et al. Prognostic value of glomerular C4d staining in patients with IgA nephritis. Int J Clin Exp Pathol. 2014;7:3299–304.
54. Vangelista A, Frasca GM, Mondini S, Bonomini V. Idiopathic IgA mesangial nephropathy: immunohistological features. Contrib Nephrol. 1984;40:167–73.
55. Ohsawa I, Kusaba G, Ishii M, Sato N, Inoshita H, Onda K, et al. Extraglomerular C3 deposition and metabolic impacts in patients with IgA nephropathy. Nephrol Dial Transplant. 2012;28:1856–64.
56. Valenzuela R, Gogate PA, Deodhar SD, Gifford RW. Hyaline arteriolar nephrosclerosis. Immunofluorescence findings in the vascular lesions. Lab Invest. 1980;43:530–4.
57. Makino H, Hironaka K, Shikata K, Nagake Y, Kumagai I, Kashihara N, et al. Mesangial matrices act as mesangial channels to the juxtaglomerular zone. Nephron. 1994;66:181–8.
58. Sterzel RB, Perfetto M, Biemesderfer D, Kashgarian M. Disposal of ferritin in the glomerular mesangium of rats. Kidney Int. 1983;23:480–8.

59. Van Es LA. Pathogenesis of IgA nephropathy. Kidney Int. 1992;41:1720–9.
60. Suzuki S, Sato H, Tsukada H, Arakawa M, Nakatomi Y. Haemophilus parainfluenzae antigen and antibody in renal biopsy samples and serum of patients with IgA nephropathy. Lancet. 1994;343:12–6.
61. Gong R, Liu Z, Li L. Mannose-binding lectin gene polymorphism associated with the patterns of glomerular immune deposition in IgA nephropathy. Scand J Urol Nephrol. 2001;35:228–32.
62. Tamano M, Fuke Y, Endo M, Ohsawa I, Fujita T, Ohi H. Urinary complement factor H in renal disease. Nephron. 2002;92:705–7.
63. Ogrodowski JL, Hebert LA, Sedmak D, Cosio FG, Tamerius J, Kolb W. Measurement of SC5b-9 in urine in patients with the nephrotic syndrome. Kidney Int. 1991;40:1141–7.
64. Endo M, Fuke Y, Tamano M, Hidaka M, Ohsawa I, Fujita T, et al. Glomerular deposition and urinary excretion of complement factor H in idiopathic membranous nephropathy. Nephron Clin Pract. 2004;97:c147–53.
65. Onda K, Ohsawa I, Ohi H, Tamano M, Mano S, Wakabayashi M, et al. Excretion of complement proteins and its activation marker C5b-9 in IgA nephropathy in relation to renal function. BMC Nephrol. 2011;12:64. doi:10.1186/1471-2369-12-64.
66. Liu L, Jiang Y, Wang L, Liu N. Urinary mannose-binding lectin is a biomarker for predicting the progression of immunoglobulin (Ig) A nephropathy. Clin Exp Immunol. 2012;169:148–55.
67. Nagamachi S, Ohsawa I, Suzuki H, Sato N, Inoshita H, Hisada A, et al. Properdin has an ascendancy over factor H regulation in complement-mediated renal tubular damage. BMC Nephrol. 2014;15:82. doi:10.1186/1471-2369-15-82.
68. Zuber J, Fakhouri F, Roumenina LT, Loirat C, Fremeaux-Bacchi V, French Study Group for aHUS/C3G. Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies. Nat Rev Nephrol. 2012;8:643–57.
69. Rosenblad T, Rebetz J, Johansson M, Békássy Z, Sartz L, Karpman D. Eculizumab treatment for rescue of renal function in IgA nephropathy. Pediatr Nephrol. 2014;29:2225–8.

Part II
Treatment

Chapter 8
How Different Are the Current Understandings of Treatments for IgA Nephropathy?

Hitoshi Suzuki

Abstract IgA nephropathy (IgAN) is a common autoimmune renal disease resulting in renal failure in patients with massive proteinuria. About 15–20 % of IgAN patients will progress to end-stage kidney disease (ESKD) within 20 years. Several risk factors for the progression of IgAN include massive proteinuria, hypertension, global sclerosis, crescent formation, and tubulointerstitial fibrosis. Worldwide, therapeutic options are limited, but include nonspecific treatments to reduce proteinuria through renin-angiotensin system inhibitors (RAS-I). Another strategy, used to control chronic inflammation, includes tonsillectomy and the use of immunosuppressive agents such as corticosteroids and mycophenolate mofetil.

A paucity of high-quality clinical trials has meant that the evaluation of immunosuppressive therapies has been difficult and there remains a great deal of confusion over the optimum treatment of patients with IgAN. Therefore, physicians have been left to manage patients with generic therapies, mainly by control of blood pressure and renin-angiotensin blockade. There are currently controversies on the definition and treatment of progressive IgAN. Here is the review about the evidence for existing treatment choices and the differences in current understanding of treatments of IgAN worldwide.

Keywords RAS inhibitor • Immunosuppressive therapy • Tonsillectomy

8.1 Introduction

More than four decades have passed since IgAN was first described by Berger and Hinglais in 1968 [1]. Patients typically present with microscopic or gross hematuria with mild to moderate proteinuria and a variable degree of renal insufficiency [2]. Accumulated experience has suggested a poor renal outcome for patients with significant proteinuria [3]. It is estimated that 15–20 % of patients with

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IgAN will reach end-stage kidney disease (ESKD) within 10 years after disease onset if left untreated [4]. The pathogenesis of IgAN is being elucidated, with new insights into the contribution of circulating immune complexes formed with aberrant glycosylated IgA1 and autoantibodies [5].

Massive proteinuria is a major risk factor for disease progression [6]. Intervention to reduce proteinuria using renin-angiotensin system inhibitors (RAS-I) is the mainstay treatment. Our current understanding of the initial pathogenic steps in IgAN provides a relatively limited rationale for immunosuppressive therapy. However, it is conceivable that immunosuppressive therapy might affect secondary inflammatory events triggered by glomerular immune deposits. Some randomized clinical trials on corticosteroid monotherapy, mycophenolate mofetil monotherapy, or immunosuppressive combination therapy have provided evidence for a benefit on either surrogate parameters, such as proteinuria, or hard end points such as renal failure. According to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, consideration for glucocorticosteroids should be given to patients with persistent proteinuria greater than or equal to 1 g per day [7]. Various therapeutic approaches, such as RAS-I, antiplatelet drugs, anticoagulants, fish oil, corticosteroids, and tonsillectomy plus steroid pulse (TSP) therapy, have been proposed for the treatment of patients with IgAN. As such, here is the review about the therapeutic options available and differences in the current understanding of the treatment of IgAN.

8.2 Supportive Treatment Strategies

Patients with IgAN who have preserved renal function, microhematuria, and minimal proteinuria generally have a benign natural history [8, 9]. However, proteinuria is a continuous risk factor for the progression of IgAN. Registry data demonstrated that a reduction of proteinuria to less than 1 g/day results in significantly improved renal function [10]. Thus, there is consensus that RAS-I should be maximized and blood pressure should be controlled before considering other forms of treatment.

8.2.1 RAS Inhibitor (RAS-I)

Antiproteinuric therapy achieved via a blockade of RAS is established firmly for IgAN patients [11]. Praga et al. also noted significantly better renal survival in patients receiving angiotensin-converting enzyme inhibitors (ACEI) as compared with those receiving other classes of antihypertensive agents, despite identical blood pressure levels over the observation period [12]. The same conclusion was reported by Coppo et al. [13]. A similar benefit was verified for angiotensin II receptor blockers (ARB) in Hong Kong [14]. However, treatment with any RAS-I was prohibited for normotensive patients in Japan by the Japanese Pharmaceutical

and Medical Devices Agency. Moreover, many physicians hesitate to prescribe RSA-I to young women of marriageable age due to the risk of teratogenicity. Of note, a significant proportion of patients will not achieve a reduction of proteinuria to less than 1 g/day despite a maximal dose of RAS-I. The choice of any additional therapy remains controversial to decrease the risk of progression.

8.2.2 Fish Oil

Fish oil contains the compound omega-3 polyunsaturated fatty acid and reduces renal inflammation by mitigating inflammatory cytokines and eicosanoids in IgAN [15]. The Mayo Clinic multicenter study tested a placebo (olive oil) versus fish oil (1.87 g of eicosapentaenoic acid and 1.36 g of docosahexaenoic acid) on 106 patients with IgAN [16]. The trial end point was a 50 % or greater rise in serum creatinine. Following a 2-year treatment period, 6 % of patients in the fish oil group, as compared to 33 % in the placebo group, had reached the trial end point ($P < 0.01$). After 4 years, only 10 % in the fish oil group, as compared to 40 % in the placebo group, had ESRD or had died ($P < 0.01$). Therapy with fish oil in the trial did not significantly reduce proteinuria when compared to the placebo.

8.2.3 Antiplatelet Agents and Anticoagulants

Less well-established non-immunosuppressive approaches to patients with IgAN include fish oil, antiplatelet drugs, and anticoagulants. Antiplatelet drugs and anticoagulants are used mainly in Asian countries for the treatment of IgAN. A few studies have suggested a benefit from dipyridamole and warfarin as compared with no medication [17, 18].

A systematic review of the benefits of fish oils, anticoagulants, tonsillectomy, and RAS-I has provided valuable insights into the role of non-immunosuppressive therapies for IgAN [19]. Evidence accumulated from 56 studies and 2838 participants showed that only RAS-I provided a useful intervention, mainly by reducing proteinuria. Other non-immunosuppressive modalities had a lack of evidence, through randomized trials, to demonstrate treatment efficacy in IgAN.

8.3 Indications of Immunosuppressive Therapy

The treatment of patients with slowly progressive IgAN or those at low risk for progression currently represents a dilemma. IgAN is an autoimmune kidney disease resulting in intrarenal inflammation and kidney injury. Immune modulation targeting the pathogenic pathway may alter the natural history of disease

progression. Although there are a few studies that convincingly describe the benefit of immunosuppression, there are an equal number of studies reporting the benefit of supportive therapy. It also noteworthy that the addition of an ARB to corticosteroid monotherapy resulted in a considerable benefit, whereas corticosteroid without a RAS-I failed to protect from progression to renal failure [20].

8.3.1 Corticosteroid

The use of corticosteroids for IgAN began in the 1980s [21, 22] and at present remains a choice for patients with moderate to severe proteinuria. In 1999, Pozzi et al. published a randomized controlled trial in patients with a glomerular filtration rate (GFR) greater than 70 mL/min. Patients were assigned randomly to supportive therapy only or additional corticosteroids [23]. In a 10-year follow-up study of the population, serum creatinine levels had doubled in 2 % of patients in the steroid group versus 30 % in the control group [24]. In 2003, Katafuchi et al. reported a randomized controlled trial in which patients administrated oral corticosteroids as compared with patients in the control group. Although renal survival was not improved by the corticosteroids, proteinuria decreased in the corticosteroid group [25]. The targets of glucocorticosteroid therapy in IgAN remain speculative, but it may improve intrarenal inflammation due to mesangial deposition of nephritogenic IgA. Nevertheless, a systematic review by the Cochrane Group identified 13 trials (623 patients) with placebo-controlled groups to assess the pros and cons of immunosuppression therapy in IgAN [26]. Analysis found that glucocorticosteroids resulted in a lower risk of ESKD (95 % CI: 0.25–0.80) and proteinuria (95 % CI: −0.72 to −0.12) in patients with IgAN.

8.3.2 Mycophenolate Mofetil

Mycophenolate mofetil (MMF) reversibly inhibits inosine monophosphate dehydrogenase (IMDPH) thus disrupting the de novo purine biosynthetic pathway required by B and T lymphocytes. Approved in 1995 by the US Food and Drug Administration (FDA) to prevent transplant rejection, MMF has been tested in proliferative lupus nephritis and shown to be non-inferior to cyclophosphamide for inducing remission [27]. The initial experience of MMF in IgAN was reported by Maes et al. [28]. Compared to the placebo group, no difference was seen in proteinuria and worsening of serum creatinine after 36 months of therapy with MMF. A North American experiment that randomized patients to MMF or placebo reported no benefit after a year of MMF therapy in patients with stage III chronic kidney disease and a mean daily proteinuria of greater than 2 g [29]. The most recent report providing longer follow-up data on 40 Chinese patients with mild histological lesions did show a benefit in reducing the composite end points of the

doubling of serum creatinine or ESKD [30]. Although MMF appears to be a promising method to reduce proteinuria and prevent ESKD, further studies are necessary to determine its efficacy in IgAN [31, 32].

8.4 Tonsillectomy Plus Steroid Pulse (TSP) Therapy

Since TSP therapy was first reported by Hotta et al. in 2001 [33], many of the benefits of TSP therapy have been reported, especially in Japan. About 50 % of patients achieved clinical remission, defined as no urinary abnormalities, 1 year after TSP therapy [34]. Pozzi et al. also reported that the clinical remission rate with TSP therapy was superior, as compared with steroid monotherapy (59.7 vs. 35.3 %, $P < 0.01$) [24]. Moreover, Xie et al. demonstrated that tonsillectomy improved renal survival in IgAN patients with an observation period of 20 years [35]. In a Chinese study, the clinical remission rate was higher in patients with tonsillectomy than in those without tonsillectomy [36]. Recently, many patients with IgAN and their families have realized the efficacy of TSP therapy through the Internet and have asked nephrologists about TSP therapy. On the other hand, Rasche et al. reported that tonsillectomy showed no efficacy in patients with progressive conditions of IgAN in a retrospective cohort study [37]. Although TSP therapy is more effective than corticosteroid therapy or antiplatelet therapy in terms of 8-year renal survival rates (82.8 % vs. 51.0 % vs. 45.1 %, respectively), there was no significant difference among the patients whose baseline serum creatinine was >2.0 mg/dl [38]. Miura et al. evaluated the efficacy of TSP therapy in a multicenter retrospective study and concluded that TSP therapy was effective for patients with an early stage, i.e., within 5 years from the onset, with the amount of proteinuria <1.1 g and serum creatinine levels <1.5 mg/dl [34]. Recently, a multicenter randomized controlled trial of TSP therapy was reported [39]. TSP therapy has greater effect in attenuating proteinuria as compared to steroid pulse therapy.

8.5 Conclusion

Despite progressive advances in our understanding of the pathogenesis of IgAN, there is still no specific treatment to inhibit the production of Gd-IgA1 and autoantibodies or to prevent its glomerular deposition. Therefore, treatment options focus on modulating immune responses and inflammatory events. Most current treatment strategies are common to other types of chronic kidney diseases, such as RAS-I, control of blood pressure, and dyslipidemia. Thus far, no medications have been approved by the FDA specifically for IgAN. The availability of new agents with novel mechanisms and activities against the humoral immune response may for the first time allow targeted treatment in IgAN.

Conflict of Interest The author declares that he has no conflict of interest.

Appendix

Results from a questionnaire for the audience at the "Clinical Symposium on IgA Nephropathy" at the 14th Asian Pacific Congress of Nephrology held in Tokyo in 2014 (President: Prof. Yasuhiko Tomino).

Questionnaire: What course of treatment would you suggest for patients with IgAN?

Case 1 46-year-old male with no medication (see Fig. 8.1 for the questionnaire result)

In January 2014, BP 124/68, proteinuria 1.5 g/day, urinary RBC 5-9/HPF, eGFR 55 mL/min/1.73 m^2. Renal biopsy: acute lesion (endocapillary hypercellularity) (+), chronic lesion (+). In May 2014, BP 124/68, proteinuria 1.5 g/day, urinary RBC 5-9/HPF, eGFR 55 mL/min/1.73 m^2.

Case 2 48-year-old female with no medication (see Fig. 8.2 for the questionnaire result)

In November 2013, BP 128/78, proteinuria 1.8 g/day, urinary RBC11-20 /HPF, eGFR 100 mL/min/1.73 m^2. Renal biopsy: acute lesion (endocapillary hypercellularity) (+). After 6 months of medication with ACEI, in May 2014, BP 118/70, proteinuria 1.2 g/day, urinary RBC 11-20/HPF, eGFR 100 mL/min/1.73 m^2.

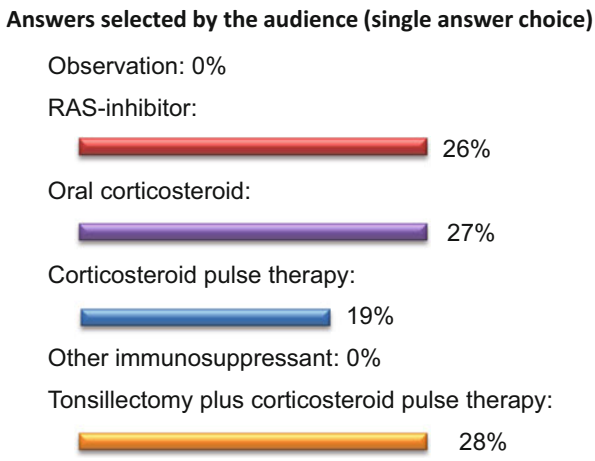

Fig. 8.1 Answers selected by the audience for Case 1

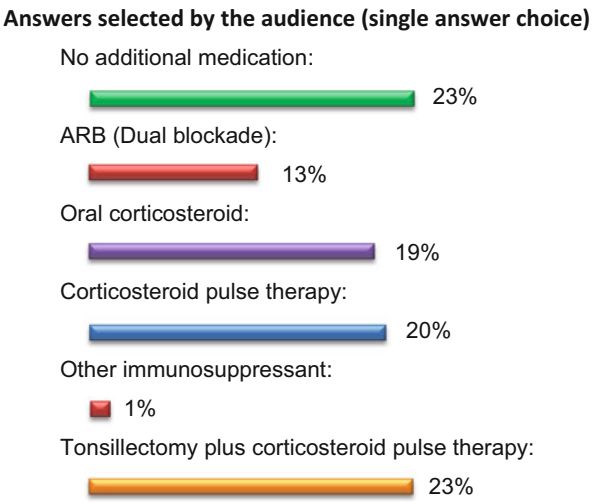

Fig. 8.2 Answers selected by the audience for Case 2

References

1. Berger J, Hinglais N. Intercapillary deposits of IgA-IgG. J Urol Nephrol. 1968;74:694–5.
2. Wyatt RJ, Julian BA. IgA nephropathy. N Engl J Med. 2013;368:2402–14.
3. Berthoux F, Mohey H, Laurent B, Mariat C, Afiani A, Thibaudin L. Predicting the risk for dialysis or death in IgA nephropathy. J Am Soc Nephrol. 2011;22:752–61.
4. D'Amico G. Natural history of idiopathic IgA nephropathy: role of clinical and histological prognostic factors. Am J Kidney Dis. 2000;36:227–37.
5. Suzuki H, Kiryluk K, Novak J, Moldoveanu Z, Herr AB, Renfrow MB, et al. The pathophysiology of IgA nephropathy. J Am Soc Nephrol. 2011;22:1795–803. doi:10.1681/ASN.2011050464.
6. Reich HN, Troyanov S, Scholey JW, Cattran DC, for the Toronto Glomerulonephritis Registry. Remission of proteinuria improves prognosis in IgA nephropathy. J Am Soc Nephrol. 2007;18:3177–83.
7. Radhakrishnan J, Cattran DC. The KDIGO practice guideline on glomerulonephritis: reading between the (guide)lines—application to the individual patient. Kidney Int. 2012;82:840–56. doi:10.1038/ki.2012.280.
8. Appel GB, Waldman M. The IgA nephropathy treatment dilemma. Kidney Int. 2006;69:1939–44.
9. Barratt J, Feehally J. Treatment of IgA nephropathy. Kidney Int. 2006;69:1934–8.
10. Reich HN, Troyanov S, Scholey JW, Cattran DC, Toronto Glomerulonephritis Registry. Remission of proteinuria improves prognosis in IgA nephropathy. J Am Soc Nephrol. 2007;18:3177–83.
11. Dillon JJ. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for IgA nephropathy. Semin Nephrol. 2004;24:218–24.
12. Praga M, Gutiérrez E, González E, Morales E, Hernández E. Treatment of IgA nephropathy with ACE inhibitors: a randomized and controlled trial. J Am Soc Nephrol. 2003;14:1578–83.
13. Coppo R, Peruzzi L, Amore A, Piccoli A, Cochat P, Stone R, et al. IgACE: a placebo-controlled, randomized trial of angiotensin-converting enzyme inhibitors in children and young people with IgA nephropathy and moderate proteinuria. J Am Soc Nephrol. 2007;18:1880–8.

14. Li PK, Leung CB, Chow KM, Cheng YL, Fung SK, Mak SK, HKVIN Study Group, et al. Hong Kong study using valsartan in IgA nephropathy (HKVIN): a double-blind, randomized, placebo-controlled study. Am J Kidney Dis. 2006;47:751–60.
15. Donadio Jr JV. Omega-3 polyunsaturated fatty acids: a potential new treatment of immune renal disease. Mayo Clin Proc. 1991;66:1018–28.
16. Donadio Jr JV, Bergstralh EJ, Offord KP, Spencer DC, Holley KE, for The Mayo Nephrology Collaborative Group. A controlled trial of fish oil in IgA nephropathy. N Engl J Med. 1994;331:1194–9.
17. Yagame M, Tomino Y, Miura M, Suga T, Endoh M, Nomoto Y, et al. Clinical effect of dipyridamole in patients with IgA nephropathy. Tokai J Exp Clin Med. 1986;11:329–33.
18. Lee GS, Woo KT, Lim CH. Controlled trial of dipyridamole and low-dose warfarin in patients with IgA nephritis with renal impairment. Clin Nephrol. 1989;31:276.
19. Reid S, Cawthon PM, Craig JC, Samuels JA, Molony DA, Strippoli GFM. Non-immunosuppressive treatment for IgA nephropathy. Cochrane Database Syst Rev. 2011. doi:10.1002/14651858.CD003962.pub2.
20. Horita Y, Tadokoro M, Taura K, Ashida R, Hiu M, Taguchi T, et al. Prednisolone co-administered with losartan confers renoprotection in patients with IgA nephropathy. Ren Fail. 2007;29:441–6.
21. Mustonen J, Pasternack A, Rantala I. The nephrotic syndrome in IgA glomerulonephritis: response to corticosteroid therapy. Clin Nephrol. 1983;20:172–6.
22. Kobayashi Y, Fujii K, Hiki Y, Tateno S. Steroid therapy in IgA nephropathy: a prospective pilot study in moderate proteinuric cases. Q J Med. 1986;61:935–43.
23. Pozzi C, Bolasco PG, Fogazzi GB, Andrulli S, Altieri P, Ponticelli C, et al. Corticosteroids in IgA nephropathy: a randomised controlled trial. Lancet. 1999;353:883–7.
24. Pozzi C, Andrulli S, Del Vecchio L, Melis P, Fogazzi GB, Altieri P, et al. Corticosteroid effectiveness in IgA nephropathy: long-term results of a randomized, controlled trial. J Am Soc Nephrol. 2004;15:157–63.
25. Katafuchi R, Ikeda K, Mizumasa T, Tanaka H, Ando T, Yanase T, et al. Controlled, prospective trial of steroid treatment in IgA nephropathy: a limitation of low-dose prednisolone therapy. Am J Kidney Dis. 2003;41:972–83.
26. Samuels JA, Strippoli GFM, Craig JC, Schena FP, Molony DA. Immunosuppressive agents for treating IgA nephropathy. Cochrane Database Syst Rev. 2003;4:CD003965.
27. Henderson L, Masson P, Craig JC, Flanc RS, Roberts MA, Strippoli GF, et al. Treatment for lupus nephritis. Cochrane Database Syst Rev. 2012;12:CD002922.
28. Maes BD, Oyen R, Claes K, Evenepoel P, Kuypers D, Vanwalleghem J, et al. Mycophenolate mofetil in IgA nephropathy: results of a 3-year prospective placebo-controlled randomized study. Kidney Int. 2004;65:1842–9.
29. Frisch G, Lin J, Rosenstock J, Markowitz G, D'Agati V, Radhakrishnan J, et al. Remission of proteinuria improves prognosis in IgA nephropathy. Nephrol Dial Transplant. 2005;20:2139–45.
30. Tang SCW, Tang AWC, Wong SSH, Leung JCK, Ho YW, Lai KN. Long-term study of mycophenolate mofetil treatment in IgA nephropathy. Kidney Int. 2010;77:543–9.
31. Tan CH, Loh PT, Yang WS, Chan CM. Mycophenolate mofetil in the treatment of IgA nephropathy: a systematic review. Singapore Med J. 2008;49:780–5.
32. Xu G, Tu W, Jiang D, Xu C. Mycophenolate mofetil treatment for IgA nephropathy: a meta-analysis. Am J Nephrol. 2009;29:362–7.
33. Hotta O, Miyazaki M, Furuta T, Tomioka S, Chiba S, Horigome I, et al. Remission of proteinuria improves prognosis in IgA nephropathy. Am J Kidney Dis. 2001;38:736–43.
34. Miura N, Imai H, Kikuchi S, Hayashi S, Endoh M, Kawamura T, et al. Tonsillectomy and steroid pulse (TSP) therapy for patients with IgA nephropathy: a nationwide survey of TSP therapy in Japan and an analysis of the predictive factors for resistance to TSP therapy. Clin Exp Nephrol. 2009;13:460–6. doi:10.1007/s10157-009-0179-1.
35. Xie Y, Chen X, Nishi S, Narita I, Gejyo F. Relationship between tonsils and IgA nephropathy as well as indications of tonsillectomy. Kidney Int. 2004;65:1135–44.

36. Chen Y, Tang Z, Wang Q, Yu Y, Zeng C, Chen H, et al. Long-term efficacy of tonsillectomy in Chinese patients with IgA nephropathy. Am J Nephrol. 2007;27:170–5.
37. Rasche FM, Schwarz A, Keller F. Tonsillectomy does not prevent a progressive course in IgA nephropathy. Clin Nephrol. 1999;51:147–52.
38. Sato M, Hotta O, Tomioka S, Horigome I, Chiba S, Miyazaki M, et al. Cohort study of advanced IgA nephropathy: efficacy and limitations of corticosteroids with tonsillectomy. Nephron Clin Pract. 2003;93:137–45.
39. Kawamura T, Yoshimura M, Miyazaki Y, Okamoto H, Kimura K, Hirano K, Special IgA Nephropathy Study Group, et al. A multicenter randomized controlled trial of tonsillectomy combined with steroid pulse therapy in patients with immunoglobulin A nephropathy. Nephrol Dial Transplant. 2014;29:1546–53. doi:10.1093/ndt/gfu020.

Chapter 9
Prognostic Indicators and Treatment of IgA Nephropathy in China

Wei-Bo Le and Zhi-Hong Liu

Abstract IgA nephropathy (IgAN) accounts for 45 % of the primary glomerulonephritis in China. The 10- and 20-year cumulative renal survival rates were 83 % and 64 %, respectively, in a cohort of 1,155 Chinese patients with IgAN. The levels of estimated glomerular filtration rate (eGFR), proteinuria, hypoproteinemia, hypertension and hyperuricemia are the five most important clinical risk factors independently associated with renal outcome. Pathologically, the lesions of mesangial proliferation and tubular interstitial fibrosis correlated independently with prognosis of patients with IgAN. IgAN patients with minimal change disease and those with recurrent macro-hematuria are considered distinct subtypes of IgAN and have a relatively favorable renal prognosis. Using repeat renal biopsy data, we found that active proliferative lesions (glomerular endocapillary hypercellularity, crescent, or necrosis) are reversible after immunosuppressive treatment. The renal pathological lesion-based guidance for treatment options provides new tools for individual therapy in IgAN patients.

Keywords IgA nephropathy • Prognosis • Treatment

9.1 Introduction

IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide and is particularly prevalent in Asia [1]. IgAN accounts for 45 % of the primary glomerulonephritis in China [2]. The clinical course of IgA nephropathy is variable, and renal outcome varies widely in patients with IgAN from different ethnic groups. Recent data have shown that patients of Pacific Asian origin with IgAN have a higher risk of progression to end-stage renal disease (ESRD) than those from North America [3]. Long-term natural history studies in developed countries have demonstrated that the rate of progression has an extremely wide range, from 10 to 25 % within 10 years and 25–50 % within 20 years [1, 4]. However, long-term renal outcome and related risk factors for IgAN in large cohorts of

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Chinese patients remain unclear. Treating IgAN remains challenging because no disease-targeted treatments for IgAN exist, and relatively a few clinical randomized controlled trials (RCTs) have been conducted.

9.2 Long-Term Renal Outcome in Chinese Patients with IgA Nephropathy

To identify long-term renal outcome of IgAN in Chinese patients, we analyzed 1,155 patients with biopsy-proven primary IgAN in the Nanjing Glomerulonephritis Registry diagnosed from 1989 to 2005 [5]. Of the 1,155 patients, 50.3 % were female. The mean age at the time of initial clinical manifestations was 31 ± 9 years old. Approximately 36 % of patients had macroscopic hematuria before renal biopsy, and 14 % of cases had a history of recurrent macroscopic hematuria. Thirty-one percent of patients had hypertension (>140/90 mmHg) before renal biopsy. Only 7 % of patients had a family history of kidney disease. The median of 24-h urinary protein excretion at biopsy was 0.89 g/day. Approximately 44 % of the enrolled patients had proteinuria >1.0 g/day, but only 7 % of the cases had proteinuria >3.5 g/day. The distribution of patients by chronic kidney disease (CKD) stage at biopsy using the MDRD formula was 47.6 % in Stage 1, 31.6 % in Stage 2, 18.3 % within Stage 3, 1.9 % within Stage 4, and 0.6 % within Stage 5.

Within a median follow-up of 5.4 years, 108 (9.4 %) patients developed ESRD (eGFR <15 mL/min/1.73 m^2, initiation of dialysis or transplantation), and 163 patients (14.1 %) achieved the combined renal outcome (50 % decline in eGFR or ESRD). As shown in Fig. 9.1a, the 10-, 15- and 20-year cumulative renal survival rates after renal biopsy, calculated by Kaplan–Meier methods, were

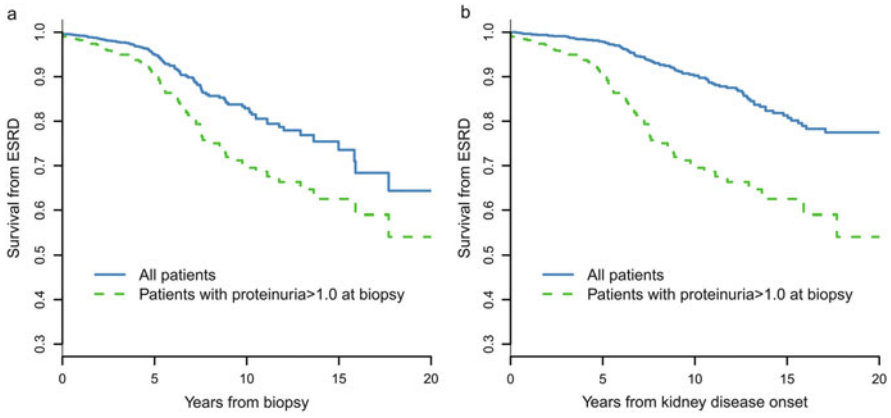

Fig. 9.1 Kaplan–Meier renal survival from renal biopsy (**a**) and disease onset (**b**) in 1,155 patients with IgAN. *ESRD* end-stage of renal disease

83 % (95 % CI, 79–87 %), 74 % (95 % CI, 67–81 %), and 64 % (95 % CI, 54–77 %), respectively. The 10-, 15- and 20-year cumulative renal survival rates after renal disease onset were 90 % (95 % CI, 88–92 %), 81 % (95 % CI, 77–85 %), and 77 % (95 % CI, 73–82 %), respectively (Fig. 9.1b).

For patients with proteinuria >1.0 g/day at biopsy, the 10-, 15- and 20-year cumulative renal survival rates from renal biopsy were 71 %, 63 %, and 54 %, respectively, and the 10-, 15- and 20-year cumulative renal survival rates from renal disease onset were 83 %, 72 %, and 67 %, respectively (Fig. 9.1).

The 20-year renal survival rate after renal biopsy in this cohort of patients (64 %) was highly similar to those of patients from Japan and Korea. A study of 1,012 patients in Japan reported that the 20-year cumulative survival rate from renal biopsy to ESRD was 66.6 % [6], and a study of 1,364 patients in Korea reported that the 20-year cumulative renal survival rate was 66.9 % [7]. The variability in renal outcome of IgAN in different studies may account for the difference in indications of kidney biopsy and health screening practice to some extent. Patients with selective biopsy indications would have lower renal survival rates. In this study, the indication of renal biopsy was relatively less selective, as suggested by the lower incidence of renal insufficiency (21.3 %), proteinuria >1.0 g/day (43.4 %), and hypertension (29.7 %) at the time of biopsy.

9.2.1 Long-Term Renal Outcome in IgA Nephropathy Patients with Recurrent Macro-Hematuria

Macro- and microscopic hematuria are frequent in patients with IgAN. However, the prognostic value of hematuria is highly complex in patients with IgAN. The persistent microscopic hematuria is associated with an increased incidence of renal failure, whereas episodic recurrent macro-hematuria (MH) is associated with relative benign renal outcomes [1, 8, 9].

Patients with recurrent hematuria (MH) (RMH, episodes of MH≥2 times, episode intervals >1 months) are a distinct subtype of IgAN [5]. Of the 1,155 patients with IgAN, 158 (14 %) of them presented with a history of RMH at biopsy. Compared with patients without a history of MH (NMH), patients with RMH were younger and more likely to be female and had lower proteinuria, a lower incidence of hypertension, a higher eGFR, a lower level of mesangial hypercellularity and segmental glomerulosclerosis, and a lower level of tubular atrophy. More importantly, as shown in Fig. 9.2, the long-term renal prognosis in RMH patients is dramatically better than that in NMH patients. The renal prognosis of patients with RMH was also better than those with isolated MH (IMH, one episode of MH) [10]. During a median follow-up of 7.9 years, the 10- and 20-year cumulative renal survival rates after biopsy, as calculated by K–M methods, were 91 % and 91 % in the RMH group, 89 % and 64 % in the IMH group, and 79 % and 57 % in the NMH group, respectively.

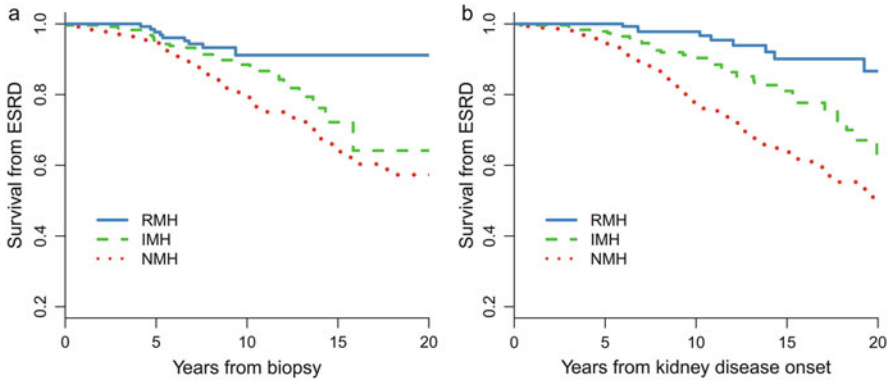

Fig. 9.2 Kaplan–Meier renal survival curve in IgAN patients with different MH patterns. *NMH* no history of macro-hematuria, *IMH* isolated onset of macro-hematuria, and *RMH* recurrent onset of macro-hematuria

Why patients with recurrent episodes of MH had relative benign renal outcomes remains unknown. It has been hypothesized that a kidney injury mechanism, mainly triggered by an upper respiratory infection, is more evident but discontinuous in patients with RMH, whereas in those without RMH, the injury mechanism is less potent but persists and could induce more severe and progressive kidney damage over time [1]. Moreover, little is known about the molecular mechanisms that cause episodic MH in IgAN [11].

9.2.2 Long-Term Renal Outcome in IgA Nephropathy Patients with Minimal Change Disease

There is another special entity of IgAN called IgAN with minimal change disease (MCD-IgAN), which was first reported in 1986 [12]. Those patients clinically present with nephrotic syndrome and a lack or mild degree of microscopic hematuria and have good response to corticosteroid therapy; meanwhile, pathologically, they have mild glomerular lesions under light microscopy, diffuse IgA-dominant depositions in mesangial region, and diffuse effacement of podocyte foot process and mesangial electron-dense deposition under electron microscopy. MCD-IgAN accounted for 2.6 % of the total biopsy-proven IgAN in our center. However, the clinicopathological characteristics and long-term renal outcome of MCD-IgAN in large cohorts have not yet been well described.

A retrospective review of 247 cases of biopsy-proven MCD-IgAN from the Glomerulonephritis Registry in Jinling Hospital was performed to characterize its clinicopathological features, treatment response, and long-term prognosis. In this cohort of patients, there was a male predominance (67.7 %), with an average age of 27.1 ± 11.0 years at biopsy. Pathological data revealed that 34 patients (13.7 %) had

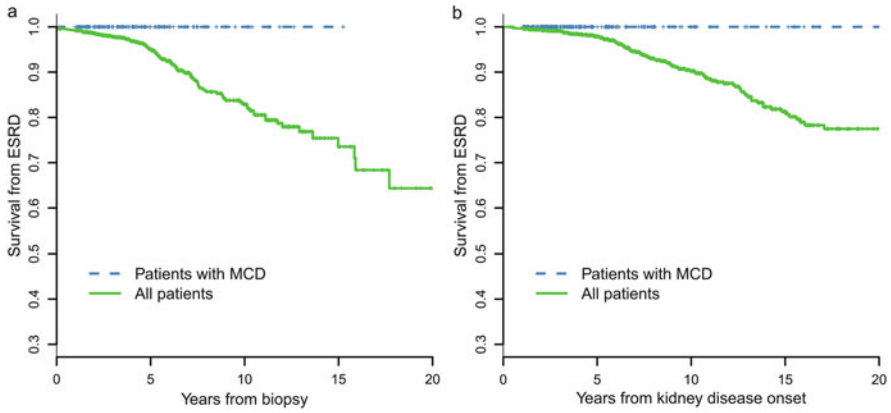

Fig. 9.3 Comparison of cumulative probabilities of renal survival between MCD-IgAN and non-MCD-IgAN patients

moderate to severe acute tubulointerstitial lesions and that 11 cases (4.5 %) had mild chronic tubulointerstitial lesions. After an 8-week course of corticosteroid therapy, a complete remission of proteinuria was observed in 216 patients (87.4 %), partial remission was observed in 21 patients (8.5 %), and no remission was observed in 10 patients (4.0 %). No patients with MCD-IgAN progressed to ESRD. MCD-IgAN patients had significantly better renal outcome compared with the cohort of 1,155 IgAN patients reported previously (Fig. 9.3).

9.3 Prognostic Indicators in IgA Nephropathy

9.3.1 Clinical Prognostic Indicators

It is important to predict which patients are at high risk of progression and should be treated. Using the 1,155-patient follow-up data, a univariate Cox regression model found that eGFR, hypertension, proteinuria, hypoproteinemia, hyperuricemia, hypercholesterolemia, hypertriglyceridemia, and body mass index (BMI) were associated with a combined renal outcome (ESRD or 50 % drop in eGFR) during follow-up. Multivariate Cox model confirmed that eGFR, proteinuria, hypoproteinemia, hypertension at presentation, and hyperuricemia were the five most important clinical predictors independently associated with renal outcome at the time of biopsy.

9.3.2 Prognostic Indicators During Follow-Up

The effects of clinical parameters during follow-up on the outcome were also examined in the 1,155 patients with IgAN. The summary measures (time-weighted averages) for proteinuria, blood pressure (MAP), and microscopic hematuria were calculated for each patient from the area under the curve of serial measurements standardized by the duration of follow-up. For instance, the time-average MAP (TA-MAP) was defined as the ratio of the area under the curve of MAP during follow-up to the duration of follow-up. The time-average blood pressure (TA-BP) was calculated with the same method as TA-MAP. Similarly, for each patient, the time-average proteinuria (TA-P) represents the area under the curve of proteinuria during follow-up divided by the years of total follow-up. As microscopic hematuria was highly skewed during the follow-up, logarithmic transformation was used to stabilize variance of the microscopic hematuria. After log transformation of microscopic hematuria, we also calculated the time-average microscopic hematuria (TA-RBC) in a similar manner. The TA-P, TA-RBC, and TA-MAP were all associated with renal outcome in both univariate and multivariate Cox models [5].

The predictive value of proteinuria and blood pressure is well defined in previous studies, whereas the predictive value of the extent of microscopic hematuria, measured as the count of urinary erythrocytes, remains uncertain; microscopic hematuria is extremely variable over time in the same patient. We did not find an association between renal outcome and the extent of microscopic hematuria at the time of renal biopsy. However, TA-RBC was associated with renal outcome when TA-RBC was used to quantify the extent of microscopic hematuria during follow-up. The multivariate Cox model showed that the risk for a combined event increased by 210 % for every ten-fold increase in microscopic hematuria.

9.3.2.1 Target Levels of Proteinuria During the Treatment of IgA Nephropathy

Proteinuria has been proven to be the most important predictor of renal failure in IgAN. However, the threshold of proteinuria above which the risk develops, and the goal of a safe proteinuria level during follow-up, remains the subject of debate. Evidence remains lacking that the long-term renal outcomes differ between patients with a proteinuria at 0.5–1.0 g/day and those at <0.5 g/day. We used the TA-P to quantify the mean exposure of proteinuria during the follow-up in patients with IgAN, and a ROC of TA-P was drawn to determine the optimal cutoffs predicting a worse renal outcome (ESRD or 50 % reduction in eGFR) [5]. The area under ROC (AUC) was 0.9 for TA-P, indicating that TA-P had high diagnostic accuracy for an unfavorable renal outcome. The optimal cutoff of TA-P was 0.97 g/day (sensitivity 83 %, specificity 84 %) in this cohort, which was approximated to 1.0 g/day to facilitate clinical practice, indicating that the relationship between TA-P and renal outcome is dramatically altered down to levels as low as 1.0 g/day. Patients with

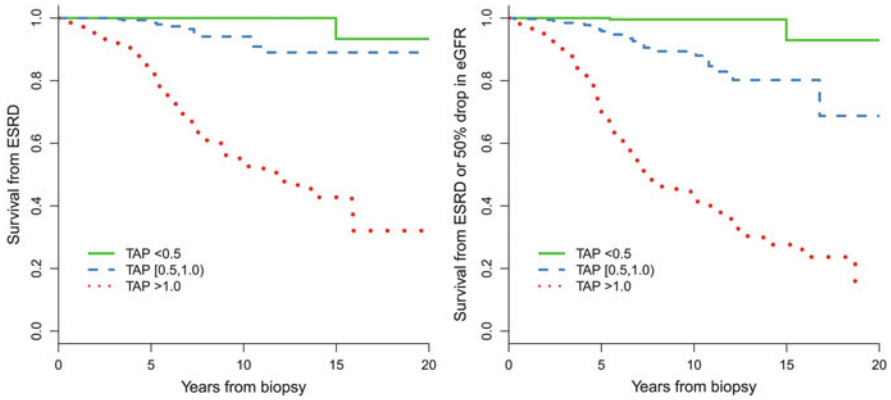

Fig. 9.4 Predictive value in renal survival of time-averaged proteinuria

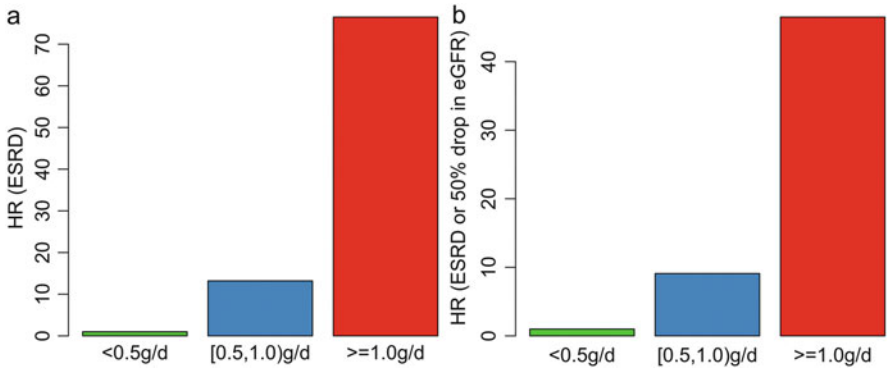

Fig. 9.5 Associations between the TA-P and hazard ratio of ESRD (**a**) and the combined renal outcome (**b**). The results were adjusted with TA-MAP, TA-RBC, and eGFR at biopsy in the multivariate Cox analysis

TA-P >1.0 g/day were associated with a 14-fold higher risk of the combined events than those with TA-P <1.0 g/day ($p < 0.001$) [2].

In addition, we found that patients with TA-P <0.5 g/day had a significantly more favorable renal outcome than those with TA-P between 0.5 and 1.0 g/day. As shown in Fig. 9.4, the cumulative renal survival from ESRD, as well as from the combined renal events in patients with TA-P 0.5–1.0, was significantly lower than those with TA-P <0.5 g/day. The multivariate Cox analysis, adjusted with TA-MAP, TA-RBC, and eGFR at biopsy, showed that patients with TA-P >1.0 g/day and patients with TA-P 0.5–0.1.0 g/day were associated with 76.5-fold ($p < 0.001$) and 13.2-fold ($p = 0.01$), respectively, increased risks of ESRD compared with those with TA-P <0.5 g/day (Fig. 9.5a). The multivariate Cox analysis also showed that patients with TA-P >1.0 g/day and patients with TA-P 0.5–0.1.0 g/ day were associated with a 46.5-fold ($p < 0.001$) and 9.1-fold

($p < 0.01$), respectively, increased risk of ESRD or 50 % drop in eGFR during follow-up than those with TA-P <0.5 g/day (Fig. 9.5b).

These results suggest that the basic goal of anti-proteinuric therapy for Chinese patients is to lower proteinuria to <1.0 g/day, whereas the optimal goal is to lower proteinuria to <0.5 g/day.

9.3.3 Pathological Prognostic Indicators

9.3.3.1 Validation of the Oxford Classification in China

The Oxford classification identified four definitive histologic lesions with high reproducibility, low collinearity, and independence of clinical factors. These lesions were mesangial hypercellularity (M), endocapillary proliferation (E), segmental sclerosis or adhesion (S), and tubular atrophy/interstitial fibrosis (T) [13, 14]. Several validation studies were performed after the Oxford classification of IgAN was published and were reviewed by Roberts [15].

A multicenter validation study of the Oxford classification was conducted in a cohort of 1,026 adult patients with IgAN from China [16]. The reproducibility (ICCs) of pathologic lesions was good in this cohort. Compared with the Oxford cohort, the Chinese cohort had a lower proportion of patients with M (43 %) and E (11 %), a higher proportion with S (83 %) and necrosis (15 %), and a similar proportion with crescents (48 %) and T (moderate, 24 %; severe, 3.3 %). The lesions M, S, E, and T, as well as crescents and necrosis, were associated strongly with proteinuria at biopsy. The lesion E, crescents, and necrosis were also strongly associated with subsequent immunosuppressive treatment. During a median follow-up of 53 months, 159 (15.5 %) patients reached the combined event (ESRD or a 50 % reduction in eGFR). Patients with M1 were associated with a 2.0-fold (95 % CI, 1.5–2.8; $p < 0.001$) risk of the combined event than patients with M0. Patients with T1/2 versus T0 were associated with a 3.7-fold (95 % CI, 2.6–5.1; $p < 0.001$) and 15.1-fold (95 % CI, 9.5–24.2; $p < 0.001$) higher risk of the combined event, respectively. The prognostic value of E, crescents, and necrosis was not associated with renal outcome in this study. Another validation study, from a single center in China, showed that the lesions S and T were independent predictive factors of ESRD [17].

We also assessed the validity of the Oxford classification of IgAN in a multicenter cohort of pediatric patients from China [18]. The clinical characteristics in this cohort were very similar to pediatric patients in the original Oxford cohort. Our study shows that tubular interstitial fibrosis was the only pathological feature independently associated with renal outcomes in Chinese pediatric patients with IgAN.

9.3.3.2 Evidence from Repeat Renal Biopsy

The active lesions (lesion E, crescents, and necrosis) are strongly associated with proteinuria at biopsy; however, these lesions were not associated with renal outcome in our validation studies of Oxford classification and in most other validation studies [15]. Recently, we evaluated histological changes in 60 patients with IgAN who received repeat biopsies after immunosuppressive treatment and found that these active lesions are reversible after immunosuppressive treatment [19]. The active lesions were markedly decreased at the second biopsy after immunosuppressive therapy (36.7 % vs. 8.3 %, $p < 0.001$; 85.0 % vs. 25.0 %, $p < 0.001$; and 51.7 % vs. 3.3 %, $p < 0.001$). However, the resolution or reduction of T was not observed in those patients. Tubular atrophy continued to progress, regardless of treatment. Reversal of the active lesions was accompanied with the clinical improvement. Patients with reversal of the active lesions exhibited significant decreases in proteinuria and hematuria after immunosuppressive treatment. The reversal of these lesions during the disease process may explain the lack of significant correlation of these lesions with clinical outcomes in this study, as well as in the patient cohort on which the original Oxford classification was based, and a number of validation studies of this classification [19].

9.4 Treatment of IgA Nephropathy in China

Despite a better understanding of the pathogenic mechanisms, there is no disease-specific treatment for patients with IgAN. To date, the treatment of IgAN has mainly been based on clinical risk factors, such as proteinuria. However, the renal pathological characteristics of IgAN may provide helpful information for decision making regarding the treatment.

9.4.1 IgA Nephropathy Patients with Minimal Change Disease (MCD-IgAN)

To evaluate the efficacy of corticosteroids for MCD-IgA patients, we conducted a single-center study of MCD-IgAN patients [20]. A total of 27 biopsy-proven adult MCD-IgAN patients were enrolled and given prednisone at a daily dose of 1 mg/kg/day (maximum 60 mg/day) prednisone until complete remission (CR), followed by gradually decreasing dosage. The cumulative CR (proteinuria <0.4 g/24 h) rates were 3.70 %, 48.1 %, 92.6 %, and 100 % after 1, 2, 4, and 8 weeks of treatment, respectively. Proteinuria at each time point after treatment was markedly decreased during follow-up. Infection, alanine aminotransferase elevation (>2-fold), fasting blood glucose (FBG) elevation (>6.2 mmol/L), and hypokalemia (<3.5 mmol/L)

occurred in 2, 5, 2, and 5 cases, respectively, but were eliminated after treatment. These results suggest that prednisone is an effective and safe therapy for IgAN patients with MCD lesions.

9.4.2 IgA Nephropathy Patients with Glomerular Active Proliferative Lesions

Patients with glomerular proliferative lesions are considered active forms of IgAN; immunosuppressive therapy may provide an additional benefit for these patients. We launched a multicenter, randomized, controlled trial to compare the efficiency and safety of the regimen of mycophenolate mofetil (MMF) plus prednisone in IgAN patients with active proliferative lesions. IgAN patients with active proliferative lesions (one of the following lesions of glomeruli: cellular and fibrocellular crescents; endocapillary hypercellularity; or necrosis) and proteinuria at 1 g/24 h were eligible. Eligible patients were randomly assigned to either MMF with prednisone (MMF 1.5 g/day for 6 months and prednisone 0.6 mg/kg/day for the first 2 months and then reduced by 0.1 mg/kg/day per month for the next 4 months, MMF group) or prednisone monotherapy (prednisone 1.0 mg/kg/day for 2 months and then reduced by 0.2 mg/kg/day per month for the next 4 months, PRED group), and both were followed for another 6 months.

The results showed that 32/86 patients (37.2 %) in the MMF group and 33/88 patients (37.5 %) in the PRED group went into complete remission, and no difference between the two groups was observed ($p > 0.05$). The overall response rate was 61/86 (70.9 %) in the MMF group and 64/88 (72.7 %) in the PRED group ($p = 0.79$). The median times to complete remission were 8.7 and 8.5 months ($p = 0.58$) for the MMF and PRED groups, respectively. The repeat renal biopsy data showed that active proliferative lesions were significantly ameliorated in both groups; the adverse event rate did not differ between the two groups. However, the incidences of newly diagnosed diabetes (13.6 % vs. 1.1 %, $p = 0.002$) and Cushing's syndrome (47.7 % vs. 18.4 %, $p < 0.001$) were higher in the PRED group than in the MMF group.

Both MMF combined with prednisone and prednisone monotherapy benefit IgAN patients with active proliferative lesions by reducing proteinuria and ameliorating active proliferative lesions. The adverse event rate was similar in the two groups, but patients administered the MMF regimen were more tolerant.

9.4.3 IgA Nephropathy Patients with Crescentic Glomerulonephritis

Crescentic IgAN is defined as IgAN with crescents in more than 50 % of glomeruli in the renal biopsy with rapidly progressive renal deterioration. In our center, the proportion of crescentic IgAN is 1.1 % in the all biopsied-proven IgAN but 16.4 % in the total crescentic glomerulonephritis [21]. Patients with crescentic IgAN have extremely poor prognosis. In 25 crescentic IgAN patients from our center, 88 % had rapidly progressive glomerulonephritis associated with a high level of serum creatinine. In 15 patients followed up for more than 6 months, all of whom were treated with immunosuppression, five were dialysis dependent, ten maintained sufficient renal function to avoid renal replacement therapy,four had a normal range of serum creatinine (<124 μmol/l) [21]. Recently, a study enrolled 113 crescentic IgAN patients from multiple centers in China, and the renal survival rates at 1, 3, and 5 years after renal biopsy were 57.4 %, 45.8 %, and 30.4 %, respectively [22]. Initial renal function is the only independent risk factor for ESRD, whereas the percentage of crescents was not independently associated with ESRD.

There is no RCT in the treatment of crescentic IgAN. The multicenter cohort study of crescentic IgAN from China suggested that immunosuppressive therapy reduced the risk of ESRD in patients with cellular or fibrocellular crescents by >50 % but not in those with high chronic tubular lesions (interstitial fibrosis >50 %) [22].

9.5 Conclusion

The 10- and 20-year cumulative renal survival rates after renal biopsy were 83 % and 64 %, respectively, in Chinese patients with IgAN. The most important clinical risk factors are proteinuria, hypertension, impaired renal function, hypoproteinemia, and hyperuricemia; histologic risk factors are mesangial hypercellularity and tubular atrophy in Chinese patients with IgAN. The repeat renal biopsy-based observations indicated that the active proliferative glomerular lesions (endocapillary hypercellularity, crescent, or necrosis) are reversible following immunosuppressive treatment. The renal pathological lesion-based guidance for treatment provides new tools for individual therapy for IgAN patients.

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. D'Amico G. Natural history of idiopathic IgA nephropathy and factors predictive of disease outcome. Semin Nephrol. 2004;24(3):179–96. doi:S0270929504000038 [pii].

2. Li LS, Liu ZH. Epidemiologic data of renal diseases from a single unit in China: analysis based on 13,519 renal biopsies. Kidney Int. 2004;66(3):920–3. doi:10.1111/j.1523-1755.2004.00837.x.
3. Barbour SJ, Cattran DC, Kim SJ, Levin A, Wald R, Hladunewich MA, et al. Individuals of Pacific Asian origin with IgA nephropathy have an increased risk of progression to end-stage renal disease. Kidney Int. 2013;84(5):1017–24. doi:10.1038/ki.2013.210.
4. Coppo R, D'Amico G. Factors predicting progression of IgA nephropathies. J Nephrol. 2005;18(5):503–12.
5. Le W, Liang S, Hu Y, Deng K, Bao H, Zeng C, et al. Long-term renal survival and related risk factors in patients with IgA nephropathy: results from a cohort of 1155 cases in a Chinese adult population. Nephrol Dial Transplant. 2012;27(4):1479–85. doi:10.1093/ndt/gfr527.
6. Moriyama T, Tanaka K, Iwasaki C, Oshima Y, Ochi A, Kataoka H, et al. Prognosis in IgA nephropathy: 30-year analysis of 1,012 patients at a single center in Japan. PLoS One. 2014;9(3):e91756. doi:10.1371/journal.pone.0091756.
7. Lee H, Kim DK, Oh KH, Joo KW, Kim YS, Chae DW, et al. Mortality of IgA nephropathy patients: a single center experience over 30 years. PLoS One. 2012;7(12):e51225. doi:10.1371/journal.pone.0051225.
8. Gutierrez E, Zamora I, Ballarin JA, Arce Y, Jimenez S, Quereda C, et al. Long-term outcomes of IgA nephropathy presenting with minimal or no proteinuria. J Am Soc Nephrol. 2012;23(10):1753–60. doi:10.1681/ASN.2012010063.
9. Moreno JA, Martin-Cleary C, Gutierrez E, Rubio-Navarro A, Ortiz A, Praga M, et al. Haematuria: the forgotten CKD factor? Nephrol Dial Transplant. 2012;27(1):28–34. doi:10.1093/ndt/gfr749.
10. Le W, Liang S, Chen H, Wang S, Zhang W, Wang X, et al. Long-term outcome of IgA nephropathy patients with recurrent macroscopic hematuria. Am J Nephrol. 2014;40(1):43–50. doi:10.1159/000364954.
11. Eitner F, Floege J. In search of a better understanding of IgA nephropathy-associated hematuria. Kidney Int. 2012;82(5):513–5. doi:10.1038/ki.2012.160.
12. Lai KN, Lai FM, Ho CP, Chan KW. Corticosteroid therapy in IgA nephropathy with nephrotic syndrome: a long-term controlled trial. Clin Nephrol. 1986;26(4):174–80.
13. Roberts IS, Cook HT, Troyanov S, Alpers CE, Amore A, Barratt J, et al. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. Kidney Int. 2009;76(5):546–56. doi:10.1038/ki.2009.168.
14. Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS, Troyanov S, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney Int. 2009;76(5):534–45. doi:10.1038/ki.2009.243.
15. Roberts IS. Oxford classification of immunoglobulin A nephropathy: an update. Curr Opin Nephrol Hypertens. 2013. doi:10.1097/MNH.0b013e32835fe65c.
16. Zeng CH, Le W, Ni Z, Zhang M, Miao L, Luo P, et al. A multicenter application and evaluation of the oxford classification of IgA nephropathy in adult Chinese patients. Am J Kidney Dis. 2012;60(5):812–20. doi:10.1053/j.ajkd.2012.06.011.
17. Shi SF, Wang SX, Jiang L, Lv JC, Liu LJ, Chen YQ, et al. Pathologic predictors of renal outcome and therapeutic efficacy in IgA nephropathy: validation of the oxford classification. Clin J Am Soc Nephrol. 2011;6(9):2175–84. doi:10.2215/CJN.11521210.
18. Le W, Zeng CH, Liu Z, Liu D, Yang Q, Lin RX, et al. Validation of the Oxford classification of IgA nephropathy for pediatric patients from China. BMC Nephrol. 2012;13:158. doi:10.1186/1471-2369-13-158.
19. Shen XH, Liang SS, Chen HM, Le WB, Jiang S, Zeng CH, et al. Reversal of active glomerular lesions after immunosuppressive therapy in patients with IgA nephropathy: a repeat-biopsy based observation. J Nephrol. 2015. doi:10.1007/s40620-014-0165-x.
20. Wang J, Juan C, Huang Q, Zeng C, Liu Z. Corticosteroid therapy in IgA nephropathy with minimal change-like lesions: a single-centre cohort study. Nephrol Dial Transplant. 2013;28(9):2339–45. doi:10.1093/ndt/gft211.

21. Tang Z, Wu Y, Wang QW, Yu YS, Hu WX, Yao XD, et al. Idiopathic IgA nephropathy with diffuse crescent formation. Am J Nephrol. 2002;22(5–6):480–6. doi:ajn22480 [pii].
22. Lv J, Yang Y, Zhang H, Chen W, Pan X, Guo Z, et al. Prediction of outcomes in crescentic IgA nephropathy in a multicenter cohort study. J Am Soc Nephrol. 2013;24(12):2118–25. doi:10.1681/ASN.2012101017.

Chapter 10
The Differences in Etiology and Treatment of IgA Nephropathy in Korea

Dong-Wan Chae

Abstract IgA nephropathy (IgAN) is the most common primary glomerulonephritis affecting young persons, the incidence of which has increased recently in Korea. Many studies related to the etiology and the pathogenesis such as various biomarkers, gene polymorphism, and intrarenal expression of various cytokines and chemokines and proteomic studies have been performed in serum, urine, and renal tissues obtained from Korean patients with IgA nephropathy. The activation of alternative pathway of complements in systemic circulation as well as local mesangial area and the activation of lectin and classic pathway of complement in some subset of patients have been shown to contribute to renal damage in IgAN. Clinical utility of Oxford classification have been verified in Korean patients, but the significance of crescent in therapeutic response and prognosis remains to be defined especially in patients with low basal estimated glomerular filtration rate (eGFR) and/or patients on the immunosuppressive therapy at the time of renal biopsy. The maintenance of proteinuria <1 g/day as recommended by KDIGO was a reasonable therapeutic target in renal protection, but the attainment of proteinuria <0.3 g/day might provide additional renal protection especially in young and otherwise healthy patients in whom a long life span is expected. Renin-angiotensin system (RAS) blockades reduced proteinuria and improved the survival of patients as well as the kidney. Various regimens of corticosteroid treatments effectively reduced proteinuria and hematuria and induced the improvement or stabilization of renal function even in patients with already decreased eGFR before treatment. Treatments by calcineurin inhibitors and sulodexide in IgAN were also reported with some positive results.

Keywords IgA nephropathy • Korea • Pathogenesis • Treatment

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IgA nephropathy (IgAN) was the most common histological diagnosis constituting 36.5 % of 4,918 renal biopsies performed in multicenters in Korea. The age of biopsy-proven diagnosis of IgAN was 37.9 ± 13.6 year, the youngest in all primary glomerular diseases in this study [unpublished result from PREMIER study].

While IgAN occupied 25.6 % of all biopsy-proven renal disease in one center during the period of 1987–1991, this proportion increased to 35.6 % during 2001–2006 [1]. Thus, IgAN is the most common primary glomerulonephritis affecting young persons, the incidence of which has increased recently in Korea.

In this chapter, clinical studies which have been performed in Korean patients with IgAN will be reviewed with a special emphasis on etiology, pathogenesis, and treatment of this disease.

10.1 Etiology and Pathogenesis

10.1.1 Viral Infections and IgA Nephropathy

Although cytomegalovirus (CMV) DNA was detected in six of ten renal biopsy specimens of IgAN, CMV protein was not detected in any specimen by indirect immunofluorescence staining with anti-CMV monoclonal antibody. Also CMV DNA but not CMV protein was also detected in biopsy specimen from 14 non-IgAN suggesting that CMV is not specifically associated with the pathogenesis of IgAN seen in Korea [2].

The prevalence of seropositive hepatitis B surface antigen (HBsAg) was 11.0 % in 172 IgAN patients which was higher than prevalence of 4.1 % in age/sex-matched general population. The cases presenting with nephrotic range proteinuria and impaired renal function were significantly higher in HBsAg-positive group than HBsAg-negative group (nephrotic proteinuria 31.6 % vs. 7.2 % and impaired renal function 42.1 % vs. 13.1 %, $p < 0.05$) [3].

Also in another report, serum HBsAg positivity was higher in patients with IgAN presenting with nephrotic syndrome than those patients presenting with non-nephrotic syndrome (7.0 % vs. 2.7 %, $p = 0.04$) [4].

But other study showed that the incidence of serum HBsAg positivity in IgAN was 4.6 % ($n = 22/360$) which was similar to the prevalence in general population. There were also no differences in the clinical characteristics such as proteinuria and estimated glomerular filtration rate (eGFR) and renal prognosis between IgAN patients with and without HBsAg. Although there were no differences in the renal function decline and urinary protein excretion between 6 patients who did and 16 patients who did not receive antiviral therapy, the number was too small to draw the conclusion. In fact, proteinuria decreased after antiviral therapy in all three patients whose basal proteinuria were greater than 0.5 g/day in this study [5].

Collectively these studies suggested that the infection of HBV could not be one of the causes of IgAN, but the presence of HBV infection might contribute to the development of higher proteinuria in patients with IgAN.

A case of development of IgAN in 30-year-old concurrent with acute hepatitis by hepatitis A virus was reported. Her laboratory examination 6 months prior to hepatitis showed normal urinalysis and renal function. Hematuria and proteinuria of 1.9 g/day with normal renal function were observed at the time of presentation of acute hepatitis. Renal biopsy revealed normal light microscopic findings with mesangial staining of IgA and mesangial electron-dense deposits. Neither evidence suggestive of the presence of viral particle in renal tissue nor IgG co-deposition was found. Hematuria and proteinuria disappeared 6 months after the resolution of hepatitis, and follow-up biopsy taken 11 months after onset showed complete disappearance of IgA deposition in renal tissues. This case suggested hepatitis A virus infection could cause the transient IgAN without acute kidney injury. Impaired clearance of IgA molecule by Kupffer cells secondary to liver damage rather than virus-induced immune response might be principal pathogenesis of IgAN in this case [6].

10.1.2 Role of Intrarenal Cytokines and Chemokines

In immunohistochemistry of renal tissue from IgAN patients [7, 8], TNF-α, IFN-γ, and IL-2 were localized dominantly in mesangial area, while IL-10 was observed primarily in renal tubules. IL-8 was noted in the periarteriolar and arteriolar area.

The level of intrarenal gene transcript of IFN-γ assessed by semiquantitative reverse-transcriptase polymerase chain reaction (RT-PCR) using internal competitors correlated with mesangial expansion, and gene transcript of IL-10 was related to interstitial fibrosis. The extent of intrarenal arteriolar lesions correlated with the IL-8 gene transcript.

The levels of intrarenal gene transcript of TNF-α and IL-1β were higher in patients with proteinuria $\geq$1 g/day than patients with proteinuria $<$1 g/day. The ratio of intrarenal gene transcript of IFN-γ/IL-10 was higher in patients with serum creatinine $\geq$1.4 mg/dL.

These studies suggested that pro-inflammatory cytokines such as TNF-α, IFN-γ, and IL-1β were involved in glomerular injuries, and IL-10 played a role in tubulointerstitial lesions, and IL-8 was related to vascular injury in IgAN.

10.1.3 Proteomic Study of IgA Nephropathy

Approximately 216 protein spots were found to be differentially expressed in the urines of IgAN patients compared with those of normal controls with 82 overexpressed and 134 under-expressed spots in IgAN by two-dimensional electrophoresis. A total of 84 differentially expressed spots representing 59 different proteins were identified in IgAN by MALDI-TOF mass spectrometry. Thirty-five proteins under-expressed in IgAN including zinc finger proteins 324 and

155, GRB2-related adaptor protein2, and c-AMP-dependent phosphodiesterase were suggested to be involved in the pathogenesis of IgAN in this study [9].

In a proteomic analysis of urinary exosome using LC-MS/MS from patients with IgAN and thin basement membrane nephropathy (TBMN) which are two most common causes of isolated hematuria, the numbers of protein spots uniquely identified in normal, IgAN, and TBMN were 790, 188, and 213, respectively. Out of these proteins, the expression level of aminopeptidase N and vasorin precursor were lower, and those of alpha-1-antitrypsin and ceruloplasmin were higher in IgAN than normal controls and TBMN. The AUCs of ROC curve for the differentiation between IgAN and TBMN were 0.813, 0.778, 0.556, and 0.993 for aminopeptidase N, vasorin precursor, alpha-1-antitrypsin, and ceruloplasmin, respectively. This study suggests that proteomic analysis of urinary exosomes, the cargo of biological information of their origin, could be a useful noninvasive diagnostic tool for IgAN [10].

Proteomic analysis on renal tissue from normal controls and patients from IgAN revealed increased expression of alpha-1-antitrypsin (AAT) especially of low molecular isoforms and fragments principally in proximal and distal tubule in IgAN renal tissues. An unidentified highly acidic proteinase different from elastase was found to cleave AAT in renal tissue. Increased nitration of tyrosine residue by oxidative injury was also noticed. This study suggests that loss of function of AAT by proteinase and nitration might contribute to pathogenesis of IgAN probably via unopposed activity of various proteinases by AAT and induction of inflammation and inhibition of extracellular matrix by polymerization of cleaved AAT [11].

10.1.4 Biomarkers

The KIM-1 (kidney injury molecule-1) was expressed at the apical side of dilated proximal tubule with the pattern of KIM-1(+) and KIM(−) cells adjacent to each other within the same tubular sections in renal tissues in a prospective observational study of 50 patients with IgAN. The expression level of KIM-1 in renal tissues correlated positively with 24-h urine protein and negatively with eGFR. The level of intrarenal KIM-1 also well correlated with E1 and T1/T2 lesions of the Oxford classification. Along with the proteinuria, renal tissue level of KIM-1 was an independent risk factor of renal survival. Although the urinary KIM-1 levels were higher in IgAN patients than normal control, urinary KIM-1 was not associated with tissue KIM-1 expression or tubulointerstitial damage [12].

The expressions of urokinase-type plasminogen activator (uPA), uPA receptor (uPAR), and plasminogen activator inhibitor (PAI)-1 were investigated by immunohistochemistry in renal biopsy specimen from 52 patients with IgAN. While uPA, uPAR, and PAI-1 were expressed in renal tubule with stronger expression in the distal tubules and collecting ducts than proximal tubules in all specimens, these molecules were not expressed in mesangium and capillary walls of glomeruli in all

specimens. On podocytes, uPA was positive in 11 cases and uPAR was positive in 38 cases including 11 uPA (+) cases. By contrast, the expression of PAI-1 was negative in all cases. There was no relationship between plasma level of uPA and PAI-1 and their staining pattern in podocytes and tubules. While there was no association between podocyte expression of uPA and uPAR and M, E, and S variables of Oxford classification, the prevalence of tubular atrophy/interstitial fibrosis is significantly lower when uPA and uPAR are expressed on podocytes. This finding suggests a possible protective effect of podocyte uPA/uPAR expression against interstitial fibrosis in IgAN [13].

Urinary excretion of β2-microglobulin, which is freely filtered at the glomerulus and subsequently reabsorbed and catabolized in proximal tubules, well correlated with serum creatinine and proteinuria in 51 patients with IgAN, 64.7 % of whom received corticosteroid therapy during follow-up. Although urinary β2-microglobulin is regarded as a marker of proximal tubular cell injury, urinary level of β2-microglobulin was neither associated with tubulointerstitial fibrosis nor tubulointerstitial inflammation in this study. Urinary β2-microglobulin was one of the predictors of renal progression in univariate analysis [14].

Heme oxygenase-1(HO-1) is known to exert an antioxidant effect by mediating the breakdown of heme to generate carbon dioxide, iron, and biliverdin which subsequently converts to bilirubin. The short (GT) repeats located in promoter of HO-1 gene upregulate enzyme activity by several folds and consequently increase the antioxidant effect of HO-1. In the analysis of 916 patients, 65 patients with short length polymorphism had lower odd ratio of impaired function than patients with 505 patients with long length polymorphism (OR = 0.216, 95 % CI 0.060–0.774, $p = 0.019$) [15]. In an analysis of 1,458 patients which include the patients of HO-1 study, the serum level of bilirubin – one of antioxidant in human body – was found to be related to renal survival. While end-stage renal disease (ESRD) occurred in 10.7 % of patients with serum bilirubin <0.4 mg/dL, the incidence of ESRD was 2.8 % in patients with serum bilirubin >0.6 mg/dL with odd ratio of developing ERSD of 0.307 [16]. Interestingly the protective effect of both HO-1 genotype and serum bilirubin level was more prominent in male, old age, normotensive patients, and patients with smaller proteinuria [15, 16]. These studies suggest that oxidative stress plays a role in the progression of IgAN, but its effect is overwhelmed by traditional strong risk factors such as hypertension and proteinuria.

Urinary angiotensinogen level showed the strongest correlation with angiotensinogen level in renal biopsy specimen measures by Western blotting and immunohistochemistry in a study of 64 patients with IgAN. Urinary angiotensinogen level showed positive correlation with initial PCR and negative correlation with initial eGFR. Interestingly, there were no differences in urinary angiotensin level and expression level of angiotensinogen in renal tissues between patients with and without renin-angiotensin system (RAS) blockade. Finally, urinary angiotensinogen level was related to proteinuria and the degree of eGFR reduction after 3 years of treatment by RAS blockade [17].

10.1.5 Genetic Studies

Genetic studies about IgAN in Korea were mostly candidate gene studies in which specific genes were chosen based on their biological function in IgAN. All of these studies showed that the frequency of allele of genes of interest did not differ between normal control and patients with IgAN suggesting no relevance of these genes to susceptibility to the development of IgAN. But various gene polymorphisms were found to affect renal progression of IgAN in studies with relatively large number of patients followed for a sufficient duration for the evaluation of progression as summarized in Table 10.1.

With regard to gene polymorphism of renin-angiotensin-aldosterone system, specific single nucleotide polymorphism (SNP) in angiotensin II type 1 receptor [18], aldosterone synthase, [18] and insertion/deletion polymorphism of angiotensin-converting enzyme [19] were not related to the progression of IgAN. While M235T SNP of angiotensinogen was related to renal progression only in male patients [18], specific SNP of chymase [20] and angiotensin II type 2 receptor [21] were related to renal progression in both sexes.

Gene polymorphism of molecules related to inflammation such as Clara cell secretory protein [22], CD 14 [23], and platelet-activating factor acetylhydrolase [19] and molecules related to extracellular matrix deposition such as megsin [24] and TGF-β [25] were associated with renal progression. Gene polymorphism affecting the activity of epoxide hydrolase which hydrolyze epoxyeicosatrienoic acid was associated with renal survival [26]. Interestingly, specific SNPs of klotho gene – an antiaging gene – were related to patients' survival as well as renal survival [27].

10.1.6 Role of Complements

The activations of alternative and lectin pathway of complements by nephritogenic polymeric IgA1 molecules are known to play an important role in the pathogenesis of IgAN.

10.1.6.1 Alternative Pathway

Mesangial deposition of C3, one of the hallmarks of the activation of alternative pathway, was observed in 73.9 % of 142 Korean patients with IgAN. While C3 deposition was observed in only 53 % of patients with histologically early stage of IgAN, it was observed in 100 % of patients with advanced stage [28].

Decreased level of serum C3 lower than normal and strong mesangial C3 deposition $\geq$2+ degree were observed in 19.2 % and 18.8 % of 343 patients, respectively. This strong C3 mesangial deposition was associated with low serum

Table 10.1 Gene polymorphisms positively associated with disease progression in Korean IgA nephropathy

Reference	Molecule	Number of patients	Polymorphism	Vs. normal control	F/U duration (months)	Renal progression	Biology
Lim et al. [22]	Clara cell secretory protein	$N = 267$	G38A	No difference	103.8 ± 52.6	AA genotype	Anti-inflammatory
		Multicenter				HR 2.34, 95 % CI 1.19–4.64	Immunomodulatory
						$P = 0.014$ (MV)	
Jung et al. [20]	Chymase	$N = 261$	CMA rs1800875	No difference	103.2 ± 52.6	AA/AG genotype	Alternative enzyme for synthesis of angiotensin II
		Single center				HR 2.351	
						95% CI 1.414–3.908	
						$P = 0.001$ (MV)	
Jung et al. [20]	Chymase	$N = 261$	CMA rs1800876	No difference	103.2 ± 52.6	CC/CT genotype	Alternative enzyme for synthesis of angiotensin II
		Single center				$\chi^2 = 4.45$	
						$P = 0.035$ (UV)	
Yoon et al. [23]	CD14	$N = 216$	159C/T	No difference	86.0 ± 51.1	CC genotype	Inflammatory responses to microorganism
		Single center				HR 3.2	
						95 % CI 1.2–8.8	
						$P = 0.025$ (MV)	

(continued)

Table 10.1 (continued)

Reference	Molecule	Number of patients	Polymorphism	Vs. normal control	F/U duration (months)	Renal progression	Biology
Kim et al. [18]	Angiotensinogen	$N = 238$	AGT M235T	No difference	102.4 ± 47.0	TT genotype	Component of renin-angiotensin system
		Multicenter				HR 5.704	
						95% CI 1.578–20.618	
						$P = 0.008$	
Lim et al. [25]	Transforming growth factor (TGF)-β1	$N = 108$, single center	C509T	Difference	At least 36	TT genotype	Anti-inflammatory
						Poor	Profibrotic activity
						Renal outcome	
						$P = 0.042$ (UV)	
						HR 2.202	
						$P = 0.138$ (MV)	
Yoon et al. [21]	Angiotensin II type 2 receptor	$N = 480$	A1818T	No difference	30.3 ± 3.3	TT/AT genotype	Counter-regulatory to the vasoconstrictor action of angiotensin II type 1 receptor
		Multicenter				HR 0.221	
						95% CI	
						0.052–0.940	
						$P = 0.041$	

Lim et al. [24]	Megsin	$N = 260$	C2093T	No difference	103.0 ± 52.4	TT genotype	Serpin
						HR 3.52	Superfamily
						95 % CI 1.69–7.34	Progressive mesangial matrix expansion
						$P = 0.001$ (MV)	
						CT genotype	
						HR 2.15	
						95 % CI 1.30–3.57	
						$P = 0.003$ (MV)	
Lim et al. [24]	Megsin	$N = 260$	C2180T	No difference	103.0 ± 52.4	CC genotype	Serpin superfamily
						HR 4.05	
						95 % CI 1.93–8.51	Progressive mesangial matrix expansion
						$P < 0.001$ (MV)	
						CT genotype	
						HR 2.35	
						95 % CI 1.40–3.94	
						$P = 0.001$ (MV)	

(continued)

Table 10.1 (continued)

Reference	Molecule	Number of patients	Polymorphism	Vs. normal control	F/U duration (months)	Renal progression	Biology
Lim et al. [24]	Megsin	$N = 260$	2093T-2180C	No difference	103.0 ± 52.4	2093 T-2180C haplotype	Serpin superfamily
		Multicenter	Haplotype			HR 2.01	
						95 % CI 1.44–2.81	Progressive mesangial matrix expansion
						$P < 0.001$ (MV)	
GO et al. [26]	Klotho	$N = 973$	G395A	N/A	50.0 ± 27.8	GA + AA genotype	Related to aging
		Multicenter				ESRD	Atherosclerosis
						$P = 0.04$ (UV)	Endothelial dysfunction
Yoon et al. [19]	ACE + PAF-AH	$N = 191$	ACE I/D	No difference	87.3 ± 50.0	DD + DI&CT + TT	Angiotensin II-forming enzyme
		Single center	C1136T			HR 4.5	Enzyme degrading PAF
						95 % CI 1.6–12.7	
						$P = 0.0039$ MV)	
Lee et al. [27]	EPHX2	$N = 401$	R287Q	No difference	74.4	GG genotype	Determines epoxyeicosatrienoic acid (EET) concentration
		Single center				ESRD	
						HR 1.83	
						95 % CI 1.13–2.96	
						$P = 0.014$ (MV)	

CMA chymase, *AGT* angiotensinogen, *ESRD* end-stage renal disease, *ACE* angiotensin-converting enzyme, *PAF-AH* platelet-activating factor acetylhydrolase, *EPHX2* epoxide hydrolase, *UV* univariate analysis, *MV* multivariate analysis

C3 level, mesangial hypercellularity, and advanced tubulointerstitial lesions. Importantly both C3 hypocomplementemia and strong mesangial C3 deposition were independent risk factor for the doubling of serum creatinine independent of basal eGFR, proteinuria, and tubulointerstitial lesions [29].

These studies suggest that the activation of alternative pathway of complements occurs in systemic circulation as well as local mesangial area and contributes significantly to the progression of IgAN.

10.1.6.2 Other Pathways

In 23 IgAN patients, glomerular C4d staining and tubular C4d staining were observed in 56.5 % and 47.8 % of patients, respectively, whereas no C4d staining was observed in tubular basement membrane, peritubular capillary, and vascular structure. The glomerular C4d staining was related to albuminuria and tubular C4d staining to higher grade of WHO classification. Tubular deposition of C4d without any co-deposition of immunoglobulin suggested the activation of lectin pathway although clear proofs were lacking [30].

Out of 221 IgAN, 8.1 % of patients had mesangial C1q staining which is a marker of activation of classic complement pathway. The co-deposition of IgG was more frequently observed in C1q(+) patients than propensity score matched C1q(−) patients (38.9 % vs. 8.3 %). C1q(+) was an independent determinant of rate of GFR loss between C1q(+) and matched C1q(−) patients [31].

These studies suggest that the activation of lectin and classic pathway of complement contribute to renal damage in some subset of patients with IgAN.

10.2 Treatment and Prognosis

10.2.1 Role of Renal Biopsy Findings in Predicting Renal Outcome

IgAN is characterized by highly variable clinical courses and the differences in response to a specific therapy resulting in highly variable renal outcome within individual patients. Even though proteinuria is generally regarded as the best predictor of renal outcome, there are substantial numbers of the patients with no proteinuria at presentation who ultimately show renal progression. Hence, many studies about the correlation between renal biopsy findings and renal progression have been performed to define a role of renal pathology for prediction of renal outcomes beyond clinical parameters.

10.2.1.1 Pathologic Grading Systems Before the Introduction of Oxford Classification

H.S. Lee's grading system developed in 1987 by incorporating mesangial proliferation, segmental lesion, crescent, and interstitial fibrosis showed good correlation with proteinuria, hypertension, and impaired renal function at the time of biopsy. Interestingly, episodes of macroscopic hematuria which is a favorable factor for renal progression in Korea were less frequent in patients with higher grade of this system [28].

Some modification of H.S. Lee's grading system with particular emphasis on crescent, segmental sclerosis, and global sclerosis which implicate, respectively, active necrotizing glomerular inflammation, podocyte depletion, and resultant irreversible glomerular damage correlated well with patients' age, CCr, 24-h urinary protein, and the prevalence of hypertension in dose-dependent manner. Moreover, this grading system predicted renal progression independent of clinical risk findings such as initial renal function and proteinuria, whereas the Hass classification did not [32].

Class IV/V lesions of WHO classification were a prognostic factor of renal progression independent of renal insufficiency (serum creatinine $\geq$1.4 mg/dL) and heavy proteinuria [33].

These studies suggest that specific histological features such as mesangial proliferation, crescent, segmental sclerosis, and advanced tubulointerstitial lesions rather than the whole system of histological classification were suggested to be significant prognostic factors independent of clinical features even before the introduction of Oxford classification.

10.2.1.2 Validation Studies of Oxford Classification

After the Oxford classification was introduced as a new histological classification system for IgAN in 2009, several studies were performed to validate the usefulness of this classification in Korean patients.

All studies identified T1 and T2 lesions, namely, advanced tubulointerstitial lesions, as a predictor of renal progression independent of clinical findings in multivariable analysis [34–36]. T1 and T2 were also predictors of renal progression in posttransplant IgAN [37]. These findings confirmed the well-established prognostic importance of tubulointerstitial lesion in essentially all glomerular diseases including IgAN.

E1 was associated with more frequent prescription of steroid in studies where steroid was infrequently used, i.e., 18 % and 11 % of subjects of study, respectively [35, 36]. But in one study in which 38 % of patients had received steroid, S1 but not E1 was associated with the more frequent use of steroid [34]. RAS blockade treatment was more frequent in patients with M1 [34, 36]. Thus, at least in current situation, where the prescription of immunosuppressive drugs is largely dependent

on the decision of individual physician without agreed guideline for immunosuppressive treatment, the reported relationship of specific Oxford lesions with steroid treatment be viewed with the consideration for criteria by which steroid was used in a specific study.

The frequency of M1, S1, E1, T1, and T2 increased along with the increasing grade of WHO classification [34] and also showed correlation with Hass classification in patients with posttransplant IgAN [37]. All MEST variables, especially S and E, correlated with activity index in semiquantitative classification, but only S and T showed relationship with chronic index [34]. Hass and Oxford classifications were comparable in providing additive predictive value for renal progression to known clinical parameters such as proteinuria and eGFR [36], but Oxford classification was superior to Haas classification in posttransplant IgAN [37]. Thus, pre-existing pathological grading systems of IgAN such as WHO and Hass classification could provide useful prognostic information as much as Oxford classification, but Oxford classification is superior to old systems in the convenience in clinical application and consistency in interpretation of pathologic findings by different pathologists.

Similar to conclusion from Oxford group, a retrospective analysis of 430 patients in which 18.8 % of patients had crescent showed that crescent was not a prognostic factor for renal progression independent of clinical findings and T lesion although patients with crescent had higher UPCR, lower eGFR, lower serum albumin level, and more prescription of RAS blockade and glucocorticoid treatment during follow-up. Because the patients in this study had a relatively good basal eGFR of 80.5 ± 24.1 ml/min/1.73 m^2, this study could not give the answer about the prognostic significance of crescent in patients having worse eGFR <30 ml/min/1.73 m^2 as Oxford classification could not [38]. But in posttransplant IgAN, 4-year graft survival after biopsy was 30.0 % in patients having crescents compared with 70.8 % patients without crescents despite the enhanced immunosuppression in the former group. Moreover, IgAN was the cause of graft failure in 66.7 % of patients with crescents, whereas IgAN was the cause of graft failure in only 13.6 % of patients without crescents [39]. Thus, the prognostic significance of crescent in IgAN remained to be defined especially in patients with low basal eGFR and/or patients on the immunosuppressive therapy at the time of renal biopsy.

10.2.2 Significance of Proteinuria in Treatment and Prognosis

10.2.2.1 Normal or Low-Grade Proteinuria at Presentation

Although the excellent prognosis is taken for granted for patients presenting with normotension, normal renal function, and normal or low-grade proteinuria, this does not apply to all such patients.

IgAN constituted 33.3 % ($n = 52$) of 156 patients who underwent renal biopsy due to isolated hematuria without proteinuria, hypertension, and azotemia. During a follow-up of mean duration of 31.6 ± 14.1 months, five patients with IgAN developed proteinuria and/or hypertension and/or eGFR <60 ml/min/1.73 m^2 [40].

In a retrospective analysis of 153 patients with IgAN presenting with benign clinical manifestation, i.e., proteinuria <0.5 g/day, normotension, and eGFR >60 ml/min at the time of renal biopsy, 31 % ($n = 36$) of patients achieved clinical remission defined as disappearance of microscopic hematuria, proteinuria <0/2 g/day, and normal renal function. But 11 patients developed proteinuria >1 g/day, three patients showed greater than 50 % increase in serum creatinine, and six patients developed ESRD. Interstitial fibrosis at renal biopsy and hypoalbuminemia were independent risk factors for the development significant proteinuria and renal progression [41].

10.2.2.2 Nephrotic Syndrome

Out of 1,076 patients, typical nephrotic syndrome was observed in 100 (10.2 %) patients, 93 of whom presented with generalized edema at initial presentation. Histologically only four patients showed typical minimal change disease-like features, and C3 deposition was observed in 91 % of patients. A total of 48 patients achieved complete remission, spontaneously in 24 patients and by immunosuppressive treatment in another 24 patients. Partial response and no response occurred in 32.0 % and 20.0 % of patients, respectively. During the median follow-up of 45.2 months, the doubling of serum creatinine occurred in 24 % of nephrotic patients compared with 7.1 % in non-nephrotic patients. In patients with nephrotic syndrome, the risk for reaching the doubling of serum creatinine was highest for patients with no response followed by partial response (HR 14.49, 95 % CI 1.14–183.76, $p = 0.04$ and HR 215, 95 % CI 15–2983, $p < 0.001$ respective for partial response and nonresponse compared with complete response). The prognosis of complete responder was excellent with only two patients reaching the doubling of serum creatinine during follow-up. In 24 patients having spontaneous complete remission, Haas IV or V classifications were observed in 11 patients. Female sex, initial serum creatinine <1.2 mg/dL, and more than 50 % reduction of proteinuria within 3 months after the onset of nephrotic syndrome were associated with likelihood of attaining spontaneous remission [4].

Among 581 patients with IgAN, 48 patients (8.3 %) presented with nephrotic syndrome. Of 25 patients who received high-dose corticosteroid, 12 patients achieved complete remission of nephrotic syndrome. Seven episodes of relapse in five patients occurred during the tapering of corticosteroids, six of which respond well to reintroduction of high-dose steroid with complete remission. Compared with nonresponders, responders were characterized by clinical features similar to minimal change disease, i.e., rapid onset of edema, higher weight gain, higher proteinuria, lower serum albumin, and lower serum creatinine, and pathological features of lower histological grade and lower mesangial IgA deposition. While

none of 12 responders did not progress to ESRD, 38 % of nonresponders to steroid and 43 % of patients who did not receive steroid treatment reached ESRD [42].

Collectively, these studies suggest that about 10 % of IgAN patients present with nephrotic syndrome in which there are considerable heterogeneity in histopathology, clinical course, response to treatment, and prognosis. Prognosis of nephrotic patients was largely determined by the reduction of proteinuria spontaneously or by steroid treatment.

10.2.2.3 Optimal Proteinuria Target for Renal Protection

Because the level of residual proteinuria attained spontaneously or by treatment was a major determinant of renal progression irrespective of risk factors at initial presentation such as eGFR, blood pressure, proteinuria, and histological findings, the optimal target for the reduction of proteinuria is always an important topic in IgAN.

In a retrospective analysis of 500 patients, the risk for developing 50 % decline in eGFR increased markedly in patients with 1.0 g/g $\leq$ TAP (time-averaged proteinuria) $\geq$2.99 g/g (HR 25.0, 95 % CI 3.17–197.0, $p = 0.002$) and TAP $\geq$3.0 (HR 244.07, 95 % CI 27.09–2198.98, $p < 0.001$) compared with patients with TAP <0.3 g/g. Although there was no difference in the development of 50 % decline in eGFR or ESRD between the patients with time-averaged proteinuria during clinical course (TAP) <0.3 g/g and patients with 0.3 g/g $\leq$ TAP $\geq$ 0.3–0.99 g/g, eGFR slope was lower in patients with TAP <0.3 g/g than patients with 0.3$\leq$ TAP $\geq$0.99 (-0.41 ± 1.68 vs. -0.73 ± 2.82 ml/min/1.73 m^2/year, $p = 0.03$) [43].

In another retrospective study of 125 patients, the risk for reaching to eGFR <15 ml/min/1.73 m^2 increased by tenfolds in patients with residual proteinuria after treatment >1.0 g/day compared with the patients with residual proteinuria <0.3 g/day. Although statistically insignificant probably due to relatively small numbers of patients, eGFR slope in patients with residual proteinuria of 0.3–0.99 was larger than patients with residual proteinuria <0.3 g/day (-1.24 ± 1.25 vs. -1.06 ± 1.69 ml/min/1.73 m^2/year, $p = 0.580$). The relapse of proteinuria more than 1 g/day, which occurred 5.2 ± 3.2 years after the initiation of treatment, was more frequent in patients with residual proteinuria of 0.3–0.99 g/day than patients with proteinuria <0.3/day (41.5 % vs. 26.3 %, $p = 0.025$) [44].

These studies suggest that the maintenance of proteinuria <1 g/day as recommended by KDIGO was a reasonable therapeutic target in renal protection, but the attainment of proteinuria <0.3 g/day might provide additional renal protection especially in young and otherwise healthy patients in whom a long life span is expected.

10.2.3 Drug Therapy

10.2.3.1 Renin-Angiotensin System Blockade (RASB)

Angiotensin-converting enzyme inhibitor (ACEI) decreased proteinuria from 3.85 ± 2.54 g/day to 1.68 ± 1.91 g/day in 24 patients in which five of whom proteinuria decreased below 0.5 g/day. ACEI also decreased the proteinuria of ten patients whose baseline proteinuria was greater than 3 g/day from 4.89 ± 1.43 g/day to 1.38 ± 1.21 g/day [45]. Insertion/deletion polymorphism of ACE gene did not influence the anti-proteinuric effect of ACEI [46].

In a trial of 4 weeks of washout period followed by 12 weeks of active treatment in which patients were randomized to once-daily losartan 50 mg/day or amlodipine 5 mg/day without any dietary restriction, all but one patient treated by losartan showed reduction in proteinuria, whereas proteinuria slightly increased in patients treated by amlodipine without no difference in blood pressure attained during the trial. Proteinuria decreased by 42.7 % from baseline after 4 weeks treatment of losartan and further reduced by 54.4 % after 12 weeks of treatment (2.3 ± 1.5 g/day, 1.4 ± 1.4 g/day, and 1.1 ± 1.2 g/day, respectively, at baseline, 4 weeks, and 12 weeks after treatment). No treatment-induced change in CCr was noted in both groups. Whereas there were no difference in serum level of TGF-ß between normal volunteer and patients with IgAN, urinary TGF-ß and reflecting renal production of TGF-ß were 20-folds higher in patients with IgAN than in normal control. Losartan but not amlodipine decreased urinary TGF-ß, but there was neither relationship between urinary TGF-ß level and proteinuria nor between decrement of urinary TGF-ß and reduction of proteinuria by losartan [47].

A crossover trial of once-daily candesartan 4 mg or placebo over 12 weeks on 19 patients who had been stably maintained on 5–7,5 mg of ramipril for at least 6 months showed the reduction of proteinuria from 4.1 ± 0.3 g/day at placebo period to 3.1 ± 0.3 g/day at combination period without change in blood pressure, serum potassium level, and renal function [48]. The addition of candesartan reduces urinary TGF-β level by 28.9 ± 6.0 %, but the reduction in proteinuria did not correlate with the reduction in urinary TGF-β level [49]. Although the combination of low dose of ACEI and angiotensin receptor blocker (ARB) reduced the proteinuria further in IgA patients having high basal proteinuria >3.0 g/day, the reduction rate in proteinuria by addition of ARB was only 12.3 ± 4.5 %, and residual proteinuria remained high in this study.

In posttransplant IgAN, more than 50 % reduction of proteinuria by enalapril was observed in 71.4 % of patients without segmental sclerosis but only 28.6 % of patients having segmental sclerosis suggestive of the inhibitory effect of segmental sclerosis on the anti-proteinuric effect of ACEI in these patients [50].

A retrospective analysis of 167 patients with IgAN biopsied in author's hospital revealed that the presence of crescents in glomeruli reduces the anti-proteinuric effects of RAS blockade administered for 1 year in the multivariable analysis adjusted for multiple factors including basal proteinuria, eGFR, and other

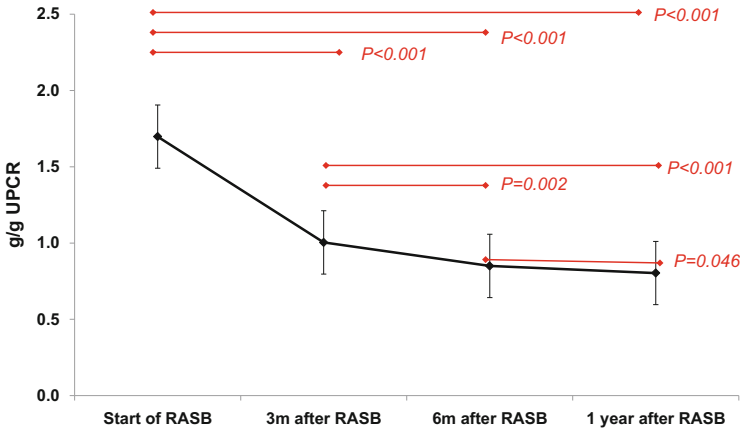

Fig. 10.1 Serial changes in UPCR after RAS blockades in patients with IgAN

histological features. In this study, most of reduction in proteinuria occurred within 3 months after RAS blockade, but further reduction of proteinuria was observed until 1 year after RAS blockade (Fig. 10.1) (unpublished results).

In the comparison between 914 IgAN patients without RAS blockade and 831 patients with RAS blockade, the rate of doubling of creatinine, ESRD, and death was higher in patients without RAS blockade (Fig. 10.2) despite the older age, lower basal eGFR, and higher prevalence of hypertension in the patients treated with RAS blockade. Interestingly, the protective effect of RAS blockade against death was significant in patients having DD genotype of insertion/deletion polymorphism of ACE (unpublished results).

Collectively, ACEI or ARB significantly reduced proteinuria in patients with IgAN with favorable long-term effects on the survival of patient as well as the kidney. The combination of ACEI and ARB further reduced the proteinuria with the further reduction of urinary TGF-β secretion. The most degree of anti-proteinuric effect of RASB was attained within 3 months after the administration of drug, but further lowering of proteinuria was observed until 1 year after treatment. Higher basal proteinuria before RASB especially more than 3 g/day and the presence of crescent or segmental sclerosis in renal biopsy decreased the proteinuria-lowering effect of RASB. Although DD genotype of ACE gene did not influence the anti-proteinuric effect of RASB, the patient's survival benefit was prominent in patients with DD genotype.

10.2.3.2 Corticosteroid

In an open label trial conducted on 50 adult patients, daily administration of 1 mg/kg of oral prednisolone for 2 months followed by tapering over 4 months on the top of ARB treatment improved mean eGFR significantly from 80.2 ± 22.7 ml/min/

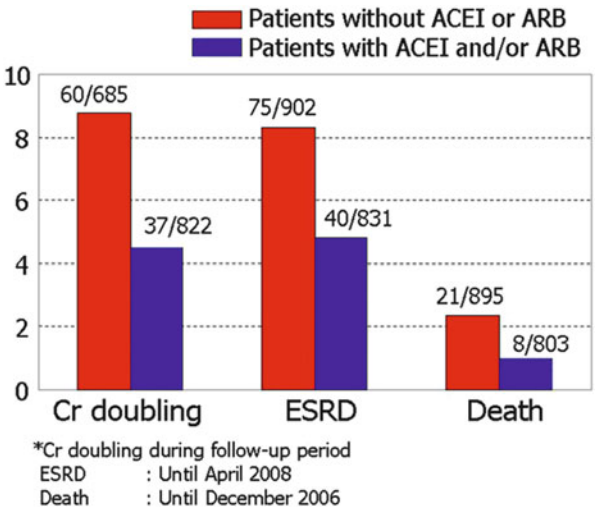

Fig. 10.2 The differences in doubling of serum creatinine, ESRD, and death according to the treatment by RAS blockades in patients with IgAN

1.73 m^2 at baseline to 93.0 ± 41.2 ml/min/1.73 m^2 and decreased UPCR 2.21 ± 2.0 g/g at baseline to 0.7 ± 0.7 g/g at 6 months after treatment. In addition the corticosteroid therapy also decreased the extent of hematuria including 16 patients in whom hematuria completely disappeared. The serum IgA level also decreased after treatment. Seven patients (14 %) who developed more than 20 % decrease in eGFR despite the corticosteroid therapy were characterized by lower eGFR, higher systolic blood pressure, and more frequent presence of crescent at baseline. Especially, the basal proteinuria of these patients was higher than respondent patients (UPCR 3.92 ± 2.00 g/g vs. 1.93 ± 1.88 g/g) in whom residual proteinuria after treatment was also higher (UPCR 1.63 ± 1.00 g/g vs. 0.61 ± 0.59 g/g) [51].

Similar regimen of oral prednisolone or deflazacort on the top of RAS blockade with good blood control also increased CCr by 11.5 ± 16.4 ml/min and decreased 24-h urine proteinuria by 4.4 ± 5.5 g/day and increased serum albumin level by 1.1 ± 2.3 g/dL in a retrospective analysis of 136 patients despite the relatively high basal proteinuria of 5.8 ± 5.6 g/day. Because the follow-up duration was short and too widely distributed and mean residual proteinuria after treatment was more than 1 g/day (1.4 ± 2.3 g/day), actual benefit of this treatment need more long-term follow-up to be confirmed [52].

The effect of intravenous pulse administration of 500 mg of methylprednisolone every 2 weeks for 6 months without accompanying oral corticosteroid administration improved the rate of eGFR decline in the 22 patients who had already progressed more than CKD 3 stage(-0.93 ± 0.87 vs. 0.14 ± 0.99 ml/min/1.73 m^2/month, respectively, before and after treatment $p = 0.007$). Ten-month dialysis-free survival after treatment was 100 % in patients with basal eGFR $\geq$30 ml/min/1.73 m^2 and 53 % in patients with eGFR $<$30 ml/min/1.73 m^2 suggesting more prominent reno-protective effect of this intermittent steroid pulse therapy in

patients having more preserved renal function before treatment. Contrary to other corticosteroid treatment, this treatment did not reduce albuminuria (UACR before and after treatment 1.71 ± 1.60 mg/g vs. 1.48 ± 1.07 mg/g) although albuminuria did not actually increase during follow-up [53].

A retrospective analysis showed that one of the main reasons for worse renal survival in IgAN than in Henöch-Schönlein purpura was earlier (durations between biopsy and steroid start: HSP vs. IgAN 9.6 ± 14.8 months vs. 25.3 ± 17.8 months) and more frequent use of steroid (HSP vs. IgAN 40.2 % vs. 14.2 %) in Henöch-Schönlein purpura. In fact, no difference in renal revival was observed between IgAN and Henöch-Schönlein purpura when matched baseline factors including steroid treatment. In fact, eGFR decreased 83.4 ml/min/1.73 m^2 to 58.5 mml/min/1.73 m^2, and UPCR increased from 1.1 to 2.2 g/g in IgAN patients before the initiation of steroid implicating that earlier and more liberal steroid use might improve the prognosis of IgAN patients [54].

In author's hospital, corticosteroid was used in 44 (15.7 %) out of 281 patients with IgAN. Compared with patients treated by RASB only, the patients to which corticosteroid was administered were characterized by lower eGFR (85.70 ± 31.55 vs. 75.14 ± 26.29 ml/min/1.73 m^2), higher UPCR (1.65 ± 1.55 vs. 2.80 ± 1.97 g/g), lower serum albumin (4.01 ± 0.39 vs. 3.76 ± 0.46 g/dL), higher percentage of glomeruli showing segmental sclerosis (8.26 ± 8.08 vs. 13.75 ± 12.26 %), and more frequent presence of advanced tubulointerstitial lesions (17.5 vs. 38.6 %). Modified Pozzi's regimen in which 500 mg instead of 1,000 mg of methylprednisolone was administered reduced proteinuria and the degree of hematuria and stabilized eGFR which had been decreasing before treatment (Fig. 10.3). The effects on the reduction of proteinuria and the stabilization of eGFR of modified Pozzi's regimen were similar between the patients whose eGFR before treatment was above and below 50 ml/min/1.73 m^2, but the extent of reduction of hematuria was greater in patients with pretreatment eGFR $\geq$50 ml/min/1.73 m^2 than those with pretreatment eGFR $<$50 ml/min/1.73 m^2. Out of 38 patients, five patients required more than two courses of corticosteroid treatment due to increased proteinuria and/or acceleration of eGFR decline after initial treatment (unpublished results).

Collectively, although there have been no settled indications for corticosteroid treatment and no agreed method of administration of corticosteroid in IgAN before the introduction of KDIGO guideline in Korea, corticosteroid treatment was effective in reducing proteinuria and inducing the improvement or stabilization of renal function even in patients with already decreased eGFR before treatment.

10.2.3.3 Calcineurin Inhibitors

A double-blind randomized trial of tacrolimus (clinicaltrial.gov identifier NCT01224028) in adult IgAN patients with UACR of 0.3−3.0 mg/g in which introduction or intensification of RAS blockade is difficult owing to further lowering of blood pressure demonstrated that the initial administration of tacrolimus of

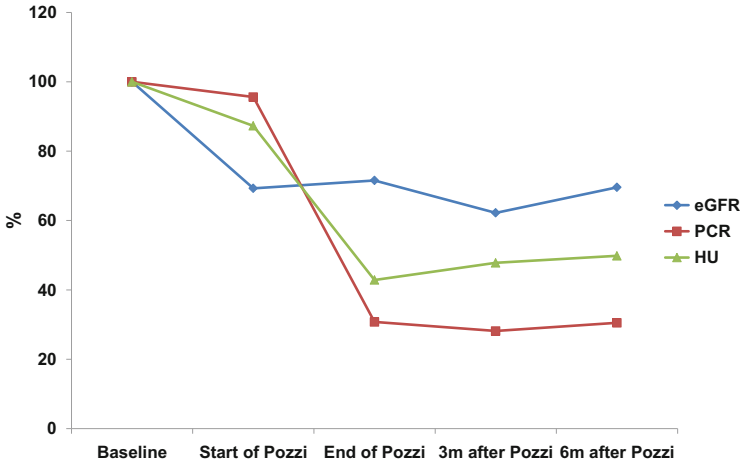

Fig. 10.3 Serial changes in eGFR, PCR, and hematuria after Pozzi's regimen in patients with IgAN

0.1 mg/kg/day adjusted to trough level of 5−10 ng/ml for 8 weeks followed by halving the dose for remaining 8 weeks reduced albuminuria greater than placebo (reduction rate of UACR: 60.2 ± 28.2 %, 62.2 ± 33.9 %, 48.5 ± 29.8 %, and 55.5 ± 24.0 %, respectively, at 4, 8, 12, and 16 weeks after tacrolimus vs. 6.8 ± 32.2 %, 2.5 ± 35.9 %, 12.7 ± 34.2 %, and 21.9 ± 30.6 %, respectively, at 4, 8, 12, and 16 weeks after placebo). Characteristically, anti-proteinuric effect of tacrolimus was most prominent when eGFR mostly decreased from baseline, and the difference in the reduction of proteinuria between tacrolimus and placebo became unapparent after halving dose of tacrolimus in patients on ARB, suggesting hemodynamic mechanism in anti-proteinuric effects of tacrolimus [55].

The combination of cyclosporine A adjusted to trough serum level of 100−200 ng/dL for 8−12 months with prednisolone of 1−2 mg/kg/day for 4 weeks followed by gradual tapering reduced 24-h urine protein from 107.1 ± 35.1 mg/m^2/h to 7.4 ± 2.4 mg/m^2/h in pediatric patients. At last follow-up, proteinuria was normalized in nine patients (64.3 %) including six patients in whom hematuria also disappeared. In the follow-up biopsies after completion of cyclosporine A, histological grading of Hass classification improved in seven patients (50 %), remained the same in three patients (21 %) and aggravated in four patients (29 %), two of whom showed the clinical improvement despite the worsening of histological findings. The degree of mesangial IgA deposition in immunofluorescence examination decreased in 50 % of patients [56].

Collectively, calcineurin inhibitors could be used for the reduction of proteinuria instead of RAS blockades in patients who are intolerable to RAS blockade due to excessive lowering of blood pressure or in patients already under corticosteroid treatment for further reduction of proteinuria. The mechanism of anti-proteinuric

effect of calcineurin inhibitor might be hemodynamic or non-hemodynamic depending on the clinical context where this drug is used.

10.2.3.4 Sulodexide

A retrospective study demonstrated that the daily administration of 50 mg of sulodexide, an oral formulation of mixture of heparan sulfate and dermatan sulfate, for 11.1 ± 2.7 months reduced the UPCR from 1.5 ± 0.6 g/g at baseline to 1.1 ± 0.7 g/g at the end of follow-up in 20 patients who had been maintained on RAS blockade with stable blood pressure more than 2 years. A quarter of patients showed more than 50 % reduction in proteinuria, and 40 % of patients showed UPCR less than 1 g/g at final follow-up. Interestingly, the anti-proteinuric effects of sulodexide were greater in patients with larger basal proteinuria [57].

Encouraged by anti-proteinuric effect in diabetic nephropathy of sulodexide, a multicenter randomized double-blind trial of daily administration of 50 mg and 150 mg of sulodexide for 6 months was conducted on 104 patients who had been maintained on RAS blockade with stable blood pressure. Although there were no differences in the primary outcome, i.e., more than 50 % reduction of UPCR, between treatment groups (12.5 % in placebo, 4.0 % in 75 mg of sulodexide, and 21.4 % in 150 mg of sulodexide), 150 mg of sulodexide significantly reduced the log UPCR of the patients within group from 6.38 ± 0.77 to 5.98 ± 0.94 in time-dependent manner ($p = 0.045$). The relatively low basal UPCR of 0.6−0.8 g/g and short duration of treatment might contribute to the negative results in this study [58].

Collectively, these studies suggested that the long-term administration of sulodexide might be effective in reducing proteinuria in patients with relatively high basal proteinuria.

10.2.3.5 Omega-3 Fatty Acid

No studies of omega-3 fatty acid in Korean patients with IgAN were published. Actually a double-blind, placebo-controlled, multicenter phase 3 trial of omega-3 fatty acid in IgAN patients with decreased renal function has been completed (clinicaltrial.gov identifier NCT 00549692), but the results are not yet published.

10.2.4 Prognosis

A retrospective analysis for 1,364 patients with IgAN showed that 10-, 20-, and 30-year renal survival rates over median period of 96 months (interquartile range (IQR) 56–187) were 82.0 %, 70.8 %, and 67.3 %, respectively. The median time to ESRD was 71 months (IQR 32–123). Initial renal function was the most important

determinant of renal survival, and hypertension, segmental sclerosis ≥20 %, hypoalbuminemia were independent risk factors for renal survival. Gross hematuria was a favorable factor for renal survival.

Ten-, 20-, and 30-year patient survival rates over median period of 101 months (IQR 38–189) were 96.3 %, 91.8 %, and 82.7 %, respectively. The median time to death was 101 months (IQR 38–189). Age was predominant risk factor for death, and hypertension, hypoalbuminemia, and the occurrence of cancer were independent risk factors for patient survival. The half of patient's death (55.7 %) occurred before reaching ESRD. The main causes of pre-ESRD death were the malignancy (30.8 %, $n = 12$), cardiovascular disease (12.8 %, $n = 5$), and infection (15.8 %, $n = 6$). Ten-year and 20-year survival rates after ESRD were 88.6 % and 66.3 %, respectively. The major causes of death after ESRD were renal-related causes, cardiovascular disease, and infection. Out of 209 patients who received immunosuppressive therapy, 24 (11.4 %) patients died. Half of these patients died of infection [59].

Compared to other primary GN, renal survival of the patients with IgAN was better than membranoproliferative glomerulonephritis, similar to focal segmental glomerulosclerosis, and worse than minimal change disease. Despite the similar renal survival, patient survival was better in IgAN than focal segmental glomerulosclerosis due to better patient survival after reaching ESRD. Compared to other primary glomerulonephritis, extrarenal morbidities such as diabetes mellitus, cancer, and cardiovascular complications occurred least in patients with IgAN during the follow-up. Mortality rate relative to age/sex-matched general population (SMR, standardized mortality ratio) was 1.43 (95 % CI 1.04–1.92) meaning IgAN patients have a little higher mortality than general population. But, the mortality rate of male patients mortality rate was similar to general population (SMR 1.22 CI 0.82–1.75), while the mortality rate of female patients was more than twofolds higher than general population [60].

While 5-year renal survival rate was 78.9 % in 223 patients biopsied between 1980 and 1993 [A-61], it was 88.0 % in 223 patients biopsied between 2002 and 2004, in whom RAS blockade, corticosteroid, and statin were prescribed in 87.0 %, 11.4 %, and 18.8 %, respectively [unpublished data].

Conflict of Interest The author declares that he has no conflict of interest.

References

1. Jae Hyun Chang, Dong Ki Kim, Hyun Wook Kim, Sun Young Park, Tae-Hyun Yoo, Beom Seok Kim, et al. Changing prevalence of glomerular diseases in Korean adults: a review of 20 years of experience. Nephrol Dial Transplant. 2009;31:2406. doi:10.1093/ndt/gfp091.
2. Park JS, Song JH, Yang WS, Kim SB, Kim YK, Hong CD. Cytomegalovirus is not specifically associated with immunoglobulin A nephropathy. J Am Soc Nephrol. 1994;4:1623.

3. Gyung Geun Han, Jeong Ha Pack, Sung Jin Bae, Sam Ryong Ji, Jeong Hyun Lim, Goang Yul Jang, et al. A clinical study of IgA nephropathy with serum Hepatitis B surface antigen. Korean J Nephrol. 2000;19:437.
4. Jwa Kyung Kim, Jeong Ho Kim, Sang Choel Lee, Ea Wha Kang, Tae Ik Chang, Sung Jin Moon, et al. Clinical features and outcomes of IgA nephropathy with nephrotic syndrome. Clin J Am Soc Nephrol. 2012;7:427. doi:10.2215/CJN.04820511.
5. In O Sun, Yu Ah Hong, Hoon Suk Park, Sun Ryoung Choi, Byung Ha Chung, Cheol Whee Park, et al. Clinical characteristics and treatment of patients with IgA nephropathy and hepatitis B surface antigen. Ren Fail. 2013;35:446. doi:10.3109/0886022X.
6. Seung Hyeok Han, Ea Wha Kang, Jeong Hae Kie, Tae Hyun Yoo, Kyu Hun Choi, Dae-Suk Han, et al. Spontaneous remission of IgA nephropathy associated with resolution of Hepatitis A. Am J Kidney Dis. 2010;56:1163. doi:10.1053/j.ajkd.2010.08.018.
7. Chun Soo Lim, Shouhuan Zheng, Yon Su Kim, Curie Ahn, Jin Suk Han, Suhnggwon Kim, et al. Th1/Th2 predominance and proinflammatory cytokines determine the clinicopathological severity of IgA nephropathy. Nephrol Dial Transplant. 2001;16:269. doi:10.1093/ndt/16.2.269.
8. Chun Soo Lim, Hyung Jin Yoon, Yon Su Kim, Curie Ahn, Jin Suk Han, Suhnggwon Kim, et al. Clinicopathological correlation of intrarenal cytokines and chemokines in IgA nephropathy. Nephrology (Carlton). 2003;8:21. doi:10.1046/j.1440-1797.2003.00128.x.
9. Mi Ra Park, Eun Hui Wang, Dong Chan Jin, Jung Ho Cha, Kweon Heang Lee, Chul Woo Yang, et al. Establishment of a 2-D human urinary proteomic map in IgA nephropathy. Proteomics. 2006;6:1066. doi:10.1002/pmic.200500023.
10. Pyong-Gon Moon, Jeong-Eun Lee, Sungyong You, Taek-Kyun Kim, Ji-Hoon Cho, In-San Kim, et al. Proteomic analysis of urinary exosomes from patients of early IgA nephropathy and thin basement membrane nephropathy. Proteomics. 2011;11:2459. doi:10.1002/pmic.201000443.
11. Noh Jin Kwak, Eun Hui Wang, Il-Young Heo, Dong-Chan Jin, Jung-Ho Cha, Kweon-Haeng Lee, et al. Proteomic analysis of alpha-1-antitrypsin in immunoglobulin A nephropathy. Proteomics Clin Appl. 2007;1:420. doi:10.1002/prca.200600288.
12. Soon Hyo Kwon, Moo Yong Park, Jin Seok Jeon, Hyunjin Noh, Soo Jeong Choi, Jin Kuk Kim, et al. KIM-1 expression predicts renal outcomes in IgA nephropathy. Clin Exp Nephrol. 2013;17:359. doi:10.1007/s10157-012-0707-2.
13. Ji Hye Lee, Mee Hye Oh, Jae Seok Park, Gyoung Jae Na, Hye Wook Gil, Jong Oh Yang, et al. Urokinase, urokinase receptor, and plasminogen activator inhibitor-1 expression on podocytes in immunoglobulin A glomerulonephritis. Korean J Intern Med. 2014;29:176. doi:10.3904/kjim.2014.29.2.176.
14. Jae Ryung Shin, Seung Min Kim, Jung Sun Yoo, Ji Yoon Park, Seul Ki Kim, Joo Hee Cho, et al. Urinary excretion of β2-microglobulin as a prognostic marker in immunoglobulin A nephropathy. Korean J Intern Med. 2011;29:334–40. doi:10.3904/kjim.2014.29.3.334
15. Ho Jun Chin, Hyun Jin Cho, Tae Woo Lee, Ki Young Na, Hyung Jin Yoon, Dong-Wan Chae, et al. The Heme Oxygenase-1 Genotype is a risk factor to renal impairment of IgA nephropathy at diagnosis, which is a strong predictor of mortality. J Korean Med Sci. 2009;24 Suppl:S30. doi:10.3346/jkms.2009.24.S1.S30.
16. Ho Jun Chin, Hyun Jin Cho, Tae Woo Lee, Ki Young Na, Kook Hwan Oh, Kwon Wook Joo, et al. The mildly elevated serum bilirubin level is negatively associated with the incidence of end stage renal disease in patients with IgA nephropathy. J Korean Med Sci. 2009;24 Suppl:S22. doi:10.3346/jkms.2009.24.S1.S22.
17. Hye Ryoun Jang, Soo Min Park, Yu ji Lee, Jung Eun Lee, Woo Seong Huh, Dae Joong Kim, et al. The origin and the clinical significance of urinary angiotensinogen in proteinuric IgA nephropathy patients. Ann Med. 2012;44:448. doi:10.3109/07853890.2011.558518.
18. Sun Moon Kim, Ho Jun Chin, Yun Kyu Oh, Yon Su Kim, Suhnggwon Kim, Chun Soo Lim. Blood pressure-related genes and the progression of IgA nephropathy. Nephron Clin Pract 2009;113:c301. doi:10.1159/000235948.

19. HJ Yoon, H Kim, HL Kim, SG Lee, S H Zheng, JH Shi, et al. Interdependent effect of angiotensin-converting enzyme and platelet-activating factor acetylhydrolase gene polymorphisms on the progression of immunoglobulin A nephropathy. Clin Genet. 2002;62:128. doi:10.1034/j.1399-0004.2002.620205.x.
20. Eun Sook Jung, Sun Moon Kim, Ho Jun Chin, Ran Hui Cha, Yun Kyu Oh, Yon Su Kim, et al. Impact of polymorphisms of the genes encoding angiotensin II-forming enzymes on the progression of IgA nephropathy. Nephron Clin Pract 2011;118:c122. doi:10.1159/000321140.
21. Hyung Jin Yoon, Ho Jun Chin, Ki Young Na, Dong Wan Chae, Suhnggwon Kim, Un Sil Jeon, et al. Association of angiotensin II Type 2 receptor gene A1818T polymorphism with progression of Immunoglobulin A nephropathy in Korean Patients. J Korean Med Sci. 2009;24 Suppl:S38. doi:10.3346/jkms.2009.24.S1.S38.
22. CS Lim, SM Kim, YK Oh, YS Kim, DW Chae, JS Han, et al. Association between the clara cell secretory protein (CC16) G38A polymorphism and the progression of IgA nephropathy. Clin Nephrol. 2007; 67:73.
23. Yoon HJ, Shin JH, Yang SH, Chae DW, Kim H, Lee DS, et al. Association of the CD14 gene-159C polymorphism with progression of IgA nephropathy. J Med Genet. 2003;40:104. doi:10.1136/jmg.40.2.104.
24. Lim CS, Kim SM, Oh YK, Joo KW, Kim YS, Han JS, et al. Megsin 2093T-2180C haplotype at the 3′ untranslated region in associated with poor renal survival in Korean IgA nephropathy patients. Clin Nephrol. 2008;70:101.
25. Lim CS, Kim YS, Chae DW, Ann C, Han JS, Kim S. Association of C-509T and T869C polymorphisms of transforming growth factor-beta1 gene with susceptibility to and progression of IgA nephropathy. Clin Nephrol. 2005;63:61.
26. Jung Pyo Lee, Seung Hee Yang, Dong Ki Kim, Hajeong Lee, Bora Kim, Joo Youn Cho, et al. In vivo activity of epoxide hydrolase according to sequence variation affects the progression of human IgA nephropathy. Am J Physiol Renal Physiol. 2011;300:F1283. doi:10.1152/ajprenal.00733.2010.
27. Gang Jae Ko, Eun Ah Lee, Un Sil Jeon, Heui Jung Pyo, Ho Jun Chin, Dong Wan Chae, et al. The association of Klotho Polymorphism with disease progression and mortality in IgA nephropathy. Kidney Blood Press Res. 2012;36:191. doi:10.1159/000343408.
28. Lee HS, Koh HI, Lee HB, Park HC. IgA nephropathy in Korea: a morphological and clinical study. Clin Nephrol. 1987;27:131.
29. Seung Jun Kim, Hyang Mo Koo, Beom Jin Lim, Hyung Jung Oh, Dong Eun Yoo, Dong Ho Shin, et al. Decreased circulating C3 levels and mesangial C3 deposition predict renal outcome in patients with IgA nephropathy. PLoS One. 2012;7:e40495. doi:10.1371/journal.pone.0040495.
30. Young In Maeng, Min Kyung Kim, Jae Bok Park, Chang Ho Cho, Hoon Kyu Oh, Woo Jung Sung, et al. Glomerular and tubular C4d depositions in IgA nephropathy: relations with histopathology and with albuminuria. Int J Clin Exp Pathol. 2013;6:904.
31. Hong Joo Lee, So Young Choi, Kyung Hwan Jeong, Ji Youn Sung, Sung Kyoung Moon, Ju Young Moon, et al. Association of C1q deposition with renal outcomes in IgA nephropathy. Clin Nephrol. 2013;80:98. doi:10.5414/CN107854.
32. Hyun Soon Lee, Myung Suk Lee, Sa Min Lee, Sang Yun Lee, Eun Sun Lee, Eun Young Lee, et al. Histological grading of IgA nephropathy predicting renal outcome: revisiting H. S. Lee's glomerular grading system. Nephrol Dial Transplant. 2005;20:342.
33. Shin Wook Kang, Kyu Hun Choi, Jong Hoon Park, Seung Woo Lee, Ho Yung Lee, Dae Suk Han, et al. Prognostic factors and renal survival rates in IgA nephropathy. Yonsei Med J. 1995;36:45.
34. Seok Hui Kang, Sun Ryoung Choi, Hoon Suk Park, Ja Young Lee, In O Sun, Hyeon Seok Hwang, et al. The Oxford classification as a predictor of prognosis in patients with IgA nephropathy. Nephrol Dial Transplant. 2012;27:252. doi:10.1093/ndt/gfr295.

35. Ho young Lee, Sul Hee Yi, Mi Seon Seo, Jin Nam Hyun, Jin Seok Jeon, Hyunjin Noh, et al. Validation of the Oxford classification of IgA nephropathy: a single-center study in Korean adults. Korean J Intern Med. 2012;27:293.
36. Kyoung Sook Park, Seung Hyeok Han, Jeong Hae Kie, Ki Heon Nam, Mi Jung Lee, Beom Jin Lim, et al. Comparison of the Haas and the Oxford classifications for prediction of renal outcome in patients with IgA nephropathy. Hum Pathol. 2014;45:236. doi:10.1016/j.humpath.2013.08.019.
37. Beom Jin Lim, Dong Jin Joo, Myoung Soo Kim, Yu Seun Kim, Soon Il Kim, Yeon hee Kim, et al. Usefulness of Oxford classification in assessing immunoglobulin A nephropathy After Transplantation. Transplantation. 2013;95:1491. doi:10.1097/TP.0b013e318291de65.
38. Mi Jung Lee, Seung Jun Kim, Hyung Jung Oh, Kwang Il Ko, Hyang Mo Koo, Chan Ho Kim, et al. Clinical implication of crescentic lesions in immunoglobulin A nephropathy. Nephrol Dial Transplant. 2014;29:356. doi:10.1093/ndt/gft398.
39. Hyeon Joo Jeong, Yu Seun Kim, Ki Hwan Kwon, Soon Il Kim, Myoung Soo Kim, Kyu Hun Choi et al. Glomerular crescents are responsible for chronic graft dysfunction in post-transplant IgA nephropathy. Pathol Int. 2004;54:837.
40. Byung Soo Kim, Yong Kyun Kim, Young Shin Shin, Young Ok Kim, Ho Cheol Song, Yong Soo Kim, et al. Natural history and renal pathology in patients with isolated microscopic hematuria. Korean J Intern Med. 2009;24:356. doi:10.3904/kjim.2009.24.4.356.
41. Hajeong Lee, Jin Ho Hwang, Jin Ho Paik, Hyun Jin Ryu, Dong Ki Kim, Ho Jun Chin, et al. Long-term prognosis of clinically early IgA nephropathy is not always favorable. BMC Nephrol. 2014;15:94. doi:10.1186/1471-2369-15-94.
42. Sun Moon Kim, Kyung Chul Moon, Kook-Hwan Oh, Kwon Wook Joo, Yon Su Kim, Curie Ahn, et al. Clinicopathologic characteristics of IgA nephropathy with steroid-responsive nephrotic syndrome. J Korean Med Sci. 2009;24 Suppl:S44. doi:10.3346/jkms.2009.24.S1.S44.
43. Ki Heon Nam, Jeong Hae Kie, Mi Jung Lee, Tae-Ik Chang, Ea Wha Kang, Dong Wook Kim, et al. Optimal proteinuria target for renoprotection in patients with IgA nephropathy. PLoS One. 2014;9(7):e101935. doi:10.1371/journal.pone.0101935.
44. Hyeon Seok Hwang, Byung Soo Kim, Young Shin Shin, Hye Eun Yoon, Joon Chang Song, Bum Soon Choi, et al. Predictors for progression in immunoglobulin A nephropathy with significant proteinuria. Nephrology (Carlton). 2010;15:236. doi:10.1111/j.1440-1797.2009.01196.x.
45. You Cheol Hwang, Tae Won Lee, Myung Jae Kim, Moon Ho Yang, Chun Gyoo Ihm. Clinical course of patients with IgA nephropathy between combined treatment of immunosuppressive agents and ACE Inhibitor and ACE Inhibitor alone. Korean J Intern Med. 2001;16:105.
46. Han SY, Kwon YJ, Jo SK, Shin JH, Cha DR, Cho WY, et al. ACE gene polymorphism and renal responsiveness to ACE inhibitors in IgA nephropathy patients. Korean J Intern Med. 2000;15:13.
47. Hyeong Cheon Park, Zhong Gao Xu, Sorae Choi, Young Suck Goo, Shin Wook Kang, Kyu Hun Choi, et al. Effect of losartan and amlodipine on proteinuria and transforming growth factor-β1 in patients with IgA nephropathy. Nephrol Dial Transplant. 2003;18:1115. doi:10.1093/ndt/gfg090.
48. Moon Jae Kim, Joon Ho Song, Ju Hyun Suh, Seoung Woo Lee, Gyoung A Kim. Additive antiproteinuric effect of combination therapy with ACE inhibitor and angiotensin II receptor antagonist: differential short-term response between IgA nephropathy and diabetic nephropathy. Yonsei Med J. 2003;44:463.
49. Song JH, Lee SW, Suh JH, Kim ES, Hong SB, Kim KA, et al. The effects of dual blockade of the renin-angiotensin system on urinary protein and transforming growth factor-beta excretion in 2 groups of patients with IgA and diabetic nephropathy. Clin Nephrol. 2003;60:318.
50. Hyeon Joo Jeong, Yu Seun Kim, Kye Won Kwon, Myoung Soo Kim, Soon Kim, Kyu Hun Choi, et al. Segmental glomerulosclerosis in IgA nephropathy after renal transplantation:

relationship with proteinuria and therapeutic response to enalapril. Clin Transplant. 2003;17:108. doi:10.1034/j.1399-0012.2003.02067.x.
51. Choi S, Lee D, Jeong KH, Moon JY, Lee SH, Lee TW, et al. Prognostic relevance of clinical and histological features in IgA nephropathy treated with steroid and angiotensin receptor blockers. Clin Nephrol. 2009;72:353. doi:10.5414/CNP72353.
52. Ji Min Jeong, Dae Hun Lim, Hyung Chul Lee, Seul Hyun Oh, Joon Seok Choi, Pyung Kyun Park, et al. Renoprotective effect of deflazacort in IgA nephropathy with proteinuria. Korean J Med. 2009;7:593.
53. Tae Young Kim, Soon Bae Kim, Su-Kil Park. The efficacy of steroid pulse therapy in patients with IgA nephropathy. Clin Nephrol. 2012;78:100. doi:10.5414/CN107418.
54. Hyung Jung Oh, Song Vogue Ahn, Dong Eun Yoo, Seung Jun Kim, Dong Ho Shin, Mi Jung Lee, et al. Clinical outcomes, when matched at presentation, do not vary between adult-onset Henöch-Schönlein purpura nephritis and IgA nephropathy. Kidney Int. 2012;82:1304. doi:10.1038/ki.2012.302.
55. Yong Chul Kim, Ho Jun Chin, Ho Suk Koo, Suhnggwon Kim. Tacrolimus decreases albuminuria in patients with IgA nephropathy and normal blood pressure: a double-blind randomized controlled trial of efficacy of tacrolimus on IgA nephropathy. PLoS One. 2013;8:e71545. doi:10.1371/journal.pone.0071545.
56. Jae Il Shin, Beom Jin Lim, Pyung Kil Kim, Jae Seung Lee, Hyeon Joo Jeong, Ji Hong Kim. Effects of cyclosporin A therapy combined with steroids and angiotensin converting enzyme inhibitors on childhood IgA nephropathy. J Korean Med Sci. 2010;25:723. doi:10.3346/jkms.2010.25.5.723.
57. Byeong Yun Yang, Hee Seon Lee, Sang Heon Song, Ihm Soo Kwak, Soo Bong Lee, Dong Won Lee, et al. Use of low-dose sulodexide in IgA nephropathy patients on renin–angiotensin system blockades. Kidney Res Clin Pract 2012;31:163.
58. Kitae Bang, Ho Jun Chin, Dong Wan Chae, Kwon Wook Joo, Yon Su Kim, Suhnggwon Kim, et al. Anti-proteinuric effect of sulodexide in immunoglobulin A nephropathy. Yonsei Med J. 2011;52:588. doi:10.3349/ymj.2011.52.4.588.
59. Hajeong Lee, Dong Ki Kim, Kook-Hwan Oh, Kwon Wook Joo, Yon Su Kim, Dong-Wan Chae, et al. Mortality of IgA nephropathy patients: a single center experience over 30 years. PLoS One. 2012;7:e51225. doi:10.1371/journal.pone.0051225.
60. Hajeong Lee, Dong Ki Kim, Kook-Hwan Oh, Kwon Wook Joo, Yon Su Kim, Dong-Wan Chae, et al. Mortality and renal outcome of primary glomerulonephritis in Korea: observation in 1,943 biopsied cases. Am J Nephrol 2013;37:74. doi:10.1159/000345960.

Chapter 11
Differences in Etiology and Treatment in Japan

Ritsuko Katafuchi

Abstract IgA nephropathy is a major glomerulonephritis in Japan, 30–50 % of primary glomerulonephritis in adults and around 20 % in children. Around 70 % of patients are found as asymptomatic hematuria and/or proteinuria.

A number of investigations concerning tonsillar abnormality have been reported, which may reflect the characteristic pathogenesis of IgA nephropathy in Japan.

Since Kobayashi et al. firstly reported a significant effect of steroids on reducing proteinuria and prevention of progression in 1986, the steroid treatment was started to be used in patients with progressive IgA nephropathy.

The effect of tonsillectomy has been reported in IgA nephropathy with chronic tonsillitis. Since Hotta et al. reported the impact of tonsillectomy and steroid pulse therapy on the remission of urinary abnormality in 2001, tonsillectomy with steroid pulse therapy has been widely spread throughout of Japan as the first line of treatment of adult patients with IgA nephropathy. However, high-level evidence of the effectiveness of such treatment on long-term outcome has been required. In 2014, Kawamura et al. reported a significantly greater antiproteinuric effect in patients treated with tonsillectomy combined with steroid pulse therapy than in those with steroid pulse monotherapy in a multicenter, randomized, controlled trial (RCT). However, since the difference was marginal, the impact of tonsillectomy combined with steroid pulse therapy on the renal outcome remains unknown.

The treatment of Japanese childhood IgA nephropathy has been determined based on several RCTs in the different subset of children with IgA nephropathy by the Japanese Pediatric IgA Nephropathy Treatment Study Group.

Keywords IgA nephropathy • Japan • Etiology • Treatment

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11.1 The Characteristics of IgA Nephropathy in Japan

IgA nephropathy is a major glomerulonephritis in Japan. The percentage of IgA nephropathy in primary glomerulonephritis is 30–50 % in adults and around 20 % in children. In addition, around 70 % of patients are found as asymptomatic hematuria and/or proteinuria by school screening system or annual health check system for employee. Out of the population with asymptomatic hematuria and/or proteinuria, 60–70 % of adults and around 30 % of children are IgA nephropathy. The incidence of IgA nephropathy was estimated to be as high as 143 cases per one million per year.

11.1.1 The Clinical and Pathological Characteristics of IgA Nephropathy in Japan

In this part, the nationwide or other main clinicopathological studies of IgA nephropathy in Japan will be introduced chronologically, as summarized in Table 11.1. In 1977, the first English paper concerning IgA nephropathy in Japan was reported by Ueda et al. [1]. They found 85 patients (28 %) with IgA nephropathy among 306 Japanese patients, who were biopsied at Tokyo Jikei University between January 1967 and December 1974. In their study, the majority of patients with IgA nephropathy presented with a mild degree of proteinuria and/or persistent microscopic hematuria, and recurrent gross hematuria was noted in 15 % of patients [1]. Light microscopic findings of IgA nephropathy were divided into minimal, focal, and diffuse proliferative glomerular lesions. Diffuse proliferative glomerular lesions were observed in 56 % of patients, one-third of whom showed small crescent formations [1]. In 1983, Kitajima et al. reported the actual state of IgA nephropathy in Japan surveyed throughout the nation by a questionnaire [2]. From 26 department of pediatrics, 500 pediatric patients and, from 27 internal medicine, 2175 adult patients were collected. IgA nephropathy accounted for 19.2 % of the children and 30.0 % of the adults among primary glomerular disease. Majority of patients, regardless children and adults, were detected by chance proteinuria and/or hematuria. 87.2 % of the children and 74.6 % of the adults had a favorable outcome. During follow-up, nephrotic syndrome developed in 4.6 % of the children and 3.7 % of the adults, and hypertension developed in 3.5 % and 10.6 % of the children and adults, respectively. 1.8 % of the children and 8.0 % of the adults developed renal failure or died [2]. In 1985, a symposium of IgA nephropathy at the annual meeting of the Japanese Society of Nephrology in 1982 was edited by Doctor Glassock and modulated by Doctor Kurokawa and summarized that IgA nephropathy is a major glomerulonephritis in Japan and a substantial fraction of patients present with so-called chance proteinuria [3]. Two cohort studies were described as summarized in Table 11.1. As for pediatric IgA nephropathy in Japan, Yoshikawa et al. reviewed the detail clinical and pathological features of 258 children with IgA

Table 11.1 Characteristics of IgA nephropathy in Japan

Year	1977	1983		1985		1988–1989	1997	2005	2006
Author [Ref]	Ueda [1]	Kitajima [2]		Glassock [3]		Yoshikawa [4]	Koyama [5]	Nozawa [9]	Wakai [7]
Source of patients	Tokyo Jikei U	Nationwide		Tokyo Jikei U	Chiba Shakai Hoken Hospital	Kobe University or Tokyo Metropolitan Children's Hospital	Nationwide	Fukushima Medical University School of Medicine	Nationwide
No. of patients (%)	85/306 Bx (28 %)	500 children	2,175 adults	243	244	258 children	502/1063 Primary GN (47 %)	181 children	2,269
Male (%)	55 (65 %)	304 (61 %)	1,157 (53 %)	67 %		60 %	53 %	59 %	1,104 (49 %)
Age	=<19 y.o. 10 (12 %)	20–24 y.o. 520 (19 %)		<29 y.o. 65 %		Mean age of onset	120 (25 %)	Mean age of onset	526 (23 %)
	20–29 y.o. 55 (65 %)	15–29 y.o. 1,381 (52 %)			A peak at 20–30 y.o.	9.3 ± 2.8 y.o. in boys	178 (37 %)	11.0 ± 2.3 y.o.	500 (22 %)
	30–39 y.o. 18 (21 %)					10.3 ± 2.4 y.o. in girls	129 (27 %)		367 (16 %)
	>=40 y.o. 2 (2 %)						58 (12 %)		40–49 y.o. 456 (20 %)
									50–59 y.o. 289 (13 %)
									60 y.o.- 131 (6 %)
Mode of onset									
Chance proteinuria and/or hematuria	47 (55 %)	371 (74 %)	1,408 (65 %)	60 %		158 (61 %)	332 (68 %)	147 (81 %)	
Acute nephritic syndrome		32 (6 %)	206 (9 %)				46 (9 %)	8 (4 %)	

(continued)

Table 11.1 (continued)

Year	1977	1983		1985		1988–1989	1997	2005	2006
Gross hematuria	15 (18 %)	70 (14 %)	280 (13 %)	18 %		68 (26 %)	36 (7 %)	26 (14 %)	
Nephrotic syndrome		7 %	5 %			32 (12 %)	16 (3 %)	9 (5 %)	76 (3 %)
Clinical manifestation at the time of biopsy									
Hypertension	8 (9 %)			10 %				18 (10 %)	414 (18 %)
Renal dysfunction	Ccr<80 9 (11 %)	Ccr<80 13 %	21 %						Cr=>1.25 mg/dl 388 (17 %)
High serum IgA		28 %	46 %	73 %		16 %			
Pathology									
Minimal	18 (21 %)	23 %	19 %		29 %	16 %	34 (7 %)	123 (68 %)	Grade I[a] 514 (24 %)
Focal	19 (22 %)	28 %	27 %		Without C 4 %	Without C 31 %	114 (23 %)		Grade II[a] 698 (33 %)
					With C 20 %	With C 28 %			
Diffuse	Without C 33 (39 %)	50 %	53 %		Without C 16 %	Without C 10 %	311 (63 %)	58 (32 %)	Grade III[a] 688 (33 %)
	With C 15 (18 %)				With C 31 %	With C 15 %			
									Grade IV[a] 212 (10 %)
Follow-up data		481 children	1,349 adults						
Follow-up duration	3 y (1y–8y 9 mo)	29 mo	39 mo				11.8 ± 6.3 y	7.3 ± 3.1 y	77 mo
Remission		20 %	7 %	13 %		71 % for 15 years		91 (50 %)	
Nephrotic syndrome		5 %	4 %	3.5 %					

Hypertension		4 %	11 %	22.5 %				12 (7 %)	
Renal failure		13 %	26 %	20 %		11 %	14 %		
ESRF	1 (1 %)			5 %			20 %	7 (4 %)	207 (9 %)
Renal survival 5 years						95 %	96 %		
10 years						94 %	85 %	92 %	
15 years						89 %	75 %		
20 years							61 %	90 %	

U university, *Bx* biopsy, *y.o.* years old, *Ccr* creatinine clearance ml/min, *C* crescent, *y* year, *mo* months, *GN* glomerulonephritis

[a]Histological grade was determined according to the clinical guidelines for the diagnosis and treatment of patients with IgA nephropathy in Japan by a joint committee of the Special Study Group on Progressive Glomerular Disease, Ministry of Health, Labour and Welfare of Japan, and the Japanese Society of Nephrology, published in 1995 [8]. Grade I is slight mesangial cell proliferation and increased matrix. Glomerulosclerosis, crescent formation, or adhesion to the Bowman's capsule is not observed. Prominent changes are not seen in the interstitium, renal tubule, or blood vessels. Grade II is slight mesangial cell proliferation and increased matrix. Glomerulosclerosis, crescent formation, or adhesion to the Bowman's capsule is seen in <10 % of all biopsied glomeruli. Interstitium, tubules, and blood vessels are the same as Grade I. Grade III is moderate, diffuse mesangial cell proliferation and increased matrix. Glomerulosclerosis, crescent formation, or adhesion to the Bowman's capsule is seen in 10–30 % of all biopsied glomeruli. Cellular infiltration is slight in the interstitium except around some sclerosed glomeruli. Tubular atrophy is slight, and mild vascular sclerosis is observed. Grade IV is severe, diffuse mesangial cell proliferation and increased matrix. Glomerulosclerosis, crescent formation, or adhesion to the Bowman's capsule is seen in >30 % of all biopsied glomeruli. When sites of sclerosis are totaled and converted to global sclerosis, the sclerosis rate is >50 % of all glomeruli. Some glomeruli also show compensatory hypertrophy. The sclerosis rate is the most important of these indices. Interstitial cellular infiltration and tubular atrophy as well as fibrosis are seen. Hyperplasia or degeneration may be seen in some intrarenal arteriolar walls

nephropathy in 1989 [4]. IgA nephropathy was the most common primary glomerulonephritis in children, and 25 % of biopsy specimens obtained between 1981 and 1985 were IgA nephropathy. A total of 60 % were boys and mean age at onset was 9.3 ± 2.8 years in boys and 10.3 ± 2.4 years in girls, and 61 % of the children were found to have microscopic hematuria and/or asymptomatic proteinuria, mainly by a school screening program, which was started by the Japanese government in 1974. The remission rate of urinary abnormality was 28 %, 58 %, and 71 % at 5, 10, and 15 years, respectively. The renal survival free from chronic renal failure was 95 %, 94 %, and 89 % at 5, 10, and 15 years, respectively [4]. In 1985 and 1993, the Research Group on Progressive Renal Diseases organized by the Ministry of Health, Labour and Welfare of Japan conducted a national survey and the results were reported by Koyama et al. in 1997 [5]. They emphasized a high prevalence and relatively poor prognosis for IgA nephropathy in Japan. Out of 1,063 patients with primary glomerulonephritis, 502 patients (47 %) were diagnosed as IgA nephropathy. Nearly 70 % of patients had no clinical symptoms and were detected by routine health examination. The mean period of observation was 11.3 ± 6.3 years. Renal survival rates were 96 %, 85 %, 75 %, and 61 % at 5, 10, 15, and 20 years, respectively. At the end of the observation, 20 % of the patients had improved, 45 % showed no change, 14 % had deteriorated, and 20 % had end-stage renal failure. The risk factor for renal failure examined by logistic multivariate analysis was serum creatinine $=>1.4$ mg/dl and proteinuria 1+ or more determined at the time of biopsy [5]. In 1995, the Research Group on Progressive Renal Disease and the Research Committee on the Epidemiology of Intractable Diseases organized by the Ministry of Health, Labour and Welfare of Japan conducted a nationwide survey on IgA nephropathy [6]. This survey identified 5,324 patients with IgA nephropathy, who had visited general physicians, nephrologists, pediatricians, or urologists in Japan during 1994. Among those patients, Wakai et al. selected 2,269 patients with IgA nephropathy from 97 clinical units in Japan, conducted a prospective cohort study from 1995 to 2002, and reported a unique scoring system to predict renal outcome in IgA nephropathy in 2006 [7]. During follow-up, 207 patients (9 %) developed end-stage renal failure (ESRF). Systolic hypertension, proteinuria, hypoproteinemia, azotemia, and a high histological grade [8] at initial biopsy were independently associated with the risk of ESRF. They developed a scoring system to estimate the 7-year ESRF risk, from eight clinical and pathological variables [7]. In 2005, Nozawa et al. reported clinicopathological features and the prognosis of 181 Japanese children with IgA nephropathy [9]. After mean follow-up of 7.3 years from onset, 91 patients of 181 (50.3 %) were in clinical remission, 24 (13.2 %) had isolated hematuria, and 59 (32.6 %) had hematuria and proteinuria. Seven patients (3.9 %) developed ESRF. Predicted renal survival rate from onset was 92.3 % at 10 years and 89.1 % at 20 years. In multivariable analysis, age at onset and chronic changes of tubulointerstitium were associated with poor outcome [9].

11.1.2 The Incidence and Prevalence of IgA Nephropathy in Japan

In 1981, the incidence of IgA nephropathy in patients with chance proteinuria and hematuria was examined by a joint effort of many institutions and supported by the National Ministry of Health and Welfare [3]. Among 335 patients (138 children and 197 adults) who received kidney biopsy because of chance proteinuria and hematuria, 33 % of children and 63 % of adult patients were IgA nephropathy [3]. Although the exact incidence or prevalence of IgA nephropathy in Japan is not known, it can be estimated that as much as 0.3 % of the population or approximately 0.3 million Japanese are suffering from IgA nephropathy, based on the data obtained on the occasion of urinary examination in school children, students, and employees [3]. According to the survey from 1993 to 1995 by the Research Committee on the Epidemiology of Intractable Diseases with the financial supports from the Ministry of Health, Labour and Welfare of Japan, the estimated annual numbers of patients treated for IgA nephropathy in 1994 were 24,000 patients (95 % confident interval 21,000–27,000) [6]. In 1996, Yamagata et al. reported a unique prospective long-term follow-up studies of 805 patients (1.4 %) with asymptomatic proteinuria and/or hematuria (478 patients with pure hematuria, 150 with hematuria and proteinuria, and 177 with proteinuria) selected in the mass screening of 56,269 adults between 1983 and 1992 [10]. Renal biopsy was performed in 151 patients in the study population and 68.2 % of these patients had IgA nephropathy. High prevalence of IgA nephropathy in the adult patients with asymptomatic proteinuria and/or hematuria selected in the mass screening was confirmed in their study. In 2002, Yamagata et al. reported a further long-term follow-up study (6.35 years, range 1.03–14.6 years) on Japanese working men to elucidate prognosis and prevalence of chronic renal diseases among proteinuric and/or hematuric subjects found in mass screening [11]. A total of 772 subjects (1.5 %) selected from 50,501 Japanese men aged 15–62 years were found to have asymptomatic hematuria ($n = 404$), hematuria and proteinuria ($n = 155$), and proteinuria ($n = 213$) during their annual urine examination and five consecutive urinalyses. Renal biopsy was performed in 168 patients and 60.7 % of these patients had IgA nephropathy. The incidence of IgA nephropathy in the present subjects was estimated to be as high as 143 cases per one million per year [11]. In 2007, the Committee for the Standardization of Renal Pathological Diagnosis and the Working Group for Renal Biopsy Database of the Japanese Society of Nephrology started the first nationwide, web-based, and prospective registry system, the Japan Renal Biopsy Registry (J-RBR), to record the pathological, clinical, and laboratory data of renal biopsies. Sugiyama reported the results of a cross-sectional study using the pathological diagnoses registered on the J-RBR in 2007 and 2008 [12]. Data were collected from 818 patients from 18 centers in 2007 and 1582 patients from 23 centers in 2008. Renal biopsies were obtained from 726 native kidneys and 92 from renal grafts in 2007 and 1,400 native kidneys and 182 renal grafts in 2008 [12]. Of the native kidneys, the most frequent pathological diagnosis was IgA

nephropathy both in 2007 (32.9 %) and 2008 (30.2 %) [12]. In 2013, Sugiyama reported the registered data from 3,336 cases in 2009 and 4,106 cases in 2010 [13]. The percentages of IgA nephropathy were 31.6 % and 30.4 %, in 2009 and 2010, respectively.

11.2 The Etiology of IgA Nephropathy Investigated by Japanese Researchers

Although the pathogenesis of IgA nephropathy is not fully determined, they include the genetic factors, abnormality of IgA molecule, abnormality of mucosal immune system such as the tonsil and intestine, infectious antigen, and food antigen. Obviously, it is not known whether the etiology of IgA nephropathy differs among different parts of the world. There has been much works done in Japan concerning the pathogenesis of IgA nephropathy. Here, investigations by Japanese researchers concerning an abnormality of IgA molecule, tonsillar abnormality, infectious antigen, and food antigen are described.

11.2.1 Abnormality of IgA1 Molecule

The accumulated evidences of a pathogenetic significance of IgA1 molecule abnormality in IgA nephropathy investigated by Hiki et al. include the existence of the dimeric form of IgA class anti-IgA antibody in the circulation [14], the increased reactivity of O-glycan(s) in the IgA1 hinge region to jacalin due to an unusual glycosylation of serum IgA1 [15], the unusual glycosylation on the hinge region of jacalin-binding IgA1 due to an insufficient conformational stiffness to the hinge peptide, resulting in the aggregation of the IgA1 molecule [16], the presence of a defect in the Gal and/or GalNAc residues in the IgA1 hinge glycopeptides [17], the aberrant exposure of the peptide core of the IgA1 hinge region by a defective N-acetylgalactosaminylation [18], the underglycosylated hinge glycopeptide of IgA1 molecules in the glomerular accumulation of IgA1 [19], and a possibility of induction of the humoral immune response due to the peptide epitope of the IgA1 hinge region aberrantly exposed by underglycosylation [20].

11.2.2 Tonsillar Abnormality

In Japan, a number of investigations of the tonsillar abnormality in IgA nephropathy have been reported.

The reports of the histochemical investigations of tonsillar abnormality in patients with IgA nephropathy include the presence of IgA1 subclass in follicular dendritic cells (FDC) of the tonsil [21], a decreased reticulization of tonsillar crypt epithelium [22], an increase in CD5+ B cells (B-1 cell) numbers in the germinal center of tonsils [23], and an increase of CD208(+) dendritic cells [24].

The reports of the studies of IgA produced in tonsil in patients with IgA nephropathy include an overproduction of asialo IgA1 in the tonsils [25], an increase in the percentage of asialo-agalacto type O-glycans in IgA1 produced by tonsillar lymphocytes [26], and a significant increase in asialo-agalacto type O-glycans in the tonsillar IgA1 hinge in IgA nephropathy [27].

The reports for the production of cytokines by tonsillar mononuclear cells or gene expression of tonsillar cells in IgA nephropathy include increased IFN-gamma production [28], increased MCP-1, IL-8 incubation with staphylococcus enterotoxin-B or lipopolysaccharide [29], an elevated frequency of T cell receptor variable (TCR V) beta 6 in tonsils [30, 31], an increase in the proportions of TCR V beta 6-positive cells in peripheral blood T cells and an enhanced expression of TCR V beta 6 in tonsillar T cells in vitro stimulation with *Haemophilus parainfluenzae* antigen [31], a high intercellular expression of IFN-gamma on the T cells isolated from tonsils, higher spontaneous productions of IgA and IFN-gamma of tonsillar mononuclear cells (TMCs), a significantly higher productions of IgA, B cell activation factor BAFF and IFN-gamma of TMCs under stimulation with unmethylated deoxycytidyl-deoxyguanosine oligodeoxynucleotide, a high BAFF expression on the CD1c cells and the BAFF production of TMCs [32], an elevated gene expression of the APOBEC2 in the tonsils [33], a decreased gene expression of beta1,3-galactosyltransferase (beta3GalT) and the core 1 beta3GalT-specific molecular chaperone, Cosmic, UDP-N-acetyl-alpha-D-galactosamine, polypeptide N-acetylgalactosaminyltransferase 2 in tonsillar CD19-positive B lymphocytes, decreased protein expression of beta3GalT in the tonsils [34], a high expression of tonsillar mucosal toll-like receptor 9 (TLR9) in 23 % of the patients with IgA nephropathy and well correlation between tonsillar TLR9 and TLR9 SNP and the efficacy of tonsillectomy with steroid pulse therapy [35], and upregulated muscle-related genes and immune-related genes and downregulated polymeric Ig receptor [36].

11.2.3 Infectious Antigen

The viruses which have been reported in relation to IgA nephropathy include adeno, herpes simplex, varicella-zoster or parainfluenza 3 [37], retrovirus [38], and entero-viruses [39]. However, Kunimoto et al. reported that they could not detect the presence of herpes simplex virus 1 and 2, varicella-zoster virus, cytomegalovirus, and Epstein-Barr virus (EBV) 1 and 2 in tonsils, renal tissues, and mouth washings from patients with IgA nephropathy [40].

The bacteria which have been reported as a candidate of the pathogenesis of IgA nephropathy include *Haemophilus parainfluenzae* [41–48], *Streptococcus* [49, 50], *Escherichia coli* [51], *Haemophilus influenzae* [51], *Staphylococcus aureus* [52, 53], and *Helicobacter pylori* [54, 55] and periodontal disease bacteria such as *Treponema* sp., *Haemophilus segnis*, and *Campylobacter rectus* [56].

11.2.4 Food Antigen

Only few reports concerning the food antigen in relation to the pathogenesis of IgA nephropathy have been published between 1988 and 1991 in Japan. Yagame et al. reported no increase in the levels of IgA-circulating immune complexes (IgA-CIC) 2 weeks after the gluten-rich diet and suggested that the short-term gluten-rich diet might not increase the levels of IgA-CIC in Japanese patients with IgA nephropathy [57]. Kuramoto et al. reported no difference in the serum level of IgG, IgA, and IgM antibody titers against six food-derived antigens (rice, soybean paste, soy sauce, egg yolk, egg white, and gluten) between the patients with IgA nephropathy and healthy controls and suggested that food antigens appear to have little relation to IgA nephropathy [58]. The glomerular deposition of food antigens was investigated in two reports; 39.3 % and 25 % of patients were positive with casein [59, 60], 69 % and 75.0 % with soybean protein [59, 60], and 3.6 % with rice protein [59].

In 1991, Coppo et al. reported a comparative investigation concerning geographical difference in the importance of food antigen as a pathogenesis of IgA nephropathy [61]. Serum IgA as antibodies to dietary antigens (Ag), as lectin-binding molecules, and as conglutinin-binding immune complexes (IgA IC) was studied in people from Italy, Australia, and Japan. Increased values of IgA IC were detected in 42.8 % of Italian patients, in 23.8 % of Australian, and in only 8 % of Japanese patients. IgA antibodies against dietary Ag were detected in 19–28.5 % of Italian patients, 0–38 % of Australians, and 0–16 % of Japanese. The relationship between IgA IC and serum concentration to alimentary component was particularly evident for Italian and Australian IgA nephropathy patients [61].

These results suggest that the dietary antigen as a pathogenesis might be less important in Japanese patients with IgA nephropathy.

11.3 The Treatment of IgA Nephropathy in Japan

11.3.1 Overview of the Treatment of IgA Nephropathy in Japan

The most conspicuous treatment of the patients with IgA nephropathy in Japan includes steroid therapy, tonsillectomy, and tonsillectomy with steroid pulse therapy.

Kobayashi et al. firstly reported a significant effect of steroids on the amount of proteinuria and prevention of progression of renal deterioration in series of retrospective studies [62–66]. Since then, Japanese nephrologists began to use steroid in patients with progressive IgA nephropathy. Although there have been many retrospective studies concerning the efficacy of steroid therapy [67–78], only a few randomized control trials have been reported in adult patients with IgA nephropathy [79–81].

The effect of tonsillectomy has been reported in patients with IgA nephropathy especially in those with chronic tonsillitis [82–89]. In 2001, Hotta et al. reported the impact of tonsillectomy and steroid pulse therapy on the remission of urinary abnormality in patients with IgA nephropathy [90]. Since then, there have been many reports published about the efficacy of such therapy [91–100], and tonsillectomy with steroid pulse therapy has been widely spread throughout Japan as the first line of treatment of adult patients with IgA nephropathy [101, 102]. However, the tonsillectomy with steroid pulse therapy was not accepted as a standard treatment of IgA nephropathy internationally due to the lack of high-level evidence of the effect of such therapy. The recent Kidney Disease: Improving Global Outcomes clinical guideline for glomerulonephritis suggests that tonsillectomy not be performed for IgA nephropathy, because no randomized controlled trial of tonsillectomy has been performed [103]. Recently, Kawamura et al. reported the results of a multicenter, randomized, controlled trial (RCT) of tonsillectomy combined with steroid pulse therapy in patients with IgA nephropathy versus steroid pulse monotherapy conducted by the Special IgA Nephropathy Study Group of the Progressive Glomerular Diseases Study Committee organized by the Ministry of Health, Labour and Welfare of Japan [104]. Although they found a significantly greater antiproteinuric effect in combined therapy, the difference was marginal. Thus, they concluded that the impact of tonsillectomy combined with steroid pulse therapy on the renal functional outcome remains to be clarified. The details of this randomized controlled trial will be described in Chap. 19.

In contrast to the treatment of the adult patients with IgA nephropathy in Japan, the treatment of Japanese pediatric patients with IgA nephropathy has been determined in evidence-based method by the Japanese pediatric IgA nephropathy treatment group. They performed several RCTs or pilot studies in the different subset of children with IgA nephropathy [105–110].

In this part, the major clinical investigations of treatment of IgA nephropathy in Japan will be described, in adult patients and pediatric patients, separately.

11.3.2 The Treatment of Adult Patients with IgA Nephropathy in Japan

11.3.2.1 Steroid Therapy

Main results of a series of the retrospective studies by Kobayashi et al., case series by Yoshimura et al., and three RCTs are summarized in Table 11.2.

In 1986, Kobayashi et al. reported the efficacy of steroid treatment in patients with IgA nephropathy, whose urinary protein was between 1.0 and 2.0 g/day [62]. A total of 14 patients were treated with steroids, and 29 patients received no steroids. They found significant reduction of urinary protein in patients with steroid treatment and deterioration of renal function in patients without steroids. The difference in the amount of proteinuria and renal function at the final observation between the patients with steroid treatment and those without it was more distinct in patients with initial creatinine clearance (Ccr) 70 ml/min or more. Thus, they concluded that treatment with steroids in IgA nephropathy may be beneficial, especially in the early stage of the disease. In 1988, Kobayashi et al. investigate the efficacy of steroids in 29 patients with IgA nephropathy whose proteinuria is 2.0 g/day or more and found that steroids were effective in patients with initial Ccr greater than 70 ml/min [64]. They suggested that steroid therapy in IgA nephropathy may be able to stabilize a progressive course, especially in the early stage of the disease. In 1989, Kobayashi et al. further investigated the efficacy of steroid therapy in IgA nephropathy patients with proteinuria between 1.0 and 2.0 g/day in the follow-up of more than 4 years and confirmed the efficacy of steroid treatment in the reduction of the amount of proteinuria and stabilization of renal function in patients with initial Ccr 70 ml/min or more [65]. In 1996, Kobayashi et al. confirmed the efficacy of steroid therapy on 10-year kidney outcome in patients with proteinuria 1–2 g/day and Ccr 70 ml/min or more [66].

The report by Yoshimura et al. in Japanese article is worthy to introduce here because it is the first one concerning the effect of steroid pulse therapy in IgA nephropathy [67]. They reported a significant decrease in urinary protein and a significant increase in glomerular filtration rate (GFR) after the methylprednisolone pulse therapy in eight patients with progressive IgA nephropathy, defined as 2+ or more urinary protein and crescents in 10 % or more glomeruli. They also found a significant reduction in the percentage of cellular crescent in the second biopsy after the treatment compared to the first biopsy. Thus, they suggested that the methylprednisolone pulse therapy significantly reduced urinary protein excretion and improved renal function through suppression of new crescent formation as well as transformation of cellular crescents to fibrocellular or fibrous crescents.

In 2000, Shoji et al. reported the result of the first RCT in Japanese patients with IgA nephropathy [79]. Inclusion criteria were diffuse mesangial proliferation, the duration of abnormal urinalysis less than 36 months, proteinuria less than 1.5 g/day, and serum creatinine level less than 1.5 mg/dL. A total of 21 patients were randomly assigned to the corticosteroid group (11 patients) and the antiplatelet

Table 11.2 Steroid treatment of adult patients with IgA nephropathy in Japan

1st author	Year	Study design	Inclusion criteria	No. of patients	No. of controls	Initial dose of steroid (mg/day)	Duration of steroid treatment	Follow-up duration	Main results				
Kobayashi [62]	1986	R	UP 1–2 g/day	14	29	PSL40 mg	19 mo	60–80 mo		Steroid group		Control	
										Initial	Last	Initial	Last
									UP (g/day)	1.2	0.7*	1.3	1.3
									Ccr (ml/min)	86	78*	86	45
									Progressive	21 %		69 %	
									ESRF	7 %		31 %	
Kobayashi [64]	1988	R	UP >= 2 g/day	29	–	PSL40 mg	12–36 mo	68–93 mo	Initial Ccr	>= 70		< 70	
									n	15		14	
										Initial	Last	Initial	Last
									UP (g/day)	3.3	1.5	3.1	1.7
									Ccr (ml/min)	83	62	51	18
									Progressive	7 (47 %)		5 (36 %)	
									ESRF	1 (7 %)		8 (57 %)	
Kobayashi [65]	1989	R	UP 1–2 g/day and followed up >= 4 years	18	42	PSL40 mg	18 mo	73–79 mo		Steroid group		Controls	
									Ccr >= 70	15 cases		31 cases	
									Stable	11 (73 %)		12 (39 %)	
									Progressive	3 (20 %)		10 (32 %)	
									ESRF	1 (7 %)		9 (29 %)	
									Ccr < 70	3 cases		11 cases	
									Stable	0 (0 %)		0 (0 %)	
									Progressive	2 (67 %)		0 (0 %)	
									ESRF	1 (33 %)		11 (100 %)	

(continued)

Table 11.2 (continued)

1st author	Year	Study design	Inclusion criteria	No. of patients	No. of controls	Initial dose of steroid (mg/day)	Duration of steroid treatment	Follow-up duration	Main results				
Kobayashi [66]	1996	R	UP 1–2 g/day and Ccr 70 or more and histological score >=7 and followed up >=10 years	20	26	PSL40mg	18 mo	10 years		Steroid group		Controls	
									Initial data				
									Proteinuria (g/day)	1.4 ± 0.4		1.3 ± 0.3	
									Ccr (ml/min)	85 ± 14		88 ± 13	
									Hypertension (%)	25		38	
									Histological score	10.7 ± 2.5		11.0 ± 3.0	
									Kidney survival				
									5 years	100 %		84 %*	
									10 years	80 %		34 %*	
Yoshimura [67]	1992	Cases	UP >= 2+ and cellular crescent >=10 % of glomeruli	8	–	2 courses of mPSL 1 g/day for 3 days	3–5 mo	3–5 mo		Pre-treatment		Post-treatment	
									UP	2.3 ± 0.5		1.1 ± 0.3**	
									GFR	83 ± 11		96 ± 10**	
									Crescent (%)	25 ± 6		16 ± 5	
Shoji [79]	2000	RCT	UP<1.5 g/day and Scr <1.5 mg/dl and diffuse mesangial proliferation (Mes pro)	11	10	PSL 0.8 mg/kg	12 mo	13.4 mo		Steroid group		Controls	
										Initial	Last	Initial	Last
									UP	0.75	0.29**	0.73	0.71
									Mes pro (%)	65	42.7**	59.3	50.7
									Increase in mm (%)	62	45.2**	63.4	56.9
									Cellular crescent (%)	7.6	0.9**	1.9	2.5
									αSMA (grade)	2.1	1.2**	1.8	1.6

Katafuchi [80]	2003	RCT	Glomerular score 4~7	43	47	PSL20 mg	24 mo	64–65 mo		Steroid group		Controls	
									ΔUP/UCR	−0.84 ± 1.78*		0.26 ± 1.65	
									ESRF: n, (%)	3 (5.7)		3 (6.4)	
Koike [81]	2008	RCT	Mild histological activities	24	24	PSL 0.4 mg/kg	24 mo	24 mo		Steroid group		Controls	
									Scr (mg/dl)	0.92 ± 0.26*		1.15 ± 0.35	
									Vascular changes	0.63 ± 0.73*		1.08 ± 0.88	
										Initial	Last	Initial	Last
									UP (g/day)	0.97	0.31**	0.89	0.68
									U-RBC/HPF	35.6	13.7**	30.1	12.4**

R retrospective study, *UP* urinary protein, *PSL* prednisolone, *mo* months, *Ccr* creatinine clearance (ml/min), *ESRF* end-stage renal failure, *n* number of patients, *Cases* case series, *mPSL* methylprednisolone, *GFR* glomerular filtration rate (ml/min), *RCT* randomized control trial, *Scr* serum creatinine mg/dl, *mm* mesangial matrix, *SMA* smooth muscle actin, *ΔUP/UCR* changes in urinary protein/creatinine ratio between initial and last follow-up, *U-RBC* urinary red blood cells, *HPF* high-power field
*Significant difference; **Significant change

group (10 patients). They found a significant reduction in proteinuria and a significant improvement of histological findings in the corticosteroid group and concluded that early treatment with corticosteroids for adult diffuse proliferative IgA nephropathy is effective in reducing renal injury.

In 2003, Katafuchi et al. reported the results of RCT of low-dose prednisolone therapy in patients with IgA nephropathy with moderate histological severity [80]. A total of 43 patients in the steroid group and 47 patients in the control group were included in their study and found a significant antiproteinuric effect of steroids, but there was no effect of steroid treatment on kidney outcome. Thus, they suggested that an insufficient dose of prednisolone in their protocol may be the reason for the discrepancy between the effect on proteinuria and kidney survival.

In 2008, Koike et al. reported the result of RCT in patients with IgA nephropathy with mild histological activities [81]. A total of 24 patients in the steroid group and 24 patients in the control group were included in their study. They found a significant decrease in the amount of proteinuria and the grade of hematuria in steroid group compared to controls and concluded that low-dose steroid therapy for IgA nephropathy patients with mild inflammatory lesions could reduce the amount of urinary protein excretion and prevent deterioration of renal function.

11.3.2.2 Tonsillectomy

The results of reports that concern the efficacy of tonsillectomy in a large number of patients with IgA nephropathy are summarized in Table 11.3.

In 1996, Tomioka et al. reported the relationship between remission rates of urinary abnormality at 1 year after tonsillectomy and clinico-pathological factors in 104 patients with IgA nephropathy, who received tonsillectomy [83]. They found that the patients with mild or moderate renal pathology had higher postoperative remission rates of proteinuria than those with advanced renal pathology, and there was no significant relationship between the efficacy of tonsillectomy and the past history of tonsillitis, age, pus plugs in the lacunae, temporary deterioration of urinary findings after tonsillectomy, and results of provocation tests.

In 2003, Xie et al. reported a clinical efficacy of tonsillectomy on long-term renal survival of patients with IgA nephropathy [85]. They reviewed the clinical course of 118 patients with IgA nephropathy, of whom 48 patients received tonsillectomy and 70 patients did not. The mean observation time was 192.9 ± 4.8 months (48–326 months). Age, gender, amount of urinary protein excretion, serum creatinine, serum IgA, blood pressure, and histopathologic findings at the time of renal biopsy and treatments during the observation period were not significantly different between patients with and without tonsillectomy. The percentage of patients who developed ESRF was significantly lower in patients with tonsillectomy than those without tonsillectomy, 10.4 % and 25.7 %, respectively. By Kaplan-Meier analysis, the renal survival rate at 240 months was significantly higher in patients with tonsillectomy than those without it (89.6 % and 63.7 %, respectively). In the multivariate Cox regression model, tonsillectomy had a

Table 11.3 Tonsillectomy with or without steroid treatment of adult patients with IgA nephropathy in Japan

1st author	Year	Study design	Inclusion criteria	Patients	Controls	Follow-up period	UP Remission (%)		OB Remission (%)		CR (UP+OB remission, %)		Long-term kidney survival			
Tonsillectomy																
Tomioka [83]	1996	R	TX+	104 TX+	–	1 year					38					
Xie [85]	2003	R	Followed up >= 5 years	48 TX+	70 TX−	193 mo								TX+		TX−
													ESRF (%)	10.4*		25.7
													20 year renal survival (%)	89.6*		63.7
Akagi [86]	2004	R	Followed up >=10 years	41 TX+	30 TX−	151–159 mo					TX+	TX−		TX+		TX−
											24.4	13.3	Renal survival rate (%)	95.1*		73.3
Maeda [89]	2012	Cohort	Scr <2.0 mg/dl and followed up >= 1 year	70 TX+ (50 with steroids)	130 TX− (19 with steroids)	7 years					*Multivariate-adjusted HR of TX for CR*		*Multivariate-adjusted HR of TX for decline GFR*			
											Model	HR (95 % CI)	Model		HR (95 % CI)	
											Age and gender adjusted	3.90* (2.46–6.18)	Age and gender adjusted		0.14* (0.02–1.03)	
											Clinical factor adjusted	4.03* (2.52–6.44)	Clinical factor adjusted		0.12* (0.02–0.89)	
											Histological factor adjusted	3.71* (2.30–5.98)	Histological factor adjusted		0.12* (0.02–0.89)	
											Treatment factor adjusted	3.06* (1.74–5.40)	Treatment factor adjusted		0.10* (0.01–0.85)	
Tonsillectomy plus steroid therapy																
Hotta [90]	2001	R	Followed up >= 36 mo	250 TX+	79 TX−	82.3 mo					48		*Probability of progressive deterioration at 10 year*			
														CR+	CR−	
														0	21 ± 5 %	
Sato [91]	2003	R	Scr >= 1.5	70		70.3 mo								Total	TSP	S	C
													n	70	30	25	15
													ESRF (%)	41.4	13.3*	56.0	73.3
Matutani [92]	2004	R	TX + steroids	186		N.D.	72		60							
Komatsu [93]	2005	Cohort	Followed up >= 6 mo	104 (29 with steroid)	133	62.3 mo	TX+	TX−	TX+	TX−	TX+	TX−		TX+		TX−
							44.2	33.1	53.8*	21.8	31.7*	16.5	ESRF (%)	8.7		15.8

(continued)

Table 11.3 (continued)

1st author	Year	Study design	Inclusion criteria	Patients	Controls	Follow-up period	UP Remission (%)		OB Remission (%)		CR (UP+OB remission, %)						Long-term kidney survival				
Miyazaki [94]	2007	Cohort	Followed up > 5 years	101		> 5 year						Total	TSP	S	T	C					
											n	101	75	18	3	5					
											CR (%)	62	69	39	33	40					
Komatsu [95]	2008	Cohort	Scr < 2.0 and H-Grade[a] >=2	35 with TSP	20 with SP	54.0 mo	TSP	SP	TSP	SP	TSP			SP				TSP		SP	
							65.7*	35.0	77.1*	45.0	54.3*			25.0			Double Scr	0		1 (5 %) (ESRF)	
Kawaguchi [96]	2010	R	OB and UP =< 0.5 g/day	388		24 mo						All	C	T	S	TSP					
											n	388	58	67	23	240					
											CR at 60 mo (%)	43.8	17.2	34.3	39.1	72.5*					
Ieiri [98]	2012	R	TSP + followed up >= 12 mo	830		81.6 mo					Duration before TSP (mo)		<36	37–84	>=85	?					
											n		338	86	71	335					
											CR (%)		87.3	73.3	42.3	43.6					
Yamamoto [100]	2013	R	Followed up >= 18 mo	208		76 mo												T	TS	TSP	C
																	n	56	33	47	72
																	Doubling Scr (%)	8.9	6.1	2.1	30.6
																	HR	0.31*	0.21	0.03*	Control
Kawamura [104]	2014	RCT	UP 1–3.5 g/day and Scr =< 1.5	33 with TSP	39 with SP	12 mo	TSP	SP	TSP	SP	TSP			SP							
							63	39	68	64	47			28							

TX tonsillectomy, *UP* urinary protein, *OB* urinary occult blood, *CR* clinical remission, i.e., disappearance of urinary protein and hematuria, *mo* months, *ESRF* end-stage renal failure, *n* number of patients, *Scr* serum creatinine (mg/dl), *HR* hazard ratio, *CI* confidence interval, *No* number of patients, *GFR* glomerular filtration rate (ml/min), *TSP* Tonsillectomy with steroid pulse therapy, *S* conventional steroid therapy only, *C* conservative therapy, *T* tonsillectomy only, *SP* steroid pulse therapy only, *?* unknown, *RCT* randomized control trial

*Significant relation or significant difference

[a]Histological grade was determined according to the second clinical guidelines for the diagnosis and treatment of patients with IgA nephropathy in Japan [8]

significant effect on renal outcome (hazard ratio, 0.22; 95 % confidence interval, 0.06–0.76). They concluded that tonsillectomy has a favorable effect on long-term renal survival in patients with IgA nephropathy.

In 2004, Akagi et al. also reported an efficacy of tonsillectomy on the improvement of long-term renal outcome in 10-year retrospective case-control study with 71 patients with IgA nephropathy [86]. Out of them, 41 patients received tonsillectomy (TX+) and 30 did not received tonsillectomy (TX−). In TX+ group, there was no relationship between long-term outcome and the results of tonsillar provocation test, although the percentage of the patients with stable renal function was significantly higher in patients with mild pathology than those with advanced pathology. They concluded although evaluation of renal pathology was useful in predicting the long-term effects of tonsillectomy in IgA nephropathy patients, the results of tonsillar provocation tests were not.

In 2012, Maeda et al. reported beneficial effects of tonsillectomy on remission and progression of IgA nephropathy in a single-center 7-year historical cohort study in 200 patients with IgA nephropathy [89]. Out of 200 patients, 70 received tonsillectomy. Tonsillectomy was associated with increased incidence of clinical remission and decreased incidence of GFR decline after adjustment for age and gender, laboratory, histological severity, or treatment variables (steroid and renin-angiotensin system inhibitors). Thus, they concluded that tonsillectomy was associated with a favorable renal outcome of IgA nephropathy in terms of clinical remission and delayed renal deterioration independent of steroid therapy.

11.3.2.3 Tonsillectomy with Steroid Therapy

The major reports that concern the efficacy of tonsillectomy and steroid therapy including steroid pulse therapy in patients with IgA nephropathy are summarized in Table 11.3.

In 2001, Hotta et al. reported the results of a retrospective investigation of renal outcome in 329 patients with IgA nephropathy with an observation period longer than 36 months [90]. Tonsillectomy was performed in 250 patients (76 %); 125 patients were treated with steroid pulse therapy. In 157 of 329 patients (48 %), disappearance of urinary abnormalities (clinical remission) was obtained. None of these 157 patients showed progressive renal deterioration, defined as a 50 % increase in serum creatinine level from baseline, during the observation period. Conversely, in patients without clinical remission, the Kaplan-Meier estimate of probability of progressive deterioration was 21 ± 5 % at 10 years. In the multivariate Cox regression model, initial serum creatinine level, histological score, tonsillectomy, and high-dose methylprednisolone therapy had a significant impact on clinical remission. Thus, they suggested that interventions aimed at achieving clinical remission have provided encouraging results applicable to managing patients with IgA nephropathy. Since their study has been published, the goal of the treatment of the patients with IgA nephropathy seems to be shifted from the prevention of the progression toward the clinical remission in Japan.

In 2003, Sato et al. reported the results of retrospective investigation in 70 patients with advanced IgA nephropathy (serum creatinine 1.5 mg/dl or higher) [91]. They

found that the incidence of ESRF was significantly lower in patients treated by steroid pulse with tonsillectomy than those treated by conventional steroid and supportive therapy at a baseline creatinine level of 1.5–2 mg/dl, but no statistical difference was observed at a level of >2 mg/dl. Thus, they concluded that steroid pulse therapy combined with tonsillectomy may be more effective than conventional steroid therapy in patients with a baseline creatinine level of 2 mg/dl or less.

In 2004, Matutani et al. reported the relationships between the remission rate of urinary abnormalities and clinical characteristics and the tonsillar findings in 186 patients with IgA nephropathy who received tonsillectomy and steroid pulse therapy [92]. The remission of proteinuria was observed in 134 patients (72 %) and remission of hematuria was observed in 111 patients (60 %). There was no significant difference in remission rate of either proteinuria or hematuria in terms of the past history of recurrent tonsillitis, episodes of synpharyngitic gross hematuria, pus plugs in the tonsillar lacunae, size of tonsils, age, and the results of tonsillar provocation tests. Thus, they suggest that it is difficult to predict the efficacy of tonsillectomy and steroid pulse therapy based on the gross appearance of tonsils, the tonsillar provocation test, or clinical episodes of tonsillitis.

In 2005, Komatsu et al. investigated the significance of prognostic factors in their cohort study in 237 patients with IgA nephropathy [93]. Steroid therapy was performed in 78 patients (32.9 %). Tonsillectomy was performed in 104 patients (43.9 %). A total of 30 patients developed ESRF. They found a significant contribution of tonsillectomy to the maintenance of renal survival and the disappearance of urinary abnormalities and that steroid therapy independently contributed to improve renal prognosis in addition to tonsillectomy. Thus, they concluded that steroid therapy and tonsillectomy can independently improve renal outcome in patients with IgA nephropathy.

In 2007, Miyazaki et al. reported an effect on clinical remission (normalization of urinary abnormality) of tonsillectomy combined with three courses of high-dose corticosteroid therapy compared to steroid monotherapy in multicenter prospective cohort study in 101 patients with IgA nephropathy observed for 5 years and concluded that the goal should be cured and released from disease at an earlier stage of IgA nephropathy [94]. In their study, the difference of efficacy on clinical remission between tonsillectomy with steroid pulse therapy and steroid monotherapy was significant only in patients with proteinuria 1.0 g/day or more. They suggested that it is necessary to reveal which clinical or histological features will most likely derive the most benefit from tonsillectomy with steroid pulse therapy, and the best strategy for each stage of IgA nephropathy should be confirmed. In addition, they reported useful data about the relapse rate, 4 % in patients treated with tonsillectomy and steroid pulse therapy and 17 % in those with steroid monotherapy.

In 2008, Komatsu et al. reported the results of a prospective, controlled study in 55 patients with IgA nephropathy [95]. A total of 35 patients received tonsillectomy with steroid pulse (TSP) therapy and 20 with steroid pulse (SP) monotherapy. At final observation, the ratios of the urinary protein and/or hematuria remission were significantly higher in TSP than in SP group. The Cox regression model showed that the combined therapy was approximately sixfold more effective in causing the disappearance of proteinuria than steroid pulse monotherapy. They concluded that

tonsillectomy combined with steroid pulse treatment can induce clinical remission in patients with IgA nephropathy.

In 2010, Kawaguchi et al. reported an effectiveness of steroid pulse therapy with tonsillectomy in 388 patients with IgA nephropathy with minimal proteinuria (daily urinary protein 0.5 g or less) [96]. During a median follow-up of 24 months, 170 patients showed clinical remission (43.8 %). They found significantly higher rate of clinical remission in patients with tonsillectomy plus steroid pulse therapy than in those with other therapies. Less severe histological findings were substantially associated with higher clinical remission rate in patients treated with tonsillectomy plus steroid pulse therapy. They concluded that tonsillectomy with steroid pulse therapy significantly increased the probability of clinical remission in IgA nephropathy patients with glomerular hematuria and minimal proteinuria, and it was more effective in those with less severe histological findings.

In 2012, Ieiri et al. reported the relationship between the duration of nephropathy and clinical remission rate in 495 patients with IgA nephropathy treated by tonsillectomy and steroid pulse therapy [98]. They found that the duration of nephropathy 36 months or less was a significant predictor of clinical remission and concluded that shorter duration of nephropathy is associated with higher likelihood of clinical remission in patients with IgA nephropathy treated by tonsillectomy and steroid pulse therapy.

In 2013, Yamamoto et al. reported the therapeutic impact of tonsillectomy and combined therapies of tonsillectomy plus steroid on the long-term prognosis in a retrospective study of 208 patients with IgA nephropathy [100]. According to the strategies for treatments, they divided patients into four groups: tonsillectomy and steroid pulse (TSP, 47 patients), tonsillectomy and oral steroid (TOS, 33 patients), tonsillectomy alone (T, 56 patients), and C group (no particular therapy, 72 patients). In multivariate analysis by the Cox regression proportional hazard model, gender, age, histological activity, dialysis induction risk, and therapy were significantly associated with doubling creatinine levels. Since hazard ratios for doubling creatinine levels compared to C group were smallest in TSP group, they concluded a combination therapy of tonsillectomy and steroid pulse had the most significant therapeutic impact compared to other therapies.

So far, nationwide surveys as for tonsillectomy with steroid pulse (TSP) therapy in patients with IgA nephropathy have been conducted by Japanese Society of Nephrology [101, 102].

In 2009, Miura et al. reported the results of the survey performed in 2006 [101]. As a primary survey, they sent a questionnaire to 848 hospitals in Japan, in order to gather information about the prevalence and efficacy of TSP therapy for patients with IgA nephropathy. As a secondary survey, they collected data from both low- and high-clinical remission (CR)-rate groups to determine which factors predicted resistance to TSP therapy. A total of 2746 patients received TSP therapy between 2000 and 2006. The CR rates 6 and 12 months after TSP therapy were 32.0 % (347/1,085) and 45.6 % (452/991), respectively. Analysis of the 30 hospitals in which TSP therapy had been performed on at least ten patients revealed that the CR rates varied from below 10–100 %. A secondary survey of ten hospitals revealed that, after correction of the CR rate from each hospital, patients could be

categorized into three groups: those with a low CR rate (122 patients in four hospitals), a middle CR rate (78 patients in four hospitals), and a high CR rate (103 patients in two hospitals). The CR rate of all patients was 54.1 %. A comparison of patient data between the low and high CR rate groups showed a significant difference in age at onset, amount of proteinuria, total protein, pathological grade, and prognostic score by Wakai et al. [7]. A multivariate logistic analysis demonstrated that resistance to TSP therapy depends on age at onset, amount of proteinuria, hematuria grade, and pathological grade. A score predicting resistance to TSP therapy could be derived by the formula: $[(-0.0330) \times (\text{age}) + (0.4772) \times \log (\text{amount of proteinuria}) - (0.0273) \times (\text{hematuria grade: 0, 1, 2, and 3}) + (0.7604) \times (\text{pathological grade: 1, 2, 3, and 4}) - 0.1894]$. From these results, they concluded that patients with either early-stage or mild to moderate IgA nephropathy easily achieve CR following TSP therapy, whereas patients with late-stage or severe disease are prone to TSP therapy resistance.

The second nationwide survey for the current status of treatments in patients with IgA nephropathy in Japan conducted in 2008 by sending questionnaires to the 1,194 teaching hospitals of the Japanese Society of Nephrology (JSN). The results were reported by Matsuzaki et al. in 2013 [102]. Among the total 376 hospitals (31.4 %) that responded, 188 hospitals (66.2 % in the internal medicine departments) performed TSP, out of which 137 hospitals (61.4 %) had begun to perform TSP in the period from 2004 to 2008. Approximately 68 % of pediatric hospitals (68 hospitals) performed combination therapy with prednisolone, azathioprine, heparin-warfarin, and dipyridamole. The remission rates for hematuria and proteinuria after TSP tended to be higher than those following other corticosteroid therapies. Almost all hospitals prescribed antiplatelet agents and renin-angiotensin system inhibitor (RAS-I). They concluded that TSP is becoming a standard treatment for adult IgA nephropathy patients in Japan in addition to popular treatments such as antiplatelet agents and RAS-I.

Recently, Kawamura et al. reported the results of RCT of tonsillectomy combined with steroid pulse therapy in patients with IgA nephropathy conducted by the Special IgA Nephropathy Study Group of the Progressive Glomerular Diseases Study Committee organized by the Ministry of Health, Labour and Welfare of Japan in 2014 [104] as shown in Table 11.3. The details of this RCT will be described in Chap. 19. Briefly, the patients with IgA nephropathy, proteinuria, and low serum creatinine were randomly allocated to receive TSP or steroid pulses alone. The primary end points were urinary protein excretion and the disappearance of proteinuria and/or hematuria. Although they found a significant antiproteinuric effect of TSP, the difference was marginal. Thus, they concluded that the impact of TSP on the renal functional outcome remains to be clarified.

11.3.2.4 Immunosuppressant Other Than Steroids

So far, there have been only few reports concerning the efficacy of immunosuppressant other than steroids in adult patients with IgA nephropathy [111, 112]. In

2000, Tsuruya et al. reported an efficacy of combination therapy using prednisolone (PSL) and cyclophosphamide (CPA) on slowing the progression of renal deterioration in 45 patients with IgA nephropathy revealing moderate to severe histological changes [111]. After treatment, they found a significant reduction in proteinuria in 26 patients treated with PSL+CPA whereas no reduction in 19 controls. The progression rate was significantly lower in patients treated with PSL+CPA than in the control group. Thus, they suggested that the immunosuppressive treatment with CPA might be useful to preserve renal function in patients with histologically advanced IgA nephropathy. In 2007, Mitsuiki et al. elongated the follow-up in patients of previous study and reported the effect of PSL+CPA on long-term renal outcome in 35 patients (27 treated patients and eight controls) with histologically advanced IgA nephropathy [112]. Renal survival at 5 years was 89.8 % in PSL+CAP group and 0 % in control group. Adverse effects of PSL+CPA were minimal and mild. They suggested that PSL+CPA therapy safely improved the renal prognosis of patients with severe IgA nephropathy.

11.3.2.5 Renin-Angiotensin System Blocking Agents

There has been only one RCT concerning the effect of renin-angiotensin system blocking agents in patients with IgA nephropathy in Japan. In 2007, Horita et al. reported the results of RCT performed to evaluate the additional effect of angiotensin II receptor blocker to steroid therapy on the reduction of proteinuria and on renal function in patients with IgA nephropathy [113]. Thirty-eight patients with IgA nephropathy (age, 33 ± 11 years; creatinine clearance, 103 ± 31 mL/min; proteinuria, 1.6 ± 0.5 g/day) were assigned into two groups that were treated with either prednisolone (PSL, 30 mg/dl, gradually tapered to 5 mg/dl over 2 years) plus 50 mg/day of losartan (LST) or PSL alone. Two years of treatment in both groups, proteinuria significantly decreased compared with baseline. Creatinine clearance was similar at the start of study in both groups, but at the end of the study, it was significantly lower in PSL alone group than in PSL plus LST group. Thus, they concluded that combined therapy with PSL plus LST appears to be more effective than PSL alone in reducing proteinuria and protecting renal function in patients with IgA nephropathy.

11.3.3 The Treatment of Pediatric Patients with IgA Nephropathy in Japan

The Japanese Pediatric IgA Nephropathy Treatment Study Group has accumulated high-level evidence according to the RCTs in different subsets of children with IgA nephropathy [105, 107–109]. The results of these RCTs and two pilot studies [106, 110] are summarized in Table 11.4.

Table 11.4 Treatment of pediatric patients with IgA nephropathy in Japan

1st author	Year	Study design	Inclusion criteria	Patients n (medication)	Controls n (medication)	Duration of treatment	Follow-up period	Main results				
Mild IgA nephropathy												
Yoshikawa [105]	1997	RCT	Focal/minimal (<=79 %) mesangial proliferation	50 (sairei-to)	51 (no drug)	2 yrs	2 yrs		Group 1 (sairei-to)		Group 2 (no drugs)	
									Start	End	Start	End
								UP	0.39 ± 0.31	0.25* ± 0.41	0.41 ± 0.48	0.43 ± 0.56
								OB	2.3 ± 1.0	1.0* ± 1.1	2.1 ± 1.1	1.8 ± 1.2
								CR n (%)	0	21 (46)*	0	5 (10)
								HBP and CRF n	0	0	0	1
Nakanishi [106]	2009	Pilot study	Focal/minimal (<=79 %) mesangial proliferation and UP/UCR => 0.2 g/gcr	40 (lisinopril)	–	2 yrs	2 yrs		Start		End point	
								UP (g/m^2/day)	0.40 (0.08–1.35)		0.18* (0.00–0.89)	
								Primary end point (UP/UCR <0.2)	0		33 (82.5 %)	
								OB (dipstick)	2.3 ± 1.0		1.0* ± 1.3	
Severe IgA nephropathy												
Yoshikawa [107]	1999	RCT	Diffuse (>80 %) mesangial proliferation	40 (prednisolone, azathioprine, heparin-warfarin, and dipyridamole, group 1)	38 (heparin-warfarin and dipyridamole, group 2)	2 yrs	2 yrs		Group 1		Group 2	
									Start	End	Start	End
								UP excretion (mean (SD))	1.35 (1.01)	0.22* (0.31)	0.98 (0.99)	0.88 (1.34)
								OB (dipstick, mean (SD))	2.9 (0.8)	0.5* (1.0)	2.7 (1.0)	1.5* (1.1)
								Serum IgA level (mg/dl)	290 (115)	229* (87)	280 (100)	281 (92)
								HBP	0	0	0	1

								CRF	0	0	0	1
								Glomerular sclerosis (%, mean (SD))	5.2 (7.7)	5.0 (6.9)	3.9 (6.1)	16.4* (23.0)
								IgA deposits (3+/2+/1+/0)	11/19/3/0	7/9/10/7*	9/16/0/0	8/15/2/0
Kamei [108]	2011	A second analysis of RCT (ref 143)	Same as above	Same as above	Same as above	2 yrs	10 yrs (0.5–18)		Group 1		Group 2	
								ESRF n (%)	2/40 (5 %)		5/34 (14.7 %)	
								10 year renal survival	97.1 %*		84.8 %	
Yoshikawa [109]	2006	RCT	Diffuse mesangial proliferation	40 (prednisolone, azathioprine, warfarin, and dipyridamole, combination)	40 (prednisolone alone)	2 yrs	2 yrs		Combination		Prednisolone alone	
									Start	End	Start	End
								Primary end point (UP<0.1 g/m^2/day)	0	36/39 (92.3 %*)	0	29/39 (74.4 %*)
								UP (g/m^2/day, mean (SD))	1.29 (1.19)	0.10* (0.15)	1.16 (1.13)	0.12* (0.16)
								OB (dipstick, mean (SD))	3.0 (0.5)	0.4* (0.8)	3.0 (0.8)	0.6* (1.0)
								Serum IgA (mg/dl, mean (SD))	276 (118)	194* (85)	245 (109)	194* (90)
								Crescent (%, mean (SD))	17.3 (16.6)	1.7* (3.0)	19.1 (17.1)	0.9* (1.9)

(continued)

Table 11.4 (continued)

1st author	Year	Study design	Inclusion criteria	Patients n (medication)	Controls n (medication)	Duration of treatment	Follow-up period	Main results				
								Sclerosed glomeruli (%, mean (SD))	5.0 (9.1)	4.6 (7.9)	3.1 (4.8)	14.6* (15.2)
								IgA deposits (mean (SD))	2.1 (0.4)	1.5* (1.0)	2.2 (0.5)	1.8* (1.2)
Yoshikawa [110]	2008	Pilot study	Diffuse mesangial proliferation	23 (prednisolone, mizoribine, heparin-warfarin, dipyridamole)	–	2 yrs	2 yrs		Start		End	
								UP remission (UP<0.1 g/m^2/day)	0		18 (80.4 %)	
								UP (g/m^2/day, median (range))	1.19 (0.74–2.38)		0.05* (0.02–023)	
								OB (dipstick, median (range))	3.1 (2.7–3.6)		0.3* (0.1–1.0)	
								Crescent (%, median (range))	35.6 (15.6–44.0)		0.4* (0.2–3.1)	
								Sclerosed glomeruli (%, median (range))	0.3 (0.1–0.4)		0.3 (0.1–2.6)	
								IgA deposits (median (range))	2.5 (1.5–2.9)		0.8* (0.1–1.8)	

n number of patients, *RCT* randomized controlled trial, *yrs* years, *UP* urinary protein, *OB* hematuria, *CR* disappearance of urinary protein and hematuria, *HBP* high blood pressure, *CRF* chronic renal failure, *UP/UCR* urinary protein/creatinine ratio (g/g creatinine), *SD* standard deviation, *ESRF* end-stage renal failure

11.3.3.1 The Treatment for Japanese Children with Mild IgA Nephropathy

In 1997, Yoshikawa et al. reported the results of RCT in 101 children with newly diagnosed IgA nephropathy showing focal/minimal mesangial proliferation [105]. The patients were randomly assigned to receive sairei-to (Chinese herbal medicine) for 2 years (group 1) or no drug for 2 years (group 2). At the end of the trial, urinary protein excretion and hematuria were significantly reduced in group 1 but were unchanged in group 2, and normal urine was observed in 46 % and in 10 % in groups 1 and 2, respectively. From these results, it was demonstrated that 2-year sairei-to treatment early in the course of disease is effective in children with IgA nephropathy showing focal/minimal mesangial proliferation.

In 2009, Nakanishi et al. reported the results of a prospective single-arm pilot trial of lisinopril (0.4 mg/kg per day) in 40 children with mild IgA nephropathy defined as morning urinary protein/creatinine ratio (uP/Cr) 0.2 g/g or more [106]. A total of 33 patients reached the primary end point (uP/Cr <0.2) during the 2-year treatment period. The cumulative disappearance rate of proteinuria determined by the Kaplan-Meier method was 80.9 %. Mean urinary protein excretion was significantly reduced from 0.40 to 0.18 g/m^2/day. Dizziness developed in five patients (12.5 %), four of whom needed the lisinopril dose reduced. Thus, they conclude that the efficacy and safety of lisinopril are acceptable for the treatment of children with mild IgA nephropathy.

11.3.3.2 The Treatment for Japanese Children with Severe IgA Nephropathy

In 1999, Yoshikawa et al. reported the results of RCT for children with severe IgA nephropathy [107]. A total of 78 patients were randomly assigned to receive either prednisolone, azathioprine, heparin-warfarin, and dipyridamole for 2 years (group 1) or heparin-warfarin and dipyridamole for 2 years (group 2). The mean urinary protein excretion, the mean serum IgA concentration, and the intensity of mesangial IgA deposition significantly decreased in group 1 patients, but remained unchanged in group 2 patients. Blood pressure and creatinine clearance were normal at the end of the trial in all but one group 2 patient, who developed chronic renal insufficiency. The percentage of glomeruli showing sclerosis was unchanged in group 1 patients, but significantly increased in group 2 patients. From these results, they concluded that treatment of children with severe IgA nephropathy with prednisolone, azathioprine, heparin-warfarin, and dipyridamole for 2 years early in the course of disease reduces immunologic renal injury and prevents increase of sclerosed glomeruli. In 2011, Kamei et al. reported long-term results of a previous RCT in children with IgA nephropathy showing diffuse mesangial proliferation [108]. The median duration of observation was 10 years (0.5–18). Two of 40 patients (5 %) who received combination therapy and 5 of 34 patients (14.7 %) who received control therapy

developed ESRF. A Kaplan-Meier plot of renal survival showed that the outcomes of patients in the combined therapy group were significantly better than those in the control therapy group. The 10-year renal survival probability of each group was 97.1 % and 84.8 %, respectively. The Cox proportional hazards model showed that the 2-year combination therapy was significantly associated with renal survival in both univariate and multivariate analyses. Thus, they concluded that 2-year combination therapy not only ameliorated the activity of the acute phase of nephritis but also improved the long-term outcome of severe childhood IgA nephropathy.

In 2006, Yoshikawa et al. reported the results of another RCT for sever childhood IgA nephropathy [109]. A total of 80 children with newly diagnosed IgA nephropathy were randomly assigned to receive either prednisolone, azathioprine, warfarin, and dipyridamole (combination) or prednisolone alone for 2 years. The primary end point was the disappearance of proteinuria, defined as urinary protein excretion <0.1 g/m^2 per day, and the secondary end points were urinary protein excretion at the end of treatment, the change in the percentage of sclerosed glomeruli during the trial, and adverse effects. Thirty-six (92.3 %) of the 39 patients who received the combination and 29 (74.4 %) of the 39 who received prednisolone alone reached the primary end point by the 2-year follow-up point, and the difference between the two groups was significant. The percentage of sclerosed glomeruli was unchanged in combination group but significantly increased in the prednisolone group. The frequency of adverse effects was similar in the two groups. Thus, they concluded that combination treatment may be better for severe IgA nephropathy than treatment with prednisolone alone.

In 2008, Yoshikawa et al. further reported the results of a pilot study of mizoribine instead of azathioprine as part of the combination therapy for treating 23 children with severe IgA nephropathy [110]. Eighteen patients reached the primary end point (urine protein/creatinine ratio <0.2) during the 2-year treatment. The cumulative disappearance rate of proteinuria determined by Kaplan-Meier was 80.4 %. Median protein excretion was significantly reduced. After treatment, the median percentage of glomeruli showing sclerosis was unchanged in comparison with that before treatment. No patients required a change of treatment. They concluded that the efficacy and safety of the mizoribine combination seem to be acceptable for treating children with severe IgA nephropathy.

11.3.3.3 Tonsillectomy for Japanese Children with IgA Nephropathy

Although tonsillectomy with steroid pulse therapy is spread widely in Japan as one of the first-line treatment in adult patients with IgA nephropathy, there have been only few reports concerning the effect of tonsillectomy in pediatric patients with IgA nephropathy.

In 2006, Kawasaki et al. reported the results of RCT of tonsillectomy plus pulse prednisolone, warfarin, and dipyridamole including methylprednisolone pulse (tonsillectomy plus pulse therapy), versus prednisolone, warfarin, and dipyridamole including mizoribine (PWDM) for the treatment of diffuse IgA nephropathy in

children [114]. A total of 32 children were randomly assigned to be treated by tonsillectomy plus pulse therapy for 2 years (Group A, 16 children) or PWDM for 2 years (Group B, 16 children). The mean urinary protein excretion after 6 months of treatment significantly decreased in both groups. The activity index in both groups was lower at the second biopsy than at the first biopsy. The chronicity index in Groups A and B did not differ between the first and second biopsy. At the latest follow-up examination, none of the patients in either group had renal insufficiency. None of the patients in Group A, but six patients in Group B experienced an acute exacerbation of IgA nephropathy as a result of tonsillitis. Thus, they suggested that tonsillectomy plus pulse therapy is as effective as PWDM in ameliorating proteinuria and histological severity in IgA nephropathy patients and in preventing acute exacerbation of IgA nephropathy by tonsillitis.

In 2009, Kawasaki et al. also reported the efficacy of tonsillectomy with methylprednisolone pulse therapy as rescue treatment for 11 children with steroid-resistant IgA nephropathy [115]. Urinary protein excretion was significantly decreased at 24.7 ± 7.3 months after tonsillectomy pulse therapy. On renal pathologic examination of six patients who underwent renal biopsy at 17.1 ± 6.9 months after tonsillectomy pulse therapy, the activity index, an index of inflammation, was lower compared to the index evaluated before the therapy, but the chronic index, an index of renal sclerosis, remained unchanged. At 24.7 ± 7.3 months after tonsillectomy pulse therapy, seven patients had normal urine and four had minor urinary abnormalities. None had active renal disease or renal insufficiency. Thus, they suggest that tonsillectomy pulse therapy may be effective as rescue treatment for steroid-resistant IgA nephropathy in childhood.

In 2012, Nishi et al. reported the efficacy of tonsillectomy for intractable childhood IgA nephropathy [116]. Patients with poor or relatively poor prognosis determined histologically, an age at least 7 years, and with proteinuria of 0.3 g/day or more despite ongoing drug treatment, are candidates for tonsillectomy. Five patients refused tonsillectomy. A total of 25 patients who received tonsillectomy were divided into two groups according to the interval between diagnosis of IgA nephropathy and tonsillectomy (within 3 years; early group vs. 3 years or later; later group). Proteinuria was reduced after tonsillectomy over 2 years of follow-up in both groups, and complete remission was achieved in ten patients, most often in early group. The patients refusing surgery failed to attain complete remission of urinary findings. Histological activity decreased in both groups, significantly in the early group. Complement component C3 deposition and activated macrophages in glomeruli decreased after tonsillectomy, especially in early group. Thus, they concluded that tonsillectomy improved clinicopathological features in relatively severe pediatric IgA nephropathy, especially in the early group, and suggested that therapeutic mechanisms may include inhibition of complement activity in glomeruli and glomerular infiltration by activated macrophages.

11.4 Clinical Guidelines for the Diagnosis and Treatment of Patients with IgA Nephropathy in Japan

So far, three clinical guidelines for the diagnosis and treatment of patients with IgA nephropathy in Japan have been published by a joint committee of the Special IgA Nephropathy Study Group of the Progressive Renal Disease Study Committee organized by the Ministry of Health, Labour and Welfare of Japan and the Japanese Society of Nephrology in 1995, 2003, and 2011 [8, 117, 118].

Table 11.5 Diagnostic criteria for IgA nephropathy according to the third version of clinical guidelines for the diagnosis and treatment of patients with IgA nephropathy in Japan

1. Clinical manifestations
The majority of cases show no symptoms, but acute nephritic symptoms may occur occasionally. The appearance of nephrotic syndrome is relatively rare. Generally, the course is gradual, but progress to end-stage renal disease occurs in 40 % of patients within 20 years
2. Urinalysis
At least three urinalyses are required for the diagnosis of urinary abnormalities, and at least two of these tests should include microscopic examination of urinary sediment in addition to routine urinalysis
A. Essential finding: persistent microscopic hematuria (Note 1)
B. Frequent finding: persistent or intermittent proteinuria
C. Occasional finding: macroscopic hematuria (Note 2)
3. Blood examination
A. Essential finding: none
B. Frequent finding: serum IgA greater than 315 mg/dl in adults (Note 3)
Definite diagnosis:
Observation of glomeruli in renal biopsy specimens is the only method of diagnosis
A. Light microscopic findings: although the main findings are mesangial proliferative changes including focal segmental to diffuse global (spherical) changes, a variety of lesions such as crescent, segmental sclerosis and global sclerosis are observed
B. Staining with fluorescence-conjugated antibody or enzyme-linked antibody: diffuse granular IgA deposition mainly present in the glomerular mesangial areas (Note 4)
C. Electron microscopic findings: highly electron-dense deposits in glomerular mesangial matrix and paramesangial areas
Addenda
1. If urinalysis findings A and B and blood examination finding B are confirmed, the probability of a diagnosis of IgA nephropathy is high. However, differential diagnosis of urological diseases should be made
2. Purpura nephritis, liver cirrhosis, and lupus nephritis may give renal biopsy findings similar to those of IgA nephropathy. These diseases can be excluded by systemic signs which are characteristic to each disease and laboratory findings

Note 1. Urinary sediment showing more than 5–6 erythrocytes/HPF
Note 2. Many patients also have upper respiratory tract infection or acute gastrointestinal symptoms
Note 3. Observed in more than half of adult patients
Note 4. IgA deposition is predominant in comparison with other immunoglobulins

The third version of clinical guidelines for the diagnosis and treatment of patients with IgA nephropathy in Japan was published in 2011 based on the evidence from a multicenter, case-control study of 287 IgA nephropathy patients with a median follow-up of 9.3 years [118]. Since the cohort contained only 26 patients aged 18 years or younger (9.1 %), these guidelines are mainly for the adult patients with IgA nephropathy.

Diagnostic criteria for IgA nephropathy according to the third version of clinical guidelines for the diagnosis and treatment of patients with IgA nephropathy in Japan are summarized in Table 11.5.

In these guidelines, four histological grades (H-Grade) I–IV were established, corresponding to <25 %, 25–49 %, 50–74 %, and 75 % or more of glomeruli exhibiting cellular/fibrocellular crescents, global sclerosis, segmental sclerosis, or fibrous crescents. The significance of histological grade for predicting long-term prognosis was reported in 2011 [119].

In addition, the clinical severity was graded by the levels of urinary protein (UP g/day) and eGFR (ml/min/1.73 m^2) at the time of renal biopsy as follows. Clinical grades (C-Grade) were defined as I, UP <0.5 g/day; II, UP 0.5 g/day or more and eGFR 60 ml/min/1.73 m^2 or more; and III, UP 0.5 g/day or more and eGFR <60 ml/min/1.73 m^2.

Furthermore, according to C-Grade and H-Grade, dialysis induction risks were stratified and classified as shown in Table 11.6.

Guidelines for treatment of IgA nephropathy in each dialysis induction risk group are summarized in Table 11.7.

Table 11.6 Stratification of dialysis induction risk for patients with IgA nephropathy

H-Grade / C-Grade	H-Grade I	H-Grade II	H-Grade III-IV
C-Grade I	Low risk	Moderate risk	High risk
C-Grade II	Moderate risk	Moderate risk	High risk
C-Grade III	High risk	High risk	Very high risk

Histological grade (H-Grade) is determined according to the percentage of glomeruli exhibiting cellular/fibrocellular crescents, global sclerosis, segmental sclerosis, or fibrous crescents as follows: I; <25 %, II; 25–49 %, III; 50–74 %, and IV; 75 % or more

Clinical grade (C-Grade) is determined by the levels of urinary protein (UP, g/day) and eGFR (ml/min/1.73 m^2) at the time of renal biopsy as follows: I; UP <0.5, II; UP 0.5 or more and eGFR 60 or more, III; UP 0.5 or more and eGFR <60

H-Grade histological grade, *C-Grade* clinical grade

Table 11.7 Guidelines for the treatment of IgA nephropathy in each dialysis induction risk group

For all patients
A. Correction of lifestyle: stop smoking, adequate intake of alcohol, management of body weight (Note 1)
B. Physical examination and laboratory data: regular checkup of blood pressure, blood test including serum creatinine, eGFR, urinalysis, urine sediment, urinary protein/creatinine ratio. 24 h urinary protein excretion and Ccr, if possible
C. Energy intake: energy intake should be determined according to age, sex, and physical activity. Standard criteria are 25–35 kcal/kg standard body weight/day. Regular checkup of body weight is required in order to evaluate if the recommended energy intake is adequate or not and modify if necessary
Guidelines for treatment of IgA nephropathy in each dialysis induction risk group
1. Low-risk group
A. Management for life:
There are no special restrictions of exercise. Correction for lifestyle should be recommended. Visits to a hospital or an outpatient clinic at least every 3–6 months
B. Diet therapy:
Avoid excessive salt intake. Avoid excessive protein intake in patients with deterioration of kidney function (0.8–1.0 g/kg standard body weight/day)
C. Drug therapy:
Antiplatelet therapy and antihypertensive therapy (Note 2) are recommended according to the amount of proteinuria, the presence or absence of hypertension, and histological findings of kidney biopsy. Steroid therapy including pulse therapy should be considered if acute active lesions are observed in glomeruli of kidney biopsy
2. Moderate-risk group
A. Management for life:
The strength of exercise should be recommended carefully according to the individual blood pressure, the amount of proteinuria, and kidney function
Visits to a hospital or an outpatient clinic at least every 1–3 months
B. Diet therapy:
Protein and salt intake should be restricted according to the individual kidney function, the amount of proteinuria, and blood pressure
The standard protein intake is 0.8–1.0 g/kg standard body weight/day. Standard salt intake is less than 6 g/day
C. Drug therapy:
Antiplatelet therapy, antihypertensive therapy (Note 2), and steroids including pulse therapy (Note 3) are recommended according to the amount of proteinuria, the presence or absence of hypertension, and histological findings of kidney biopsy. Especially, if acute active lesions are observed in glomeruli of kidney biopsy and the patients reveal urinary protein 0.5 g/day or more and eGFR 60 ml/min/1.73 m^2 or more, steroid therapy including pulse therapy is strongly recommended
3. High-risk group
A. Management for life
The strength of exercise should be recommended carefully according to the individual blood pressure, the amount of proteinuria, and kidney function
Visits to a hospital or an outpatient clinic once a month. Pregnancy and delivery should be carefully managed

(continued)

Table 11.7 (continued)

B. Diet therapy:
Protein and salt intake should be restricted according to the individual kidney function, the amount of proteinuria, and blood pressure
The standard protein intake is 0.6–0.8 g/kg standard body weight/day. Standard salt intake is less than 6 g/day. Potassium restriction should be recommended if necessary
C. Drug therapy:
Antiplatelet therapy, antihypertensive therapy, and steroids including pulse therapy are recommended according to the amount of proteinuria, the presence or absence of hypertension, and histological findings of kidney biopsy. Especially, if acute active lesions are observed in glomeruli of kidney biopsy and the patients reveal urinary protein 0.5 g/day or more and eGFR 60 ml/min/1.73 m^2 or more, steroid therapy including pulse therapy is strongly recommended
4. Very high-risk group
A. Management for life:
Same as high-risk group. Pregnancy and delivery required extremely careful management
B. Diet therapy:
Salt restriction (less than 6 g/day) and protein intake restriction (0.6–0.8 g/kg standard body weight/day) are recommended
Potassium restriction should be recommended if necessary
C. Drug therapy:
Same as high-risk group. Treatment for chronic renal failure if necessary. If chronic lesions are predominant in the glomeruli of kidney biopsy, indication of steroid therapy including pulse therapy should be carefully considered.

Note 1. The standard body weight [height^2 × 22] (kg) is recommended

Note 2. The first choice of antihypertensive drug is angiotensin-converting enzyme blocker or angiotensin II receptor blocker. If the blood pressure does not reach the target level, diuretics or calcium channel blocker is considered as the second choice

Note 3. Consultation with nephrologists is necessary. The efficacy of tonsillectomy with steroid pulse therapy is under investigation

eGFR estimated glomerular filtration rate (ml/min/1.73 m^2), *Ccr* creatinine clearance (ml/min)

11.5 Guidelines for the Treatment of Childhood IgA Nephropathy

Based on the high-level evidence according to the RCTs in different subsets of children with IgA nephropathy, the Japanese Pediatric IgA Nephropathy Treatment Study Group established "Guidelines for the treatment of childhood IgA nephropathy" [120] as summarized in Table 11.8.

Table 11.8 Guidelines for the treatment of childhood IgA nephropathy

The treatment of mild childhood IgA nephropathy
The definition of mild childhood IgA nephropathy
The childhood IgA nephropathy filled with all the following criteria
Clinical findings: mild proteinuria (early morning urinary protein/creatinine ratio less than 1.0 g/g creatinine)
Pathological findings: moderate or more mesangial proliferation, crescent, adhesion, or sclerosis observed in less than 80 % of glomeruli and crescent in less than 30 % of glomeruli
Guidelines for treatment
Either one of the following treatment is recommended
1. Angiotensin-converting enzyme blocker:
Lisinopril 0.4 mg/kg/day once a day (maximum dose: 20 mg/day) (Note 1)
2. Chinese herb:
Sairei-to one pack/day, twice a day (body weight 20 kg or less); two packs/day, twice a day (body weight 20–40 kg); three packs/day, three times a day (body weight 40 kg or more) (Note 2)
Note 1: Start from low dose and gradually increase in dosage with paying attention to side effect. The teratogenicity as side effect should be well explained to the girls in childbearing age. If they desire to bear children, the drug should be discontinued
Note 2: One pack of sairei-to is 3 g of TUMURA sairei-to granules and 2.7 g of KANEBOU sairei-to granules
The treatment of severe childhood IgA nephropathy
The definition of mild childhood IgA nephropathy
The childhood IgA nephropathy filled with all the following criteria
Clinical findings: severe proteinuria (early morning urinary protein/creatinine ratio 1.0 or more g/g creatinine)
Pathological findings: moderate or more mesangial proliferation, crescent, adhesion, or sclerosis observed in 80 % or more of glomeruli and crescent in 30 % or more of glomeruli
*These guidelines do not cover the patients with rapidly progressive glomerulonephritis syndrome
Guidelines for treatment
Combination treatment (cocktail treatment) with adrenocorticosteroid, immunosuppressant, anticoagulant, and antiplatelet drug for 2 years is recommended
Adrenocorticosteroid: oral prednisolone (1). 2 mg/kg/day (maximum dose: 80 mg/day), three times a day, daily for 4 weeks
(2). Then, 2 mg/kg/day, once a day, alternative day and gradually taper and discontinue. Standard duration of treatment is 2 years
Immunosuppressant: oral azathioprine (Note 1) or mizoribine (Note 1)
Azathioprine; 2 mg/kg/day (maximum dose: 100 mg/day), once a day, for 2 years
Mizoribine; 4 mg/kg/day (maximum dose: 150 mg/day), twice a day, for 2 years
Anticoagulant: Oral warfarin potassium (Note 1), once a day in the morning. Dosage should be adjusted for 20–50 % of thrombotest
Start with 0.5–1.0 mg/day for safety
Keep under a condition of shading light
Antiplatelet drug: oral dipyridamole; start with 3 mg/kg/day, three times a day, and 1 week later, if no side effect occurs, 6–7 mg/kg/day (maximum dose: 300 mg/day)
Note 1: The teratogenicity as side effect should be well explained to the girls in childbearing age. If they desire to bear children, the drug should be discontinued

Conflict of Interest The author declares that she has no conflict of interest.

References

1. Ueda Y, Sakai O, Yamagata M, Kitajima T, Kawamura K. IgA glomerulonephritis in Japan. Contrib Nephrol. 1977;4:36–47.
2. Kitajima T, Murakami M, Sakai O. Clinicopathological features in the Japanese patients with IgA nephropathy. Jpn J Med. 1983;22:219–22.
3. Glassock RJ, Kurokawa K, Yoshida M, Sakai O, Okada M, Shigematsu H, et al. IgA nephropathy in Japan. Am J Nephrol. 1985;5:127–37.
4. Yoshikawa N, Ito H, Nakamura H. IgA nephropathy in children from Japan. Clinical and pathological features. Child Nephrol Urol. 1988–1989;9:191–9.
5. Koyama A, Igarashi M, Kobayashi M. Natural history and risk factors for immunoglobulin A nephropathy in Japan. Research Group on Progressive Renal Diseases. Am J Kidney Dis. 1997;29:526–32.
6. Ohno Y, Kawamura T, Tamakoshi A, Wakai K, Aoki R, Kojima M, et al. Epidemiology of diseases of unknown etiology, specified as "intractable diseases". J Epidemiol. 1996;6 (3 Suppl):S87–94.
7. Wakai K, Kawamura T, Endoh M, Kojima M, Tomino Y, Tamakoshi A, et al. A scoring system to predict renal outcome in IgA nephropathy: from a nationwide prospective study. Nephrol Dial Transplant. 2006;21:2800–8.
8. Tomino Y, Sakai H, Special Study Group (IgA Nephropathy) on Progressive Glomerular Disease. Clinical guidelines for immunoglobulin A (IgA) nephropathy in Japan, second version. Clin Exp Nephrol. 2003;7:93–7.
9. Nozawa R, Suzuki J, Takahashi A, Isome M, Kawasaki Y, Suzuki S, et al. Clinicopathological features and the prognosis of IgA nephropathy in Japanese children on long-term observation. Clin Nephrol. 2005;64:171–9.
10. Yamagata K, Yamagata Y, Kobayashi M, Koyama A. A long-term follow-up study of asymptomatic hematuria and/or proteinuria in adults. Clin Nephrol. 1996;45:281–8.
11. Yamagata K, Takahashi H, Tomida C, Yamagata Y, Koyama A. Prognosis of asymptomatic hematuria and/or proteinuria in men. High prevalence of IgA nephropathy among proteinuric patients found in mass screening. Nephron. 2002;91:34–42.
12. Sugiyama H, Yokoyama H, Sato H, Saito T, Kohda Y, Nishi S, Committee for Standardization of Renal Pathological Diagnosis and Working Group for Renal Biopsy Database, Japanese Society of Nephrology, Tokyo, Japan, et al. Japan Renal Biopsy Registry: the first nationwide, web-based, and prospective registry system of renal biopsies in Japan. Clin Exp Nephrol. 2011;15:493–503.
13. Sugiyama H, Yokoyama H, Sato H, Saito T, Kohda Y, Nishi S, Committee for Standardization of Renal Pathological Diagnosis, Committee for Kidney Disease Registry, Japanese Society of Nephrology, et al. Japan Renal Biopsy Registry and Japan Kidney Disease Registry: Committee report for 2009 and 2010. Clin Exp Nephrol. 2013;17:155–73.
14. Hiki Y, Saitoh M, Kobayashi Y. Serum IgA class anti-IgA antibody in IgA nephropathy. Nephron. 1991;59:552–60.
15. Hiki Y, Iwase H, Saitoh M, Saitoh Y, Horii A, Hotta K, et al. Reactivity of glomerular and serum IgA1 to jacalin in IgA nephropathy. Nephron. 1996;72:429–35.
16. Hiki Y, Iwase H, Kokubo T, Horii A, Tanaka A, Nishikido J, et al. Association of asialogalactosyl beta 1-3N-acetylgalactosamine on the hinge with a conformational instability of Jacalin-reactive immunoglobulin A1 in immunoglobulin A nephropathy. J Am Soc Nephrol. 1996;7:955–60.

17. Hiki Y, Tanaka A, Kokubo T, Iwase H, Nishikido J, Hotta K, et al. Analyses of IgA1 hinge glycopeptides in IgA nephropathy by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. J Am Soc Nephrol. 1998;9:577–82.
18. Kokubo T, Hiki Y, Iwase H, Tanaka A, Nishikido J, Hotta K, et al. Exposed peptide core of IgA1 hinge region in IgA nephropathy. Nephrol Dial Transplant. 1999;14:81–5.
19. Hiki Y, Kokubo T, Iwase H, Masaki Y, Sano T, Tanaka A, et al. Underglycosylation of IgA1 hinge plays a certain role for its glomerular deposition in IgA nephropathy. J Am Soc Nephrol. 1999;10:760–9.
20. Kokubo T, Hashizume K, Iwase H, Arai K, Tanaka A, Toma K, et al. Humoral immunity against the proline-rich peptide epitope of the IgA1 hinge region in IgA nephropathy. Nephrol Dial Transplant. 2000;15:28–33. 1414.
21. Kusakari C, Nose M, Takasaka T, Yuasa R, Kato M, Miyazono K, et al. Immunopathological features of palatine tonsil characteristic of IgA nephropathy: IgA1 localization in follicular dendritic cells. Clin Exp Immunol. 1994;95:42–8.
22. Sato Y, Hotta O, Taguma Y, Takasaka T, Nose M. IgA nephropathy with poorly developed lymphoepithelial symbiosis of the palatine tonsils. Nephron. 1996;74:301–8.
23. Kodama S, Suzuki M, Arita M, Mogi G. Increase in tonsillar germinal centre B-1 cell numbers in IgA nephropathy (IgAN) patients and reduced susceptibility to Fas-mediated apoptosis. Clin Exp Immunol. 2001;123:301–8.
24. Takechi H, Oda T, Hotta O, Yamamoto K, Oshima N, Matsunobu T, et al. Clinical and immunological implications of increase in CD208+ dendritic cells in tonsils of patients with immunoglobulin A nephropathy. Nephrol Dial Transplant. 2013;28(12):3004–13.
25. Itoh A, Iwase H, Takatani T, Nakamura I, Hayashi M, Oba K, et al. Tonsillar IgA1 as a possible source of hypoglycosylated IgA1 in the serum of IgA nephropathy patients. Nephrol Dial Transplant. 2003;18:1108–14.
26. Horie A, Hiki Y, Odani H, Yasuda Y, Takahashi M, Kato M, et al. IgA1 molecules produced by tonsillar lymphocytes are under-O-glycosylated in IgA nephropathy. Am J Kidney Dis. 2003;42:486–96.
27. Hiki Y, Horie A, Yasuda Y, Iwase H, Sugiyama S. IgA nephropathy and tonsils – an approach from the structure of IgA1 produced by tonsillar lymphocytes. Acta Otolaryngol Suppl. 2004;555:28–31.
28. Fujieda S, Suzuki S, Sunaga H, Yamamoto H, Seki M, Sugimoto H, et al. Production of interferon-gamma by tonsillar mononuclear cells in IgA nephropathy patients. Acta Otolaryngol. 2000;120:649–54.
29. Kuki K, Gotoh H, Hayashi M, Hujihara K, Tamura S, Yamanaka N. Immunity of tonsil and IgA nephropathy – relationship between IgA nephropathy and tonsillitis. Acta Otolaryngol Suppl. 2004;555:6–9.
30. Takahara M, Kishibe K, Nozawa H, Harabuchi Y. T-cell repertoire in the tonsils of patients with IgA nephropathy. Acta Otolaryngol Suppl. 2004;555:25–7.
31. Nozawa H, Takahara M, Yoshizaki T, Goto T, Bandoh N, Harabuchi Y. Selective expansion of T cell receptor (TCR) V beta 6 in tonsillar and peripheral blood T cells and its induction by in vitro stimulation with Haemophilus parainfluenzae in patients with IgA nephropathy. Clin Exp Immunol. 2008;151:25–33.
32. Goto T, Bandoh N, Yoshizaki T, Nozawa H, Takahara M, Ueda S, Hayashi T, Harabuchi Y. Increase in B-cell-activation factor (BAFF) and IFN-gamma productions by tonsillar mononuclear cells stimulated with deoxycytidyl-deoxyguanosine oligodeoxynucleotides (CpG-ODN) in patients with IgA nephropathy. Clin Immunol. 2008;126:260–9.
33. Iio K, Nagasawa Y, Iwatani H, Yamamoto R, Horii A, Okuzaki D, et al. Microarray analysis of tonsils in immunoglobulin A nephropathy patients. Biochem Biophys Res Commun. 2010;19(393):565–70.
34. Inoue T, Sugiyama H, Hiki Y, Takiue K, Morinaga H, Kitagawa M, et al. Differential expression of glycogenes in tonsillar B lymphocytes in association with proteinuria and renal dysfunction in IgA nephropathy. Clin Immunol. 2010;136:447–55.

35. Sato D, Suzuki Y, Kano T, Suzuki H, Matsuoka J, Yokoi H, et al. Tonsillar TLR9 expression and efficacy of tonsillectomy with steroid pulse therapy in IgA nephropathy patients. Nephrol Dial Transplant. 2012;27:1090–7.
36. Iwatani H, Iio K, Nagasawa Y, Yamamoto R, Horii A, Okuzaki D, et al. Microarray analysis of tonsils of IgA nephropathy patients. Adv Otorhinolaryngol. 2011;72:75–8.
37. Tomino Y, Yagame M, Suga T, Miura M, Endoh M, Nomoto Y, et al. Detection of viral antigens in patients with IgA nephropathy. Jpn J Med. 1989;28:159–64.
38. Kanno Y, Suzuki H, Okada H, Nakazato Y, Saruta T. Retroviral infection in peripheral mononuclear cells in patients with IgA nephropathy. Clin Nephrol. 1997;47:211–6.
39. Takahashi A, Kawasaki Y, Yoshida K, Mochizuki K, Isome M, Honzumi K, et al. Detection of enteroviruses in renal biopsies from patients with immunoglobulin A nephropathy. Pediatr Nephrol. 2005;20(11):1578–82.
40. Kunimoto M, Hayashi Y, Kuki K, Mune M, Yamada Y, Tamura S, et al. Analysis of viral infection in patients with IgA nephropathy. Acta Otolaryngol Suppl. 1993;508:11–8.
41. Suzuki S, Nakatomi Y, Sato H, Tsukada H, Arakawa M. Haemophilus parainfluenzae antigen and antibody in renal biopsy samples and serum of patients with IgA nephropathy. Lancet. 1994;343(8888):12–6.
42. Suzuki S, Nakatomi Y, Odani S, Sato H, Gejyo F, Arakawa M. Circulating IgA, IgG, and IgM class antibody against Haemophilus parainfluenzae antigens in patients with IgA nephropathy. Clin Exp Immunol. 1996;104:306–11.
43. Suzuki S, Gejyo F, Nakatomi Y, Odani S, Sato H, Arakawa M. Role of IgA, IgG, and IgM antibodies against Haemophilus parainfluenzae antigens in IgA nephropathy. Clin Nephrol. 1996;46:287–95.
44. Suzuki S, Fujieda S, Sunaga H, Sugimoto H, Yamamoto C, Kimura H, et al. Immune response of tonsillar lymphocytes to Haemophilus parainfluenzae in patients with IgA nephropathy. Clin Exp Immunol. 2000;119(2):328–32.
45. Suzuki S, Fujieda S, Sunaga H, Yamamoto C, Kimura H, Gejyo F. Synthesis of immunoglobulins against Haemophilus parainfluenzae by tonsillar lymphocytes from patients with IgA nephropathy. Nephrol Dial Transplant. 2000;15(5):619–24.
46. Fujieda S, Suzuki S, Sunaga H, Yamamoto H, Seki M, Sugimoto H, et al. Induction of IgA against Haemophilus parainfluenzae antigens in tonsillar mononuclear cells from patients with IgA nephropathy. Clin Immunol. 2000;95:235–43.
47. Ogura Y, Suzuki S, Shirakawa T, Masuda M, Nakamura H, Iijima K, et al. Haemophilus parainfluenzae antigen and antibody in children with IgA nephropathy and Henoch-Schönlein nephritis. Am J Kidney Dis. 2000;36:47–52.
48. Sunaga H, Oh M, Takahashi N, Fujieda S. Infection of Haemophilus parainfluenzae in tonsils is associated with IgA nephropathy. Acta Otolaryngol Suppl. 2004;555:15–9.
49. Kukuminato Y, Hamamoto M, Kataura A. Role of serum antibodies to streptococci in patients with IgA nephropathy. Acta Otolaryngol Suppl. 1993;508:6–10.
50. Nishikawa Y, Shibata R, Ozono Y, Ichinose H, Miyazaki M, Harada T, et al. Streptococcal M protein enhances TGF-beta production and increases surface IgA-positive B cells in vitro in IgA nephropathy. Nephrol Dial Transplant. 2000;15(6):772–7.
51. Hirabayashi A, Yorioka N, Oda H, Sekiguchi Y, Kuramoto A, Okushin S, et al. Involvement of bacterial antigens in immunoglobulin A nephropathy. Hiroshima J Med Sci. 1996;45:113–7.
52. Koyama A, Sharmin S, Sakurai H, Shimizu Y, Hirayama K, Usui J, et al. Staphylococcus aureus cell envelope antigen is a new candidate for the induction of IgA nephropathy. Kidney Int. 2004;66:121–32.
53. Shimizu Y, Seki M, Kaneko S, Hagiwara M, Yoh K, Yamagata K, et al. Patients with IgA nephropathy respond strongly through production of IgA with low avidity against Staphylococcus aureus. Contrib Nephrol. 2007;157:139–43.

54. Kusano K, Tokunaga O, Ando T, Inokuchi A. Helicobacter pylori in the palatine tonsils of patients with IgA nephropathy compared with those of patients with recurrent pharyngotonsillitis. Hum Pathol. 2007;38:1788–97.
55. Kusano K, Inokuchi A, Fujimoto K, Miyamoto H, Tokunaga O, Kuratomi Y, et al. Coccoid Helicobacter pylori exists in the palatine tonsils of patients with IgA nephropathy. J Gastroenterol. 2010;45:406–12.
56. Nagasawa Y, Iio K, Fukuda S, Date Y, Iwatani H, Yamamoto R, et al. Periodontal disease bacteria specific to tonsil in IgA nephropathy patients predicts the remission by the treatment. PLoS One. 2014;9(1):e81636.
57. Yagame M, Tomino Y, Eguchi K, Miura M, Suga T, Endoh M, et al. Levels of circulating IgA immune complexes after gluten-rich diet in patients with IgA nephropathy. Nephron. 1988;49:104–6.
58. Kuramoto T, Yano N, Miyazaki M, Endoh M, Nomoto Y, Sakai H. No increase in antibodies to six food antigens in Japanese patients with IgA nephropathy. Tokai J Exp Clin Med. 1991;16:239–44.
59. Sato M, Kojima H, Takayama K, Koshikawa S. Glomerular deposition of food antigens in IgA nephropathy. Clin Exp Immunol. 1988;73:295–9.
60. Sato M, Kojima H, Kino K, Koshikawa S. Effects of neutral pepsin on the deposition of dietary antigens in glomeruli from IgA nephropathy. Clin Exp Immunol. 1990;81:137–41.
61. Coppo R, Amore A, Roccatello D, Gianoglio B, Molino A, Piccoli G, et al. IgA antibodies to dietary antigens and lectin-binding IgA in sera from Italian, Australian, and Japanese IgA nephropathy patients. Am J Kidney Dis. 1991;17:480–7.
62. Kobayashi Y, Fujii K, Hiki Y, Tateno S. Steroid therapy in IgA nephropathy: a prospective pilot study in moderate proteinuric cases. Steroid therapy in IgA nephropathy: a prospective pilot study in moderate proteinuric cases. Q J Med. 1986;61:935–43.
63. Kobayashi Y, Hiki Y, Fujii K, Kurokawa A, Kamiyana M, Tateno S. IgA nephropathy: heterogeneous clinical pictures and steroid therapy in progressive cases. Semin Nephrol. 1987;7:382–5.
64. Kobayashi Y, Fujii K, Hiki Y, Tateno S, Kurokawa A, Kamiyama M. Steroid therapy in IgA nephropathy: a retrospective study in heavy proteinuric cases. Nephron. 1988;48:12–7.
65. Kobayashi Y, Hiki Y, Fujii K, Kurokawa A, Tateno S. Moderately proteinuric IgA nephropathy: prognostic prediction of individual clinical courses and steroid therapy in progressive cases. Nephron. 1989;53:250–6.
66. Kobayashi Y, Hiki Y, Kokubo T, Horii A, Tateno S. Steroid therapy during the early stage of progressive IgA nephropathy. A 10-year follow-up study. Nephron. 1996;72:237–42.
67. Yoshimura M, Kida H, Saito Y, Takaeda M, Sugioka G. Effects of methylprednisolone pulse therapy on progressive IgA nephropathy. Article in Japanese. Nihon Jinzo Gakkai Shi. 1991;33:761–8.
68. Honda K, Nitta K, Kobayashi H, Uchida K, Kawashima A, Horita S, et al. Clinical significance of histological grading and staging for predicting the effectiveness of steroid therapy in IgA nephropathy. Clin Exp Nephrol. 2000;4:241–50.
69. Tomiyoshi Y, Sakemi T, Ikeda Y, Ohtsuka Y, Nakamura M, Fujisaki T. Cellular crescents and segmental glomerular necrosis in IgA nephropathy are indicative of the beneficial effects of corticosteroid therapy. Intern Med. 2001;40:862–6.
70. Kuriki M, Asahi K, Asano K, Sakurai K, Eiro M, Suzuki H, et al. Steroid therapy reduces mesangial matrix accumulation in advanced IgA nephropathy. Nephrol Dial Transplant. 2003;18:1311–5.
71. Uzu T, Harada T, Ko M, Yamato M, Takahara K, Yamauchi A. Effect of corticosteroid therapy on the progression of IgA nephropathy with moderate proteinuria. Clin Exp Nephrol. 2003;7:210–4.
72. Moriyama M, Honda K, Nitta K, Yumura W, Nihei H. The effectiveness of steroid therapy for patients with advanced IgA nephropathy and impaired renal function. Clin Exp Nephrol. 2004;8:237–42.

73. Suzuki T, Yamamoto T, Ohura M, Fujigaki Y, Yonemura K, Kimura M, et al. Clinicopathologic findings relevant to disappearance or relapse of proteinuria following corticosteroid treatment in IgA nephropathy patients with proteinuria of 0.5 to 2.0 g/day. Clin Exp Nephrol. 2004;8:243–9.
74. Suzuki S, Joh K. Applicability of steroid therapy in 275 adult patients with IgA nephropathy determined using a histological scoring system and degree of proteinuria. Clin Exp Nephrol. 2004;8:109–16.
75. Katafuchi R, Ninomiya T, Mizumasa T, Ikeda K, Kumagai H, Nagata M, et al. The improvement of renal survival with steroid pulse therapy in IgA nephropathy. Nephrol Dial Transplant. 2008;23:3915–20.
76. Harada K, Akai Y, Yamaguchi Y, Kimura K, Nishitani Y, Nakatani K, et al. Prediction of corticosteroid responsiveness based on fibroblast-specific protein 1 (FSP1) in patients with IgA nephropathy. Nephrol Dial Transplant. 2008;23:3152–9.
77. Shimizu A, Takei T, Uchida K, Tsuchiya K, Nitta K. Predictors of poor outcomes in steroid therapy for immunoglobulin A nephropathy. Nephrol (Carlton). 2009;14:521–6.
78. Tatematsu M, Yasuda Y, Morita Y, Sakamoto I, Kurata K, Naruse T, et al. Complete remission within 2 years predicts a good prognosis after methylprednisolone pulse therapy in patients with IgA nephropathy. Clin Exp Nephrol. 2012;16:883–91.
79. Shoji T, Nakanishi I, Suzuki A, Hayashi T, Togawa M, Okada N, et al. Early treatment with corticosteroids ameliorates proteinuria, proliferative lesions, and mesangial phenotypic modulation in adult diffuse proliferative IgA nephropathy. Am J Kidney Dis. 2000;35:194–201.
80. Katafuchi R, Ikeda K, Mizumasa T, Tanaka H, Ando T, Yanase T, et al. Controlled, prospective trial of steroid treatment in IgA nephropathy: a limitation of low-dose prednisolone therapy. Am J Kidney Dis. 2003;41:972–83.
81. Koike M, Takei T, Uchida K, Honda K, Moriyama T, Horita S, et al. Clinical assessment of low-dose steroid therapy for patients with IgA nephropathy: a prospective study in a single center. Clin Exp Nephrol. 2008;12:250–5.
82. Iino Y, Ambe K, Kato Y, Nakai A, Toriyama M, Saima K, et al. Chronic tonsillitis and IgA nephropathy. Clinical study of patients with and without tonsillectomy. Acta Otolaryngol Suppl. 1993;508:29–35.
83. Tomioka S, Miyoshi K, Tabata K, Hotta O, Taguma Y. Clinical study of chronic tonsillitis with IgA nephropathy treated by tonsillectomy. Acta Otolaryngol Suppl. 1996;523:175–7.
84. Yamabe H, Osawa H, Inuma H, Kaizuka M, Tamura N, Tsunoda S, et al. Deterioration of urinary findings after tonsil stimulation in patients with IgA nephropathy. Acta Otolaryngol Suppl. 1996;523:169–71.
85. Xie Y, Nishi S, Ueno M, Imai N, Sakatsume M, Narita I, et al. The efficacy of tonsillectomy on long-term renal survival in patients with IgA nephropathy. Kidney Int. 2003;63 (5):1861–7.
86. Akagi H, Kosaka M, Hattori K, Doi A, Fukushima K, Okano M, et al. Long-term results of tonsillectomy as a treatment for IgA nephropathy. Acta Otolaryngol Suppl. 2004;555:38–42.
87. Nishi S, Xie Y, Ueno M, Imai N, Suzuki Y, Iguchi S, et al. A clinicopathological study on the long-term efficacy of tonsillectomy in patients with IgA nephropathy. Acta Otolaryngol Suppl. 2004;555:49–53.
88. Akagi H, Doi A, Kosaka M, Hattori K, Kariya S, Fukushima K, et al. Indication criteria for tonsillectomy in IgA nephropathy patients. Adv Otorhinolaryngol. 2011;72:50–2.
89. Maeda I, Hayashi T, Sato KK, Shibata MO, Hamada M, Kishida M, et al. Tonsillectomy has beneficial effects on remission and progression of IgA nephropathy independent of steroid therapy. Nephrol Dial Transplant. 2012;27:2806–13.
90. Hotta O, Miyazaki M, Furuta T, Tomioka S, Chiba S, Horigome I, et al. Tonsillectomy and steroid pulse therapy significantly impact on clinical remission in patients with IgA nephropathy. Am J Kidney Dis. 2001;38:736–43.

91. Sato M, Hotta O, Tomioka S, Horigome I, Chiba S, Miyazaki M, et al. Cohort study of advanced IgA nephropathy: efficacy and limitations of corticosteroids with tonsillectomy. Nephron Clin Pract. 2003;93:c137–45.
92. Matutani S, Honma R, Adachi M, Hotta O. Clinical observation of palatine tonsils with IgA nephropathy. Acta Otolaryngol Suppl. 2004;555:58–61.
93. Komatsu H, Fujimoto S, Hara S, Sato Y, Yamada K, Eto T, et al. Multivariate analysis of prognostic factors and effect of treatment in patients with IgA nephropathy. Ren Fail. 2005;27:45–52.
94. Miyazaki M, Hotta O, Komatsuda A, Nakai S, Shoji T, Yasunaga C, et al. A multicenter prospective cohort study of tonsillectomy and steroid therapy in Japanese patients with IgA nephropathy: a 5-year report. Contrib Nephrol. 2007;157:94–8.
95. Komatsu H, Fujimoto S, Hara S, Sato Y, Yamada K, Kitamura K. Effect of tonsillectomy plus steroid pulse therapy on clinical remission of IgA nephropathy: a controlled study. Clin J Am Soc Nephrol. 2008;3:1301–7.
96. Kawaguchi T, Ieiri N, Yamazaki S, Hayashino Y, Gillespie B, Miyazaki M, et al. Clinical effectiveness of steroid pulse therapy combined with tonsillectomy in patients with immunoglobulin A nephropathy presenting glomerular haematuria and minimal proteinuria. Nephrology (Carlton). 2010;15:116–23.
97. Kaneko T, Hirama A, Ueda K, Fujino T, Utsumi K, Iino Y, et al. Methylprednisolone pulse therapy combined with mizoribine following tonsillectomy for immunoglobulin A nephropathy: clinical remission rate, steroid sparing effect, and maintenance of renal function. Clin Exp Nephrol. 2011;15:73–8.
98. Ieiri N, Hotta O, Sato T, Taguma Y. Significance of the duration of nephropathy for achieving clinical remission in patients with IgA nephropathy treated by tonsillectomy and steroid pulse therapy. Clin Exp Nephrol. 2012;16:122–9.
99. Ochi A, Moriyama T, Takei T, Uchida K, Nitta K. Comparison between steroid pulse therapy alone and in combination with tonsillectomy for IgA nephropathy. Int Urol Nephrol. 2013;45:469–76.
100. Yamamoto Y, Hiki Y, Nakai S, Yamamoto K, Takahashi K, Koide S, et al. Comparison of effective impact among tonsillectomy alone, tonsillectomy combined with oral steroid and with steroid pulse therapy on long-term outcome of immunoglobulin A nephropathy. Clin Exp Nephrol. 2013;17:218–24.
101. Miura N, Imai H, Kikuchi S, Hayashi S, Endoh M, Kawamura T, et al. Tonsillectomy and steroid pulse (TSP) therapy for patients with IgA nephropathy: a nationwide survey of TSP therapy in Japan and an analysis of the predictive factors for resistance to TSP therapy. Clin Exp Nephrol. 2009;13:460–6.
102. Matsuzaki K, Suzuki Y, Nakata J, Sakamoto N, Horikoshi S, Kawamura T, et al. Nationwide survey on current treatments for IgA nephropathy in Japan. Clin Exp Nephrol. 2013;17:827–33.
103. KDIGO Clinical Practice Guideline for Glomerulonephritis. Chapter 10: immunoglobulin a nephropathy. Kidney Int Suppl. 2012;2:209–17.
104. Kawamura T, Yoshimura M, Miyazaki Y, Okamoto H, Kimura K, Hirano K, et al. A multicenter randomized controlled trial of tonsillectomy combined with steroid pulse therapy in patients with immunoglobulin A nephropathy. Nephrol Dial Transplant. 2014;29:1546–53.
105. Yoshikawa N, Ito H, Sakai T, Takekoshi Y, Honda M, Awazu M, et al. A prospective controlled study of sairei-to in childhood IgA nephropathy with focal/minimal mesangial proliferation. Article in Japanese. Nihon Jinzo Gakkai Shi. 1997;39:503–6.
106. Nakanishi K, Iijima K, Ishikura K, Hataya H, Awazu M, Sako M, et al. Efficacy and safety of lisinopril for mild childhood IgA nephropathy: a pilot study. Pediatr Nephrol. 2009;24:845–9.
107. Yoshikawa N, Ito H, Sakai T, Takekoshi Y, Honda M, Awazu M, et al. A controlled trial of combined therapy for newly diagnosed severe childhood IgA nephropathy. J Am Soc Nephrol. 1999;10:101–9.

108. Kamei K, Nakanishi K, Ito S, Saito M, Sako M, Ishikura K, et al. Long-term results of a randomized controlled trial in childhood IgA nephropathy. Clin J Am Soc Nephrol. 2011;6:1301–7.
109. Yoshikawa N, Honda M, Iijima K, Awazu M, Hattori S, Nakanishi K, Japanese Pediatric IgA Nephropathy Treatment Study Group, et al. Steroid treatment for severe childhood IgA nephropathy: a randomized, controlled trial. Clin J Am Soc Nephrol. 2006;1:511–7.
110. Yoshikawa N, Nakanishi K, Ishikura K, Hataya H, Iijima K, Honda M, et al. Combination therapy with mizoribine for severe childhood IgA nephropathy: a pilot study. Pediatr Nephrol. 2008;23:757–63.
111. Tsuruya K, Harada A, Hirakata H, Mitsuiki K, Johko T, Kondoh H, et al. Combination therapy using prednisolone and cyclophosphamide slows the progression of moderately advanced IgA nephropathy. Clin Nephrol. 2000;53:1–9.
112. Mitsuiki K, Harada A, Okura T, Higaki J. Histologically advanced IgA nephropathy treated successfully with prednisolone and cyclophosphamide. Clin Exp Nephrol. 2007;11:297–303.
113. Horita Y, Tadokoro M, Taura K, Ashida R, Hiu M, Taguchi T, et al. Prednisolone co-administered with losartan confers renoprotection in patients with IgA nephropathy. Ren Fail. 2007;29:441–6.
114. Kawasaki Y, Takano K, Suyama K, Isome M, Suzuki H, Sakuma H, et al. Efficacy of tonsillectomy pulse therapy versus multiple-drug therapy for IgA nephropathy. Pediatr Nephrol. 2006;21:1701–6.
115. Kawasaki Y, Suyama K, Abe Y, Ushijima Y, Sakai N, Takano K, et al. Tonsillectomy with methylprednisolone pulse therapy as rescue treatment for steroid-resistant IgA nephropathy in children. Tohoku J Exp Med. 2009;218:11–6.
116. Nishi H, Sugimoto K, Fujita S, Miyazaki K, Miyazawa T, Sakata N, et al. Effect and therapeutic mechanisms of tonsillectomy for childhood IgA nephropathy. Nephrology (Carlton). 2012;17:658–64.
117. Sakai H, Abe K, Kobayashi Y, Koyama A, Shigematsu H, Harada T, et al. Clinical guidelines of IgA nephropathy. Nihon Jinzo Gakkai Shi. 1995;37:417–21.
118. No author. Clinical guides for immunoglobulin A (IgA) nephropathy in Japan, third version. Article in Japanese. Nihon Jinzo Gakkai Shi. 2011;53:123–35.
119. Kawamura T, Joh K, Okonogi H, Koike K, Utsunomiya Y, Miyazaki Y, et al. A histologic classification of IgA nephropathy for predicting long-term prognosis: emphasis on end-stage renal disease. J Nephrol. 2013;26:350–7.
120. Yoshikawa N, Igarashi T, Ishikura K, Kaku Y, Nakazato H, Kamei K, et al. Guidelines for the treatment of childhood IgA nephropathy. Article in Japanese. Nihon Jinzo Gakkai Shi. 2008;50:31–41.

Chapter 12
IgA Nephropathy from the VALIGA European Study: Differences in Treatment Approaches Within Europe

Rosanna Coppo

Abstract The VALIGA – Validation Study of the Oxford Classification of IgA Nephropathy (IgAN) – was aimed at investigating in a large cohort of European patients with various clinical presentations the prognostic value of the pathology features indicated by the Oxford classification (MEST score). In the 1,147 patients enrolled, the value of MEST to predict the renal function decline was validated, except for the endocapillary lesions, which showed prognostic value only in early stages of IgAN with mild proteinuria. In the VALIGA cohort, most of the patients (86 %) received renin-angiotensin system (RAS) blockade, and half of them had also immunosuppressive regimens (mostly oral or pulse corticosteroids (CSs), seldom associated with other immunosuppressants including azathioprine, cyclophosphamide, and mycophenolate mofetil). The benefit on renal function decline of CS regimen in 523 patients was observed to be significant in comparison to the 624 cases who did not receive it.

In Europe the frequency of IgAN and the rate of progression to end-stage renal failure greatly differ in various countries. Among the factors which may be responsible for this variability, including genetic conditioning and environmental influences, differences in treatment approaches could be taken into account. From the VALIGA cohort, we observed that CS treatment, mostly associated with RAS inhibition, was frequently adopted in Southern Europe, while Northern Europe tended to use RAS blockade alone. A difference in clinical outcome of patients with IgAN was observed between these two geographical European areas suggesting a role of different treatment regimens.

VALIGA Study of the ERA-EDTA Immunonephrology Working Group: VALIGA Steering Committee, nephrologists, and pathologist collaborators are listed in Appendix.

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12.1 Prevalence and Natural History of IgA Nephropathy in Europe

IgA nephropathy (IgAN) is known to be the most common glomerular disease in the world, but, in spite of decades of research, the final outcome of individual patients presenting with IgAN is still insufficiently defined due to the extreme variability of progression toward end-stage renal disease (ESRD) [1–4].

IgAN is mostly frequent in Asia, but it is reported as the most frequent glomerular disease also in Europe, with an incidence of 8–25 new cases/year/pmarp (per million of age-related population) in adults and 3–5 new cases/year/pmarp in children [5, 6]. In Europe the frequency of IgAN at renal biopsy ranges from 19 to 51 % of renal biopsies performed in various countries (Table 12.1) [7–10]. This difference within Europe may be due to different renal biopsy policies, limited to patients with >1 g/day proteinuria in association with microscopic hematuria in some countries, or more largely indicated also for patients with minor proteinuria when associated with persistent microscopic hematuria or when glomerular filtration rate (GFR) is declining, in other countries. Apart from this bias, some true variability may be dependent from genetic factors, as suggested by large genome-wide associated studies (GWAS) which detected an increase in seven single nucleotide polymorphism (SNP) genetic risk score in IgAN with eastward and northward distance from Africa [11]. The same gradient was observed also in European countries, with higher frequency in northeast countries, as in Scandinavia.

Apart from genetic conditioning, exposure to different environmental factors may be considered, including diet, intestinal microbiota, alcohol intake, or chronic intestinal diseases favoring high intestinal permeability (e.g., celiac disease, which is unevenly distributed in Europe) [12, 13]. Finally different pathogen exposure in various European countries due to the climatic variability might also be considered.

IgAN is a major cause of need of dialysis and transplantation worldwide, with renal survival ranging from 95 % to 77 % at 10 years [2–4, 14]. There is a higher

Table 12.1 Frequency of diagnosis of IgA nephropathy (IgAN) in different European countries according to published literature [5–10] and by an inquiry answered by national coordinators of European registries of renal biopsies in native kidneys

Country	% of IgAN
Spain	24
France	33
Italy	37
Czech Republic	37
UK	39
Estonia	35
Poland	51
Sweden	30
Norway	19
Finland	40

prevalence of patients entering dialysis because of IgAN in Northern European countries in comparison to Southern ones (ERA-EDTA Registry, unpublished data presented at 2013 ERA-EDTA Congress), suggesting various risk factors not only for development of IgAN but also for progression, including a different genetic conditioning for factors favoring the sclerotic progression of renal disease [15]. However, it is also possible that the variability of treatment choice pays a role and this has never been explored before.

In Norway at 10 years, 77 % of patients with IgAN survive to end-stage renal disease (ESRD) [16], while this survival observed after 20 years in most reports from Southern Europe (Spain, France, Italy) [17, 18]. Furthermore in Norway also patients with low progression at 10 years can develop ESRD later on suggesting particularly aggressive forms of IgAN or a failure of treatment.

12.2 Risk Factors for Progression of IgA Nephropathy

There is a need for detecting new risk factors for the progression of IgAN, in order to identify patients deserving a more early and aggressive therapy meanwhile avoiding overtreatment of benign cases who will never lose their renal function. Indeed about 20 % of patients enter during the follow-up persistent remission [19].

The role of pathology lesions detected at renal biopsy as risk factors for the progression of IgAN has been enlightened by the Oxford classification of IgAN study [20–22]. This collaborative work identified four pathological features (mesangial proliferation (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), and tubular atrophy/interstitial fibrosis (T), resulting in a MEST score) which predicted renal outcome independently from all clinical indicators at the time of renal biopsy and during follow-up. However, the limited number of patients enrolled in the Oxford classification (265 cases) and their heterogeneous origin (from four continents) indicated a need for validation studies. Several validation studies have been published (reviewed in [23]) over the following years with variable results, but all had in common the limitation of investigating small cohorts, with the exception of a Chinese study on 1,026 cases [24]. In small cohorts, different baseline features (age, eGFR, sclerotic lesions, treatments) were likely to condition the final results.

12.3 The VALIGA Cohort Investigated: Patients and Analysis Methods

ERA-EDTA Immunonephrology Working Group VALIGA (Validation Study of the Oxford Classification of IgAN), granted by the ERA-EDTA Immunonephrology Working Group, aimed at investigating a large number of European

patients with various clinical presentations encompassing the whole spectrum of IgAN, looking for the prognostic value of the pathology features indicated by the Oxford study [25]. The enrolment criteria allowed also the inclusion of patients who did not enter the original Oxford study, as those presenting at renal biopsy with mild proteinuria (<0.5 g/day) or having an already advanced form of IgAN, with residual glomerular filtration rate (e-FGFR) <30 ml/min/1.73 m^2. The VALIGA study had a very successful enrolment accounting for 1,147 patients with IgAN with renal biopsy material available for central review and suitable data sets at renal biopsy and during the follow-up. This study has produced the largest single cohort reported in the worldwide literature on patients with IgAN, comparable only to the Chinese cohort [24].

Clinical data were collected by the coordinating center in Turin, Italy, from 55 nephrology and pathology institutions of 13 European countries (Fig. 12.1) scored by the local pathologists. Each renal biopsy was centrally reviewed in Oxford, UK. Statistical analysis was done in Montreal, Canada. The outcomes (rate of renal function decline and the combined survival from a 50 % reduction of renal function or end-stage renal failure) were detected over a median follow-up

Fig. 12.1 European map of the centers participating in the Validation Study of the Oxford Classification of IgAN (VALIGA) in Europe. The study enrolled 1,147 patients with IgA nephropathy from 55 centers from 13 European countries, which were followed for a median of 4.8 years

of 4.8 years. In patients with an initial proteinuria <0.5 g/day, the outcome considered was the survival from 30 % reduction in eGFR.

The VALIGA cohort [25] was well representative of the whole spectrum of the disease. Ethnicity was for 97 % Caucasian, and gender was 73 % men. Patients' mean age was 36 years; 15 % of the patients were children. At renal biopsy their mean eGFR was 73 ml/min/1.73 m^2 and proteinuria 1.3 (0.6–2.6) g/day. Patients were presenting different degrees of proteinuria and various stages of chronic kidney disease at renal biopsy (Fig. 12.2). The mean yearly loss of the eGFR was 1.8 ml/min/1.73 m^2/year. The combined end point of 50 % reduction of renal function or end-stage renal failure was reached in 16 % of the cases. The renal function survival from the combined end point was 74 % at 10 years.

VALIGA patients had mesangial proliferative changes (M1) in 28 % of the cases, endocapillary hypercellularity (E1) in 11 %, segmental glomerulosclerosis (S1) in 70 %, and tubulointerstitial changes (T1 or T2) in 21 %. Moreover 28 % had arteriolar damage and 7 % crescents. The lesions were differently distributed according to baseline proteinuria and renal function, with a clear increase in MEST score in patients with high levels of proteinuria.

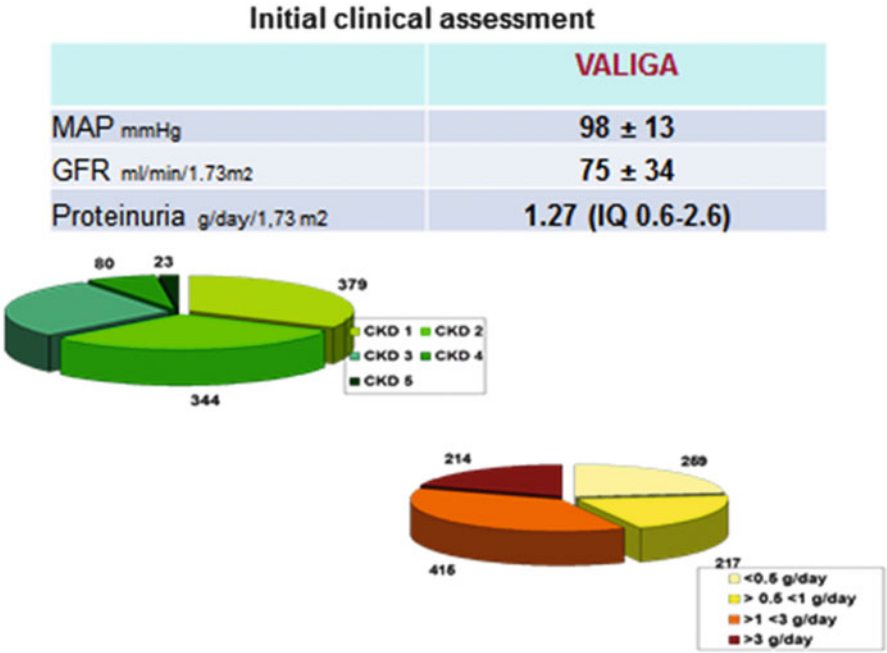

Fig. 12.2 Clinical data at initial assessment of patients with IgA nephropathy enrolled in VALIGA. *MAP* mean arterial blood pressure, *GFR* glomerular filtration rate, *CKD* chronic kidney disease stages

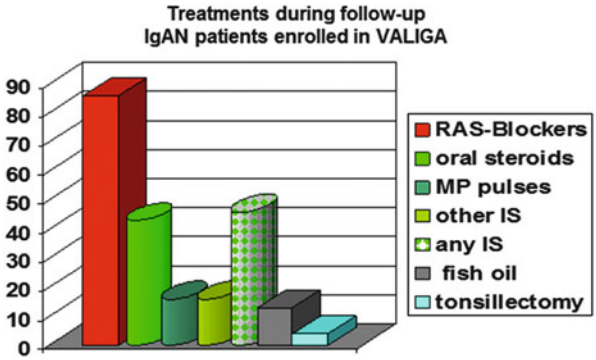

Fig. 12.3 Distribution of treatments in patients with IgA nephropathy enrolled in VALIGA

12.4 Risk Factors for Progression in the VALIGA Cohort

In the whole VALIGA cohort, the value of the MEST score to predict the rate of renal function decline as well as survival without ESRD or 50 % reduction in initial GFR was validated, except for the E lesion, rare within these patients.

The value of mesangial proliferation was assessed not only in the whole cohort but also in subgroups of patients with early diagnosis and proteinuria <0.5 g/day and even in those with renal biopsy in advanced stages, with eGFR <30 ml/min/1.73 m^2. In patients with low proteinuria, mesangial proliferation and endocapillary hypercellularity significantly influenced the survival from progression to levels of proteinuria ≥ 1 g/day and ≥ 2 g/day. In patients with reduced renal function at renal biopsy, mesangial proliferation maintained its value as a predictive factor.

12.5 The Effect of Therapy on Progression of VALIGA Patients

The VALIGA cohort gathered 1,147 patients with IgAN from 13 European countries. This large database allowed an analysis on the possible long-term benefits of CS, in patients with any level of GFR, including those patients with an initial eGFR ≤ 50 ml/min/1.73 m^2 [26].

Most of the patients (86 %) received renin-angiotensin system (RAS) blockade and half of them had also immunosuppressive regimens (mostly oral or pulse corticosteroids (CSs), seldom associated with other immunosuppressants including azathioprine, cyclophosphamide, and mycophenolate mofetil) (Fig. 12.3). In the VALIGA cohort, 523 patients (46 %) received corticosteroids (CSs)/immunosuppression and 624 (54 %) did not.

Since this was a retrospective registry, it reflected the spontaneous attitude for treating patients with IgAN. The European nephrologists chose to treat with CS patients with signs of clinical activity, including high proteinuria and low eGFR,

and pathology signs of potentially progressive disease, including high MEST score. However, in spite of most frequent risk factor for progression, the outcome of patients who had received CS was significantly better than those who did not. After therapy eGFR increased and proteinuria decreased, both significantly.

The benefits of CS were further assessed using a propensity score, identifying 184 patients treated with CS and RAS inhibitors to 184 patients using RAS blockers only, who were similar for clinical and pathological data. The renal outcomes of the patients who received CS in addition to RAS blockade resulted to be significantly better than in patients who had RAS inhibition alone as far as rate of renal function decline and proteinuria reduction were concerned [26].

12.6 Differences in Treatment Approaches Within Europe

As mentioned above, the large VALIGA cohort allowed a sub-analysis of subjects with IgAN enrolled in different European countries. We aimed at investigating differences in clinical and pathological features and the influence of immunosuppressive regimen on the final outcome. We considered 247 VALIGA patients enrolled in East-Northern Europe (including the Netherlands, England, Scotland, Estonia, Poland, and Sweden) and 600 cases from South Europe (Italy).

Patients from Northern and Southern Europe had rather similar demographic and clinical features at renal biopsy (Table 12.2). Gender distribution and mean age at renal biopsy were similar (70 and 73 % of males, respectively, in the two cohorts),

Table 12.2 Baseline data of patients with IgA nephropathy enrolled in Northern European countries (England, Scotland, Estonia, Poland, and Sweden) and in Southern Europe (Italy)

	VALIGA Northern EU countries	VALIGA Southern EU countries
Number of patients	274	600
Male (%)	70	73
Age (years)	34.3 ± 15	36 ± 17.5
Pediatric subjects (%)	15	19
eGFR (ml/min/1.73 m^2)	77 ± 30	76 ± 31
Proteinuria (g/day)	1.5 (0.6–3.1)	1.8 (0.5–2.3)
MAP (mmHg)	99 ± 13	97 ± 13
Pathology features		
M1 (%)	33	25
E1 (%)	14	9
S1 (%)	74*	65
T1–T2 (%)	23+	18
Follow-up		
Duration of follow-up (years)	6.8 ± 4.6	5.8 ± 4
Follow-up proteinuria (g/day)	1 (0.4–1.7)	0.7 (0.4–1.5)

Significance of the difference. *$p < 0.01$; +$p < 0.02$

Table 12.3 Clinical outcome of patients with IgA nephropathy enrolled in Northern European countries (England, Scotland, Estonia, Poland, and Sweden) and in Southern Europe (Italy)

	VALIGA Northern EU countries	VALIGA Southern EU countries
Number of patients	247	600
Treatment		
RAS blockade (%)	84	84
Steroids/immunosuppressors (%)	28	53
Outcome		
Rate of renal function decline (ml/min/1.73 m^2/year)	-3.2 ± 6.6*	-0.8 ± 6.6
50 % decrease in eGFR	22*	9.5
ESRD	16*	8.3
50 % decrease in eGFR or ESRD (%)	23.5*	11.2

Significance of the difference *$p < 0.001$

with a mean age of 34 and 36 years and similar proportion of children (15–19 %). Also baseline eGFR, proteinuria, and mean arterial blood pressure (MAP) were similar in patients with IgAN enrolled in Northern and in Southern Europe (mean eGFR 77 ± 30 and 76 ± 31 ml/min/1.73 m^2, median proteinuria 1.5 and 1.8 g/day, MAP 99 and 97 mmHg, respectively). Pathology features were slightly worse in patients enrolled in Northern Europe in comparison to those in Southern Europe for all the MEST scores, with significantly higher S and T scores, in spite of similar mean baseline values of eGFR and proteinuria. The follow-up was 4.8–5.8 years, with median follow-up proteinuria of 1 and 0.7 g/day, respectively, in patients from North and South Europe (Table 12.2).

The treatment options chosen by the nephrologists in different European countries (Table 12.3) were similar in the use of RAS blockade (84 % in both European geographic areas), while there was a huge difference in the use of CS/IS, prescribed to 28 % only of IgAN patients in Northern Europe versus 53 % in Southern Europe.

The outcome was significantly worse ($p < 0.001$) in VALIGA patients enrolled in Northern Europe for each parameter investigated (Table 12.3), including the rate of eGFR decline (3.2 versus -0.8 ml/min/1.73 m^2/year), 50 % decrease in eGFR (22 % versus 9.5 %), ESRD (16 % versus 8.3 %), and the combined end point of 50 % decrease in eGFR or ESRD (23.5 % versus 11.2 %).

Hence, the unadjusted outcome of patients with IgAN enrolled in VALIGA centers of Northern Europe was significantly worse than what was found in patients from Southern Europe, in spite of similar clinical baseline data, and the most relevant risk factor detected was significantly higher use of CS/IS regimens in patients from Southern Europe.

12.7 Conclusion

The VALIGA study provided a large cohort of patients with IgAN with various clinical presentations and different treatments. It was useful not only to validate the MEST score in predicting the renal function decline but also in getting insight into the possible benefit of immunosuppressive therapy in addition to RAS blockade in comparison to RAS blockade as monotherapy. The major novelty in the results from the two publications from VALIGA study [25, 26] includes the value of mesangial and endocapillary hypercellularity particularly in early stages of IgAN and the protective effects on renal functional decline of CS/IS treatments added on RAB blockade in comparison to RAS inhibition alone.

In Europe the frequency of IgAN and the rate of progression to end-stage renal failure greatly differ in various countries, with eastward and northward. Among the factors which may be responsible for this variability, like genetic as well as environmental factors, differences in treatment approaches to IgAN could be taken into account. From the VALIGA cohort, we observed that CS/IS treatment, mostly associated with RAS inhibition, was frequently adopted in Southern Europe, while Northern Europe tended to use RAS blockade alone. A difference in clinical outcome of patients with IgAN was observed between these two geographical European areas in association with different treatment regimens.

Conflict of Interest The authors declare that they have no conflict of interest.

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Appendix

VALIGA Steering Committee

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References

1. Wyatt RJ, Julian BA. IgA nephropathy. N Engl J Med. 2013;20(368):2402–14.
2. Radford Jr MG, Donadio Jr JV, Bergstralh EJ, Grande JP. Predicting renal outcome in IgA nephropathy. J Am Soc Nephrol. 1997;8:199–207.
3. Berthoux FC, Mohey H, Afiani A. Natural history of primary IgA nephropathy. Semin Nephrol. 2008;28:4–9.
4. Moriyama T, Tanaka K, Iwasaki C, Oshima Y, Ochi A, Kataoka H, Itabashi M, Takei T, Uchida K, Nitta K. Prognosis in IgA nephropathy: 30-year analysis of 1,012 patients at a single center in Japan. PLoS One. 2014;9(3):e01756. doi:10.1371/journal.pone.0091756.
5. McGrogan A, Franssen CF, de Vries CS. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. Nephrol Dial Transplant. 2011;26:414–30.
6. Pesce F, Schena FP. Worldwide distribution of glomerular diseases: the role of renal biopsy registries. Nephrol Dial Transplant. 2010;25:334–6.
7. Schena FP. Survey of the Italian Registry of Renal Biopsies. Frequency of the renal diseases for 7 consecutive years. The Italian Group of Renal Immunopathology. Nephrol Dial Transplant. 1997;12:418–26.
8. Zaza G, Bernich P, Lupo A; 'Triveneto' Register of Renal Biopsies (TVRRB). Incidence of primary glomerulonephritis in a large North-Eastern Italian area: a 13-year renal biopsy study. Nephrol Dial Transplant. 2013;2:367–72.
9. Verde E, Quiroga B, Rivera F, López-Gómez JM. Renal biopsy in very elderly patients: data from the Spanish Registry of Glomerulonephritis. Am J Nephrol. 2012;3:230–7.
10. Maixnerova D, Bauerova L, Skibova J, Rysava R, Reiterova J, Merta M, Honsova E, Tesar V. The retrospective analysis of 343 Czech patients with IgA nephropathy–one centre experience. Nephrol Dial Transplant. 2012;27:1492–8.
11. Kiryluk K, Li Y, Sanna-Cherchi S, Rohanizadegan M, Suzuki H, Eitner F, Snyder HJ, Choi M, Hou P, Scolari F, Izzi C, Gigante M, Gesualdo L, Savoldi S, Amoroso A, Cusi D, Zamboli P, Julian BA, Novak J, Wyatt RJ, Mucha K, Perola M, Kristiansson K, Viktorin A, Magnusson PK, Thorleifsson G, Thorsteinsdottir U, Stefansson K, Boland A, Metzger M, Thibaudin L, Wanner C, Jager KJ, Goto S, Maixnerova D, Karnib HH, Nagy J, Panzer U, Xie J, Chen N, Tesar V, Narita I, Berthoux F, Floege J, Stengel B, Zhang H, Lifton RP, Gharavi AG. Geographic differences in genetic susceptibility to IgA nephropathy: GWAS replication study and geospatial risk analysis. PLoS Genet. 2012;8(6):e1002765. doi:10.1371/journal.pgen.1002765. Epub 2012 Jun 21. PubMed PMID: 22737082; PubMed Central PMCID: PMC3380840.
12. Kaartinen K, Niemela O, Syrjanen J, Porsti I, Harmoinen A, Pasternack A, Huhtala H, Mustonen J. Alcohol consumption and kidney function in IgA glomerulonephritis. Nephron Clin Pract. 2009;112:c86–93.
13. Welander A, Sundelin B, Fored M, Ludvigsson JF. Increased risk of IgA nephropathy among individuals with celiac disease. J Clin Gastroenterol. 2013;47:678–83.
14. Geddes CC, Rauta V, Gronhagen-Riska C, Bartosik LP, Jardine AG, Ibels LS, Pei Y, Cattran DC. A tricontinental view of IgA nephropathy. Nephrol Dial Transplant. 2003;18:1541–8.
15. Kiryluk K, Novak J, Gharavi AG. Pathogenesis of immunoglobulin A nephropathy: recent insight from genetic studies. Annu Rev Med. 2013;64:339–56.
16. Bjørneklett R, Vikse BE, Bostad L, Leivestad T, Iversen BM. Long-term risk of ESRD in IgAN; validation of Japanese prognostic model in a Norwegian cohort. Nephrol Dial Transplant. 2012;27:1485–91.
17. Manno C, Torres DD, Rossini M, Pesce F, Schena FP. Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy. Nephrol Dial Transplant. 2009;24:3694–701.
18. Gutiérrez E, Hernández E, Morales E, Praga M. Immunoglobulin therapy and IgA nephropathy. Nefrologia. 2007;27:765–6.

19. Gutiérrez E, Zamora I, Ballarín JA, Arce Y, Jiménez S, Quereda C, Olea T, Martínez-Ara J, Segarra A, Bernis C, García A, Goicoechea M, García de Vinuesa S, Rojas-Rivera J, Praga M, Grupo de Estudio de Enfermedades Glomerulares de la Sociedad Española de Nefrología (GLOSEN). Long-term outcomes of IgA nephropathy presenting with minimal or no proteinuria. J Am Soc Nephrol. 2012;23:1753–60.
20. Working Group of the International IgA Nephropathy Network and the Renal Pathology Society, Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS, Troyanov S, Alpers CE, Amore A, Barratt J, Berthoux F, Bonsib S, Bruijn JA, D'Agati V, D'Amico G, Emancipator S, Emma F, Ferrario F, Fervenza FC, Florquin S, Fogo A, Geddes CC, Groene HJ, Haas M, Herzenberg AM, Hill PA, Hogg RJ, Hsu SI, Jennette JC, Joh K, Julian BA, Kawamura T, Lai FM, Leung CB, Li LS, Li PK, Liu ZH, Mackinnon B, Mezzano S, Schena FP, Tomino Y, Walker PD, Wang H, Weening JJ, Yoshikawa N, Zhang H. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney Int. 2009;76:534–45.
21. Working Group of the International IgA Nephropathy Network and the Renal Pathology Society, Roberts IS, Cook HT, Troyanov S, Alpers CE, Amore A, Barratt J, Berthoux F, Bonsib S, Bruijn JA, Cattran DC, Coppo R, D'Agati V, D'Amico G, Emancipator S, Emma F, Feehally J, Ferrario F, Fervenza FC, Florquin S, Fogo A, Geddes CC, Groene HJ, Haas M, Herzenberg AM, Hill PA, Hogg RJ, Hsu SI, Jennette JC, Joh K, Julian BA, Kawamura T, Lai FM, Li LS, Li PK, Liu ZH, Mackinnon B, Mezzano S, Schena FP, Tomino Y, Walker PD, Wang H, Weening JJ, Yoshikawa N, Zhang H. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. Kidney Int. 2009;76:546–56.
22. Working Group of the International IgA Nephropathy Network and the Renal Pathology Society, Coppo R, Troyanov S, Camilla R, Hogg RJ, Cattran DC, Cook HT, Feehally J, Roberts IS, Amore A, Alpers CE, Barratt J, Berthoux F, Bonsib S, Bruijn JA, D'Agati V, D'Amico G, Emancipator SN, Emma F, Ferrario F, Fervenza FC, Florquin S, Fogo AB, Geddes CC, Groene HJ, Haas M, SI H, Jennette JC, Joh K, Julian BA, Kawamura T, Lai FM, Li LS, Li PK, Liu ZH, Mezzano S, Schena FP, Tomino Y, Walker PD, Wang H, Weening JJ, Yoshikawa N, Zhang H. The Oxford IgA nephropathy clinicopathological classification is valid for children as well as adults. Kidney Int. 2010;77:921–7.
23. Lv J, Shi S, Xu D, Zhang H, Troyanov S, Cattran DC, Wang H. Evaluation of the Oxford classification of IgA nephropathy: a systematic review and meta-analysis. Am J Kidney Dis. 2013;62:891–9.
24. Zeng CH, Le W, Ni Z, Zhang M, Miao L, Luo P, Wang R, Lv Z, Chen J, Tian J, Chen N, Pan X, Fu P, Hu Z, Wang L, Fan Q, Zheng H, Zhang D, Wang Y, Huo Y, Lin H, Chen S, Sun S, Wang Y, Liu Z, Liu D, Ma L, Pan T, Zhang A, Jiang X, Xing C, Sun B, Zhou Q, Tang W, Liu F, Liu Y, Liang S, Xu F, Huang Q, Shen H, Wang J, Shyr Y, Phillips S, Troyanov S, Fogo A, Liu ZH. A multicenter application and evaluation of the oxford classification of IgA nephropathy in adult Chinese patients. Am J Kidney Dis. 2012;60:812–20.
25. Coppo R, Troyanov S, Bellur S, Cattran D, Cook HT, Feehally J, Roberts IS, Morando L, Camilla R, Tesar V, Lunberg S, Gesualdo L, Emma F, Rollino C, Amore A, Praga M, Feriozzi S, Segoloni G, Pani A, Cancarini G, Durlik M, Moggia E, Mazzucco G, Giannakakis C, Honsova E, Sundelin BB, Di Palma AM, Ferrario F, Gutierrez E, Asunis AM, Barratt J, Tardanico R, Perkowska-Ptasinska A, on behalf of the VALIGA study of the ERA-EDTA Immunonephrology Working Group. Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments. Kidney Int. 2014;86:828–36.
26. Tesar V, Troyanov S, Bellur S, Verhave JC, Cook HT, Feehally J, Roberts IS, Cattran D, Coppo R; on behalf of the VALIGA study of the ERA-EDTA Immunonephrology Working Group. Corticosteroids in IgA Nephropathy: a retrospective analysis from the VALIGA Study. J Am Soc Nephrol. 2015 Feb 12; pii: ASN.2014070697. [Epub ahead of print] PubMed

Chapter 13
Differences in Etiology and Treatment in Scandinavian Countries

Jukka Mustonen, Kati Kaartinen, Jaana Syrjänen, and Ilkka Pörsti

Abstract We here review the studies of IgA nephropathy (IgAN) performed in the Scandinavian countries Denmark, Finland, Iceland, Norway, and Sweden, with emphasis on the etiologic and prognostic factors as well as the treatment of IgAN. During the last decades, most of the published studies about IgAN have come from Sweden and Finland, whereas there are only few reports from the other Scandinavian countries thus far.

Keywords IgA nephropathy • IgA glomerulonephritis • Scandinavian countries

13.1 General Aspects

IgAN was first described almost 50 years ago [1]. The diagnostic hallmark of IgAN is the predominance of glomerular IgA deposits, either alone or with IgG, IgM, or both. Complement C3 deposits are also almost always present [2]. A rare subgroup of primary glomerulonephritis is IgA-IgM nephropathy, in which there are heavy deposits of both IgA and IgM in the glomerular mesangium [3]. Glomerular IgA deposition can be clinically totally silent or "lanthanic" [4, 5]. The ratio of subjects with "lanthanic" glomerular deposits of IgA to those with clinically overt disease can be estimated about 80–1 [4]. In a study from Finland, it was observed that 6.8 % of the necropsy cases from people, who had committed suicide or had encountered violent death, had mesangial IgA deposits [6].

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13.2 Epidemiology and Natural Course

The prevalence of nephritis among young Finnish men was examined in a study 30 years ago [7]. During an 8-year period (1975–1982), 174 military conscripts (out of a total of 314,000) were studied in Helsinki University Central Hospital because of hematuria and/or proteinuria. A representative renal biopsy sample was available from 171 cases. Morphological analysis showed that 131 patients had glomerulonephritis, IgAN being the most common type as it was found in 70 patients [7].

A study about the epidemiology and prognosis of glomerulonephritis in Denmark from the years 1985 to 1997 showed that the prognosis of mesangioproliferative glomerulonephritis was unaffected by the presence of IgA deposits in immunofluorescence examination of the renal biopsies [8]. Based on these findings, the annual incidence of IgAN was estimated to be 1.8 cases per million, placing the Danish residents to the lowest end of the spectrum of IgAN incidence in populations [8].

A major finding in a Finnish study, based on the kidney biopsy registry of Tampere University Hospital, was that the annual incidence of a biopsy-proven glomerulonephritis, 17.6 per population of 100,000, was much higher than in any of the European registries [9]. IgAN was the most common glomerulonephritis, representing one third of all glomerulonephritides. Two other studies, one from Australia and one from France, with a corresponding high biopsy rate as in the above study, showed similar figures [10, 11]. There are no significant time trends in the incidence of IgAN during the last decades in Finland. It was also presumed that there is at least a tenfold true incidence of IgAN in the Finnish population when compared with the number of subjects requiring renal replacement therapy, assuming an unrestricted access to replacement therapy [9].

A recent study from Norway analyzed the mortality of 633 IgAN patients during a mean follow-up time of 11.8 years corresponding a total of 7,464 person-years [12]. The major new finding was that the age- and sex-adjusted mortality rate in Norwegian patients was approximately twofold higher when compared with the general population. A surprising finding was also that in IgAN patients, end-stage renal disease (ESRD) occurred 3.2 times more frequently than pre-ESRD deaths [12].

Geddes et al. [13] studied the long-term outcome of IgAN on three continents. They found significant variability in renal survival between centers, with 10-year actual survival rates of 95.7 %, 87.0 %, 63.9 %, and 61.6 % in Helsinki, Sydney, Glasgow, and Toronto, respectively ($P < 0.001$). This was concluded to be consistent with the hypothesis that geographical variability in the outcome of IgAN is largely explained by lead-time bias and inclusion of milder cases in centers with apparent good outcome. However, these findings do not exclude the possibility that some of the variability is due to other factors such as genetics, diet, or treatment [13].

Several clinical aspects of IgAN in children have been studied by a Swedish group. They reported that childhood IgAN is not a benign disease, as after a median

follow-up of 5 years, a number of children had impaired renal function [14]. Moreover, a rising excretion rate of IgG may be a marker of progressive disease [15], while boys with proteinuria showed a significant decrease in renal function [16]. Therefore, children with IgAN should be carefully monitored with adequate glomerular filtration rate (GFR) measurements and urine protein analyses [17]. The value of early diagnosis of IgAN has recently been emphasized by Tomino [18].

The progression of Henoch-Schönlein nephritis was studied in a material of 42 adult patients by a group in Helsinki, Finland. Renal survival 10 years after biopsy was 91 %, and the only factor that was statistically significantly related to progression was proteinuria >1.0 g/24 h [19].

Recently, the value of the Oxford classification was studied in 99 pediatric IgAN patients with a follow-up of more than 5 years in Sweden. Three of the four histology lesions, namely, mesangial hypercellularity score >0.5, presence of endocapillary hypercellularity or tubular atrophy/interstitial fibrosis of >25 %, and also presence of crescents, were valid in predicting poor outcome in the cohort examined [20].

The natural long-term outcome of childhood IgAN was evaluated in a Finnish retrospective study [21]. After a mean follow-up of 19 years, 71 % of patients had abnormal renal findings and 39 % were receiving antihypertensive treatment at their latest follow-up visit. Pregnancy complications were common: 55 % of the pregnancies had been complicated by proteinuria and/or hypertension, and the prematurity rate was 30 % [21].

Swedish authors evaluated if graft survival rates after renal transplantation are better in IgAN patients when compared to those with other original renal diseases. Rejection rates were not reduced in IgAN, and survival of grafts and patients were not better than for the matched controls [22]. In another study by the same group, it was shown that no specific human leukocyte antigen (HLA) is a risk factor for the recurrence of IgAN in renal grafts and that cumulative graft survival was not reduced in living versus cadaveric donor recipients [23].

The aim of a study performed recently in Finland and Spain was to determine the incidence of IgAN recurrence, as assessed by protocol biopsies during the first 2 years after transplantation, and to determine predictive factors for the recurrence [24]. IgA recurrence rate was 32 %. The histological diagnosis was not accompanied by abnormalities in the urinalysis in half of the patients. Full DR match in HLA analyses and the use of cyclosporine were factors associated with non-recurrence [24].

A broad spectrum of clinical presentations and variable prognosis is typical for IgAN. The genetic risk of IgAN, based on replicated genome-wide association studies, is highest in Asians, intermediate in Europeans, and lowest in Africans, and there seems to be increased prevalence of kidney failure in Northern Europe [25]. Country-specific prevalence of IgAN demonstrates a trend for increased risk in the Nordic countries, with the highest prevalence in Northern European countries Sweden, Finland, and Iceland, while the prevalence is lower in Norway and in Denmark [25].

13.3 Pathogenesis

In a Finnish study almost 30 years ago, a single dose of subcutaneously administered inactivated mumps virus vaccine was administered to male patients with IgAN and IgM glomerulonephritis and to healthy controls. It turned out that IgAN patients were high responders for IgA and IgG antibody production, whereas patients with IgM glomerulonephritis were low responders, especially for IgA antibody production [26].

In the second vaccination study by the same group, oral polio vaccine was examined in 51 IgAN patients and 44 healthy controls [27]. Again, IgAN patients showed an enhanced antibody response compared with controls, and they presented with higher frequency of strong increases in neutralizing antibody titers as well as higher levels of virus-specific IgA-class antibodies. The responses in IgG-class antibodies showed similar activity in both groups. The IgA antibodies synthesized by the patients seemed to be functionally competent antibodies. It was concluded that in IgAN patients, augmentation of antigen-specific IgA response occurs and is induced by different antigens and via different routes of inoculation [27].

In a Swedish study, stimulation of peripheral blood monocyte cells with a polyclonal activator resulted in a threefold increase in synthesis of both IgA subclasses with a preference for IgA1 ribonucleic acid (RNA). It was concluded that increased cytokine production and hyperresponsiveness to polyclonal stimulation may play an important role in the increased synthesis of IgA in IgAN [28].

Swedish authors have demonstrated that patients with IgAN have circulating IgA antibodies against collagen IV alpha chains [29]. In another study from Sweden, the occurrence of anti-C1q antibodies was demonstrated in both IgAN and systemic lupus erythematosus (SLE) nephritis, which was considered to suggest a similar pathogenic mechanism involved in these renal disorders [30]. In one study, the degree of monocyte activation as measured by monocyte respiratory burst was studied in IgAN. The study demonstrated a higher monocyte respiratory burst in patients with IgAN when compared to the cells obtained from healthy controls, as well as a significant reduction in this parameter after a relatively short time (1 month) of treatment with 20 mg of atorvastatin daily [31].

A recent study from Iceland was set up to determine if defective glycosylation might promote IgA antibody deposition and subsequently influence the clinical prognosis in IgAN [32]. The subjects included 44 patients and 46 controls, and it turned out that increased IgA glycosylation in IgAN was associated with low levels of IgA, concomitant glomerular IgA1 and IgA2 deposits, and poor clinical outcome. Altogether, about 20 % of the patients had detectable glomerular IgA2 deposits [32]. One Japanese group has also reported IgA2 in the glomerular deposits of some IgAN patients [33].

The role of streptococcal infection in IgAN has been studied by Swedish authors. They have shown that mesangial IgA deposits co-localize with streptococcal IgA-binding regions of M proteins [34], and that children with IgAN have high antibody levels to IgA-binding streptococcal M proteins [35]. In a recent report,

they demonstrated that IgA-binding M4 protein binds preferentially to galactose-deficient polymeric IgA1 and that these proteins together induce excessive pro-inflammatory responses and proliferation of human mesangial cells. Thus, tissue deposition of streptococcal IgA-binding M proteins may contribute to the pathogenesis of IgAN [36]. These findings are interesting as B cells in the tonsil may be linked to the production of nephritogenic galactose-deficient IgA, which subsequently induces polymeric IgA1 and IgA/IgG immune complex formation [37].

In another Swedish study, the gene and protein expression of proteoglycans were investigated in biopsies from 19 IgAN patients and 14 healthy kidney donors [38]. Distinct patterns of gene expression were seen in glomerular and tubulointerstitial cells. Three of the proteoglycans investigated were found to be upregulated in glomeruli: perlecan, decorin, and biglycan. Perlecan gene expression negatively correlated with albumin excretion and progress of the disease. Abundant decorin protein expression was found in sclerotic glomeruli, but not in unaffected glomeruli from IgAN patients or in controls. Transforming growth factor beta (TGF-ß) was upregulated both on gene and protein level in the glomeruli. Upregulation of biglycan and decorin, as well as TGF-ß itself, indicated that the regulation of TGF-ß, and other profibrotic markers could play a role in IgAN pathology [38].

13.4 Genetics

Immunoglobulin heavy chain switch region gene polymorphism was studied in three European populations. Patients and controls from the UK, Italy, and Finland were included. It was concluded that these genes are not important in conferring disease susceptibility to IgAN in any of the countries studied [39].

In another study, HLA-DP gene polymorphism was studied in the same above three European populations to determine whether ethnic variation exists in the genetic susceptibility for IgAN [40]. The frequency distribution of the DPA1 and DPB1 fragments was found to be similar between these Caucasoid IgAN patient groups when compared with their respective controls. These results suggested that HLA-DP region genes were not important in conferring disease susceptibility to IgAN and did not influence clinical disease expression [40].

The third study with the same three IgAN populations did not demonstrate a consistent association between HLA-DQ region and IgAN [41]. It was concluded that there is no single DQ allele which predisposes to IgAN in these populations. The proportion of patients presenting with macroscopic hematuria and renal impairment varied between the three groups, and this might have influenced the results [41].

Complement component C4 phenotyping and C4 isotope quantification were performed in 93 IgAN patients from Southern Sweden. Phenotype frequencies did not deviate from those of healthy controls. However, the findings suggested that

homozygous C4A deficiency predisposes to the development of end-stage renal failure in IgAN [42].

In a material of 168 IgAN patients from Finland, it was shown that patients with angiotensin-converting enzyme (ACE) genotype II (insertion-insertion) have a more favorable prognosis than those with genotypes ID/DD (deletion-deletion). In patients with the ACE genotype II, renal function deteriorated very seldom, and the degree of proteinuria decreased during the follow-up when compared with proteinuria observed at time of diagnosis [43].

Another study from Finland evaluated the polymorphism of the important cytokine genes of inflammation *interleukin-1ß (IL-1ß)*, *tumor necrosis factor-α (TNF-α)*, *interleukin-6 (IL-6)*, *and interleukin-1 receptor antagonist (IL-1RA)* in 167 patients with IgAN and 400 healthy controls. The carriage of *ILß2* and *IL1RN*2* together with non-carriage of *TNF2* increase the risk of IgAN fivefold. However, no association was found between IgAN progression and cytokine gene polymorphism during the follow-up time of 6–17 (median 11) years from renal biopsy [44].

Genetic factors that predispose to sporadic IgAN were investigated in a high-throughput single nucleotide polymorphism (SNP) association study in 732 patients with biopsy-proven IgAN and 503 control subjects from Canada, France, and Finland. Two significant association signals were found at *IL5RA* and *TNFRSF6B*, the latter being a gene that encodes a decoy receptor for a TNF family ligand that causes IgA in mice when overexpressed [45]. As discussed by the authors, they were unable to confirm a previous report that found a genetic association at the selectin gene cluster with IgAN in Japanese patients [46].

A group from Sweden has studied many genetic factors in a clinical material of about 200 biopsy-proven IgAN patients. They have found that TGF-ß1 gene is an important contributor to the susceptibility to IgAN, but no differences in genotype frequencies between the non-progression and the progression groups of the patients could be found [47]. In another study by the group, interferon regulatory factor 5 (IRF5), signal transducer and activator of transcription (STAT4), and TNF receptor-associated factor 1-complement component 5 (TRAF1-C5) polymorphisms did not show an association with susceptibility and/or severity of IgAN. Further, the results did not support an overlap in genetic susceptibility between patients with lupus nephritis and IgAN [48]. There was no association between CD89 gene polymorphism and susceptibility to IgA, but there was an association between the levels of soluble CD89-IgA complexes in serum and the severity of IgAN [49]. In the cohort of Swedish Caucasian IgAN patients, it was found that the variants of HLA-DRB1 were associated with IgAN, of which the HLA-DRB1*03 revealed a strong protective effect of IgAN. The conclusion was that involvement of adaptive immunity may be of importance in the development of IgAN [50].

13.5 Etiology

IgAN was originally described as a primary glomerulonephritis [1] and was also found in patients with the Henoch-Schönlein syndrome (HSS) [51]. Soon thereafter, it was found that glomerular IgA deposits are often present in patients with alcoholic liver cirrhosis [52]. Primary IgAN and HSS are considered to be parts of the spectrum of IgA-related diseases [53]. A clinical spectrum was also visible in a previous Finnish material, as some patients had a fully developed HSS and some only had a purpuric rash in addition to IgAN [54].

13.5.1 Associated Diseases

In two Finnish studies, associated diseases were found in 54–62 % among IgAN patients [54, 55]. These diseases did not include various acute infectious illnesses that are known to provoke the clinical manifestations of IgAN. Interestingly, in many of these diseases, a high serum IgA concentration has been documented: ankylosing spondylitis, psoriatic arthritis, systemic lupus erythematosus, rheumatoid arthritis (RA), idiopathic pulmonary siderosis, chronic bronchitis, pulmonary fibrosis, sarcoidosis, alcoholic liver cirrhosis, celiac disease (CD), HSS, scleroderma, and certain neoplastic diseases as discussed below [54, 55].

Case reports of IgAN associated with chronic viral infections such as hepatitis C and B and human immunodeficiency virus (HIV) have been reported in the literature. However, the prevalence of these infections is quite low in the Scandinavian countries as compared to many other parts of the world. This may explain why no such reports have emerged from Scandinavia.

In many reports during the 1970s and 1980s, IgAN was reported to coexist with several types of diseases including rheumatic, gastrointestinal, hepatic, dermatologic, ophthalmologic, hematologic, neoplastic, and unclassified diseases, as reviewed by Mustonen and Pasternack [55]. In 1984, Australian authors suggested that IgAN should be regarded as a syndrome, and they divided IgAN into primary and secondary forms [56].

One study examined whether there were any differences in the clinical, histopathologic, or immunologic features in IgAN between the patient groups with associated diseases and those without any extrarenal diseases [57]. The only discovered differences were higher prevalence of renal interstitial cell infiltrates and IgA deposited along glomerular capillary walls in patients with associated diseases. No differences were observed in the severity or prognosis between these two groups of patients [57].

Without an understanding of the pathogenesis of primary IgAN, it remains difficult to dissect out those diseases in which there is only an association with primary IgAN by chance versus those diseases in which there might be shared pathophysiology [58].

13.5.2 Malignancies

In 1978, two IgAN patients with bronchial carcinoma and Henoch-Schönlein purpura were described [59]. Later, we reported two cases of patients with a bronchial small cell carcinoma coexisting with IgAN [60]. One of the patients had also a purpuric rash suggestive of HSS. It was calculated that a causal relationship between bronchial carcinoma and IgAN was very likely [60]. Some years later, we reported four more IgAN patients with a malignancy: carcinoma of the tongue, nasopharyngeal papilloma, retroperitoneal liposarcoma, and pancreatic carcinoma [61]. Interestingly, many of these malignancies affect mucosal membranes and have been shown to associate with high serum IgA levels. As we concluded then, the relationship between neoplastic diseases and IgAN still remains unresolved [61].

13.5.3 Rheumatic Diseases

The prevalence of IgAN in the Finnish population has been estimated to be 1.3 % [6]. The corresponding prevalence in a Finnish renal biopsy material of patients with RA was 8 %, which suggests that IgAN is more common than expected in patients with RA [62]. Among 37 RA patients with mesangial glomerulonephritis (MesGN), there were two main patterns of the nephropathy. Immunofluorescence study showed mesangial IgM deposits as the sole or main finding in 25 patients [62]. This finding closely resembles morphologically the so-called IgM nephropathy [63]. IgAN was found in 9 out of 37 patients. The biopsy indications were quite liberal, since five of these patients had microscopic hematuria and proteinuria, while four subjects had only hematuria as the clinical manifestation of IgAN. The intensity of mesangial IgA deposition, graded from – to +++, correlated significantly with the age of the patients, duration of RA, class of functional capacity, erythrocyte sedimentation rate, and especially with the serum IgA level in the whole group of 37 patients. The prevalence and the concentrations of IgA-rheumatoid factor (RF) were especially high in patients with IgAN [62]. It was suggested that RFs may be involved in the renal injury in these patients and that MesGN represents an extra-articular manifestation of the basic rheumatic disease [62]. Mesangial proliferative glomerulonephritis with IgA deposits has also been reported to be the most common type of nephropathy in Japanese patients with RA [64]. The authors suggested that IgA-RF may play little pathogenetic part in the development of IgAN in RA [64].

13.5.4 Celiac Disease and Intestinal Tract

In 1983, we documented the occurrence of IgAN in three patients with CD, two of whom had also dermatitis herpetiformis (DH) [5]. Both CD and DH are characterized by gluten-sensitive enteropathy. All patients presented with elevated serum IgA levels as well as dermal IgA deposits either in the papillary pattern typical of DH or within the dermal vessel walls.

Glomerular immunopathology was studied in 25 patients with newly diagnosed CD [65]. None of the subjects had any clinical signs of renal disease. Glomeruli were obtained by atraumatic fine-needle aspiration biopsy [66], and the specimens were studied by indirect immunofluorescence for immunoglobulin and complement [67]. Mesangial IgA deposits were found in eight (32 %) of the patients, but C3 was not present in any of them. IgA-class circulating immune complexes, antireticulin and antigliadin antibodies, as well as IgA-RF occurred more often in patients with IgA deposits than in those without mesangial IgA. These results suggested that glomerular IgA deposits are frequently present in untreated CD without inducing overt clinical glomerulonephritis [65].

To clarify possible intestinal mucosal involvement in IgAN, 17 patients with IgAN underwent gastroscopic examination and small bowel mucosal findings were studied [68]. In all specimens, the mucosal architecture was normal. The amount of gamma-delta T cells and the total amount of T cells, as indicated by cluster of differentiation 3+ (CD3+) positivity, were both significantly increased in IgAN patients when compared to patients who had undergone gastroscopy because of dyspepsia and who served as controls. The number of alpha-beta T cells was also higher in IgAN patients. Villous epithelium of the patients disclosed a significant increase in the expression of HLA-DR antigen and GroEL stress protein. A conclusion was made that ongoing small bowel inflammation and stress are present in IgAN. Despite normal morphology that excludes CD, there is reason to believe that intestinal mucosa is involved in the pathogenesis of IgAN [68].

Intestinal inflammation in IgAN was further studied by using duodenal biopsy specimens of the same 17 IgAN patients as above [69]. The amount of CD3+ cells and cyclooxygenase-2 (COX-2)-positive cells was significantly increased, and J-chain-producing plasma cells were decreased in IgAN patients compared to controls. CD3+ cells were coexpressed with COX-2 protein and COX-2-positive cells also expressed CD45RO antigen. The number of lymphocytes and COX-2 expression correlated with serum IgA level. COX-2-positive subepithelial fibroblasts were a conspicuous finding in IgAN. Also, in CD68+ and CD15+ cells, a significant increase was seen. These results clearly indicate that small bowel inflammation in IgAN is presented as an increased number of mucosal inflammatory cells. However, polymeric IgA production is decreased. Active intestinal inflammation in IgAN was strongly related with serum IgA, proteinuria, and hematuria. Subepithelial bowel fibroblasts seemed also to be involved in the process [69].

CD is strongly associated with the HLA-DQ2 and DQ8 haplotypes [70]. In one study, we sought to establish how common CD is in patients with IgAN and

whether the possible association can be explained by similar HLA-DQ status [71]. A total of 223 adult patients with IgAN were studied. Eight patients (3.6 %) with IgAN were found to have also CD. All CD cases had the HLA-DQ2 or HLA-DQ8 haplotype, but these haplotypes were not more common in 168 IgAN patients eligible for haplotyping than in their controls. As many as 14 % of HLA-DQ2-positive patients with IgAN had CD. It was concluded that patients with IgAN carry a risk of contracting CD. This association cannot be explained by a similar accumulation of HLA-DQ haplotypes. A hypothesis was presented that increased intestinal permeability in IgAN may predispose genetically susceptible patients to CD [71].

In a Swedish population-based prospective cohort study comprising 27,160 individuals with CD and no previous renal disease, seven (0.026 %) individuals with CD developed IgAN. An increased risk of biopsy-verified IgAN among individuals with CD was threefold, even after adjustment for prior liver disease and country of birth [72].

Rectal mucosal inflammatory reaction to gluten was examined in 27 patients with IgAN and 18 controls in a study performed by authors from Sweden and Norway [73]. The rectal mucosal production of nitric oxide and release of myeloperoxidase and eosinophil cationic protein were measured. Gluten reactivity was observed in 8 of 27 IgAN patients but in none of the controls. A hypothesis was presented that subclinical inflammation to gluten might be involved in the pathogenesis of IgAN in a subgroup of patients [73].

A study made by the authors from Sweden, Norway, and Iceland evaluated rectal mucosal sensitivity to soy and cow's milk protein in 28 IgAN patients by using a recently developed mucosal patch technique. Approximately half of the patients had a rectal mucosal sensitivity to these proteins, suggesting immune reactivity against these antigens in IgAN [74].

The aim of a recent study from the USA was to evaluate a large series of kidney biopsy specimens to define the spectrum and relative frequencies of inflammatory bowel disease (IBD)-associated kidney abnormalities [75]. Eighty-three of 33,713 renal biopsy specimens were from patients with IBD, so 54 cases were suffering from Crohn's disease and 38 from ulcerative colitis. IgAN was the most common diagnosis in these patients, which suggested a shared pathophysiology between intestinal and kidney disease [75]. A previous Finnish material of 230 IgAN patients included only two cases with ulcerative colitis and none with Crohn's disease as an associated disease [55].

In a recent comprehensive review by Coppo [76], a tempting new hypothesis for a strong intestine-kidney connection in IgAN was presented. This may include abnormal response to microbiota with alterations of the intestinal barrier, including increased absorption of alimentary antigens and bacterial toxins, triggering mucosal-associated lymphoid tissue (MALT) activation, and subclinical intestinal inflammation [76].

In a genome-wide association study (GWAS) of IgAN, six new significant associations were identified [77]. Interestingly, most of the loci found were either directly associated with the risk of IBD or maintenance of the intestinal epithelial

barrier and response to mucosal pathogens. Moreover, the study demonstrated significant overlap of these loci with the loci for other autoimmune and inflammatory disorders, such as RA, systemic sclerosis, alopecia areata, Graves' disease, follicular lymphoma, and type 1 diabetes [77].

13.5.5 Vascular Diseases

In a material of 221 adult IgAN patients, we demonstrated that vascular diseases are notably common in them [78]. The patients had significantly more frequent coronary heart disease and cerebrovascular disease than the general population in Finland. Especially, patients with progressive IgAN had elevated risk of developing vascular disease. Vascular changes seen in renal biopsy specimens of the patients signify an elevated risk of vascular diseases [78]. This is interesting, as it is possible that IgA-mediated inflammation may modify the vascular injury associated with hypertension and atherosclerosis in IgAN [79]. To our knowledge, there are no studies published in which the incidence or prevalence of vascular diseases has been compared between IgAN patients from different countries.

13.6 Progression

In our own study, body mass index (BMI) was higher at the time of renal biopsy among those IgAN patients who showed progression of renal disease during follow-up when compared with those who did not progress [80]. In a French study, excessive body weight at the time of diagnosis has also been shown to be an independent risk factor for chronic renal failure in IgAN [81]. Moreover, it was recently reported in Japanese IgAN patients that even slightly elevated BMI is a risk factor for the progression of the disease [82]. Our group has observed in prospective studies that in addition to the well-known risk factors age, hypertension, and proteinuria, several metabolic factors such as hypertriglyceridemia, hyperuricemia, and hyperinsulinemia are also risk factors for the progression of IgAN [80, 83]. In another study, we evaluated the impact of inflammatory markers and observed that also sensitive C-reactive protein, serum albumin, and white blood cell count were associated with the progression of IgAN [84].

We have also shown that many metabolic factors are associated with renal morphologic alterations in IgAN [85]. These factors that play a central role in the metabolic or insulin resistance syndrome possibly have a pathogenic role also in the progression of IgAN. Serum uric acid may have an independent role in the development of tubulointerstitial lesions as well as being associated with inflammation in renal tissue in IgAN [85].

In a material of 204 IgAN patients, we focused on leukocyte infiltrations and cytokines of the renal biopsy specimens [86]. We found that the parameters

reflecting tubulointerstitial inflammation (leukocyte common antigen, CD3, CD68, interleukin-1β, and interleukin-10) predict the deterioration of renal function in IgAN during a median follow-up of 10 years. This was also seen in patients whose serum creatinine was normal at the time of renal biopsy [86]. In the Oxford classification, four of the histologic variables, namely mesangial hypercellularity, segmental glomerulosclerosis, endocapillary hypercellularity, and tubular atrophy/interstitial fibrosis were shown to have independent influences in predicting renal outcome of IgAN [87]. We suggest that tubulointerstitial inflammation should also be taken into account when evaluating the prognosis of a patient with IgAN.

The prevalence of metabolic syndrome (MetS) was found to be 39 % in patients with IgAN, corresponding to that of the general Finnish population [88]. Furthermore, the presence of MetS was significantly associated with the progression of IgAN in univariate analysis. However, in multivariate analysis, MetS was no more a significant prognostic determinant, suggesting that it is not an independent prognostic variable in IgAN [88].

In a Japanese study, alcohol consumption was suggested to have a protective effect against developing IgAN [89], but this finding could not be confirmed in another study by the same investigators [90]. According to our study, alcohol consumption, as determined by interviews about the amount of alcohol intake, combined with the measurement of a specific biomarker of alcohol abuse, might have a favorable impact of the progression of IgAN [91]. When the study population of 158 patients was divided by gender, the kidney function during the follow-up of 6 years was found to be best among light drinkers in women and among moderate drinkers in men. As we discussed, the question about the safe level of alcohol use remains to be determined, and this might also be different between men and women [91].

Some years ago, a new scoring system to predict renal outcome in IgAN was published [92]. It was based on a large cohort of 2,238 patients followed in 97 clinical units in Japan. In a recent study from Norway, this Japanese prognostic model was also found to be applicable in the prediction of 10-year risk of ESRD in Norwegian IgAN patients [93]. This indicates that the prognosis of IgAN is similar in Japan and Norway.

An active group from Sweden has recently reported several factors that are associated with the progression of IgAN. They found that the plasma levels of soluble interleukin-2 receptor alpha predicts renal outcome in IgAN, providing support for the view that IgAN is a T-cell-driven disease [94]. Patients with IgAN and an increased apolipoprotein B/apolipoprotein A-I ratio have a significantly higher risk of developing ESRD when compared with patients with a low ratio. This result was suggested to strengthen the hypothesis that similar mechanisms may be involved in progressive renal and cardiovascular disease [95]. Circulating fibroblast growth factor-23 (FGF23) was also found to associate with albuminuria and disease progression in patients with IgAN. A question was expressed whether FGF23 modifies albuminuria or fibrosis as a part of an “off-target” effect that has been evidenced in the cardiovascular system [96].

13.7 Treatment

A wealth of modalities have been used in the treatment of IgAN: modulation of immune response by many drugs and plasma exchange, antigen elimination including tonsillectomy, anticoagulant/antithrombotic/fibrinolytic agents, diet therapies, antihypertensive/anti-proteinuric agents, lipid-lowering therapy, miscellaneous other therapies and combination therapies as well as renal replacement therapy, and transplantation [2, 97]. There are no national guidelines for the treatment of IgAN in any Scandinavian country (personal communication from the Presidents of Danish, Finnish, Norwegian, and Swedish Societies of Nephrology and Iceland Renal Association).

In 1983, we published the first report of corticosteroid treatment in IgAN [98]. Six patients with nephrotic syndrome and IgAN were treated with oral corticosteroids. Three of them with mild glomerular histologic alterations responded to treatment, while three patients with moderate to marked mesangial changes associated with segmental sclerosing or proliferative lesions showed no response. We concluded that corticosteroid treatment was justified when the nephrotic syndrome was due to IgAN and only minor glomerular changes were observed [98].

This finding has since been confirmed in many other reports from several countries, and there has been much discussion about the relationship between IgAN and minimal change disease (MCD) [99–103]. It has been suggested that these patients might have either MCD with glomerular IgA deposits, a distinct variant of IgAN, or that the nephropathies occur sequentially as two separate disorders [104].

It has later been observed that also some nephrotic IgAN patients with quite severe glomerular sclerosing or proliferative changes go into clinical remission during immunosuppressive drug therapy, after cessation of therapy, or spontaneously [104].

There are some rather old case reports where the addition of cyclophosphamide or azathioprine to corticosteroid therapy seemed to cause the disappearance of the nephrotic syndrome in IgAN with minimal glomerular changes [99, 105, 106].

In a study from Sweden, the effects of beta-blocking agents and the angiotensin-converting enzyme inhibitor enalapril as antihypertensive drugs were compared in 47 IgAN patients. GFR was determined by 51Cr-EDTA clearance. The deterioration of GFR was faster in patients treated with beta-blocking agents than in the other group of patients [107].

In a Swedish retrospective study, the authors examined 43 children, of whom 24 had Henoch-Schönlein nephritis (HSN) and 19 had primary IgAN [108]. The median age at onset was 12 years, and the subjects were followed for a median of 3 years. The patients were treated with corticosteroids, cyclophosphamide, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. The effects of treatment did not differ between patients with HSN and primary IgAN [108].

In a Swedish study, IgAN patients were given a fish oil product with a high dose of omega-3 polyunsaturated fatty acids (w-3-PUFA) or corn oil in a prospective, double-blind, randomized setting [109]. By 6 months, fish oil treatment resulted in a slight reduction in GFR compared to the start, whereas no change in GFR was observed in the corn oil group. The urinary total protein and red blood cell excretions were not affected in any of the groups [109]. There are other studies of fish oil treatment in IgAN with varying results. Although this therapy is widely prescribed in IgAN, further studies in this area are required before any firm conclusions can be drawn [110].

According to a recent case report from Sweden, early initiation of anti-C5 antibody eculizumab therapy in patients with progressive IgAN may have a beneficial effect by blocking the complement-mediated inflammation [111]. A patient with rapidly progressive crescentic IgAN was treated, in addition to intravenous methylprednisolone pulses and mycophenolate mofetil, also with eculizumab for a total period of 3 months. The treatment led to temporary clinical improvement with stabilization of the GFR and reduction of proteinuria [111].

A pilot study was performed in Sweden, in which oral budesonide 8 mg/day was given to 16 patients with IgAN for 6 months, followed by a 3-month follow-up period [112]. An enteric formulation of the locally acting budesonide, designed to release the active compound in the ileocecal region, was used in the study. The targeted release was hypothesized to exert its effects by local immunosuppression, and the local administration minimized the systemic side effects seen with oral corticosteroids. The treatment had a significant lowering effect on urine albumin excretion accompanied by a minor reduction of serum creatinine. Budesonide was suggested to represent a new treatment of IgAN, the findings clearly warranting further investigation [112].

A subsequent NEFIGAN Trial is a randomized, placebo-controlled study that has just been performed in 56 centers in ten European countries including Denmark, Finland, and Sweden from Scandinavia. This study evaluates the efficacy and safety of two different daily doses (8 and 16 mg) of budesonide in a modified-release capsule formula in the treatment of patients with primary IgAN at risk of developing ESRD. The first results will be available in 2015.

In our opinion, several determinants should be taken into account when deciding the treatment of an individual IgAN patient: the age and gender and associated diseases of the patient, past history and clinical course of IgAN including blood pressure values, the level of proteinuria and GFR, as well as glomerular, tubulointerstitial, and vascular changes of the renal biopsy of the patient.

In conclusion, IgAN presents usually as primary glomerulonephritis, but in many cases, it may also be a part of some systemic disease. Secondary IgAN is seen most commonly in patients with liver disease or mucosal inflammation, in particular affecting the gastrointestinal tract. The highest prevalence of IgAN in the Nordic countries has been found in Sweden, Finland, and Iceland, while the prevalence is lower in Norway and in Denmark. There are no specific national guidelines for the treatment of IgAN in Scandinavian countries. Several clinical,

laboratory, and renal histopathologic findings influence the treatment strategy of a patient with IgAN.

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Berger J, Hinglais N. Les depots intercapillaires d´IgA-IgG. J Urol Nephrol. 1968;74:694–5.
2. Wyatt RJ, Julian BA. IgA nephropathy. N Engl J Med. 2013;368:2402–14. doi:10.1056/NEJMra1206793.
3. Mustonen JT, Rantala IS, Helin HJ, Pasternack AI. IgA-IgM nephropathy. A subgroup of primary mesangial glomerulonephritis. Am J Clin Pathol. 1991;95:863–6.
4. Coppo R, Feehally J, Glassock RJ. IgA nephropathy at two score and one. Kidney Int. 2010;77:181–6. doi:10.1038/ki.2009.427.
5. Helin H, Mustonen J, Reunala T, Pasternack A. IgA nephropathy associated with celiac disease and dermatitis herpetiformis. Arch Pathol Lab Med. 1983;107:324–7.
6. Varis J, Rantala I, Pasternack A, Oksa H, Jäntti M, Paunu ES, et al. Immunoglobulin and complement deposition in glomeruli of 756 subjects who had committed suicide or met with a violent death. J Clin Pathol. 1993;46:607–10.
7. Pettersson E, von Bonsdorff M, Törnroth T, Lindholm H. Nephritis among young Finnish men. Clin Nephrol. 1984;22:217–22.
8. Heaf J, Lokkegaard H, Larsen S. The epidemiology and prognosis of glomerulonephritis in Denmark 1985–1997. Nephrol Dial Transplant. 1999;14:1889–97.
9. Wirta O, Mustonen J, Helin H, Pasternack A. Incidence of biopsy-proven glomerulonephritis. Nephrol Dial Transplant. 2008;23:193–200. doi:10.1093/ndt/gfm564.
10. Briganti EM, Dowling J, Finlay M, Hill PA, Jones CL, Kincaid-Smith PS, et al. The incidence of biopsy-proven glomerulonephritis in Australia. Nephrol Dial Transplant. 2001;16:1364–7.
11. Simon P, Ramee MP, Boulahrouz R, Stanescu C, Charasse C, Ang KS, et al. Epidemiologic data of primary glomerular diseases in western France. Kidney Int. 2004;66:905–8. doi:10.1111/j.1523-1755.2004.00834.x.
12. Knoop T, Vikse BE, Svarstad E, Leh S, Reisaeter AV, Bjorneklett R. Mortality in patients with IgA nephropathy. Am J Kidney Dis. 2013;62:883–90. doi:10.1053/j.ajkd.2013.04.019.
13. Geddes CC, Rauta V, Gronhagen-Riska C, Bartosik LP, Jardine AG, Ibels LS, et al. A tricontinental view of IgA nephropathy. Nephrol Dial Transplant. 2003;18:1541–8.
14. Widstam-Attorps UC, Berg UB. Urinary protein excretion and renal function in children with IgA nephropathy. Pediatr Nephrol. 1991;5:279–83.
15. Berg UB, Bohman SO, Widstam-Attorps U. Renal histological changes in relation to renal function and urinary protein excretion in IgA nephropathy. Arch Dis Child. 1991;66:593–7.
16. Berg UB. Long-term follow up of renal function in IgA nephropathy. Arch Dis Child. 1991;66:588–92.
17. Berg UB, Widstam-Attorps UC. Follow-up of renal function and urinary protein excretion in childhood IgA nephropathy. Pediatr Nephrol. 1993;7:123–9.
18. Tomino Y. Immunoglobulin A, nephropathy and chronic kidney disease. Nephrol (Carlton). 2010;15 Suppl 2:23–6. doi:10.1111/j.1440-1797.2010.01307.x.
19. Rauta V, Törnroth T, Gronhagen-Riska C. Henoch-Schoenlein nephritis in adults-clinical features and outcomes in Finnish patients. Clin Nephrol. 2002;58:1–8.
20. Edström Halling S, Söderberg MP, Berg UB. Predictors of outcome in paediatric IgA nephropathy with regard to clinical and histopathological variables (Oxford classification). Nephrol Dial Transplant. 2012;27:715–22. doi:10.1093/ndt/gfr339.

21. Ronkainen J, Ala-Houhala M, Autio-Harmainen H, Jahnukainen T, Koskimies O, Merenmies J, et al. Long-term outcome 19 years after childhood IgA nephritis: a retrospective cohort study. Pediatr Nephrol. 2006;21:1266–73. doi:10.1007/s00467-006-0163-x.
22. Freese P, Norden G, Olausson M, Nyberg G. Rejection rates in kidney transplant patients with and without IgA nephropathy. Nephrol Dial Transplant. 1997;12:2385–8.
23. Freese P, Svalander C, Norden G, Nyberg G. Clinical risk factors for recurrence of IgA nephropathy. Clin Transplant. 1999;13:313–7.
24. Ortiz F, Gelpi R, Koskinen P, Manonelles A, Räisänen-Sokolowski A, Carrera M, et al. IgA nephropathy recurs early in the graft when assessed by protocol biopsy. Nephrol Dial Transplant. 2012;27:2553–8. doi:10.1093/ndt/gfr664.
25. Kiryluk K, Novak J, Gharavi AG. Pathogenesis of immunoglobulin A nephropathy: recent insight from genetic studies. Annu Rev Med. 2013;64:339–56. doi:10.1146/annurev-med-041811-142014.
26. Pasternack A, Mustonen J, Leinikki P. Humoral immune response in patients with IgA and IgM glomerulonephritis. Clin Exp Immunol. 1986;63:228–33.
27. Leinikki PO, Mustonen J, Pasternack A. Immune response to oral polio vaccine in patients with IgA glomerulonephritis. Clin Exp Immunol. 1987;68:33–8.
28. Baskin B, Pettersson E, Rekola S, Smith CI, Islam KB. Studies of the molecular basis of IgA production, subclass regulation and class-switch recombination in IgA nephropathy patients. Clin Exp Immunol. 1996;106:509–17.
29. Cederholm B, Wieslander J, Bygren P, Heinegard D. Patients with IgA nephropathy have circulating anti-basement membrane antibodies reacting with structures common to collagen I, II, and IV. Proc Natl Acad Sci U S A. 1986;83:6151–5.
30. Gunnarsson I, Ronnelid J, Lundberg I, Jacobson SH. Occurrence of anti-C1q antibodies in IgA nephropathy. Nephrol Dial Transplant. 1997;12:2263–8.
31. Lundberg S, Lundahl J, Gunnarsson I, Jacobson SH. Atorvastatin-induced modulation of monocyte respiratory burst in vivo in patients with IgA nephropathy: a chronic inflammatory kidney disease. Clin Nephrol. 2010;73:221–8.
32. Kolka R, Valdimarsson H, Bodvarsson M, Hardarson S, Jonsson T. Defective immunoglobulin A (IgA) glycosylation and IgA deposits in patients with IgA nephropathy. APMIS. 2013;121:890–7. doi:10.1111/apm.12051.
33. Hisano S, Matsushita M, Fujita T, Endo Y, Takebayashi S. Mesangial IgA2 deposits and lectin pathway-mediated complement activation in IgA glomerulonephritis. Am J Kidney Dis. 2001;38:1082–8. doi:10.1053/ajkd.2001.28611.
34. Schmitt R, Carlsson F, Morgelin M, Tati R, Lindahl G, Karpman D. Tissue deposits of IgA-binding streptococcal M proteins in IgA nephropathy and Henoch-Schonlein purpura. Am J Pathol. 2010;176:608–18. doi:10.2353/ajpath.2010.090428.
35. Schmitt R, Lindahl G, Karpman D. Antibody response to IgA-binding streptococcal M proteins in children with IgA nephropathy. Nephrol Dial Transplant. 2010;25:3434–6. doi:10.1093/ndt/gfq346.
36. Schmitt R, Stahl AL, Olin AI, Kristoffersson AC, Rebetz J, Novak J, et al. The combined role of galactose-deficient IgA1 and streptococcal IgA-binding M protein in inducing IL-6 and C3 secretion from human mesangial cells: implications for IgA nephropathy. J Immunol. 2014;193:317–26. doi:10.4049/jimmunol.1302249.
37. Suzuki Y, Suzuki H, Nakata J, Sato D, Kajiyama T, Watanabe T, et al. Pathological role of tonsillar B cells in IgA nephropathy. Clin Dev Immunol. 2011;2011:639074. doi:10.1155/2011/639074.
38. Ebefors K, Granqvist A, Ingelsten M, Molne J, Haraldsson B, Nystrom J. Role of glomerular proteoglycans in IgA nephropathy. PLoS ONE. 2011;6:e18575. doi:10.1371/journal.pone.0018575.
39. Moore RH, Hitman GA, Sinico RA, Mustonen J, Medcraft J, Lucas EY, et al. Immunoglobulin heavy chain switch region gene polymorphisms in glomerulonephritis. Kidney Int. 1990;38:332–6.

40. Moore RH, Hitman GA, Medcraft J, Sinico RA, Mustonen J, Lucas EY, et al. HLA-DP region gene polymorphism in primary IgA nephropathy: no association. Nephrol Dial Transplant. 1992;7:200–4.
41. Fennessy M, Hitman GA, Moore RH, Metcalfe K, Medcraft J, Sinico RA, et al. HLA-DQ gene polymorphism in primary IgA nephropathy in three European populations. Kidney Int. 1996;49:477–80.
42. Wopenka U, Thysell H, Sjoholm AG, Truedsson L. C4 phenotypes in IgA nephropathy: disease progression associated with C4A deficiency but not with C4 isotype concentrations. Clin Nephrol. 1996;45:141–5.
43. Syrjänen J, Huang XH, Mustonen J, Koivula T, Lehtimäki T, Pasternack A. Angiotensin-converting enzyme insertion/deletion polymorphism and prognosis of IgA nephropathy. Nephron. 2000;86:115–21. doi:45728.
44. Syrjänen J, Hurme M, Lehtimäki T, Mustonen J, Pasternack A. Polymorphism of the cytokine genes and IgA nephropathy. Kidney Int. 2002;61:1079–85. doi:10.1046/j.1523-1755.2002.00193.x.
45. Liu XQ, Paterson AD, He N, St George-Hyslop P, Rauta V, Gronhagen-Riska C, et al. IL5RA and TNFRSF6B gene variants are associated with sporadic IgA nephropathy. J Am Soc Nephrol. 2008;19:1025–33. doi:10.1681/ASN.2007091013.
46. Takei T, Iida A, Nitta K, Tanaka T, Ohnishi Y, Yamada R, et al. Association between single-nucleotide polymorphisms in selectin genes and immunoglobulin A nephropathy. Am J Hum Genet. 2002;70:781–6. doi:10.1086/339077.
47. Vuong MT, Lundberg S, Gunnarsson I, Wramner L, Seddighzadeh M, Hahn-Zoric M, et al. Genetic variation in the transforming growth factor-beta1 gene is associated with susceptibility to IgA nephropathy. Nephrol Dial Transplant. 2009;24:3061–7. doi:10.1093/ndt/gfp079.
48. Vuong MT, Gunnarsson I, Lundberg S, Svenungsson E, Wramner L, Fernstrom A, et al. Genetic risk factors in lupus nephritis and IgA nephropathy – no support of an overlap. PLoS ONE. 2010;5:e10559. doi:10.1371/journal.pone.0010559.
49. Vuong MT, Hahn-Zoric M, Lundberg S, Gunnarsson I, van Kooten C, Wramner L, et al. Association of soluble CD89 levels with disease progression but not susceptibility in IgA nephropathy. Kidney Int. 2010;78:1281–7. doi:10.1038/ki.2010.314.
50. Vuong MT, Lundberg S, Gunnarsson I, Wramner L, Lundstrom E, Fernstrom A, et al. Genetic evidence for involvement of adaptive immunity in the development of IgA nephropathy: MHC class II alleles are protective in a Caucasian population. Hum Immunol. 2013;74:957–60. doi:10.1016/j.humimm.2013.04.016.
51. Berger J. IgA glomerular deposits in renal disease. Transplant Proc. 1969;1:939–44.
52. Manigand G, Morel-Maroger L, Simon J, Deparis M. Lesions renales glomerulaires et cirrhose du foie: note preliminaire sur les lesions histologiques de rein au cours des cirrhoses hepatiques, d'après 20 prelevements biopsiques. Rev Eur Etudes Clin Biol. 1970;15:989–96.
53. Nakamoto Y, Asano Y, Dohi K, Fujioka M, Iida H, Kida H, et al. Primary IgA glomerulonephritis and Schonlein-Henoch purpura nephritis: clinicopathological and immunohistological characteristics. Q J Med. 1978;47:495–516.
54. Mustonen J. IgA glomerulonephritis and associated diseases. Ann Clin Res. 1984;16:161–6.
55. Mustonen J, Pasternack A. Associated diseases in IgA nephropathy. In: Clarkson AR, editor. IgA nephropathy. Boston: Martinus Nijhoff Publishing; 1987. p. 47–65.
56. Clarkson AR, Woodroffe AJ, Bannister KM, Lomax-Smith JD, Aarons I. The syndrome of IgA nephropathy. Clin Nephrol. 1984;21:7–14.
57. Mustonen J, Pasternack A, Helin H, Nikkilä M. Clinicopathologic correlations in a series of 143 patients with IgA glomerulonephritis. Am J Nephrol. 1985;5:150–7.
58. Pouria S, Barratt J. Secondary IgA nephropathy. Semin Nephrol. 2008;28:27–37. doi:10.1016/j.semnephrol.2007.10.004.
59. Cairns SA, Mallick NP, Lawler W, Williams G. Squamous cell carcinoma of bronchus presenting with Henoch-Schonlein purpura. Br Med J. 1978;2:474–5.

60. Mustonen J, Helin H, Pasternack A. IgA nephropathy associated with bronchial small-cell carcinoma. Am J Clin Pathol. 1981;76:652–6.
61. Mustonen J, Pasternack A, Helin H. IgA mesangial nephropathy in neoplastic diseases. Contrib Nephrol. 1984;40:283–91.
62. Korpela M, Mustonen J, Teppo AM, Helin H, Pasternack A. Mesangial glomerulonephritis as an extra-articular manifestation of rheumatoid arthritis. Br J Rheumatol. 1997;36:1189–95.
63. Helin H, Mustonen J, Pasternack A, Antonen J. IgM-associated glomerulonephritis. Nephron. 1982;31:11–6.
64. Nakano M, Ueno M, Nishi S, Suzuki S, Hasegawa H, Watanabe T, et al. Determination of IgA- and IgM-rheumatoid factors in patients with rheumatoid arthritis with and without nephropathy. Ann Rheum Dis. 1996;55:520–4.
65. Pasternack A, Collin P, Mustonen J, Reunala T, Rantala I, Laurila K, et al. Glomerular IgA deposits in patients with celiac disease. Clin Nephrol. 1990;34:56–60.
66. Pasternack A, Helin H, Törnroth T, Rantala I, Väisänen J, Rahka R. Aspiration biopsy of the kidney with a new fine needle: a way to obtain glomeruli for morphological study. Clin Nephrol. 1978;10:79–84.
67. Rantala I, Laasonen A, Pasternack A, Mustonen J. Immunofluorescence microscopy of paraffin-embedded human kidney specimens obtained by fine-needle aspiration biopsy. Am J Clin Pathol. 1983;79:489–92.
68. Rantala I, Collin P, Holm K, Kainulainen H, Mustonen J, Mäki M. Small bowel T cells, HLA class II antigen DR, and GroEL stress protein in IgA nephropathy. Kidney Int. 1999;55:2274–80. doi:10.1046/j.1523-1755.1999.00471.x.
69. Honkanen T, Mustonen J, Kainulainen H, Myllymaki J, Collin P, Hurme M, et al. Small bowel cyclooxygenase 2 (COX-2) expression in patients with IgA nephropathy. Kidney Int. 2005;67:2187–95. doi:10.1111/j.1523-1755.2005.00324.x.
70. Sollid LM, Markussen G, Ek J, Gjerde H, Vartdal F, Thorsby E. Evidence for a primary association of celiac disease to a particular HLA-DQ alpha/beta heterodimer. J Exp Med. 1989;169:345–50.
71. Collin P, Syrjänen J, Partanen J, Pasternack A, Kaukinen K, Mustonen J. Celiac disease and HLA DQ in patients with IgA nephropathy. Am J Gastroenterol. 2002;97:2572–6. doi:10.1111/j.1572-0241.2002.06025.x.
72. Welander A, Sundelin B, Fored M, Ludvigsson JF. Increased risk of IgA nephropathy among individuals with celiac disease. J Clin Gastroenterol. 2013;47:678–83. doi:10.1097/MCG.0b013e318284792e.
73. Smerud HK, Fellstrom B, Hallgren R, Osagie S, Venge P, Kristjansson G. Gluten sensitivity in patients with IgA nephropathy. Nephrol Dial Transplant. 2009;24:2476–81. doi:10.1093/ndt/gfp133.
74. Smerud H, Fellstrom B, Hallgren R, Osagie S, Venge P, Kristjansson G. Gastrointestinal sensitivity to soy and milk proteins in patients with IgA nephropathy. Clin Nephrol. 2010;74:364–71.
75. Ambruzs JM, Walker PD, Larsen CP. The histopathologic spectrum of kidney biopsies in patients with inflammatory bowel disease. Clin J Am Soc Nephrol. 2014;9:265–70. doi:10.2215/CJN.04660513.
76. Coppo R. The intestine-renal connection in IgA nephropathy. Nephrol Dial Transplant. 2015;30:360–6. doi:10.1093/ndt/gfu343.
77. Kiryluk K, Li Y, Scolari F, Sanna-Cherchi S, Choi M, Verbitsky M, et al. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. Nat Genet. 2014;46:1187–96. doi:10.1038/ng.3118.
78. Myllymäki J, Syrjänen J, Helin H, Pasternack A, Kattainen A, Mustonen J. Vascular diseases and their risk factors in IgA nephropathy. Nephrol Dial Transplant. 2006;21:1876–82. doi:10.1093/ndt/gfl062.
79. Coppo R, Feehally J. Is progression of IgA nephropathy conditioned by genes regulating atherosclerotic damage? Nephrol Dial Transplant. 2009;24:3573–5. doi:10.1093/ndt/gfp524.

80. Syrjänen J, Mustonen J, Pasternack A. Hypertriglyceridaemia and hyperuricaemia are risk factors for progression of IgA nephropathy. Nephrol Dial Transplant. 2000;15:34–42.
81. Bonnet F, Deprele C, Sassolas A, Moulin P, Alamartine E, Berthezene F, et al. Excessive body weight as a new independent risk factor for clinical and pathological progression in primary IgA nephritis. Am J Kidney Dis. 2001;37:720–7.
82. Shimamoto M, Ohsawa I, Suzuki H, Hisada A, Nagamachi S, Honda D, et al. Impact of body mass index on progression of IgA nephropathy among Japanese patients. J Clin Lab Anal. 2014. doi:10.1002/jcla.21778.
83. Kaartinen K, Syrjänen J, Pörsti I, Harmoinen A, Pasternack A, Huhtala H, et al. Insulin resistance and the progression of IgA glomerulonephritis. Nephrol Dial Transplant. 2007;22:778–83. doi:10.1093/ndt/gfl704.
84. Kaartinen K, Syrjänen J, Pörsti I, Hurme M, Harmoinen A, Pasternack A, et al. Inflammatory markers and the progression of IgA glomerulonephritis. Nephrol Dial Transplant. 2008;23:1285–90. doi:10.1093/ndt/gfm782.
85. Myllymäki J, Honkanen T, Syrjänen J, Helin H, Rantala I, Pasternack A, et al. Uric acid correlates with the severity of histopathological parameters in IgA nephropathy. Nephrol Dial Transplant. 2005;20:89–95. doi:10.1093/ndt/gfh584.
86. Myllymäki JM, Honkanen TT, Syrjänen JT, Helin HJ, Rantala IS, Pasternack AI, et al. Severity of tubulointerstitial inflammation and prognosis in immunoglobulin A nephropathy. Kidney Int. 2007;71:343–8. doi:10.1038/sj.ki.5002046.
87. Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS, Troyanov S, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney Int. 2009;76:534–45. doi:10.1038/ki.2009.243.
88. Kaartinen K, Syrjänen J, Pörsti I, Harmoinen A, Huhtala H, Mustonen J. Metabolic syndrome in IgA glomerulonephritis. Nephron Extra. 2014;4:138–45. doi:10.1159/000365591.
89. Wakai K, Kawamura T, Matsuo S, Hotta N, Ohno Y. Risk factors for IgA nephropathy: a case-control study in Japan. Am J Kidney Dis. 1999;33:738–45.
90. Wakai K, Nakai S, Matsuo S, Kawamura T, Hotta N, Maeda K, et al. Risk factors for IgA nephropathy: a case-control study with incident cases in Japan. Nephron. 2002;90:16–23.
91. Kaartinen K, Niemelä O, Syrjanen J, Pörsti I, Harmoinen A, Pasternack A, et al. Alcohol consumption and kidney function in IgA glomerulonephritis. Nephron Clin Pract. 2009;112:c86–93. doi:10.1159/000213086.
92. Goto M, Wakai K, Kawamura T, Ando M, Endoh M, Tomino Y. A scoring system to predict renal outcome in IgA nephropathy: a nationwide 10-year prospective cohort study. Nephrol Dial Transplant. 2009;24:3068–74. doi:10.1093/ndt/gfp273.
93. Bjorneklett R, Vikse BE, Bostad L, Leivestad T, Iversen BM. Long-term risk of ESRD in IgAN; validation of Japanese prognostic model in a Norwegian cohort. Nephrol Dial Transplant. 2012;27:1485–91. doi:10.1093/ndt/gfr446.
94. Lundberg S, Lundahl J, Gunnarsson I, Sundelin B, Jacobson SH. Soluble interleukin-2 receptor alfa predicts renal outcome in IgA nephropathy. Nephrol Dial Transplant. 2012;27:1916–23. doi:10.1093/ndt/gfr554.
95. Lundberg S, Gunnarsson I, Jacobson SH. Impact of the apolipoprotein B/apolipoprotein A-I ratio on renal outcome in immunoglobulin A nephropathy. Scand J Urol Nephrol. 2012;46:148–55. doi:10.3109/00365599.2011.644635.
96. Lundberg S, Qureshi AR, Olivecrona S, Gunnarsson I, Jacobson SH, Larsson TE. FGF23, albuminuria, and disease progression in patients with chronic IgA nephropathy. Clin J Am Soc Nephrol. 2012;7:727–34. doi:10.2215/CJN.10331011.
97. Mustonen J, Syrjänen J, Rantala I, Pasternack A. Clinical course and treatment of IgA nephropathy. J Nephrol. 2001;14:440–6.
98. Mustonen J, Pasternack A, Rantala I. The nephrotic syndrome in IgA glomerulonephritis: response to corticosteroid therapy. Clin Nephrol. 1983;20:172–6.

99. di Barbiano BG, Mazzucco G, Casanova S, Radaelli L, Monga G, Minetti L. Steroid-sensitive nephrotic syndrome with mesangial IgA deposits: a separate entity? Observation of two cases. Am J Nephrol. 1986;6:141–5.
100. Furuse A, Hiramatsu M, Adachi N, Karashima S, Hattori S, Matsuda I. Dramatic response to corticosteroid therapy of nephrotic syndrome associated with IgA nephropathy. Int J Pediatr Nephrol. 1985;6:205–8.
101. Gonzalo A, Mampaso F, Teruel JL, Ortuno J. Steroid-responsive nephrotic syndrome with IgA deposits. Nephron. 1988;48:84–5.
102. Rambausek M, Waldherr R, Rauterberg W, Andrassy K, Ritz E. Mesangial IgA nephropathy and idiopathic nephrotic syndrome. Nephron. 1987;47:190–3.
103. Sinnassamy P, O'Regan S. Mesangial IgA deposits with steroid responsive nephrotic syndrome: probable minimal lesion nephrosis. Am J Kidney Dis. 1985;5:267–9.
104. Mustonen J, Pasternack A, Helin H. The course of disease in patients with nephrotic syndrome and IgA nephropathy. Semin Nephrol. 1987;7:374–6.
105. Abreo K, Wen SF. A case of IgA nephropathy with an unusual response to corticosteroid and immunosuppressive therapy. Am J Kidney Dis. 1983;3:54–7.
106. Mustonen J, Pasternack A. A patient with IgA GN with steroid-dependent nephrotic syndrome. Am J Kidney Dis. 1984;4:210–1.
107. Rekola S, Bergstrand A, Bucht H. Deterioration rate in hypertensive IgA nephropathy: comparison of a converting enzyme inhibitor and beta-blocking agents. Nephron. 1991;59:57–60.
108. Edström Halling S, Söderberg MP, Berg UB. Treatment of severe Henoch-Schonlein and immunoglobulin A nephritis. A single center experience. Pediatr Nephrol. 2009;24:91–7. doi:10.1007/s00467-008-0990-z.
109. Pettersson EE, Rekola S, Berglund L, Sundqvist KG, Angelin B, Diczfalusy U, et al. Treatment of IgA nephropathy with omega-3-polyunsaturated fatty acids: a prospective, double-blind, randomized study. Clin Nephrol. 1994;41:183–90.
110. Boyd JK, Cheung CK, Molyneux K, Feehally J, Barratt J. An update on the pathogenesis and treatment of IgA nephropathy. Kidney Int. 2012;81:833–43. doi:10.1038/ki.2011.501.
111. Rosenblad T, Rebetz J, Johansson M, Bekassy Z, Sartz L, Karpman D. Eculizumab treatment for rescue of renal function in IgA nephropathy. Pediatr Nephrol. 2014;29:2225–8. doi:10.1007/s00467-014-2863-y.
112. Smerud HK, Barany P, Lindstrom K, Fernstrom A, Sandell A, Pahlsson P, et al. New treatment for IgA nephropathy: enteric budesonide targeted to the ileocecal region ameliorates proteinuria. Nephrol Dial Transplant. 2011;26:3237–42. doi:10.1093/ndt/gfr052.

Chapter 14
The Implication of the KDIGO Clinical Practice Guidelines on Management of IgA Nephropathy

Philip Kam-tao Li and Kai Ming Chow

Abstract The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline published by the expert panel addresses the treatment approach to IgA nephropathy. The KDIGO Work Group commissioned a systematic review of randomized trial evidence, evaluated the evidence, made recommendations, indicated the level of evidence supporting those recommendations, used GRADE methodology, and reported conflicts of interest. This provides important guidance for the care of patients with IgA nephropathy, with emphasis on treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers to decrease proteinuria. The treatment goal of blood pressure depends on the level of proteinuria (<125/75 mmHg if initial proteinuria is >1 g/day and <130/80 mmHg if proteinuria is <1 g/day). The use of steroid, mycophenolate mofetil, fish oil, and tonsillectomy was discussed in the guidelines. Research suggestions were also made in areas that the current level of evidences is low.

Keywords KDIGO • Clinical practice guideline • Evidence-based medicine • Randomized controlled trial

14.1 Introduction

Management of IgA nephropathy remains controversial despite an improved understanding of the disease mechanisms. Consensus for the best treatment protocol of IgA nephropathy is lacking for many reasons, one of the most important reasons being the relatively few randomized, controlled clinical trials. Other key difficulties with managing IgA nephropathy is the heterogeneity of the disease, absence of disease-specific treatment, and small number of event rates with short-term follow-up, as is the case with most published trials in IgA nephropathy.

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In addition, evidence-based guidelines for the management of IgA nephropathy had not been available until the publication of the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Glomerulonephritis [1]. In other words, this is the first document of expert panel guidelines on managing glomerulonephritis including IgA nephropathy. The chapter on IgA nephropathy laid the groundwork on this field, making treatment recommendations for primary IgA nephropathy. Notably, it is intended to provide guidance rather than a strict set of rules. With the publication of KDIGO guidelines, a commonly agreed approach of managing IgA nephropathy is gaining momentum. Guidelines, as quoted recently by Krumholz HM, "should inform but not dictate, guide but not enforce, and support but not restrict" [2]. The guidelines are therefore not supposed to tell us what to do for every difficult patient in every situation; they will remind us what we know and what we do not know. On the other hand, the evidence-based KDIGO guidelines must be put in context with the concept that its utility is meant for physicians in all parts of the world, where most medications recommended should be available at reasonably low cost [3].

KDIGO is a not-for-profit organization incorporated under Belgium law and is led by an international board of directors, independent of established medical associations [4]. Basic elements for high-quality guidelines, such as those listed by the Institute of Medicine, include the utilization of systematic literature review as the starting point, transparent disclosure of methods for all development steps, multidisciplinary development group and involvement of relevant stakeholders in the external review process, disclosure and active management of (financial and nonfinancial) conflicts of interests, and the use of the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology [5].

The KDIGO Work Group sought to improve transparency by using the GRADE methodology which enables an important distinction between the quality of the evidence and the strength of the recommendation. The Work Group made clear that they are classifying the strength of recommendation as Level 1 or Level 2. The two levels of recommendations are determined by the strength of the evidence supporting the recommendation, the net medical benefit, values and preferences, and costs. Level 1 recommendation can be translated as "We recommend," implying that most patients in their situation would want the recommended course of action and only a small proportion would not. Another implication of Level 1 recommendation is that it is unlikely to change even with the results of future research. Level 2 evidence, translated as "We suggest," refers to the situation in which the majority of patients would want the recommended course of action, but many would not. Further research, under this circumstance, is considered worthwhile. Quality of the evidence, in turn, was characterized by four different levels, as either high (A), moderate (B), low (C), or very low (D).

In line with the process of developing KDIGO guidelines, we discuss the implication of managing IgA nephropathy, highlight the published commentary on the KDIGO guidelines on IgA nephropathy, and report relevant literature available after the publication of KDIGO guidelines.

14.2 Major Implications of KDIGO Guidelines

Table 14.1 summarizes the salient Level 1 and 2 treatment recommendations [1]. It should be stressed that IgA nephropathy represents a wide spectrum of clinical presentations, and optimized supportive therapy remains the cornerstone of treating IgA nephropathy. In terms of supportive therapy, the KDIGO guidelines emphasized control of blood pressure and proteinuria by up-titration of an ACE inhibitor (ACEI) or angiotensin II receptor blocker.

The rationale of the KDIGO guidelines is based on moderate-quality evidence to suggest that proteinuria more than 1 g/day is associated with an accelerated decline in kidney function, in a dose-dependent fashion and independent of other risk factors. The strongest evidence ("We recommend") points to a proteinuria

Table 14.1 The essence of treatment recommendation by KDIGO clinical practice guideline

Recommendation
Long-term ACEI or ARB or ARB treatment when proteinuria is >1 g/day, with up-titration of the drug depending on blood pressure (1B)
Suggestions
Proteinuria
ACEI or ARB if proteinuria is between 0.5 and 1 g/day (in children, between 0.5 and 1 g/day per 1.73 m^2) (2D)
ACEI or ARB be titrated upward as far as tolerated to achieve proteinuria <1 g/day (2C)
6-month course of corticosteroid therapy in patients with persistent proteinuria ≥1 g/day despite 3–6 months of optimized supportive care (including ACEI or ARB and blood pressure control) and GFR >50 ml/min per 1.73 m^2 (2C)
Fish oil if persistent proteinuria ≥1 g/day despite 3–6 months of optimized supportive care (including ACEI or ARB and blood pressure control) (2D)
Blood pressure
Treatment goal of <130/80 mmHg in patients with proteinuria <1 g/day (not graded)
Treatment goal of <125/75 mmHg when initial proteinuria is >1 g/day (not graded)
Rapidly declining GFR
Supportive care for AKI in IgA nephropathy, with a kidney biopsy performed during an episode of macroscopic hematuria showing only ATN and intratubular erythrocyte casts (2C)
Steroids and cyclophosphamide in patients with IgA nephropathy and rapidly progressive crescentic IgA nephropathy, analogous to the treatment of ANCA vasculitis (2D)
Treatment as for MCD in nephrotic patients showing pathological findings of MCD with mesangial IgA deposits on kidney biopsy (2B)
Treatments not suggested
Immunosuppressive therapy in patients with GFR <30 ml/min per 1.73 m^2 unless there is crescentic IgA nephropathy with rapidly deteriorating kidney function (2C)
Mycophenolate mofetil (2C)
Antiplatelet agents (2C)
Tonsillectomy (2C)

Abbreviation: *ACEI* angiotensin-converting enzyme inhibitor, *AKI* acute kidney injury, *ANCA* anti-neutrophil cytoplasmic antibody, *ARB* angiotensin receptor blocker, *ATN* acute tubular necrosis, *GFR* glomerular filtration rate, *MCD* minimal change disease

(in adults) cutoff of 1 g/day (Table 14.1), below which (and sustained) a favorable outcome is achieved. There is valid concern that an increased risk starts with proteinuria above 0.5 g/day ("We suggest").

Noting the less controversial proteinuria cutoff of 1 g/day in adults, the KDIGO guidelines suggest additional treatment when the proteinuria is persistently more than 1 g/day despite 3–6 months of optimized supportive care (including ACEI or angiotensin II receptor blocker and blood pressure control). Choices ("we suggest") include fish oil, a 6-month course of corticosteroid therapy, or both. The guidelines do not address how to choose between fish oil and corticosteroid, but the corticosteroid therapy should be restricted to patients with glomerular filtration rate of more than 50 ml/min per 1.73 m^2 of body surface area according to the KDIGO guidelines (Table 14.1). Furthermore, the preferred dosage regimen for corticosteroids (combined pulse and oral steroids versus purely oral regimen) cannot be commented. The guidelines also draw attention to the potential of more side effects with high-dose pulse corticosteroids, as reported in non-IgA nephropathy patients [1].

It is important to take precaution and keep in mind that the KDIGO guidelines include mostly Level 2 evidence ("We suggest") and much less Level 1 recommendation ("We recommend"). This is partly because of the considerable lack of randomized controlled trials, among which patient numbers seldom exceed 200. Another important purpose of the KDIGO guidelines is the opportunity to prioritize areas in need of research. For example, there is no randomized controlled trial of treatment in crescentic IgA nephropathy.

14.3 Published Commentaries of KDIGO Guidelines

Since the publication of KDIGO guidelines, a few reviews had been published on the topic of IgA nephropathy [6, 7] and evaluation of the guidelines [8]. In particular, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) [9] and the Canadian Society of Nephrology [10] made specific comments on the chapter of IgA nephropathy.

Much insight can be gleaned from the discussion from these two documents [9, 10]. Their focuses were summarized in Table 14.2. A few points deserve mentioning. First, both commentaries highlighted the corticosteroid treatment threshold for IgA nephropathy: trial of corticosteroids should only be considered in patients with preserved renal function or glomerular filtration rate above 50 ml/min per 1.73 m^2. Admittedly, this is reasonable to draw such conclusion based on the inclusion criteria and subject profiles of the three major trials of corticosteroids [11–13]. Nonetheless, concern about corticosteroid side effects explains the need to emphasize the treatment criteria. The Canadian commentary advises the consideration of corticosteroids at the level of the individual patients, taking into account of their relative contraindications to steroid therapy [10]. And, as highlighted by the US commentary [9], a meta-analysis of corticosteroid treatment in IgA nephropathy

Table 14.2 Published comments on KDIGO clinical practice guideline concerning IgA nephropathy

Commentary source	Critiques, remarks, and rationale	Implication and suggestion
National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) US commentary [9]	No trials showing ACEI or ARB decrease the risk for ESRD from IgA nephropathy	No need to decrease proteinuria to <0.5 g/day/1.73 m^2 in children
	No objective evidence for superiority of proteinuria goal <0.5 g/day per 1.73 m^2 to <1.0 g/day per 1.73 m^2 in children	Target blood pressure goals in children based on gender and age norms outlined by the National Institutes of Health (NIH) Task Force on Blood Pressure Control in Children, aiming for blood pressure below the 95th percentile
	Agree with the additional benefit of corticosteroids	
	Agree with not treating with cyclophosphamide or azathioprine	Trial of corticosteroids restricted to patients with preserved renal function (concept about "point of no return")
	Generally agree with not using mycophenolate mofetil, but there may be some benefit in patients of Asian ancestry	Reasonable to use mycophenolate mofetil as an alternative agent if corticosteroids fail or are poorly tolerated in patients of Asian ancestry
	Conflicting evidence on efficacy of fish oil supplements but there is little risk	Suggest future research comparing racial differences in response to immunosuppressive agents
	Low-quality evidence to the benefit of antiplatelet therapy (and expected low adherence to the three-times-daily regimen with dipyridamole)	Suggest using fish oil as stated Suggest not using antiplatelet agents
	No benefit of tonsillectomy alone	Suggest tonsillectomy should not be routinely performed, but there may be benefit when tonsillectomy is combined with corticosteroids (and with recurrent bouts of tonsillitis and macroscopic hematuria)
	Observational studies support the use of steroids plus cyclophosphamide for crescentic IgA nephropathy	Suggest the use of steroids and cyclophosphamide in rapidly progressive crescentic IgA nephropathy (as well as those with rapid deterioration in GFR without ATN and with crescents approaching 50 % of glomeruli on biopsy)
	Sampling error affects renal biopsy interpretation	

(continued)

Table 14.2 (continued)

Commentary source	Critiques, remarks, and rationale	Implication and suggestion
Canadian Society of Nephrology commentary [10]	Lack of RCT evidence on blood pressure targets: opinion-based target of 130/80 versus 125/75 mmHg	A full 6-month trial of corticosteroids is not required prior to determination if the patient is likely to "respond" and benefit from corticosteroids
	Benefits of corticosteroids should be judged at individual patient level and relative contraindications	Suggest evaluation of histologic pattern (that predicts patient response to corticosteroids)
	No comment on recurrent proteinuria after stopping corticosteroid therapy (and adjunctive role of azathioprine)	Suggest 3 g/day purified polyunsaturated fatty acid (as lowest effective dose)
	Challenge for individual patients to meet and maintain the fish oil formulation target	

Abbreviation: *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ATN* acute tubular necrosis, *ESRD* end-stage renal disease, *GFR* glomerular filtration rate, *RCT* randomized controlled trial

suggested an increased efficacy with shorter-term high-dose therapy compared to longer-term low-dose therapy [14]. Second, the controversy of using mycophenolate mofetil can be demonstrated by the different views from the two commentaries. The US commentary generally agreed with the recommendation not to use mycophenolate mofetil in patients with IgA nephropathy, but hinted on the racial differences in the response to mycophenolate mofetil [9]. The benefit of mycophenolate mofetil in Asian patients, as shown in the reduction of proteinuria, a decrease in rate of decline in glomerular filtration rate and end-stage renal disease risk after 6 years of follow-up [15, 16], was acknowledged in the commentary. On the other hand, the Canadian commentary argued against the use of mycophenolate mofetil and reminded us the potential toxicity (including severe pneumonia such as *Pneumocystis* pneumonia) as observed in observational studies, in line with what were recommended by the KDIGO guidelines.

14.4 New Literature After Publication of KDIGO Guidelines

Do we have new data on managing IgA nephropathy after the publication of KDIGO guidelines? A few clinical trials and updated publications are available.

The 2014 blood pressure guidelines from the Eighth Joint National Committee (JNC 8) deserve discussion. One of their recommendations (with a weak expert opinion graded E) advises blood pressure goal of 140/90 mmHg in patients aged 18 years or older with chronic kidney disease [17]. This appears to deviate from the more stringent blood pressure goal listed in KDIGO guidelines on managing IgA nephropathy (Table 14.1). However, it should be emphasized that, in clinical practice, the up-titration of ACEI or angiotensin II receptor blocker in patients with IgA nephropathy is more often driven by the proteinuria reduction need than the blood pressure lowering need. The pertinent question, in other words, is whether a stringent blood pressure might confer risk in patients with IgA nephropathy.

New clinical trial is also available on management strategies of early IgA nephropathy. The KDIGO guidelines did not address the treatment of IgA nephropathy patients with a proteinuria lower than 0.5 g/day, although these patients are often not treated (and are monitored periodically). The best data now come from a randomized trial of 60 Chinese patients with IgA nephropathy, protein excretion less than 0.5 g/day (mean 0.11 g/day), normal blood pressure, and renal function [18]. They were randomized to ramipril 2.5 mg daily or no treatment for 5 years. No treatment benefit was reported, in support of a watchful waiting strategy in this group of early IgA nephropathy patients [18].

Some patients have proteinuria at least 0.75 g/day after renin-angiotensin system blockade. The Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy (STOP-IgAN) trial [19] randomized these patients to supportive care (including a target blood pressure of 125/75 mmHg) and to immunosuppression. The addition of glucocorticoid (with or without cyclophosphamide and azathioprine) did not significantly improve the renal outcomes [19]. There are subsets of patients who cannot achieve urinary protein excretion below 1 g/day despite proper supportive therapy. One approach is focused on further drug treatment aiming at additional antiproteinuric strategies. The results of two open-label trials of oral vitamin D calcitriol have now provided signals of benefit in addition to best supportive care (including renin-angiotensin-aldosterone system blockade) [20, 21].

Another approach, particularly in Japan, is to target tonsils as a source of abnormal IgA that forms immune complexes and deposits in the glomeruli. The KDIGO guidelines explicitly advise against the use of tonsillectomy (Table 14.1). Although randomized trials are lacking, a recent multicenter randomized trial recruited 80 Japanese patients, who were randomized to receive tonsillectomy with steroid pulses or steroid pulses alone. They showed nonsignificantly higher remission rates, defined as proteinuria reduction to below 0.3 g/g creatinine and hematuria to less than five cells per high-power field, in the tonsillectomy plus steroid pulse group [22]. This study was limited by the small sample size, limited statistical power, short duration of follow-up (12 months), patient crossover to alternative treatment group, addition of ACEI or angiotensin II receptor blocker during follow-up course, and patient loss (nearly 20 %) [23]. Given the invasive nature of surgery, an accompanied commentary of the study concluded that data do not support the contention that tonsillectomy should be used in the absence of clear

otorhinolaryngological indication [23]. In a recent meta-analysis of tonsillectomy for IgA nephropathy, it is also suggested that data should be interpreted with caution, apart from its limited generalizability (when most studies involved Japanese population) [24].

14.5 Conclusion

Before the availability of new approaches to IgA nephropathy, the current KDIGO guidelines provide the highest-quality evidence for managing patients with primary IgA nephropathy. Additional information on management of recurrent IgA nephropathy (after renal transplantation) and relevance of the guidelines to the recent Oxford Classification of IgA nephropathy [25] should be sought.

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. KDIGO clinical practice guidelines for glomerulonephritis – chapter 10: immunoglobulin A nephropathy. Kidney Int Suppl. 2012;2:S209–17
2. Krumholz HM. The new cholesterol and blood pressure guidelines: perspective on the path forward. JAMA. 2014;311:1403–5.
3. KDIGO clinical practice guidelines for glomerulonephritis – chapter 2: general principles in the management of glomerular disease. Kidney Int Suppl. 2012;2:S156–62
4. Eckardt KU, Kasiske BL. Kidney disease: improving global outcomes. Nat Rev Nephrol. 2009;5:650–7.
5. AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care. 2003;12:18–23.
6. Wyatt RJ, Julian BA. IgA nephropathy. N Engl J Med. 2013;368:2402–14.
7. Floege J, Feehally J. Treatment of IgA nephropathy and Henoch-Schönlein nephritis. Nat Rev Nephrol. 2013;9:320–7.
8. Radhakrishnan J, Cattran DC. The KDIGO practice guideline on glomerulonephritis: reading between the (guide)lines – application to the individual patient. Kidney Int. 2012;82:840–56.
9. Beck L, Bomback AS, Choi MJ, Holzman LB, Langford C, Mariani LH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for glomerulonephritis. Am J Kidney Dis. 2013;62:403–41.
10. Cybulsky AV, Walsh M, Knoll G, Hladunewich M, Bargman J, Reich H, et al. Canadian Society of Nephrology Commentary on the 2012 KDIGO clinical practice guideline for glomerulonephritis: management of glomerulonephritis in adults. Am J Kidney Dis. 2014;63:363–77.
11. Pozzi C, Andrulli S, Del Vecchio L, Melis P, Fogazzi GB, Altieri P, et al. Corticosteroid effectiveness in IgA nephropathy: long-term results of a randomized, controlled trial. J Am Soc Nephrol. 2004;15:157–63.

12. Manno C, Torres DD, Rossini M, Pesce F, Schena FP. Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy. Nephrol Dial Transplant. 2009;24:3694–701.
13. Lv J, Zhang H, Chen Y, Li G, Jiang L, Singh AK, et al. Combination therapy of prednisolone and ACE inhibitor versus ACE-inhibitor therapy alone in patients with IgA nephropathy: a randomized controlled trial. Am J Kidney Dis. 2009;53:26–32.
14. Lv J, Xu D, Perkovic V, Ma X, Johnson DW, Woodward M, et al. Corticosteroid therapy in IgA nephropathy. J Am Soc Nephrol. 2012;23:1108–16.
15. Tang S, Leung JC, Chan LY, Lui YH, Tang CS, Kan CH, et al. Mycophenolate mofetil alleviates persistent proteinuria in IgA nephropathy. Kidney Int. 2005;68:802–12.
16. Tang SC, Tang AW, Wong SS, Leung JC, Ho YW, Lai KN. Long-term study of mycophenolate mofetil treatment in IgA nephropathy. Kidney Int. 2010;77:543–9.
17. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311:507–20.
18. Li PK, Kwan BC, Chow KM, Leung CB, Szeto CC. Treatment of early immunoglobulin A nephropathy by angiotensin-converting enzyme inhibitor. Am J Med. 2013;126:162–8.
19. Rauen T, Eitner F, Fitzner C, Sommerer C, Zeier M, Otte B, et al. Intensive supportive care plus immunosuppresion in IgA nephropathy. N Engl J Med. 2015;373:2225–36.
20. Szeto CC, Chow KM, Kwan BC, Chung KY, Leung CB, Li PK. Oral calcitriol for the treatment of persistent proteinuria in immunoglobulin A nephropathy: an uncontrolled trial. Am J Kidney Dis. 2008;51:724–31.
21. Liu LJ, Lv JC, Shi SF, Chen YQ, Zhang H, Wang HY. Oral calcitriol for reduction of proteinuria in patients with IgA nephropathy: a randomized controlled trial. Am J Kidney Dis. 2012;59:67–74.
22. Kawamura T, Yoshimura M, Miyazaki Y, Okamoto H, Kimura K, Hirano K, et al. A multicenter randomized controlled trial of tonsillectomy combined with steroid pulse therapy in patients with immunoglobulin A nephropathy. Nephrol Dial Transplant. 2014;29:1546–53.
23. Zand L, Fervenza FC. Does tonsillectomy have a role in the treatment of patients with immunoglobulin A nephropathy. Nephrol Dial Transplant. 2014;29:1456–9.
24. Liu LL, Wang LN, Jiang Y, Yao L, Dong LP, Li ZL, et al. Tonsillectomy for IgA nephropathy: a meta-analysis. Am J Kidney Dis. 2015;65:80–7.
25. Working Group of the International IgA Nephropathy Network and the Renal Pathology Society, Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney Int. 2009;76:534–45.

Chapter 15
Japanese Clinical Practice Guidelines for IgA Nephropathy: Difference from KDIGO Guidelines

Kazuo Takahashi, Ryohei Yamamoto, and Yukio Yuzawa

Abstract In Japan, the Progressive Renal Dysfunction Research Group of the Ministry of Health, Labour and Welfare (MHLW) and the Japanese Society of Nephrology (JSN) developed the Clinical Practice Guides for Immunoglobulin A (IgA) Nephropathy (IgAN) for the first time in 1995. Thereafter, they published its second version in 2002 and third version in 2011. Meanwhile, the Kidney Disease: Improving Global Outcomes (KDIGO) published the Clinical Practice Guidelines for Glomerulonephritis in 2011. The Progressive Renal Dysfunction Research Group of MHLW and JSN developed the Clinical Practice Guidelines for Immunoglobulin A Nephropathy 2014 as an evidence-based guideline to make it more suitable for clinical practice in Japan. In this article, we describe the outlines of the Japanese guidelines and the differences between the Japanese and KDIGO guidelines. These practical guidelines provide evidence-based optimum treatment and will lead to new clinical trials raised from clinical questions in IgAN.

Keywords IgA nephropathy • Evidence-based clinical practice guidelines • Clinical questions • Japanese Society of Nephrology (JSN) • The Ministry of Health, Labour and Welfare (MHLW) of Japan Progressive Renal Diseases Research Group

15.1 Introduction

Immunoglobulin A (IgA) nephropathy (IgAN) is the most common primary glomerulonephritis, and patients typically require dialysis when the disease progresses to end-stage renal failure. As the incidence of IgAN is high in Asian populations,

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including Japanese, establishing a treatment strategy in Japan is strongly warranted. In 1995, the joint committee of the Special Study Group of the Progressive Renal Dysfunction Research Group of the Ministry of Health, Labour and Welfare (MHLW) and the Japanese Society of Nephrology (JSN) developed the Clinical Practice Guides for IgAN for the first time. Its second version was published with a partial amendment in 2002. The third version [1], published in 2011, analyzed data from a multicenter study conducted mainly by the Research Group for IgAN in the Progressive Renal Dysfunction Research Group of MHLW to propose a novel prognostic classification (risk stratification for dialysis), adding clinical severity to histological severity. These clinical practice guides present clear prognostic criteria and treatment guidelines according to the criteria. Therefore, these guides have been widely used in clinical practice or pathological diagnosis, and they have contributed to the diagnosis and treatment of IgAN in Japan.

Meanwhile, Kidney Disease: Improving Global Outcomes (KDIGO) internationally published the Clinical Practice Guidelines for Glomerulonephritis in 2011 [2]. Recommendation grades based on the systematic review of clinical studies and the quality of evidence as a basis for determination of the strength of the recommendations are shown in the KDIGO Clinical Guidelines for Glomerulonephritis. IgAN is described in Chap. 10. However, careful evaluation was required to verify whether the KDIGO Clinical Guidelines for Glomerulonephritis was applicable to the actual clinical situation of IgAN in Japan, because in Japan, IgAN has been detected in routine checkups in the early stage, prognosis of IgAN has been classified in many cases according to the third version of the Clinical Guides for IgAN, and tonsillectomy has been performed in many cases. Therefore, establishing practice guidelines for IgAN that are adjusted to the situation in Japan is warranted. Responding to this need, the Progressive Renal Dysfunction Research Group of MHLW and JSN decided to develop the evidence-based Clinical Guidelines for IgA Nephropathy 2014. Thus, they established the Clinical Guidelines for IgA Nephropathy 2014 Advisory Committee (Fig. 15.1). Against this background, the Clinical Guidelines for IgA Nephropathy 2014 was published [3]. It is the first-ever-published comprehensive guideline only focusing on IgAN.

15.2 Characteristics of the Japanese Clinical Guidelines for IgA Nephropathy

The purpose of the Clinical Guidelines for IgA Nephropathy 2014 was to define evidence-based clinical guidelines that reflect the clinical situation of IgAN in Japan. This guideline is developed to provide answers to clinical questions (CQs) that nephrologists may encounter in the clinical practice for the treatment of IgAN. Each answer is shown as a statement, and recommendation grades based on the evidence-based levels are noted for each statement in the treatment section (Table 15.1). It was not aimed at creating an exhaustive textbook but at supporting clinical decisions by answering questions raised by nephrologists in clinical

Fig. 15.1 Working group for the development of Clinical Guidelines for IgA Nephropathy, Progressive Renal Diseases Research by the Japanese Society of Nephrology, and Research on Intractable Disease by the Ministry of Health, Labour and Welfare of Japan

Table 15.1 Rating description of the guideline recommendations

Recommendation grade
A. Strongly recommended for implementation in routine clinical practice because of sufficient evidence
B. Recommended for implementation in routine clinical practice because of some evidence
C1. Might be implemented in routine clinical practice despite insufficient evidence
C2. Not recommended for implementation in routine clinical practice because of insufficient evidence
D. Not recommended for implementation in routine clinical practice because of evidence that it might be harmful to patients

The current guideline is developed along with the Medical Information Network Distribution Service, which is the clearinghouse for clinical practice guidelines developed in Japan. Five grades of recommendations (from A to D) were set based on the agreement among the members of the working group for the development of clinical guidelines on IgA nephropathy (informal consensus method)

practice and establishing a standard treatment. With the aim of comprehensively supporting nephrologists in the treatment of IgAN in clinical settings, the Clinical Guidelines for IgA Nephropathy 2014 Advisory Committee independently evaluated the results of principal randomized parallel-group clinical trials published to date (Figs. 15.2 and 15.3) and presented the scheme of indications for preventive intervention of renal dysfunction progression in this guideline (Fig. 15.4). Now, the indications of therapeutic interventions of IgAN are mainly based on GFR and urinary protein level in this guideline and also the evidence-based practice

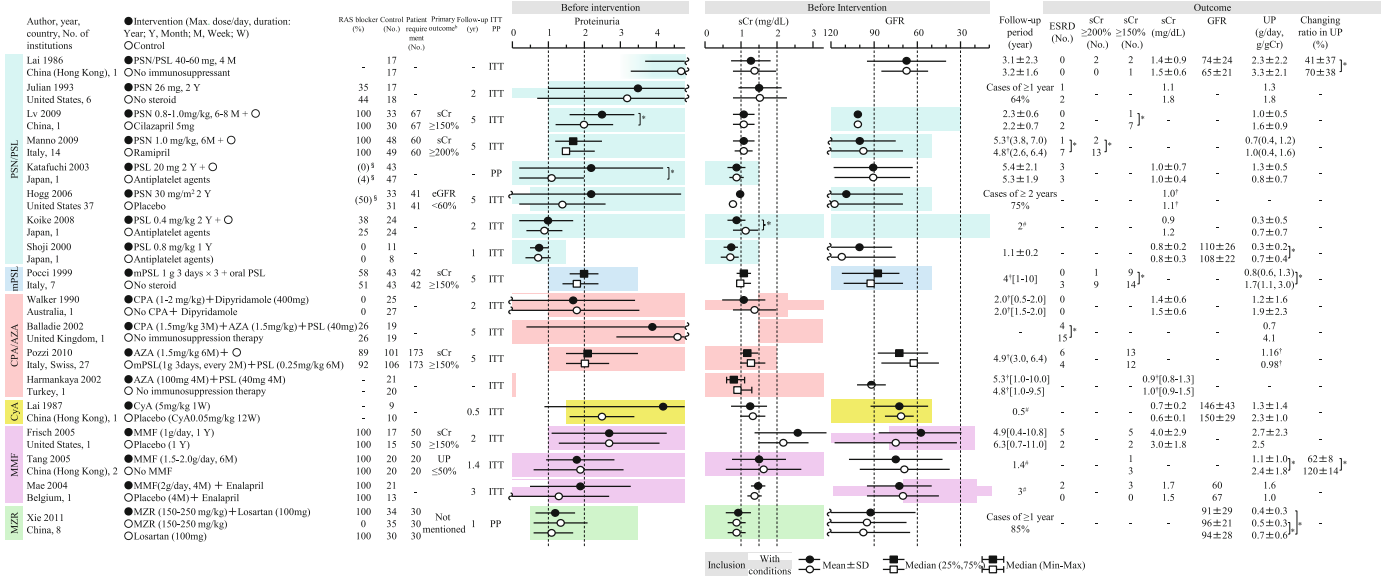

Fig. 15.2 Summary of the randomized controlled trials of corticosteroids and immunosuppressive agents in adult IgAN patients. *AZA* azathioprine, *CPA* cyclophosphamide, *CyA* cyclosporin, *ITT* intention to treat, *MMF* mycophenolate mofetil, *mPSL* methylprednisolone, *MZR* mizoribine, *PP* pet protocol, *PSL* prednisolone, *PSN* prednisone. Mean ± SD, median (25 %, 75 %), mean or median [range]. -NA, $*P < 0.05$, [§]administration rate before intervention, [#]scheduled follow-up period, [†]median. [a]Indicated when the administration period is limited. [b]Indicated only when the number needed to treat is calculated

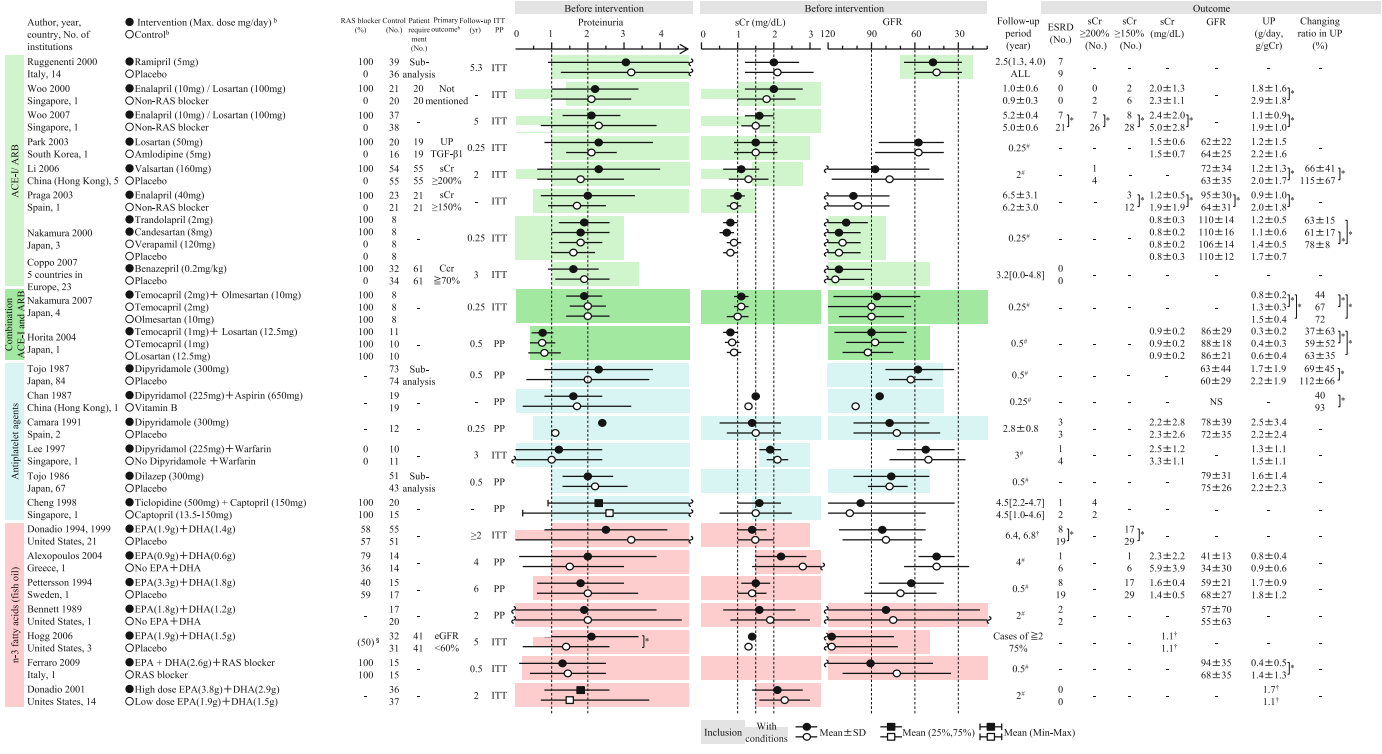

Fig. 15.3 Summary of the randomized controlled trials of RAS blockers, antiplatelet agents, and fish oils in adult patients with IgAN. *EPA* eicosapentaenoic acid, *DHA* docosahexaenoic acid, *ITT* intention to treat, *NS* not significant, *PP* pet protocol, *SI* selectivity index. Mean ± SD, median (25 %, 75 %), mean or median [range]. -NA, $*P < 0.05$, [§]administration rate before intervention, [#] scheduled follow-up period, [†]median. [a]Indicated only when administration period is limited. [b]The approved maximum daily dose (mg) of antihypertensive drug in Japan/JNC7 recommended dose in the United States (mg): amlodipine (10/10), enalapril (10/40), olmesartan (40/40), captopril (150/100), candesartan cilexetil (12/32), temocapril hydrochloride (4/−), trandolapril (2/4), valsartan (160/320), benazepril hydrochloride (10/40), verapamil (360/360), ramipril (−/10), and losartan potassium (100/100). [c]Indicated only when the number needed to treat is calculated

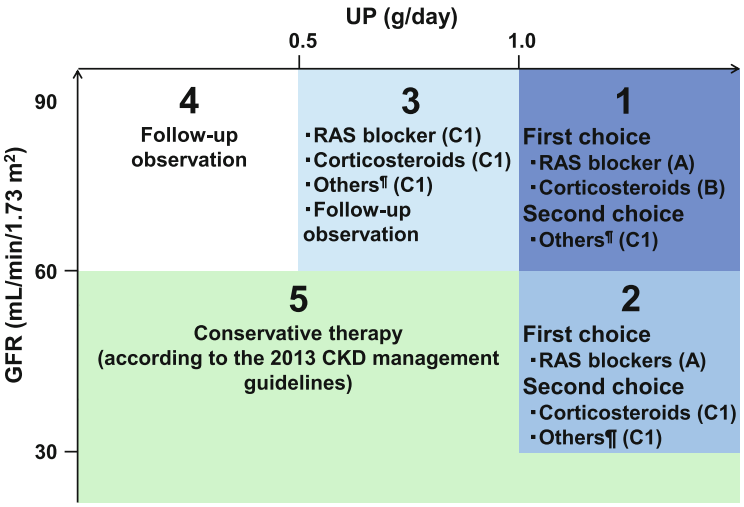

Fig. 15.4 Outline of the treatment of IgAN in adults, with a focus on the prevention of renal dysfunction. Others: tonsillectomy (combined with high-dose pulse corticosteroid therapy) and therapy with nonsteroidal immunosuppressive agents, antiplatelet agents, and n-3 fatty acids (fish oil). This figure shows the indications for treatment intervention, based mainly on the results (Figs. 15.2 and 15.3) of RCTs, often focusing on renal function and amount of urinary protein excreted as patient inclusion/exclusion criteria. In actual clinical practice, besides renal function and urinary protein level, other factors such as renal histopathological findings and age should also be considered to carefully decide the indications for these treatment interventions. Hypertension (CKD Guideline, Chap. 4), salt intake (Chaps. 3 and 4), lipid disorders (Chap. 14), glucose intolerance (Chap. 9), obesity (Chap. 15), smoking (Chap. 2), anemia (Chap. 7), CKD mineral and bone disorders (CKD-MBD, Chap. 8), and metabolic acidosis (Chap. 3) should also be managed as necessary

guideline for the treatment of chronic kidney disease (CKD) [4]. The Clinical Guidelines for IgA Nephropathy 2014 also describe the characteristics and treatment of pediatric IgAN.

The Clinical Guidelines for IgA Nephropathy 2014 comprehensively covers the concept, diagnosis, pathology, epidemiology, and adverse effects of treatment, as well as the standard treatment of IgAN (Table 15.2), actively presenting the data obtained from Japanese patients in figures and tables. IgAN can be definitely diagnosed when kidney biopsy results show IgA deposition within the renal glomerular mesangium. However, glomerular IgA deposition can occur in normal kidneys. Thus, Japanese guidelines define IgAN as follows: IgAN is a disease characterized by urinary findings suggestive of glomerulonephritis; predominantly, IgA is deposited in the glomeruli, with no evidence of other underlying diseases. Glomerular hematuria and proteinuria are urinary findings that suggest glomerulonephritis.

Pathological lesions which are commonly seen in IgAN are shown in the figure panels. Differences in pathological classification between the Japanese severity

Table 15.2 Table of contents of the Japanese Clinical Guidelines for IgA Nephropathy

I. Introduction
1. Definition and background
2. Pathogenesis and pathophysiology
1. Overview
2. Genetics
3. Abnormal IgA molecules
4. Mucosal immunity
5. IgA1 glomerular deposition
6. Glomerular damage
II. Diagnosis
1. Diagnosis
2. Clinical manifestations and laboratory findings
1. Clinical symptoms and physical examination findings
2. Urinalysis findings
3. Blood biochemistry findings
4. Indications for renal biopsy
5. Features of childhood IgA nephropathy
3. Pathological findings
4. Classification
5. Atypical forms of IgA nephropathy
1. Minimal change nephrotic disease (MCD) with mesangial IgA deposits
2. Acute kidney injury (AKI) associated with macroscopic hematuria
3. Crescentic IgA nephropathy
III. Epidemiology, prognosis, and follow-up
1. Incidence and prevalence
2. Natural course
3. Changes in prognosis with changes in treatment guidelines
4. Clinical predictors of progression at the time of initial examination or renal biopsy
5. Clinical predictors of progression during follow-up
6. Remission of urinary findings and its significance
7. Follow-up
IV. Treatment
1. A summary of the management of IgAN in adults, with a focus on prevention of renal dysfunction
2. Clinical questions (CQs) about immunosuppressive therapy (adults)
CQ1. Are corticosteroids recommended in IgA nephropathy?
CQ2. Is tonsillectomy combined with steroid pulse therapy recommended?
CQ3. Is tonsillectomy (alone) recommended?
CQ4. Are nonsteroidal immunosuppressive agents recommended?
3. CQs about immunosuppressive therapy (children)
CQ1. Is immunosuppressive therapy recommended in childhood IgA nephropathy?
CQ2. Is combination “cocktail” therapy recommended in childhood IgA nephropathy?
4. CQs about supportive therapy (adults)

(continued)

Table 15.2 (continued)

CQ1. Are RAS blockers recommended in IgA nephropathy?
CQ2. Are antiplatelet agents recommended in IgA nephropathy?
CQ3. Are n-3 fatty acids (fish oil) recommended in IgA nephropathy?
5. CQs about lifestyle and dietary guidance in IgA nephropathy
CQ1. Should limitation of salt intake be recommended?
CQ2. Should restricted protein intake be recommended?
CQ3. Should weight loss be recommended?
CQ4. Should exercise restriction be recommended?
CQ5. Should smoking cessation be recommended?
6. Adverse events associated with steroid therapy and immunosuppressive agents

classification and the Oxford classification are described in detail. The Clinical Guidelines for IgA Nephropathy 2014 has a supplemental material section that contains structured abstracts of the clinical trials published to date.

15.3 Summary of the Management of IgA Nephropathy in Adults, with a Focus on the Prevention of Renal Dysfunction

In Japan, the major potential treatment modalities for adult IgAN are the use of renin-angiotensin system (RAS) blockers, corticosteroids, nonsteroidal immunosuppressive agents, antiplatelet agents, and n-3 fatty acids (fish oil) and tonsillectomy (with corticosteroid pulse therapy). Based on the results of several randomized controlled trials (RCTs), we evaluated the reduction of proteinuria and preservation of kidney function in response to the therapeutic interventions (Figs. 15.2 and 15.3). Because the entry criteria of the majority of the RCTs included GFR and urinary protein levels, the indications of these therapeutic interventions are mainly based on GFR and urinary protein level in this guideline. Age and renal histological lesions may potentially provide clinically useful information on indications of these therapeutic interventions. Interventions to optimize blood pressure, salt intake, lipid and glucose metabolism, body weight, and smoking habits should be considered, if necessary (Fig. 15.4).

15.3.1 Adult IgA Nephropathy Patients with CKD Stages G1–G2 and Urinary Protein Levels >1.0 g/day

The first-line therapy includes RAS blockers and/or corticosteroid therapy. The second-line therapy includes immunosuppressive agents, antiplatelet agents, tonsillectomy (plus high-dose pulse corticosteroids), fish oil, and others.

These patients are the most common candidates for RCTs and given RAS blockers (grade A) and corticosteroids (grade B) as first-line therapy. These patients are predicted to have poor prognosis of renal function. Therefore, active intervention with the first-line therapy should be considered. The second-line therapy should be considered as a combination therapy with the first-line therapy or if the first-line therapy is unavailable for some reason.

15.3.2 Adult IgA Nephropathy Patients with CKD Stage G3 and Urinary Protein Levels >1.0 g/day

The first-line therapy includes RAS blockers. The second-line therapy includes corticosteroid therapy, immunosuppressive agents, antiplatelet agents, tonsillectomy (plus high-dose pulse corticosteroids), fish oil, and others.

These patients are predicted to have extremely poor prognosis of renal function. Therefore, active intervention with RAS blockers (grade A) as first-line therapy should be considered. Because the efficacy of corticosteroids has not been examined in these patients in RCTs, corticosteroids are classified as second-line therapy. The second-line therapy can be considered as a combination therapy with the first-line therapy or if the first-line therapy is unavailable for some reason.

15.3.3 Adult IgA Nephropathy Patients with CKD Stages G1–G3 and Urinary Protein Levels Between 0.50 and 0.99 g/day

We suggest therapeutic interventions as shown in Fig. 15.4 to prevent proteinuria at urinary protein levels >1.0 g/day, which is closely associated with accelerated decline in kidney function. Furthermore, urinary protein levels between 0.5 and 0.99 g/day are reportedly a high-risk factor of decline in kidney function.

Currently, the necessity of intervention for patients with IgAN whose urinary protein levels are between 0.50 and 0.99 g/day is less certain because the clinical significance for such patients has not been established yet as a predictor of prognosis of renal function and only a few RCTs have been conducted with these patients. However, some studies reported urinary protein levels of 0.50–0.99 g/day as a relative prognostic factor of renal function, and progression to proteinuria at urinary protein levels ≥1.00 g/day, which is a definite poor prognostic factor of renal function, should be prevented. Therefore, interventions should be examined in consideration of benefits and risks.

15.3.4 Adult IgA Nephropathy Patients with CKD Stages G1–G2 and Urinary Protein Levels <0.5 g/day

We recommend annual examination of patients because urinary protein levels <0.5 g/day with preserved renal function carry a favorable impact on long-term outcome.

The prognosis of renal function in patients with IgAN can be favorable if the urinary protein level is <0.50 g/day and the CKD stage is G1–G3. However, careful follow-up is required because gradual increase in proteinuria and decrease in renal function have been observed in some patients. When any finding indicating poor prognosis of renal function other than proteinuria/renal function is found on kidney biopsy or other examinations, intervention should be examined in consideration of benefits and risks.

15.3.5 Adult IgA Nephropathy Patients with CKD Stages G3–G5 and Urinary Protein Levels <1.0 g/day

We recommend supportive therapy according to the evidence-based Clinical Practice Guidelines for CKD 2013 [4].

15.4 How the Japanese Guidelines Differ from the KDIGO Guidelines

Although both the Japanese Clinical Guidelines for IgA Nephropathy 2014 and Chap. 10 in the KDIGO Clinical Practice Guidelines for Glomerulonephritis evaluated indications for intervention for IgAN based mainly on the results of RCTs, they have some differences. One of the major differences is the usage of different criteria to determine the strength of intervention recommendations. The KDIGO guidelines do not indicate an intervention if its efficacy has not been demonstrated in RCTs, whereas the Japanese guidelines indicate that such an intervention be used as second-line therapy if non-RCTs or cohort studies suggested the efficacy of the intervention.

Another major difference is the strength of the recommendations for RAS blockers and corticosteroids. The Japanese guidelines position both RAS blockers and corticosteroids as first-line therapy for IgAN patients with CKD stages G1–G2 and urinary protein levels >1.0 g/day. By contrast, the KDIGO guidelines indicate corticosteroids for patients with persistent proteinuria at urinary protein levels ≥1 g/day despite treatment with RAS blockers, because of a concern about adverse effects due to corticosteroid administration.

Tonsillectomy is not recommended for patients with IgAN, unless for tonsil-related diseases, in the KDIGO guidelines. The Japanese guidelines state that tonsillectomy combined with steroid pulse therapy may improve urinary findings in patients with IgAN and lower the progression of renal dysfunction. This may also

Table 15.3 Summary of recommendation grades in the treatment of IgAN (adults)

Immunosuppressive therapy
Corticosteroids
[**Recommendation grade B**] To control the progression of renal dysfunction in patients with IgAN with urinary protein levels ≥1 g/day and CKD stages G1–2, a short course of high-dose oral steroid therapy (prednisolone at dose of 0.8–1.0 mg/kg for about 2 months, followed by gradual tapering over about 6 months) is recommended
[**Recommendation grade B**] To control the progression of renal dysfunction in patients with IgAN with urinary protein levels ≥1 g/day and CKD stages G1–2, steroid pulse therapy (methylprednisolone 1 g for 3 days by infusion [or intravenously] every other month, 3 times + prednisolone 0.5 mg/kg every other day for 6 months) is recommended
[**Recommendation grade C1**] Steroid therapy may reduce proteinuria in patients with IgAN with urinary protein levels of 0.5–1.0 g/day and CKD stages G1–2, and this may also be considered a treatment option
Tonsillectomy combined with steroid pulse therapy
[**Recommendation grade C1**] Tonsillectomy combined with steroid pulse therapy may improve urinary findings in patients with IgAN and inhibit renal dysfunction progression. This may also be considered a treatment option
Tonsillectomy (**alone**)
[**Recommendation grade C1**] Tonsillectomy may improve urinary findings in patients with IgAN and inhibit the renal dysfunction progression. This may also be considered as a treatment option
Nonsteroidal immunosuppressive agents
[**Recommendation grade C1**] Cyclophosphamide, azathioprine, cyclosporine, mycophenolate mofetil, and mizoribine may improve the renal prognosis in IgAN patients. They may also be considered treatment options (off-label use)
Supportive therapy
*RAS blockers**
[**Recommendation grade A**] RAS blockers control the progression of renal dysfunction in IgAN patients with urinary protein levels ≥1.0 g/day and CKD stages G1–3b; therefore, their use is recommended
[**Recommendation grade C1**] RAS blockers may reduce proteinuria in IgAN patients with urinary protein levels of 0.5–1.0 g/day. They may be considered treatment options
*RAS blockers for IgAN patients without hypertension have off-label use in Japan
Antiplatelet agents
[**Recommendation grade C1**] Dipyridamole may be effective in reducing proteinuria and controlling the progression of renal dysfunction. This may be considered as a treatment option
[**Recommendation grade C1**] Dilazep hydrochloride (dilazep) may be effective in reducing proteinuria, and it may be considered as a treatment option
n-3 fatty acids (fish oil)
[**Recommendation grade C1**] n-3 fatty acids (fish oil) may improve renal prognosis in IgAN patients. They may be considered as a treatment option

be considered a treatment option, as the RCT conducted by the Progressive Renal Dysfunction Research Group of the MHLW reported that tonsillectomy combined with steroid pulse therapy was found to be more effective than steroid pulse therapy alone in reducing urinary protein [5]. To establish more amount of substantial evidence, the superiority of tonsillectomy combined with steroid pulse therapy should be further investigated. No RCT of tonsillectomy alone has been conducted. Previous studies may have shown the long-term efficacy of tonsillectomy in cases of IgAN. Therefore, according to the current clinical practices in Japan, tonsillectomy alone may also be considered as a treatment option.

15.5 Summary of the Guidelines

We summarize the recommendation grades of the Japanese guidelines in Table 15.3. The Clinical Guidelines for IgA Nephropathy 2014 was developed in accordance with the Japanese clinical practice for the treatment of IgAN. Publishing a comprehensive practice guideline suitable for Japanese clinical practice may provide an optimum treatment and encourage new clinical trials based on clinical questions.

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Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Japanese Society of Nephrology. Clinical guides for immunoglobulin A (IgA) nephropathy in Japan, third version. Nihon Jinzo Gakkai shi. 2011;53(2):123–35.
2. KDIGO Clinical Practice Guideline for Glomerulonephritis. Chapter 10: immunoglobulin A nephropathy. Kidney Int Suppl. 2012;2(2):209–17.
3. Japanese Society of Nephrology. JSN and MHWL clinical practice guidelines for IgA nephropathy 2014. Nihon Jinzo Gakkai shi. 2015;57(1):5–137.
4. Japanese Society of Nephrology. Special issue: evidence-based practice guideline for the treatment of CKD. Nihon Jinzo Gakkai shi. 2013;55(5):585–860.
5. Kawamura T, Yoshimura M, Miyazaki Y, Okamoto H, Kimura K, Hirano K, et al. A multicenter randomized controlled trial of tonsillectomy combined with steroid pulse therapy in patients with immunoglobulin A nephropathy. Nephrol Dial Transplant. 2014;29(8):1546–53.

Chapter 16
Limitations of RAS Blockade in IgA Nephropathy

Ryohei Yamamoto

Abstract In KDIGO guideline and Japanese guidelines published recently, the renin-angiotensin system (RAS) blockade by angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) was regarded as the major therapeutic modality of IgA nephropathy (IgAN) with higher evidence level, compared with other modalities including corticosteroids. Multiple randomized controlled trials (RCTs) demonstrated antiproteinuric efficacy of RAS blockade in IgAN patients. However, only a limited number of RCTs with the longer follow-up period reported that RAS blockade improved the renal prognosis of IgAN patients with urinary protein $\geq$1 g/day, who were at high risk of end-stage kidney disease. Besides a lack of evidence to understand the magnitude of benefit and the possible risk of RAS blockade, some questions remain to be examined. First, it is uncertain whether renal histological lesions affect renoprotective effects of RAS blockade. Second, the target level of urinary protein after RAS blockade is unknown. Third, RAS blockade is contraindicated in pregnant women. RAS blockade is the first-line therapeutic modality. In spite of the first-line therapeutic modality of IgAN, further studies are essential to elucidate the magnitude of benefit and the potential risk of RAS blockade in IgAN patients with a wide range of clinical characteristics.

Keywords Angiotensin-converting enzyme inhibitor (ACEI) • Angiotensin receptor blocker (ARB) • Renal histology • Target level of urinary protein • Pregnancy

16.1 Introduction

Renin-angiotensin system (RAS) blockade by angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) is now regarded as a first-line therapeutic modality in patients with IgA nephropathy (IgAN) [1–3]. Two systematic reviews published in 2009 [4] and 2011 [5], including 11 and 30 randomized controlled trials (RCTs), respectively, showed RAS blockade

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decrease urinary protein in IgAN patients and suggested its renoprotective effect on IgAN. Based on the current cumulative evidence, Kidney Disease: Improving Global Outcomes (KDIGO) published the Clinical Practice Guideline for Glomerulonephritis in 2012, including Chap. 10: Immunoglobulin A Nephropathy [1]. The Japanese Society of Nephrology (JSN) independently published Evidence-Based Clinical Practice Guideline for CKD 2013, including Chap. 10: Immunoglobulin A Nephropathy [6], and Clinical Practice Guidelines for IgA Nephropathy 2014 [7], which reflected the practice patterns of IgAN in Japan.

Although these IgAN guidelines stated that RAS blockade was investigated most extensively and had the highest quality of evidence among therapeutic modalities of IgAN (Tables 16.1 and 16.2), more and better evidence is essential to understand the magnitude of benefit and the possible risk and which specific types of IgAN patients might have the greatest potential for benefit. This review, first, summarizes the cumulative evidence of RCTs assessing efficacy of RAS blockade in IgAN patients and, second, discusses several clinical questions to be addressed.

16.2 RAS Blockade in IgA Nephropathy Patients in KDIGO Guideline and Japanese Guidelines

In KDIGO Clinical Practice Guideline for Glomerulonephritis, strength of recommendation of RAS blockade is different between IgAN patients with proteinuria >1 g/day and those with proteinuria <1 g/day. KDIGO guideline *recommends* RAS blockade in IgAN patients with proteinuria >1 g/day (statement 10.2.1, grade 1B), whereas it *suggests* RAS blockade in those with proteinuria between 0.5 and 1 g/day (statement 10.2.2, grade 2D) (Table 16.1). The rationales for the different strength of recommendation on RAS blockade are, first, that moderate-quality evidence identified proteinuria >1 g/day as a risk factor of accelerated decline in GFR [8] and, second, that the majority of randomized trials using ACEI or ARB recruited IgAN patients mainly with proteinuria >1 g/day (Tables 16.3a, 16.3b, 16.3c, 16.3d, 16.4a, 16.4b, 16.4c, 16.4d, 16.5a, 16.5b, 16.5c, and 16.5d). Interestingly, KDIGO guideline suggests IgAN patients with persistent proteinuria ≥1 g/day, despite 3–6 months of optimized supportive care (including ACEIs or ARBs and blood pressure control), and GFR >50 mL/min per 1.73 m^2, receive a 6-month course of corticosteroid therapy (statement 10.3.1, grade 2C). As an initial therapy in IgAN patients with proteinuria ≥1 g/day, RAS blockade takes priority over corticosteroid therapy.

Two Japanese guidelines, Evidence-Based Clinical Practice Guideline for CKD 2013 and Evidence-Based Clinical Practice Guideline for IgA Nephropathy 2014, have a similar difference in strength of recommendation for RAS blockade in different clinical characteristics of IgAN patients. The guidelines recommend RAS blockade for IgAN patients with proteinuria ≥1 g/day and eGFR ≥30 mL/min per 1.73 m^2 (grade A) and suggest RAS blockade for IgAN patients with

Table 16.1 RAS blockade and use of corticosteroids in IgAN patients in KDIGO clinical guideline for glomerulonephritis [1]

Chapter	Recommendation statement	Grade
10.2	Antiproteinuric and antihypertensive therapy	
10.2.1	We *recommend* long-term ACEI or ARB treatment when proteinuria is >1 g/day, with up-titration of the drug depending on blood pressure	1B
10.2.2	We *suggest* ACEI or ARB treatment if proteinuria is between 0.5 and 1 g/day (in children, between 0.5 and 1 g/day per 1.73 m^2)	2D
10.3.3	We *suggest* the ACEI or ARB be titrated upward as far as tolerated to achieve proteinuria <1 g/day	2C
10.3.4	In IgAN, use blood pressure treatment goals of <130/80 mmHg in patients with proteinuria <1 g/day and <125/75 mmHg when initial proteinuria is >1 g/day	Not graded
10.3	Corticosteroids	
10.3.1	We suggest that patients with persistent proteinuria ≥1 g/day, despite 3–6 months of optimized supportive care (including ACEI or ARBs and blood pressure control) and GFR >50 mL/min per 1.73 m^2, receive a 6-month course of corticosteroid therapy	2C

(1) Strength of recommendation: grade 1–2

Grade 1, "we recommend"

– Implications for clinicians: Most patients should receive the recommended course of action

– Implications for patients: Most people in your situation would want the recommended course of action and only a small proportion would not

– Implications for policy: The recommendation can be evaluated as a candidate for developing a policy or a performance measure

Grade 2, "we suggest"

– Implications for clinicians: The majority of people in your situation would want the recommended course of action, but many would not

– Implications for patients: Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences

– Implications for policy: The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined

(2) Quality of evidence: grade A–D

Grade A, "high"

– We are confident that the true effect lies close to that of the estimate of the effect

Grade B, "moderate"

– The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Grade C, "low"

– The true effect may be substantially different from the estimate of the effect

Grade D, "very low"

– The estimate of effect is very uncertain and often will be far from the truth

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *GFR* glomerular filtration rate, *IgAN* IgA nephropathy, *KDIGO* kidney disease: improving global outcomes, *RAS* renin-angiotensin system

proteinuria between 0.5 and 1.0 g/day and eGFR ≥60 mL/min per 1.73 m^2 (grade C1). Contrary to the KDIGO guideline, Japanese guidelines give no priority to RAS blockade over corticosteroid therapy except recommendation grade.

Table 16.2 RAS blockade and use of corticosteroids in IgAN patients in Japanese Evidence-Based Clinical Practice Guideline for CKD 2013 [6, 56] and IgAN 2014

No	Clinical questions and statements	Grade
2	Are RAS inhibitors recommended for decreasing urinary protein and preserving renal function in patients with IgAN?	
	We recommend treatment with RAS inhibitors for patients with proteinuria ≥1 g/day and eGFR ≥30 mL/min/1.73 m^2 (CKD G1 to G3b) because of their effect of preservation of renal function	A
	We suggest treatment with RAS inhibitors if proteinuria is between 0.5 and 1.0 g/day because of their antiproteinuric effect	C1
3	Are corticosteroids recommended for decreasing urinary protein and preserving renal function in patients with IgAN?	
	We recommend that patients with proteinuria ≥1 g/day and eGFR ≥60 mL/min/1.73 m^2 (CKD G1 to G2) receive a 6-month course of high-dose oral corticosteroids therapy (6-month regime of oral prednisone starting with 0.8–1 mg/kg/day for 2 months and then reduced gradually for the next 4 months)	B
	We recommend that patients with proteinuria ≥1 g/day and eGFR ≥60 mL/min/1.73 m^2 (CKD G1 to G2) receive high-dose pulse corticosteroids therapy (i.v. bolus injections of 1 g methylprednisolone for 3 days each at months 1, 3, and 5, followed by 0.5 mg/kg oral prednisone on alternate days for 6 months)	B
	We tentatively suggest using corticosteroids for patients with proteinuria less than 1 g/day and eGFR ≥60 mL/min/1.73 m^2 (CKD G1 to G2) because of their antiproteinuric effect	C1

Strength of recommendation: grade A–D
Grade A, strongly recommended because the scientific basis is strong
Grade B, recommended because there is some scientific basis
Grade C1, recommended despite having only a weak scientific basis
Grade C2, not recommended because there is only a weak scientific basis
Grade D, not recommended because scientific evidence shows the treatment to be ineffective or harmful
ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *IgAN* IgA nephropathy, *RAS* renin-angiotensin system

16.3 Randomized Controlled Trials Assessing Efficacy of RAS Blockade in IgA Nephropathy Patients

The current cumulative evidence supporting these guidelines is reviewed in this section. I searched MEDLINE via PubMed until May 2015 for randomized controlled trials enrolling IgAN patients. After excluding non-RCT studies and RCTs published in non-English languages, we retrieved 84 RCTs, including 22 RCTs assessing efficacy of RAS blockade in IgAN. Their details are described below.

Table 16.3a Study protocols of RCTs assessing efficacy of ACEI vs. no RAS blockade in IgAN patients

Author year	Interventions (dose)	Duration	Age	BP	Renal function	UP	Histology
Parallel group trials							
Praga 2003 [9]	Enalapril (≤40 mg)	ND (76 months)	Adult	0–2 antihypertensive drugs	SCr ≤1.5 mg/dL	≥0.5 g/day	ND
	No RAS blockade			No malignant hypertension			
Li 2013 [10]	Ramipril (2.5 mg)	60 months	18–65 years	Normal blood pressure	SCr <120 μmol/L	<0.5 g/day	ND
	No treatment						
Coppo 2007 [11]	Benazepril (≤0.2 mg/kg)	36 months	3–35 years	BP <140/90 mmHg (adults)	eGFR >50 mL/min/1.73 m^2	1.0–3.4 g/day	ND
	Placebo			BP <95 % (children)			
Kanno 2005 [12]	ACEI (≤2 mg)[a]	≥3 years	ND	No previous ACEI	ND	ND	ND
	Amlodipine (5 mg)						
Ruggenenti 2000 [13]	Ramipril (≤5 mg)	63 months	18–70 year	BP <220/115 mmHg	Ccr 20–70 mL/min/1.73 m^2	≥1.0 g/day	ND
	Placebo[b]						
Bannister 1995 [14]	Enalapril (ND)	12 months	ND	Hypertension	GFR 30–90 mL/min	ND	ND
	Nifedipine (ND)						
Nakamura 2000 [15]	Trandolapril (2 mg)	3 months	ND	Normal blood pressure (BP <140/90 mmHg)	Ccr >80 mL/min/1.73 m^2	≤3.0 g/day	ND
	Candesartan (8 mg)						
	Verapamil (120 mg)						
	Placebo						

(continued)

Table 16.3a (continued)

Author year	Interventions (dose)	Duration	Age	BP	Renal function	UP	Histology
Crossover trials							
Maschio 1994 [16]	Fosinopril (20 mg)	4 months	ND	Normal blood pressure	SCr <1.4 mg/dL	≥1.0 g/day	ND
	Placebo			(BP <140/90 mmHg)	Ccr >90 mL/min/ 1.73 m^2		
Ikeda 1989 [17] (sub)	Captopril (ND)	ND	ND	ND	ND	ND	ND
	Nicardipine (ND)						

ACEI angiotensin-converting enzyme inhibitor, *BP* blood pressure, *Ccr* creatinine clearance, *CKD* chronic kidney disease, *eGFR* estimated GFR, *GFR* glomerular filtration rate, *IgAN* IgA nephropathy, *RAS* renin-angiotensin system, *SCr* serum creatinine, *UP* urinary protein

[a]Temocapril (≤2 mg) or trandolapril (≤2 mg)

[b]The patients' code was opened at 27th month of randomization

Table 16.3b Baseline characteristics of IgAN patients included in RCTs assessing efficacy of ACEI vs. no RAS blockade

Author year	Interventions	N	Age (Year)	SBP/DBP or MAP (mmHg)	SCr (mg/dL)		GFR (mL/min)	UP	Histology
Parallel group trials									
Praga 2003 [9]	Enalapril	23	27.8 ± 12	102 ± 11	1 ± 0.2	Ccr	102 ± 25	2 ± 1.3 g/day	ND
	No RAS blockade	21	29.9 ± 12.3	98 ± 12	0.9 ± 0.2		99 ± 22	1.7 ± 0.8	
Li 2013 [10]	Ramipril	30	42.2 ± 11.0	115.5 ± 13.0/ 69.6 ± 10.3	0.88 ± 0.19[c]	eGFR	106.8 ± 20.9 per1.73 m^2	0.10 ± 0.13 g/gCr	Haas' [57] and
	No treatment	30	41.0 ± 7.5	114.2 ± 16.3/ 70.1 ± 9.3	0.85 ± 0.14[c]		102.9 ± 15.2	0.12 ± 0.13 g/gCr	To's [58]
Coppo 2007 [11]	Benazepril	32	21.8 ± 6.3	122.59 ± 9.0/ 77.81 ± 8.0	ND	Ccr	113.2 ± 23.5 per 1.73 m^2	1.61 ± 0.70 g/day per 1.73 m^2	ND
	Placebo	34	19.3 ± 6.1	117.06 ± 11.0/ 72.09 ± 9.0			114.1 ± 19.0	1.87 ± 0.74	
Kanno 2005 [12]	ACEI[a]	26	35 ± 10[b]	143 ± 15[b]/87 ± 10[b]	1.07 ± 0.66[b]	Ccr	92.8 ± 31.6[b]	1.09 ± 0.82[b] g/day	TIF index
	Amlodipine	23	35 ± 14[b]	140 ± 14[b]/83 ± 10[b]	1.02 ± 0.38[b]		90.8 ± 34.1[b]	1.10 ± 0.72[b]	
Ruggenenti 2000 [13]	Ramipril	39	42.3 ± 12.9	142.8 ± 16.3/ 91.8 ± 9.9	1.96 ± 0.73	Cio	48.1 ± 20.3 per 1.73 m^2	3.05 ± 2.17 g/day	ND
	Placebo	36	45.9 ± 11.2	137.6 ± 12.8/ 89.3 ± 8.0	2.12 ± 0.94		44.2 ± 16.7	3.19 ± 1.93	
Bannister 1995 [14]	Enalapril	13	49 [34–74]	116 ± 9.0[b]	ND	C_{DTPA}	74.6 ± 24.9[b]	ND	ND
	Nifedipine	10	53 [32–69]	114 ± 7.5[b]			62.5 ± 13.8[b]		
Nakamura [15] 2000	Trandolapril	8	32.6 [18–54]	118 ± 14/80 ± 6	0.8 ± 0.2	Ccr	108 ± 16 per 1.73 m^2	1.9 ± 0.7 g/day	ND
	Candesartan	8		118 ± 16/78 ± 6	0.7 ± 0.2		112 ± 14	1.8 ± 0.8	
	Verapamil	8		116 ± 12/82 ± 8	0.9 ± 0.2		110 ± 12	1.8 ± 0.6	
	Placebo	8		120 ± 12/80 ± 8	0.8 ± 0.2		112 ± 12	1.6 ± 0.6	

(continued)

Table 16.3b (continued)

Author year	Interventions	N	Age (Year)	SBP/DBP or MAP (mmHg)	SCr (mg/dL)		GFR (mL/min)	UP	Histology
Crossover trials									
Maschio [16] 1994	Fosinopril	39	33.2 ± 11.4 [18–58]	92.8 ± 9.1	1.0 ± 0.2	Ccr	103 ± 23 per 1.73 m^2	1.74 ± 0.84 g/day	ND
	Placebo								
Ikeda [17] 1989 (sub)	Captopril	4	40.5 ± 12.6	167.5 ± 21.4/ 110.0 ± 14.0	ND	Ccr	78.0 ± 20.5	2.9 ± 0.6 g/day	ND
	Nicardipine								

Mean ± SD, median [range]

ACEI angiotensin-converting enzyme inhibitor, *Ccr* creatinine clearance, C_{DTPA} ^{99m}Tc-diethylenetriaminepentaacetic acid clearance, *Cio* iohexol clearance, *Cr* creatinine, *eGFR* estimated GFR, *GFR* glomerular filtration rate, *IgAN* IgA nephropathy, *MAP* mean arterial pressure, *RAS* renin-angiotensin system, *RCT* randomized controlled trial, *SBP/DBP* systolic and diastolic blood pressure, *SCr* serum creatinine, *TIF* tubulointerstitial fibrosis, *UP* urinary protein

[a]Temocapril or trandolapril

[b]SE was multiplied by √N to calculate SD

[c]An original unit, μmol/L, was divided by 88.4 for conversion to mg/dL

Table 16.3c Outcomes of renal function in RCTs assessing efficacy of ACEI vs. no RAS blockade in IgAN patients

Author year	Interventions	N	Follow-up	ESKD (N)	ΔSCr ≥100 % (N)	ΔSCr ≥50 % (N)	SCr at last visit (mg/dL)		GFR at last visit (mL/min)	ΔGFR (mL/min per 1.73 m^2)
Parallel group trials										
Praga 2003 [9]	Enalapril	23	78 ± 37 [36–120] months	ND	ND	3	1.2 ± 0.5	Ccr	95 ± 30	ND
	No RAS blockade	21	74 ± 36 [29–108]			12*	1.9 ± 1.9		64 ± 31*	
Li 2013 [10]	Ramipril	30	60 month	ND	ND	ND	ND	eGFR	108.1 ± 29.0 per 1.73 m^2	0.39 ± 2.57 per year
	No treatment	30							105.7 ± 17.7	0.59 ± 1.63
Coppo 2007 [11]	Benazepril	32	35[b] [0–58] mo	0	ND	ND	ND	Ccr	124.0 ± 31 per 1.73 m^2	ND
	Placebo	34	38[b] [3–53] mo	0					109.3 ± 29.8*	
Kanno 2005 [12]	ACEI[a]	26	≥36 months	ND	ND	ND	1.18 ± 1.33[d]	Ccr	85.5 ± 28.0[d]	ND
	Amlodipine	23					1.23 ± 2.01[d]		85.5 ± 35.5[d]	
Ruggenenti 2000 [13]	Ramipril	39	30.0[b] (16.4–47.5) mo[c]	7	ND	ND	ND	Cio	ND	0.36 ± 0.56[d] per month
	Placebo[b]	36		9						0.55 ± 0.78[d]
Bannister 1995 [14]	Enalapril	13	12 months	ND	ND	ND	ND		ND	ND
	Nifedipine	10								
Nakamura 2000 [15]	Trandolapril	8	3 months	ND	ND	ND	0.8 ± 0.3	Ccr	110 ± 14 per 1.73 m^2	ND
	Candesartan	8					0.8 ± 0.2		110 ± 16	
	Verapamil	8					0.8 ± 0.2		106 ± 14	
	Placebo	8					0.8 ± 0.3		110 ± 12	

(continued)

Table 16.3c (continued)

Author year	Interventions	N	Follow-up	ESKD (N)	ΔSCr ≥100 % (N)	ΔSCr ≥50 % (N)	SCr at last visit (mg/dL)		GFR at last visit (mL/min)	ΔGFR (mL/min per 1.73 m^2)
Crossover trials										
Maschio 1994 [16]	Fosinopril	39	3 months	ND	ND	ND	ND	Ccr	105 ± 23 per 1.73 m^2	ND
	Placebo								107 ± 25	
Ikeda 1989 [17] (sub)	Captopril	4	ND	ND	ND	ND	ND	Ccr	71.9 ± 25.3	ND
	Nicardipine								77.5 ± 20.4	

Mean ± SD, [range], (25–75 %)

ACEI angiotensin-converting enzyme inhibitor, *Ccr* creatinine clearance, C_{DTPA} ^{99m}Tc-diethylenetriaminepentaacetic acid clearance, *Cio* iohexol clearance, *Cr* creatinine, *eGFR* estimated GFR, *ESKD* end-stage kidney disease, *GFR* glomerular filtration rate, *IgAN* IgA nephropathy, *RAS* renin-angiotensin system, *RCT* randomized controlled trial, *TIF* tubulointerstitial fibrosis, *ΔGFR* a decrease in GFR from the baseline value, *ΔSCr* an increase in serum creatinine from the baseline value

*$P < 0.05$ (vs. ACEI intervention)

[a]Temocapril or trandolapril

[b]Median

[c]Follow-up period of the whole cohort including IgAN patients ($N = 75$) and other CKD patients ($N = 277$)

[d]SE was multiplied by √N to calculate SD

Table 16.3d Outcomes of urinary protein in RCTs assessing efficacy of ACEI vs. no RAS blockade in IgAN patients

Author year	Interventions	N	Follow-up	At last visit		At 12th month		At 3rd month		Histology
				UP (g/day)	ΔUP (%)	UP (g/day)	ΔUP (%)	UP (g/day)	ΔUP (%)	
Parallel group trials										
Praga 2003 [9]	Enalapril	23	78 ± 37 [36–120] months	0.9 ± 1	ND	1.2 ± 1.1	36 ± 40.1	ND	ND	ND
	No RAS blockade	21	74 ± 36 [29–108]	2 ± 1.8*		1.8 ± 1.5	−23 ± 79*			
Li 2013 [10]	Ramipril	30	60 months	ND	ND	ND	ND	ND	ND	ND
	No treatment	30								
Coppo 2007 [11]	Benazepril	32	35[b] [0–58] mo	0.94 ± 0.98 per 1.73m^2	ND	0.96 ± 0.68 per 1.73 m^2	ND	ND	ND	ND
	Placebo	34	38[b] [3–53] mo	1.80 ± 1.34*		ND				
Kanno 2005 [12]	ACEI[a]	26	≥36 months	0.79 ± 1.84[d]	ND	ND	ND	ND	ND	ND
	Amlodipine	23		1.33 ± 2.91[d]						
Ruggenenti 2000 [13]	Ramipril	39	30.0[b] (16.4–47.5) mo[c]	ND	ND	ND	ND	ND	ND	ND
	Placebo[b]	36								
Bannister 1995 [14]	Enalapril	13	12 months	ND	ND	ND	ND	ND	ND	ND
	Nifedipine	10								
Nakamura 2000 [15]	Trandolapril	8	3 months	1.2 ± 0.5	36.8 ± 15.2	ND	ND	1.2 ± 0.5	36.8 ± 15.2	ND
	Candesartan	8		1.1 ± 0.6	38.9 ± 16.6			1.1 ± 0.6	38.9 ± 16.6	
	Verapamil	8		1.4 ± 0.5	22.2 ± 8.4*			1.4 ± 0.5	22.2 ± 8.4*	
	Placebo	8		1.7 ± 0.7	ND			1.7 ± 0.7	ND	

(continued)

Table 16.3d (continued)

Author year	Interventions	N	Follow-up	At last visit		At 12th month		At 3rd month		Histology
				UP (g/day)	ΔUP (%)	UP (g/day)	ΔUP (%)	UP (g/day)	ΔUP (%)	
Crossover trials										
Maschio 1994 [16]	Fosinopril	39	3 months	1.37 ± 0.98	ND	ND	ND	1.37 ± 0.98	ND	ND
	Placebo			1.79 ± 1.20*				1.79 ± 1.20		
Ikeda 1989 [17]	Captopril	4	ND	1.4 ± 0.6	ND	ND	ND	ND	ND	ND
	Nicardipine			2.5 ± 0.7						

Mean ± SD, [range], (25–75 %)

ACEI angiotensin-converting enzyme inhibitor, *IgAN* IgA nephropathy, *RAS* renin-angiotensin system, *RCT* randomized controlled trial, *UP* urinary protein, *ΔUP* decrease in UP from the baseline value

*$P < 0.05$ (vs. ACEI intervention)

[a]Temocapril or trandolapril

[b]Median

[c]Follow-up period of the whole cohort including IgAN patients ($N = 75$) and other CKD patients ($N = 277$)

[d]SD was calculated multiplying SE by √N

Table 16.4a Study protocols of RCTs assessing efficacy of ARB vs. no RAS blockade in IgAN patients

Author year	Interventions (dose)	Duration	Age (yr)	BP	Renal function	UP (g/day)	Histology
Parallel group trials							
Li 2006 [18]	Valsartan (≤160 mg)	104 weeks	≥18	No malignant hypertension	SCr <2.8 mg/dL and UP ≥1.0 g/d	ND	
	Placebo				or SCr 1.4–2.8 mg/dL		
Horita 2007 [19]	Losartan (12.5 mg) + PSL (≤30 mg)	24 months	ND	Normal blood pressure	eCcr >50 mL/min/ 1.73 m^2	1.0–2.6	Katafuchi's scale [54] 4–7
	PSL (≤30 mg)			(BP <140/ 90 mmHg)			
Shimizu 2008 [20]	Losartan (≤25 mg)	12 months	ND	Normal blood pressure	eGFR >50 mL/min/ 1.73 m^2	≥0.4	ND
	Antiplatelet			(BP <140/ 90 mmHg)			
Xie 2011 [21]	Losartan (100 mg) + MZR (≤250 mg)	12 months	14–70	ND	SCr <4.0 mg/dL[a]	0.5–3.5	ND
	Losartan (100 mg)						
	MZR (≤250 mg)						
Nakamura 2000 [15]	Trandolapril (2 mg)	3 months	ND	Normal blood pressure	Ccr >80 mL/min/1.73 m^2	≤3.0	ND
	Candesartan (8 mg)			(BP <140/ 90 mmHg)			
	Verapamil (120 mg)						
	Placebo						
Park 2003 [22]	Losartan (50 mg)	12 weeks	ND	Hypertension	SCr <3.0 mg/dL	≥1.0	ND
	Amlodipine (5 mg)			Systolic BP ≤210 mmHg			

BP blood pressure, *Ccr* creatinine clearance, *CKD* chronic kidney disease, *eCcr* estimated Ccr, *eGFR* estimated glomerular filtration rate, *MZR* mizoribine, *PSL* prednisolone, *SCr* serum creatinine, *UP* urinary protein

[a]An original unit, μmol/L, was divided by 88.4 for conversion to mg/dL

Table 16.4b Baseline characteristics of IgAN patients included in RCTs assessing efficacy of ARB vs. no RAS blockade

Author year	Interventions	N	Age (Year)	SBP/DBP or MAP (mmHg)	SCr (mg/dL)		GFR (mL/min)	UP (g/day)	Histology
Parallel group trial									
Li 2006 [18]	Valsartan	54	40 ± 10	136 ± 20/81 ± 11	1.11 ± 0.48	eGFR	87 ± 36 per 1.73m^2	1.8 ± 1.2	ND
	Placebo	55	41 ± 9	137 ± 17/83 ± 14	1.29 ± 0.54		78 ± 38	2.3 ± 1.7	
Horita 2007 [19]	Losartan + PSL	20	34 ± 12	120 ± 8/73 ± 6	0.8 ± 0.2	Ccr	104 ± 36 per 1.73 m^2	1.6 ± 0.6	Katafuchi's [59]
	PSL	18	32 ± 10	121 ± 7/75 ± 7	0.7 ± 0.1		103 ± 28	1.6 ± 0.4	
Shimizu 2008 [20]	Losartan	18	36.0 ± 8.5	119.3 ± 10.8/ 74.8 ± 7.5	1.0 ± 0.2	eGFR	72.0 ± 15.9	0.81 ± 0.52	Taneda's [60]
	Antiplatelet	18	35.7 ± 8.1	122.1 ± 9.6/ 73.4 ± 12.1	0.9 ± 0.2		75.4 ± 18.1	0.73 ± 0.36	
Xie 2011 [21]	Losartan + MZR	34	33.68 ± 10.29	101.15 ± 9.94	0.96 ± 0.37[a]	eGFR	91.50 ± 29.83 per 1.73 m^2	1.21 ± 0.56	ND
	MZR	35	33.63 ± 11.71	97.61 ± 8.54	0.90 ± 0.25[a]		95.63 ± 28.31	1.35 ± 0.74	
	Losartan	30	33.67 ± 11.62	101.13 ± 9.88	0.88 ± 0.26[a]		97.85 ± 32.87	1.12 ± 0.54	
Nakamura 2000 [15]	Trandolapril	8	32.6 [18–54]	118 ± 14/80 ± 6	0.8 ± 0.2	Ccr	108 ± 16 per 1.73 m^2	1.9 ± 0.7	ND
	Candesartan	8		118 ± 16/78 ± 6	0.7 ± 0.2		112 ± 14	1.8 ± 0.8	
	Verapamil	8		116 ± 12/82 ± 8	0.9 ± 0.2		110 ± 12	1.8 ± 0.6	
	Placebo	8		120 ± 12/80 ± 8	0.8 ± 0.2		112 ± 12	1.6 ± 0.6	
Park 2003 [22]	Losartan	20	39.3 ± 8.7	131 ± 16/89 ± 9	ND	Ccr	63 ± 22 per 1.73 m^2	2.3 ± 1.5	ND
	Amlodipine	16	44.3 ± 13.4	131 ± 12/86 ± 11			63 ± 24	2.1 ± 0.7	

Mean ± SD, [range]

ARB angiotensin II receptor blocker, *Ccr* creatinine clearance, *DBP* diastolic blood pressure, *eGFR* estimated GFR, *GFR* glomerular filtration rate, *IgAN* IgA nephropathy, *MAP* mean arterial pressure, *MZR* mizoribine, *PSL* prednisolone, *RAS* renin-angiotensin system, *RCT* randomized controlled trial, *SBP* systolic blood pressure, *SCr* serum creatinine, *UP* urinary protein

[a]An original unit, μmol/L, was divided by 88.4 for conversion to mg/dL

Table 16.4c Outcomes of renal function in RCTs assessing efficacy of ARB vs. no RAS blockade in IgAN patients

Author year	Interventions	N	Follow-up	ESKD (N)	ΔSCr ≥100 % (N)	ΔSCr ≥50 % (N)	SCr at last visit (mg/dL)		GFR at last visit (mL/min)	ΔGFR (mL/min)
Parallel group trial										
Li 2006 [18]	Valsartan	54	104 weeks	ND	1	ND	ND	eGFR	72.36 ± 34.20 per 1.73 m^2	5.62 ± 6.79 per year
	Placebo	55			4				63.39 ± 34.79	6.98 ± 6.17
Horita 2007 [19]	Losartan + PSL	20	24 months	ND	ND	0	0.8 ± 0.2	Ccr	100 ± 38 per 1.73 m^2	ND
	PSL	18				4*	0.9 ± 0.2		84 ± 34	
Shimizu 2008 [20]	Losartan	18	12 months	ND	ND	ND	0.9 ± 0.3	eGFR	71.8 ± 17.1 per 1.73 m^2	ND
	Antiplatelet	18					0.9 ± 0.4		76.1 ± 17.3	
Xie 2011 [21]	Losartan + MZR	34	12 months	ND	ND	ND	ND	eGFR	90.86 ± 28.65 per 1.73 m^2	ND
	MZR	35							95.62 ± 21.28	
	Losartan	30							93.57 ± 27.86	
Nakamura 2000 [15]	Trandolapril	8	3 months	ND	ND	ND	0.8 ± 0.3	Ccr	110 ± 14 per 1.73 m^2	ND
	Candesartan	8					0.8 ± 0.2		110 ± 16	
	Verapamil	8					0.8 ± 0.2		106 ± 14	
	Placebo	8					0.8 ± 0.3		110 ± 12	
Park 2003 [22]	Losartan	20	12 weeks	ND	ND	ND	1.5 ± 0.6	Ccr	62 ± 22 per 1.73 m^2	ND
	Amlodipine	16					1.5 ± 0.7		64 ± 25	

Mean ± SD

ARB angiotensin II receptor blocker, *Ccr* creatinine clearance, *eGFR* estimated GFR, *ESKD* end-stage kidney disease, *GFR* glomerular filtration rate, *IgAN* IgA nephropathy, *RAS* renin-angiotensin system, *RCT* randomized controlled trial, *ΔGFR* a decrease in GFR from the baseline value, *ΔSCr* an increase in serum creatinine from the baseline value

*$P < 0.05$ for Fisher's exact test (vs. ARB group), although not reported in the study

Table 16.4d Outcomes of urinary protein and renal histology in RCTs assessing efficacy of ARB vs. no RAS blockade in IgAN patients

Author year	Interventions	N	Follow-up	At last visit		At 12th month		At 3rd month		Histology
				UP (g/day)	ΔUP (%)	UP (g/day)	ΔUP (%)	UP (g/day)	ΔUP (%)	
Parallel group trials										
Li 2006 [18]	Valsartan	54	104 weeks	1.23 ± 1.25	33.5 ± 40.8	1.45 ± 1.30	ND	ND	ND	ND
	Placebo	55		1.97 ± 1.67*	−15.0 ± 67.2*	2.54 ± 1.85*				
Horita 2007 [19]	Losartan + PSL	20	24 months	0.3 ± 0.2[a]	ND	0.4 ± 0.2[a]	ND	ND	ND	ND
	PSL	18		0.5 ± 0.2[a]*		0.6 ± 0.2[a]*				
Shimizu 2008 [20]	Losartan	18	12 months	0.39 ± 0.42	ND	0.39 ± 0.42	ND	0.48 ± 0.38	ND	ND
	Antiplatelet	18		0.66 ± 0.41		0.66 ± 0.41		0.70 ± 0.44		
Xie 2011 [21]	Losartan + MZR	34	12 months	0.43 ± 0.25	61 ± 23	0.43 ± 0.25	61 ± 23	0.70 ± 0.48	30 ± 53	ND
	MZR	35		0.51 ± 0.28	54 ± 30	0.51 ± 0.28	54 ± 30	0.86 ± 0.49	26 ± 43	
	Losartan	30		0.68 ± 0.56	25 ± 83	0.68 ± 0.56	25 ± 83	0.59 ± 0.38	44 ± 30	
Nakamura 2000 [15]	Trandolapril	8	3 months	1.2 ± 0.5	36.8 ± 15.2	ND	ND	1.2 ± 0.5	36.8 ± 15.2	ND
	Candesartan	8		1.1 ± 0.6	38.9 ± 16.6			1.1 ± 0.6	38.9 ± 16.6	
	Verapamil	8		1.4 ± 0.5	22.2 ± 8.4*			1.4 ± 0.5	22.2 ± 8.4*	
	Placebo	8		1.7 ± 0.7	ND			1.7 ± 0.7	ND	
Park 2003 [22]	Losartan	20	12 weeks	1.2 ± 1.5	ND	ND	ND	1.2 ± 1.5	ND	ND
	Amlodipine	16		2.2 ± 1.6				2.2 ± 1.6		

Mean ± SD

ARB angiotensin II receptor blocker, *IgAN* IgA nephropathy, *RAS* renin-angiotensin system, *RCT* randomized controlled trial, *UP* urinary protein, *ΔUP* decrease in UP from the baseline value

*$P < 0.05$ vs. ARB intervention

[a]Measured from a figure

Table 16.5a Study protocols of RCTs assessing efficacy of ACEI and/or ARB vs. no RAS blockade in IgAN patients

Author year	Interventions, dose	Duration	Age	BP	Renal function and UP	Histology
Parallel group trials						
Woo 2007 [23]	Enalapril (≤10 mg) and/or losartan (≤100 mg)	5 years	ND	Hypertension	SCr >1.6 mg/dL	ND
	No RAS blockade			Systolic BP ≤210 mmHg	or SCr ≤1.6 mg/dL and UP ≥1.0 g/day	
Woo 2000 [24]	Enalapril (≤10 mg) and/or losartan (≤100 mg)	ND	ND	ND	SCr 1.4–5.0 mg/dL	ND
	No RAS blockade				or SCr <1.4 mg/dL and UP ≥1.0 g/day	

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *BP* blood pressure. *GFR* glomerular filtration rate, *IgAN* IgA nephropathy, *RAS* renin-angiotensin system, *RCT* randomized controlled trial, *SCr* serum creatinine, *UP* urinary protein

Table 16.5b Baseline characteristics of IgAN patients included in RCTs assessing efficacy of ACEI and/or ARB vs. no RAS blockade

Author year	Interventions	N	Age (Year)	SBP/DBP (mmHg)C	SCr (mg/dL)	GFR (mL/min)	UP (g/day)
Parallel group trials							
Woo 2007 [23]	Enalapril and/or losartan	37	36 ± 11	135 ± 12/85 ± 7	1.6 ± 0.4	ND	2.1 ± 0.8
	No RAS blockade	38	34 ± 11	132 ± 12/86 ± 6	1.5 ± 0.4		2.3 ± 1.6
Woo 2000 [24]	Enalapril and/or losartan	21	39 ± 10	ND	2.0 ± 0.8	ND	2.2 ± 1.2
	No RAS blockade	20	37 ± 6		1.8 ± 0.8		2.1 ± 1.1

Mean ± SD

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *BP* blood pressure, *DBP* diastolic blood pressure, *GFR* glomerular filtration rate, *IgAN* IgA nephropathy, *RAS* renin-angiotensin system, *RCT* randomized controlled trial, *SBP* systolic blood pressure, *SCr* serum creatinine, *UP* urinary protein

Table 16.5c Outcomes of renal function in RCTs assessing efficacy of ACEI and/or ARB vs. no RAS blockade in IgAN patients

Author year	Interventions	N	Follow-up	ESKD (N)	ΔSCr≥100 % (N)	ΔSCr≥50 % (N)	SCr at last visit (mg/dL)	GFR at last visit (mL/min)	ΔGFR (mL/min)
Parallel group trials									
Woo 2007 [23]	Enalapril and/or losartan	37	62 ± 5 months	7	7	8	2.4 ± 2.0	ND	ND
	No RAS blockade	38	60 ± 7	21**	26**	28**	5.0 ± 2.8*		
Woo 2000 [24]	Enalapril and/or losartan	21	13 ± 5 months	0	0	2	2.0 ± 1.3	ND	ND
	No RAS blockade	20	12 ± 4	0	2	6	2.3 ± 1.1		

Mean ± SD

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *ESKD* end-stage kidney disease, *GFR* glomerular filtration rate, *IgAN* IgA nephropathy, *RAS* renin-angiotensin system, *RCT* randomized controlled trial, *ΔGFR* a decrease in GFR from the baseline value, *ΔSCr* an increase in serum creatinine from the baseline value

*$P < 0.05$ vs. ACEI and/or ARB intervention; **$P < 0.05$ for Fisher's test (vs. ACEI and/or ARB intervention), although not reported in the study

†Median

Table 16.5d Outcomes of urinary protein and renal histology in RCTs assessing efficacy of ACEI and/or ARB vs. no RAS blockade in IgAN patients

Author year	Interventions	N	Follow-up	At last visit		At 12th month		At 3rd month		Histology
				UP (g/day)	ΔUP (%)	UP (g/day)	ΔUP (%)	UP (g/day)	ΔUP (%)	
Parallel group trials										
Woo 2007 [23]	Enalapril and/or losartan	37	62 ± 5 months	1.1 ± 0.9	39.6 ± 64.3	ND	ND	ND	ND	ND
	No RAS blockade	38	60 ± 7	1.9 ± 1.0*	−14.9 ± 109.1**					
Woo 2000 [24]	Enalapril and/or losartan	21	13 ± 5 months	1.8 ± 1.6	5.5 ± 102.4	ND	ND	ND	ND	ND
	No RAS blockade	20	12 ± 4	2.9 ± 1.8	−49.8 ± 70.5					

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *IgAN* IgA nephropathy, *RAS* renin-angiotensin system, *RCT* randomized controlled trial, *UP* urinary protein, *ΔUP* decrease in UP from the baseline value

*$P < 0.05$ vs. ACEI and/or ARB intervention; **$P < 0.05$ for *t*-test (vs. ACEI and/or ARB intervention), although not reported in the study

16.3.1 *Efficacy of ACEI vs. No RAS Blockade in Randomized Controlled Trials*

Tables 16.3a, 16.3b, 16.3c, and 16.3d listed nine randomized controlled trials [9–17], which assessed efficacy of ACEI compared with no RAS blockade in IgAN patients. Among seven parallel group trials [9–15] and two crossover trials [16, 17], three [11, 13, 15] and one [16] trial(s) were placebo-controlled trials, respectively. Two trials reported the subgroup analysis of IgAN patients [13, 17].

A Spanish group reported an open-label randomized trial in a single hospital with the longest observational period of 76 ± 36 (range 29–120) months. They enrolled 44 IgAN patients with mainly CKD stage G1-2 and 1–3 g/day of urinary protein. They demonstrated that significantly lower incidence rate of 50 % increase of serum creatinine level in 23 patients with enalapril ($n = 3$), compared with 21 patients without RAS blockade ($n = 12$). They also showed that significantly higher creatinine clearance and lower urinary protein at the end of follow-up in the enalapril group, compared with RAS blockade group (creatinine clearance [mL/min] of enalapril group vs. no RAS blockade group, 95 ± 30 vs. 64 ± 31; urinary protein [g/day], 0.9 ± 1 vs. 2 ± 1.8).

A Chinese group reported the second longest trial with a 60-month observational period at a single Chinese hospital [10]. Contrary to the Spanish study [9], they enrolled 60 patients with <0.5 g/day of urinary protein, who were at lower risk of poor renal prognosis. Between the ramipril group and the no-treatment group, eGFR at the end of observation and incidence of urinary protein ≥ 1 g/day were comparable. This study suggested IgAN patients with <0.5 g/day had no obvious benefit of ramipril.

IgA Nephropathy and ACE Inhibitors (IgACE) trial is a multicenter, randomized, double-blind, placebo-controlled trial at 23 hospitals in Italy, France, Germany, Sweden, and Portugal. The IgACE trial included 64 IgAN patients aged 9–35 years with 1.0–3.5 g/day of urinary protein and eGFR >50 mL/min/1.73 m^2 [11]. Although the study was planned to enroll 122 patients, Coppo et al. reported a preliminary result after enrolling 66 patients. Compared with the placebo group ($n = 34$), the benazepril group ($n = 32$) had significantly higher creatinine clearance and lower urinary protein at the end of median 38 months of the observation period (creatinine clearance, 124.0 ± 31 vs. 109.3 ± 29.8 mL/min per 1.73 m^2; urinary protein 0.94 ± 0.98 vs. 1.80 ± 1.34 g/day per 1.73 m^2).

Other trials with the shorter observational period did not show an obvious renoprotective effect of ACEIs, probably because of a shorter observational period. Some trials show significant reduction of urinary protein in the ACEI group.

16.3.2 *Efficacy of ARB vs. No RAS Blockade in Randomized Controlled Trials*

Efficacy of ARB vs. no RAS blockade was examined in six parallel group trials [15, 18–22], including two placebo-controlled trials (Tables 16.4a, 16.4b, 16.4c, and 16.4d) [15, 18]. The longest observational period of ARB trials was 2 years, much shorter than ACEI trials, suggesting that these studies were remarkably underpowered to examine renoprotective effect of ARB.

Hong Kong study using valsartan in IgA nephropathy (HKVIN), the longest trial, enrolled 109 IgAN patients with (1) serum creatinine <2.8 mg/dL and urinary protein ≥ 1.0 g/day or (2) serum creatinine 1.4–2.8 mg/dL [18]. The incidence of 100 % increase of serum creatinine level ($N = 1$ and four in the valsartan group and placebo group, respectively) and GFR at the end of the observation (72.36 ± 34.20 vs. 63.39 ± 34.79 mL/min per 1.73 m^2) were not significantly different, but a linear mixed model adjusting for average blood pressure and urinary protein suggested that decrease in eGFR was significantly different between the valsartan group and the placebo group. In contrast, a significant decrease in urinary protein was observed in the valsartan group, compared with the placebo group.

A Japanese trial by Horita et al. examined a renoprotective effect of losartan in patients with prednisolone. During the 2-year observational period, four patients without losartan developed 50 % increase in serum creatinine level, whereas no patients with losartan did ($P < 0.001$ for Fisher's exact test), despite an obviously underpowered comparison. An antiproteinuric effect of losartan was observed, contrary to the HKVIN trial.

Other four trials did not show significant differences of GFR and urinary protein except a significant decrease in urinary protein in the candesartan group, compared with the verapamil group, in a Japanese trial.

16.3.3 *Efficacy of ACEI and/or ARB vs. No RAS Blockade in Randomized Controlled Trials*

A Singaporean trial, including 75 IgAN patient with (1) serum creatinine >1.6 mg/dL or (2) serum creatinine <1.4 mg/dL and urinary protein ≥ 1.0 g/day, demonstrated that RAS blockade using enalapril and/or losartan suppressed the incidences of ESKD and ≥ 100 % and ≥ 50 % increase of serum creatinine level during the 5-year observational period [23]. The trial also showed antiproteinuric effect of RAS blockade. The same study group reported an antiproteinuric effect of RAS blockade in another previous 1-year trial [24].

16.3.4 *Efficacy of ACEI vs. ARB in Randomized Controlled Trials*

Efficacy of ACEI vs. ARB was assessed in five parallel group trials [15, 25–28], including one placebo-controlled trial [15] and one crossover trial (Tables 16.6a, 16.6b, 16.6c, and 16.6d) [29]. A Singaporean trial, the largest trial of RAS blockade in IgAN patients ever reported, assigned 210 IgAN patients with CKD stage 3 and/or urinary protein $\geq$1 g/day into 6-year treatments of normal dose of enalapril (20 mg), low dose of enalapril (10 mg), high dose of losartan (200 mg), or normal dose of losartan (100 mg) [25]. After the 6-year treatment, eCcr was highest and a GFR decrease was lowest in the high-dose losartan group, whereas eCcr and its decrease were comparable between normal-dose enalapril (20 mg) and losartan (100 mg) (normal-dose enalapril vs. losartan; eCcr 41.3 ± 27.9 vs. 40.2 ± 27.6 mL/min; eCcr decrease 3.5 ± 3.3 vs. 3.5 ± 3.2 mL/min per year). However, a conflicting result was observed in the incidence of ESKD, which was highest in the normal-dose ACEI. Similar to the results of eCcr, urinary protein was lowest in high-dose losartan group and comparable between normal-dose enalapril and losartan.

Five other short trials of the $\leq$6-month observational period reported that GFR and urinary protein were comparable between ACEI and ARB group.

16.3.5 *Efficacy of Dual vs. Single Blockade in Randomized Controlled Trials*

Efficacy of dual vs. single blockade was assessed in two parallel group trials [26, 27] and two crossover trials [29, 30], including a subgroup analysis of IgAN patients in a placebo-controlled trial [30] (Tables 16.7a, 16.7b, 16.7c, and 16.7d). All trials demonstrated an antiproteinuric effect of dual RAS blockade, compared with single blockade. However, the follow-up period of these trials was $\leq$6 months, indicating that the trials were obviously underpowered to assess a renoprotective effect of RAS blockade on GFR.

16.4 Histological Lesions and Renoprotective Effect of RAS Blockade

Along with GFR, urinary protein, and blood pressure, renal histological lesions is one of the major renal prognostic factors of IgAN. Probably because of no standard renal histological classification of IgAN before Oxford classification published on 2009 [31, 32], only a single trial included renal histological lesions as one of entry

Table 16.6a Study protocols of RCTs assessing efficacy of ACEI vs. ARB in IgAN patients

Author year	Interventions, dose	Duration	Age	BP	Renal function	UP (g/day)	Histology
Parallel group trials							
Woo 2009 [25]	Enalapril (20 mg)	6 years	ND	ND	CKD stage 3 or UP	≥1 g/day	ND
	Enalapril (10 mg)						
	Losartan (200 mg)						
	Losartan (100 mg)						
Horita 2004 [26]	Temocapril (1 mg) + Losartan (12.5 mg)	6 months	ND	Normal blood pressure	eCcr >50 mL/min/1.73 m^2	≥0.4	ND
	Temocapril (1 mg)			(BP <140/90 mmHg)			
	Losartan (12.5 mg)						
Nakamura 2000 [15]	Trandolapril (2 mg)	3 months	ND	Normal blood pressure	Ccr >80 mL/min/1.73 m^2	≤3.0	ND
	Candesartan (8 mg)			(BP <140/90 mmHg)			
	Verapamil (120 mg)						
	Placebo						
Nakamura 2007 [27]	Temocapril (2 mg) + Olmesartan (10 mg)	3 months	ND	Normal blood pressure	ND	ND	ND
	Temocapril (2 mg)			(BP <140/90 mmHg)			
	Olmesartan (10 mg)						
Perico 1998 [28]	Enalapril (20 mg)	4 weeks	20–65 years	ND	SCr <2.5 mg/dL	0.5–4.0	ND
	Irbesartan (100 mg)						
Crossover trials							
Russo 2001 [29]	Enalapril (≤20 mg) + Losartan (≤100 mg)	8 weeks	ND	Normal blood pressure	Ccr >90 mL/min/1.73 m^2	1.0–3.0	ND
	Enalapril (≤20 mg)			(BP <140/90 mmHg)			
	Losartan (≤100 mg)						

ACEI angiotensin-converting enzyme inhibitor, *BP* blood pressure, *Ccr* creatinine clearance, *CKD* chronic kidney disease, *eCcr* estimated Ccr, *ND* not described, *RAS* renin-angiotensin system, *SCr* serum creatinine, *UP* urinary protein

Table 16.6b Baseline characteristics of IgAN patients included in RCTs assessing efficacy of ACEI vs. ARB in IgAN patients

Author year	Interventions	N	Age (Year)	SBP/DBP or MAP (mmHg)	SCr (mg/dL)		GFR (mL/min)	UP	Histology
Parallel group trials									
Woo 2009 [25]	Enalapril (20 mg)	63	32 ± 10[a]	134 ± 11/83 ± 7	ND	eCcr	62 ± 20.8	2.2 ± 1.6	3 items
	Enalapril (10 mg)	43	34 ± 11[a]	132 ± 12/86 ± 5			60.9 ± 19.8	2.3 ± 1.5	
	Losartan (200 mg)	61	34 ± 10[a]	132 ± 12/84 ± 7			63.5 ± 24.2	2.2 ± 0.9	
	Losartan (100 mg)	40	32 ± 12[a]	132 ± 12/85 ± 7			61.2 ± 18.4	2.0 ± 0.9	
Horita 2004 [26]	Temocapril + Losartan	11	39.6 ± 10.4	121 ± 9/73 ± 11	0.83 ± 0.19	eCcr	91.5 ± 24.6 per 1.73 m^2	0.75 ± 0.30 g/day	9 semiquantitative score
	Temocapril	10	39.6 ± 10.8	121 ± 8/78 ± 8	0.85 ± 0.21		92.5 ± 17.2	0.73 ± 0.36	
	Losartan	10	42.7 ± 12.0	124 ± 5/80 ± 5	0.88 ± 0.17		88.3 ± 19.8	0.81 ± 0.44	
Nakamura 2000 [15]	Trandolapril	8	32.6 [18–54]	118 ± 14/80 ± 6	0.8 ± 0.2	Ccr	108 ± 16 per 1.73 m^2	1.9 ± 0.7 g/day	ND
	Candesartan	8		118 ± 16/78 ± 6	0.7 ± 0.2		112 ± 14	1.8 ± 0.8	
	Verapamil	8		116 ± 12/82 ± 8	0.9 ± 0.2		110 ± 12	1.8 ± 0.6	
	Placebo	8		120 ± 12/80 ± 8	0.8 ± 0.2		112 ± 12	1.6 ± 0.6	
Nakamura 2007 [27]	Temocapril + Olmesartan	8	31 ± 7	116 ± 10/68 ± 9	1.1 ± 0.2	Ccr	86.8 ± 30.0	1.9 ± 0.5 g/day	Modified NIH score [61]
	Temocapril	8	31 ± 8	117 ± 5/68 ± 6	1.1 ± 0.2		90.6 ± 28.4	2.0 ± 0.5	
	Olmesartan	8	34 ± 7	119 ± 6/70 ± 5	1.0 ± 0.3		90.2 ± 22.0	2.0 ± 0.6	
Perico 1998 [28]	Enalapril	11	31[b] [20–54]	136 ± 13/82 ± 12	1.22[b] [0.9–2.14]	Cin	63 ± 23 per 1.73 m^2	1.44 ± 1.10 g/day	ND
	Irbesartan	9	46[b] [34–65]	152 ± 14*/92 ± 9*	1.36[b] [0.86–2.43]		56 ± 18	2.48 ± 2.02	
Crossover trials									
Russo 2001 [29]	Enalapril + Losartan	10	25.0 ± 5.7[c]	118.5 ± 11.7[c]/ 75.9 ± 5.7[c]	ND	Ccr	109.6 ± 26.6[c] per 1.73 m^2	1.52 ± 1.17[c] g/d	ND
	Enalapril								
	Losartan								

Mean ± SD, [range]

ACEI angiotensin-converting enzyme inhibitor, *Ccr* creatinine clearance, *Cin* inulin clearance, *DBP* diastolic blood pressure, *eCcr* estimated Ccr, *MAP* mean arterial pressure, *RAS* renin-angiotensin system, *SBP* systolic blood pressure, *SCr* serum creatinine, *UP* urinary protein

*$P < 0.05$ vs. ACEI intervention

[a]At kidney biopsy

[b]Median

[c]SD was calculated multiplying SE by √N

Table 16.6c Outcomes of renal function in RCTs assessing efficacy of ACEI vs. ARB in IgAN patients

Author year	Interventions	N	Follow-up	ESKD (N)	ΔSCr ≥100 % (N)	ΔSCr ≥50 % (N)	SCr at last visit (mg/dL)		GFR at last visit (mL/min)	ΔGFR (mL/min)
Parallel group trials										
Woo 2009 [25]	Enalapril (20 mg)	63	74 ± 2 months	19	ND	ND	ND	eCcr	41.3 ± 27.9	3.5 ± 3.3 per year
	Enalapril (10 mg)	43	75 ± 2	9					42.3 ± 26.6	3.2 ± 2.6
	Losartan (200 mg)	61	75 ± 3	7					59.1 ± 31.8*	0.7 ± 3.1*
	Losartan (100 mg)	40	74 ± 3	9					40.2 ± 27.6	3.5 ± 3.2
Horita 2004 [26]	Temocapril + Losartan	11	6 months	ND	ND	ND	0.91 ± 0.23	eCcr	85.7 ± 29.1 per 1.73 m^2	ND
	Temocapril	10					0.89 ± 0.22		87.5 ± 17.9	
	Losartan	10					0.92 ± 0.23		85.8 ± 20.7	
Nakamura 2000 [15]	Trandolapril	8	3 months	ND	ND	ND	0.8 ± 0.3	Ccr	110 ± 14 per 1.73 m^2	ND
	Candesartan	8					0.8 ± 0.2		110 ± 16	
	Verapamil	8					0.8 ± 0.2		106 ± 14	
	Placebo	8					0.8 ± 0.3		110 ± 12	
Nakamura 2007 [27]	Temocapril + Olmesartan	8	3 months	ND	ND	ND	ND		ND	ND
	Temocapril	8								
	Olmesartan	8								
Perico 1998 [28]	Enalapril	119	4 weeks	ND	ND	ND	ND	Cin	65 ± 25 per 1.73 m^2	ND
	Irbesartan								55 ± 11	

(continued)

Table 16.6c (continued)

Author year	Interventions	N	Follow-up	ESKD (N)	ΔSCr ≥100 % (N)	ΔSCr ≥50 % (N)	SCr at last visit (mg/dL)		GFR at last visit (mL/min)	ΔGFR (mL/min)
Crossover trials										
Russo 2001 [29]	Enalapril + Losartan	10	8 weeks	0	ND	ND	ND	Ccr	110 ± 38^{a} per 1.73 m^2	ND
	Enalapril			0					108 ± 28^{a}	
	Losartan			0					111 ± 28^{a}	

Mean ± SD

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *Ccr* creatinine clearance, *Cin* inulin clearance, *eCcr* estimated Ccr, *ESKD* end-stage kidney disease, *GFR* glomerular filtration rate, *IgAN* IgA nephropathy, *RAS* renin-angiotensin system, *RCT* randomized controlled trial, *ΔGFR* a decrease in GFR from the baseline value, *ΔSCr* an increase in serum creatinine from the baseline value

*$P < 0.05$ for *t*-test vs. ACEI intervention (enalapril 20 mg in Woo 2009 [25]), although not reported in the study

[a]SD was calculated multiplying SE by √N

Table 16.6d Outcomes of urinary protein and renal histology in RCTs assessing efficacy of ACEI vs. ARB in IgAN patients

Author year	Interventions	N	Follow-up	At last visit		At 12th month		At 3rd month		Histology
				UP (g/day)	ΔUP (%)	UP (g/day)	ΔUP (%)	UP (g/day)	ΔUP (%)	
Parallel group trials										
Woo 2009 [25]	Enalapril (20 mg)	63	74 ± 2 months	1.7 ± 1.0	ND	ND	ND	ND	ND	ND
	Enalapril (10 mg)	43	75 ± 2	1.7 ± 0.9						
	Losartan (200 mg)	61	75 ± 3	1.2 ± 0.8**						
	Losartan (100 mg)	40	74 ± 3	1.6 ± 0.9						
Horita 2004 [26]	Temocapril + Losartan	11	6 months	0.28 ± 0.20	63 ± 21[b]	ND	ND	0.54 ± 0.20	ND	ND
	Temocapril	10		0.44 ± 0.31	41 ± 16[b]			0.52 ± 0.30		
	Losartan	10		0.55 ± 0.38	37 ± 11[b]			0.67 ± 0.47		
Nakamura 2000 [15]	Trandolapril	8	3 months	1.2 ± 0.5	36.8 ± 15.2	ND	ND	1.2 ± 0.5	36.8 ± 15.2	ND
	Candesartan	8		1.1 ± 0.6	38.9 ± 16.6			1.1 ± 0.6	38.9 ± 16.6	
	Verapamil	8		1.4 ± 0.5	22.2 ± 8.4*			1.4 ± 0.5	22.2 ± 8.4*	
	Placebo	8		1.7 ± 0.7	ND			1.7 ± 0.7	ND	
Nakamura 2007 [27]	Temocapril + Olmesartan	8	3 months	0.8 ± 0.2	55.7[b]	ND	ND	0.8 ± 0.2	55.7[b]	Modified NIH score [61]
	Temocapril	8		1.3 ± 0.3	33.0[b]			1.3 ± 0.3	33.0[b]	
	Olmesartan	8		1.5 ± 0.4	27.6[b]			1.5 ± 0.4	27.6[b]	
Perico 1998 [28]	Enalapril	11	4 weeks	0.72 ± 0.39	39 ± 28	ND	ND	ND	ND	ND
	Irbesartan	9		1.54 ± 1.46	45 ± 20					

(continued)

Table 16.6d (continued)

Author year	Interventions	N	Follow-up	At last visit		At 12th month		At 3rd month		Histology
				UP (g/day)	ΔUP (%)	UP (g/day)	ΔUP (%)	UP (g/day)	ΔUP (%)	
Crossover trials										
Russo 2001 [29]	Enalapril + Losartan	10	8 weeks	0.57 ± 0.38[a]	44[b]	ND	ND	ND	ND	ND
	Enalapril			0.95 ± 0.51[a, b]	34[b]					
	Losartan			1.01 ± 0.82[a, b]	37[b]					

Mean ± SD

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *IgAN* IgA nephropathy, *RAS* renin-angiotensin system, *RCT* randomized controlled trial, *UP* urinary protein, *ΔUP* decrease in UP from the baseline value

*$P < 0.05$ vs. ACEI intervention (enalapril 20 mg in Woo 2009 [25]); **$P < 0.05$ for *t*-test vs. ACEI intervention (enalapril 20 mg in Woo 2009 [25]), although not reported in the study

[a]SD was calculated multiplying SE by √N

[b]Measured from a figure

Table 16.7a Study protocols of RCTs assessing efficacy of dual blockade vs. single blockade in IgAN patients

Author year	Interventions, dose	Duration	Age	BP	Renal function	UP	Histology
Parallel group trials							
Horita 2004 [26]	Temocapril (1 mg) + Losartan (12.5 mg)	6 months	ND	Normal blood pressure	eCcr >50 mL/min/1.73 m^2	≥0.4 g/day	ND
	Temocapril (1 mg)			(BP <140/90 mmHg)			
	Losartan (12.5 mg)						
Nakamura 2007 [27]	Temocapril (2 mg) + Olmesartan (10 mg)	3 months	ND	Normal blood pressure	ND	ND	ND
	Temocapril (2 mg)			(BP <140/90 mmHg)			
	Olmesartan (10 mg)						
Crossover trials							
Kim 2003 [30] (sub)	Candesartan (4 mg) + ramipril (≥5 mg)	12 weeks	ND	BP <130/80 mmHg with use of ramipril ≥5 mg	Ccr 25–90 mL/min/1.73 m^2	>1.0 g/day	ND
	Placebo + Ramipril (≥5 mg)						
Russo 2001 [29]	Enalapril (≤20 mg) + Losartan (≤100 mg)	8 weeks	ND	Normal blood pressure	Ccr >90 mL/min/1.73 m^2	1.0–3.0 g/day	ND
	Enalapril (≤20 mg)			(BP <140/90 mmHg)			
	Losartan (≤100 mg)						

BP blood pressure, *Ccr* creatinine clearance, *CKD* chronic kidney disease, *eCcr* estimated Ccr, *PSL* prednisolone, *SCr* serum creatinine, *UP* urinary protein

Table 16.7b Baseline characteristics of IgAN patients included in RCTs assessing efficacy of dual vs. single RAS blockade in IgAN patients

Author year	Interventions	N	Age (Year)	SBP/DBP or MAP (mmHg)	SCr (mg/dL)		GFR (mL/min)	UP (g/day)	Histology
Parallel group trials									
Horita 2004 [26]	Temocapril + Losartan	11	39.6 ± 10.4	121 ± 9/73 ± 11	0.83 ± 0.19	eCcr	91.5 ± 24.6 per 1.73 m^2	0.75 ± 0.30	9 semiquantitative score
	Temocapril	10	39.6 ± 10.8	121 ± 8/78 ± 8	0.85 ± 0.21		92.5 ± 17.2	0.73 ± 0.36	
	Losartan	10	42.7 ± 12.0	124 ± 5/80 ± 5	0.88 ± 0.17		88.3 ± 19.8	0.81 ± 0.44	
Nakamura 2007 [27]	Temocapril + Olmesartan	8	31 ± 7	116 ± 10/68 ± 9	1.1 ± 0.2	Ccr	86.8 ± 30.0	1.9 ± 0.5	Modified NIH score [61]
	Temocapril	8	31 ± 8	117 ± 5/68 ± 6	1.1 ± 0.2		90.6 ± 28.4	2.0 ± 0.5	
	Olmesartan	8	34 ± 7	119 ± 6/70 ± 5	1.0 ± 0.3		90.2 ± 22.0	2.0 ± 0.6	
Crossover trials									
Kim 2003 [30]	Candesartan + Ramipril	19	30 ± 4[a] [24–38]	92 ± 8[a]	ND	Ccr	65.3 ± 25.7[a] per 1/73 m^2	4.0 ± 1.7[a]	ND
	Placebo + Ramipril								
Russo 2001 [29]	Enalapril + Losartan	10	25.0 ± 5.7	118.5 ± 11.7/ 75.9 ± 5.7	ND	Ccr	109.6 ± 26.6 per 1.73 m^2	1.52 ± 1.17	
	Enalapril								
	Losartan								

Mean ± SD, [range]

Ccr creatinine clearance, *DBP* diastolic blood pressure, *eCcr* estimated Ccr, *MAP* mean arterial pressure, *RAS* renin-angiotensin system, *SBP* systolic blood pressure, *SCr* serum creatinine, *UP* urinary protein

[a]SD was calculated multiplying SE by √N

Table 16.7c Outcomes of renal function in RCTs assessing efficacy of dual blockade vs. single RAS blockade in IgAN patients

Author year	Interventions	N	Follow-up	ESKD (N)	ΔSCr ≥100 % (N)	ΔSCr ≥50 % (N)	SCr at last visit (mg/dL)		GFR at last visit (mL/min)	ΔGFR (mL/min)
Parallel group trials										
Horita 2004 [26]	Temocapril + Losartan	11	6 months	ND	ND	ND	0.91 ± 0.23	eCcr	85.7 ± 29.1 per 1.73 m^2	ND
	Temocapril	10					0.89 ± 0.22		87.5 ± 17.9	
	Losartan	10					0.92 ± 0.23		85.8 ± 20.7	
Nakamura 2007 [27]	Temocapril + Olmesartan	8	3 months	ND	ND	ND	ND	ND		ND
	Temocapril	8								
	Olmesartan	8								
Crossover trials										
Kim 2003 [30]	Candesartan + Ramipril	19	12 weeks	ND	ND	ND	ND	Ccr	64.7 ± 25.4[a] per 1.73 m^2	ND
	Placebo + Ramipril								65.4 ± 25.0[a]	
Russo 2001 [29]	Enalapril + Losartan	10	8 weeks	0	ND	ND	ND	Ccr	110 ± 12 per 1.73 m^2	ND
	Enalapril			0					108 ± 9	
	Losartan			0					111 ± 9	

Ccr creatinine clearance, *eCcr* estimated Ccr, *ESKD* end-stage kidney disease, *GFR* glomerular filtration rate, *IgAN* IgA nephropathy, *RAS* renin-angiotensin system, *RCT* randomized controlled trial, *ΔGFR* a decrease in GFR from the baseline value, *ΔSCr* an increase in serum creatinine from the baseline value
[a]SD was calculated multiplying SE by √N

Table 16.7d Outcomes of urinary protein and renal histology in RCTs assessing efficacy of dual vs. single RAS blockade in IgAN patients

Author year	Interventions	N	Follow-up	At last visit		At 12th month		At 3rd month		Histology
				UP (g/day)	ΔUP (%)	UP (g/day)	ΔUP (%)	UP (g/day)	ΔUP (%)	
Parallel group trials										
Horita 2004 [26]	Temocapril + Losartan	11	6 months	0.28 ± 0.20	63.2 ± 21.4^{b}	ND	ND	0.54 ± 0.20	ND	ND
	Temocapril	10		0.44 ± 0.31	41.3 ± 15.9^{b}**			0.52 ± 0.30		
	Losartan	10		0.55 ± 0.38	36.6 ± 10.8^{b}**			0.67 ± 0.47		
Nakamura 2007 [27]	Temocapril + Olmesartan	8	3 months	0.8 ± 0.2	55.7^{b}	ND	ND	0.8 ± 0.2	55.7^{b}	Modified NIH score [61]
	Temocapril	8		1.3 ± 0.3*	33.0^{b}*			1.3 ± 0.3*	33.0^{b}*	
	Olmesartan	8		1.5 ± 0.4*	27.6^{b}*			1.5 ± 0.4*	27.6^{b}*	
Crossover trials										
Kim 2003 [30]	Candesartan + Ramipril	19	12 weeks	3.1 ± 1.3^{a}	ND	ND	ND	3.1 ± 1.3^{a}	ND	ND
	Placebo + Ramipril			4.3 ± 0.9^{a}*				4.3 ± 0.9^{a}*		
Russo 2001 [29]	Enalapril + Losartan	10	8 weeks	0.57 ± 0.38	64^{b}	ND	ND	ND	ND	ND
	Enalapril			0.95 ± 0.51^{b}*	34^{b}*					
	Losartan			1.01 ± 0.82^{b}*	37^{b}*					

IgAN IgA nephropathy, *RAS* renin-angiotensin system, *RCT* randomized controlled trial, *UP* urinary protein, *ΔUP* decrease in UP from the baseline value
*$P < 0.05$ vs. dual RAS blockade; **$P < 0.05$ for *t*-test vs. dual RAS blockade, although not reported in the study
[a]SD was calculated multiplying SE by √N
[b]Measured from a figure

criteria [19] and a limited number of trials showed the baseline renal histological lesions [10, 12, 19, 20, 25–27].

A very interesting Japanese trial assessed a renal histological effect of dual RAS blockade, compared with single blockade [27]. Compared with patients with single blockade using temocapril 2 mg or olmesartan 10 mg, patients with dual blockade had significantly lower activity index scored by mesangial cell proliferation, segmental cellular crescent formation, and mononuclear interstitial infiltration, whereas no significant change of chronicity scored by global glomerulosclerosis, fibrous crescents, focal segmental glomerulosclerosis, interstitial fibrosis, and tubular atrophy. This trial suggested that dual blockade might be more beneficial in patients with higher activity index.

Few studies assessed whether renal histological lesions affect a renoprotective effect of RAS blockade or not. In contrast, an association between immunosuppressive therapy and renal histological lesions was reported in several studies. A retrospective longitudinal study reported a significant effect modification between mesangial hypercellularity of Oxford classification and immunosuppressive therapy, suggesting that mesangial hypercellularity potentially predicted a renoprotective effect of immunosuppressive therapy [31]. A Japanese RCT assessing efficacy of oral prednisolone showed endocapillary proliferation was associated with response of urinary protein to prednisolone therapy [33].

It is uncertain whether renal histological lesions predict a renoprotective effect of RAS blockade or not. Further studies are essential to identify the clinical characteristics of IgAN patients who are more responsive to RAS blockade, including renal histological lesions, especially Oxford classification with high reproducibility [32] and clinical relevance [31].

16.5 Target Level of Urinary Protein in RAS Blockade in IgA Nephropathy Patients

Although a number of RCTs demonstrated that RAS blockade improved renal prognosis of IgAN, the optimal target levels of the surrogate markers in IgAN patients with RAS blockage remains unknown. No one doubts that the most promising candidate is urinary protein level. Several cohort studies of IgAN reported that time-averaged urinary protein (TAP) during the observational period had more predictive power than baseline urinary protein at first presentation [8, 34] or diagnosis by kidney biopsy [35–37]. A prospective cohort study including 542 IgAN patients enrolled in the Toronto Glomerulonephritis Registry since 1974 showed TAP >1 g/day were significantly associated with poor renal prognosis, compared with those with TAP <1 g/day [8]. A more interesting finding of this report was that renal prognosis between the patients with TAP <0.3 g/day and those with 0.3–1.0 g/day were comparable, suggesting that urinary protein <1.0 g/day was the target level to suppress progression of IgAN. A Korean retrospective cohort

study including 500 IgAN patients also reported similar findings [37]. However, they suggested that the ultimate optimal goal of urinary protein was <0.3 g/day because the slope of eGFR decline was lower in patients with TAP 0.3–0.99 g/day, compared with those with TAP <0.3 g/day (-0.73 ± 2.82 and -0.41 ± 1.68 mL/min per 1.73 m^2 per year, $P = 0.03$, respectively). A larger Chinese cohort study including 1,155 IgAN patients enrolled in Nanjing Glomerulonephritis Registry between 1989 and 2005 identified TAP 0.5–1.0 g/day as a significant predictor of 50 % decrease in eGFR or ESKD, compared with TAP <0.5 g/day (vs. TAP <0.5 g/day; multivariate-adjusted hazard ratio 9.1 (95 % confidence interval 2.7–30.0), $P < 0.001$) [35]. The differences in the findings of these might be due to sample size, TAP categorization, and/or their practice patterns.

Strictly speaking, these previous cohort studies provided no direct evidence suggesting the optimal target level of urinary protein in IgAN patients with RAS blockades, because multiple interventions affected TAP, including RAS blockade, immunosuppression by corticosteroids, use of fish oils, and others. Response of urinary protein to RAS blockade and use of corticosteroid is remarkably different from that to corticosteroids. Randomized crossover trials demonstrated that an antiproteinuric effect of RAS blockade was reversible within 1 month of discontinuation of RAS blockade [16, 29]. On the contrary, urinary protein level decreases even after the end of corticosteroid therapy. An Italian randomized controlled trial including 86 IgAN patients with urinary protein ≥1 g/day reported that 19 (44 %) of 43 patients with 6-month treatment of corticosteroid showed a minimal response defined as urinary protein <1.0 g/day at the end of the treatment and, interestingly, 31 (72 %) patients did 6 months after the end of 6-month corticosteroid treatment [38]. In 43 patients without corticosteroid treatment, minimal response was observed in 9 (21 %) and 13 (30 %) patients within 6 and 12 months of the follow-up period, respectively. Other randomized controlled trials also confirmed that an irreversible antiproteinuric effect of corticosteroids, even in combination with RAS blockade [39, 40].

Different antiproteinuric responses to RAS blockade and immunosuppression by corticosteroids raise a question whether or not the optimal therapeutic target level of urinary protein is comparative in IgAN patients with RAS blockade and those with corticosteroids. For example, is an IgAN patient with 1.0 g/day of urinary protein 6 months after finishing 6-month corticosteroid therapy at similar risk of ESKD, compared with a patient who has 1.0 g/day of urinary protein after 12-month RAS blockade? Few studies reported an association between urinary protein level after therapeutic intervention and subsequent renal prognosis of IgAN. A small Japanese cohort study including 141 IgAN patients interestingly reported that the patients with <0.4 g/day of urinary protein 6 months after 6-month corticosteroid therapy were at significantly lower risk of 50 % increase of serum creatinine level, compared with those with >1.0 g/day of urinary protein, suggesting that the optimal therapeutic target of urinary protein in patients with RAS blockade might be <0.4 g/day [41]. Regarding RAS blockade, some study reported that decrease in urinary protein within 1 year of RAS blockade was associated with better renal prognosis [9]. However, no study assessed an association between urinary protein

level after initiating RAS blockade and subsequent renal prognosis. Further studies are essential to disclose the optimal therapeutic target level of urinary protein in patients with RAS blockade.

16.6 RAS Blockade in Pregnant IgA Nephropathy Patients

Because IgA nephropathy is common in younger generation [42], pregnancy is of great interest to female IgAN patients of childbearing age. Previous studies reported that pregnancy was very common in IgAN patients. An Italian prospective cohort study reported that 136 (51.0 %) of 223 female patients aged 18–35 years became pregnant during a median follow-up of 10 years [43]. In a Chinese retrospective cohort study, 62 (25.9 %) of 239 female patients aged 18–40 years had at least one pregnancy during a mean follow-up of 4 years [44]. Both studies suggested that pregnancy was unlikely to affect renal prognosis in the patients with preserved renal function. In addition to the renoprotective treatment strategy, physicians should keep in mind the pregnancy of IgAN patients.

Although RAS blockade is the first-line therapeutic modality of IgAN, both ACEIs and ARBs are strictly contraindicated in pregnancy because of a well-known fetopathy, particularly during the second and third trimesters [45]. Fetal RAS blockade syndrome is characterized by oligohydramnios, neonatal renal failure, hypotension, fetal pulmonary hypoplasia, patent ductus arteriosus, joint contractures, and hypocalvaria [46]. Many of the infants with fetal RAS blockade syndrome progress to ESKD and/or death. Experimental studies and human morphological studies suggest that the combinations of severe fetal hypotension, hypoxia, and loss of a functional RAS result in reduced renal blood flow leading to a marked decline in glomerular filtration pressure [47].

Contrary to second- or third-trimester RAS blockade, the teratogenic effect of first-trimester RAS blockade is controversial. A retrospective cohort study using Tennessee Medicaid data of 29,507 infants identified the first-trimester exposure to ACEIs as a significant predictor of major congenital malformations, especially those of the cardiovascular and central nervous systems, compared with no exposure to antihypertensive drugs (risk ratio 2.71 [95 % confidence interval 1.72–4.27]), whereas fetal exposure to other antihypertensive medications during the first trimester did not confer an increased risk (0.66 [0.25–1.75]) [48]. However, subsequent studies, including Swedish Medical Birth Register study [49], National Birth Defects Prevention Study [50], and Kaiser Permanente Northern California study [51], failed to ascertain that the first-trimester RAS blockade was associated with higher incidence rate of major congenital malformations, compared with use of other hypertensive drugs. A systematic review suggested that RAS blockade was not significantly associated with a higher risk of major congenital malformations, compared with use of other antihypertensive drugs [52].

In current guidelines for hypertension, RAS blockade is not recommend for pregnant women and women who have a plan of pregnancy. In 2013 European

Society of Cardiology and European Society of Hypertension (ESC/ESH) guidelines for the management of arterial hypertension, ACEIs, or ARBs should be avoided in women with childbearing potential [53]. Similarly, The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014) recommend that RAS blockade should be avoided in women who may become pregnant [54]. They stress that administration should be carefully performed only after confirming their wishes for pregnancy and plans even in those who may become pregnant. British NICE clinical guideline 107 of hypertension in pregnancy recommend telling women with ACEIs or ARBs that there is an increased risk of congenital abnormalities if these drugs are taken during pregnancy and stopping antihypertensive treatment in women taking ACEIs or ARBs if they become pregnant (preferably within two working days of notification of pregnancy) and offer alternatives [55].

Although RAS blockade is regarded as one of the main treatment modalities of IgAN, female patients of childbearing age and their physicians should keep its teratogenic effect in mind. The physicians should provide them with enough information about its adverse effect before starting RAS blockade.

16.7 Conclusion

Current cumulative evidence strongly suggests that RAS blockade is most promising therapeutic modalities of IgAN. However, RAS blockade has a number of clinical issues to be addressed. Further studies are essential to elucidate the magnitude of benefit and the potential risk of RAS blockade in IgAN patients with a wide range of clinical characteristics.

Conflict of Interest The author declares that he has no conflict of interest.

References

1. KDIGO clinical practice guideline for glomerulonephritis, chapter 10: immunoglobulin A nephropathy. Kidney Int Suppl. 2012;2:209–17.
2. Canetta PA, Kiryluk K, Appel GB. Glomerular diseases: emerging tests and therapies for IgA nephropathy. Clin J Am Soc Nephrol. 2013;9(13):617–25.
3. Wyatt RJ, Julian BA. IgA nephropathy. N Engl J Med. 2013;368:2402–14.
4. Cheng J, Zhang W, Zhang XH, He Q, Tao XJ, Chen JH. ACEI/ARB therapy for IgA nephropathy: a meta analysis of randomised controlled trials. Int J Clin Pract. 2009;63:880–8.
5. Reid S, Cawthon PM, Craig JC, Samuels JA, Molony DA, Strippoli GF. - Non-immunosuppressive treatment for IgA nephropathy. Cochrane Database Syst Rev. 2011;3, CD003962.
6. Evidence-based clinical practice guideline for CKD 2013. Clin Exp Nephrol. 2014;18:346–423.

7. Japanese society of n. [JSN and MHLW clinical practice guidelines for IgA nephropathy 2014]. Nihon Jinzo Gakkai Shi. 2015;57:5–137.
8. Reich HN, Troyanov S, Scholey JW, Cattran DC. Remission of proteinuria improves prognosis in IgA nephropathy. J Am Soc Nephrol. 2007;18:3177–83.
9. Praga M, Gutierrez E, Gonzalez E, Morales E, Hernandez E. Treatment of IgA nephropathy with ACE inhibitors: a randomized and controlled trial. J Am Soc Nephrol. 2003;14:1578–83.
10. Li PK, Kwan BC, Chow KM, Leung CB, Szeto CC. Treatment of early immunoglobulin A nephropathy by angiotensin-converting enzyme inhibitor. Am J Med. 2013;126:162–8.
11. Coppo R1, Peruzzi L, Amore A, Piccoli A, Cochat P, Stone R, et al. IgACE: a placebo-controlled, randomized trial of angiotensin-converting enzyme inhibitors in children and young people with IgA nephropathy and moderate proteinuria. J Am Soc Nephrol. 2007;18:1880–8.
12. Kanno Y, Okada H, Yamaji Y, Nakazato Y, Suzuki H. Angiotensin-converting-enzyme inhibitors slow renal decline in IgA nephropathy, independent of tubulointerstitial fibrosis at presentation. Q J Med. 2005;98:199–203.
13. Ruggenenti P, Perna A, Gherardi G, Benini R, Remuzzi G. Chronic proteinuric nephropathies: outcomes and response to treatment in a prospective cohort of 352 patients with different patterns of renal injury. Am J Kidney Dis. 2000;35:1155–65.
14. Bannister KM, Weaver A, Clarkson AR, Woodroffe AJ. Effect of angiotensin-converting enzyme and calcium channel inhibition on progression of IgA nephropathy. Contrib Nephrol. 1995;111:184–92.
15. Nakamura T, Ushiyama C, Suzuki S, Hara M, Shimada N, Sekizuka K, et al. Effects of angiotensin-converting enzyme inhibitor, angiotensin II receptor antagonist and calcium antagonist on urinary podocytes in patients with IgA nephropathy. Am J Nephrol. 2000;20:373–9.
16. Maschio G, Cagnoli L, Claroni F, Fusaroli M, Rugiu C, Sanna G, et al. ACE inhibition reduces proteinuria in normotensive patients with IgA nephropathy: a multicentre, randomized, placebo-controlled study. Nephrol Dial Transplant. 1994;9:265–9.
17. Ikeda T, Nakayama D, Gomi T, Sakurai J, Yamazaki T, Yuhara M. Captopril, an angiotensin I-converting enzyme inhibitor, decreases proteinuria in hypertensive patients with renal diseases. Nephron. 1989;52:72–5.
18. Li PK, Leung CB, Chow KM, Cheng YL, Fung SK, Mak SK, et al. Hong Kong study using valsartan in IgA nephropathy (HKVIN): a double-blind, randomized, placebo-controlled study. Am J Kidney Dis. 2006;47:751–60.
19. Horita Y, Tadokoro M, Taura K, Ashida R, Hiu M, Taguchi T, et al. Prednisolone co-administered with losartan confers renoprotection in patients with IgA nephropathy. Ren Fail. 2007;29:441–6.
20. Shimizu A, Takei T, Uchida K, Tsuchiya K, Nitta K. Low-dose losartan therapy reduces proteinuria in normotensive patients with immunoglobulin A nephropathy. Hypertens Res. 2008;31:1711–7.
21. Xie Y, Huang S, Wang L, Miao L, Zhang A, Li Y, et al. Efficacy and safety of mizoribine combined with losartan in the treatment of IgA nephropathy: a multicenter, randomized, controlled study. Am J Med Sci. 2011;341:367–72.
22. Park HC, Xu ZG, Choi S, Goo YS, Kang SW, Choi KH, et al. Effect of losartan and amlodipine on proteinuria and transforming growth factor-beta1 in patients with IgA nephropathy. Nephrol Dial Transplant. 2003;18:1115–21.
23. Woo KT, Lau YK, Zhao Y, Liu FE, Tan HB, Tan EK, et al. Disease progression, response to ACEI/ATRA therapy and influence of ACE gene in IgA nephritis. Cell Mol Immunol. 2007;4:227–32.
24. Woo KT, Lau YK, Wong KS, Chiang GS. ACEI/ATRA therapy decreases proteinuria by improving glomerular permselectivity in IgA nephritis. Kidney Int. 2000;58:2485–91.
25. Woo KT, Chan CM, Tan HK, Choong HL, Foo M, Vathsala A, et al. Beneficial effects of high-dose losartan in IgA nephritis. Clin Nephrol. 2009;71:617–24.

26. Horita Y, Tadokoro M, Taura K, Suyama N, Taguchi T, Miyazaki M, et al. Low-dose combination therapy with temocapril and losartan reduces proteinuria in normotensive patients with immunoglobulin a nephropathy. Hypertens Res. 2004;27:963–70.
27. Nakamura T, Inoue T, Sugaya T, Kawagoe Y, Suzuki T, Ueda Y, et al. Beneficial effects of olmesartan and temocapril on urinary liver-type fatty acid-binding protein levels in normotensive patients with immunoglobin A nephropathy. Am J Hypertens. 2007;20:1195–201.
28. Perico N, Remuzzi A, Sangalli F, Azzollini N, Mister M, Ruggenenti P, et al. The antiproteinuric effect of angiotensin antagonism in human IgA nephropathy is potentiated by indomethacin. J Am Soc Nephrol. 1998;9:2308–17.
29. Russo D, Minutolo R, Pisani A, Esposito R, Signoriello G, Andreucci M, et al. Coadministration of losartan and enalapril exerts additive antiproteinuric effect in IgA nephropathy. Am J Kidney Dis. 2001;38:18–25.
30. Kim MJ, Song JH, Suh JH, Lee SW, Kim GA. Additive antiproteinuric effect of combination therapy with ACE inhibitor and angiotensin II receptor antagonist: differential short-term response between IgA nephropathy and diabetic nephropathy. Yonsei Med J. 2003;44:463–72.
31. Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS, Troyanov S, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney Int. 2009;76:534–45.
32. Roberts IS, Cook HT, Troyanov S, Alpers CE, Amore A, Barratt J, et al. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. Kidney Int. 2009;76:546–56.
33. Katafuchi R, Ninomiya T, Nagata M, Mitsuiki K, Hirakata H. Validation study of oxford classification of IgA nephropathy: the significance of extracapillary proliferation. Clin J Am Soc Nephrol. 2011;6:2806–13.
34. Hwang HS, Kim BS, Shin YS, Yoon HE, Song JC, Choi BS, et al. Predictors for progression in immunoglobulin A nephropathy with significant proteinuria. Nephrology. 2010;15:236–41.
35. Le W, Liang S, Hu Y, Deng K, Bao H, Zeng C, et al. Long-term renal survival and related risk factors in patients with IgA nephropathy: results from a cohort of 1155 cases in a Chinese adult population. Nephrol Dial Transplant. 2012;27:1479–85.
36. Li X, Liu Y, Lv J, Shi S, Liu L, Chen Y, et al. Progression of IgA nephropathy under current therapy regimen in a Chinese population. Clin J Am Soc Nephrol. 2014;9:484–9.
37. Nam KH, Kie JH, Lee MJ, Chang TI, Kang EW, Kim DW, et al. Optimal proteinuria target for renoprotection in patients with IgA nephropathy. PLoS One. 2014;9, e101935.
38. Pozzi C, Andrulli S, Del Vecchio L, Melis P, Fogazzi GB, Altieri P, et al. Corticosteroid effectiveness in IgA nephropathy: long-term results of a randomized, controlled trial. J Am Soc Nephrol. 2004;15:157–63.
39. Lv J, Zhang H, Chen Y, Li G, Jiang L, Singh AK, et al. Combination therapy of prednisone and ACE inhibitor versus ACE-inhibitor therapy alone in patients with IgA nephropathy: a randomized controlled trial. Am J Kidney Dis. 2009;53:26–32.
40. Manno C, Torres DD, Rossini M, Pesce F, Schena FP. Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy. Nephrol Dial Transplant. 2009;24:3694–701.
41. Hirano K, Kawamura T, Tsuboi N, Okonogi H, Miyazaki Y, Ikeda M, et al. The predictive value of attenuated proteinuria at 1 year after steroid therapy for renal survival in patients with IgA nephropathy. Clin Exp Nephrol. 2013;17:555–62.
42. Geddes CC, Rauta V, Gronhagen-Riska C, Bartosik LP, Jardine AG, Ibels LS, et al. A tricontinental view of IgA nephropathy. Nephrol Dial Transplant. 2003;18:1541–8.
43. Limardo M, Imbasciati E, Ravani P, Surian M, Torres D, Gregorini G, et al. Pregnancy and progression of IgA nephropathy: results of an Italian multicenter study. Am J Kidney Dis. 2010;56:506–12.
44. Liu Y, Ma X, Lv J, Shi S, Liu L, Chen Y, et al. Risk factors for pregnancy outcomes in patients with IgA nephropathy: a matched cohort study. Am J Kidney Dis. 2014;64:730–6.

45. European Society of G, Association for European Paediatric C, German Society for Gender M, Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. ESC guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:3147–97.
46. Pucci M, Sarween N, Knox E, Lipkin G, Martin U. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in women of childbearing age: risks versus benefits. Exp Rev Clin Pharmacol. 2015;8:221–31.
47. Polifka JE. Is there an embryopathy associated with first-trimester exposure to angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists? A critical review of the evidence. Birth Defects Res A Clin Mol Teratol. 2012;94:576–98.
48. Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med. 2006;354:2443–51.
49. Lennestal R, Otterblad Olausson P, Kallen B. Maternal use of antihypertensive drugs in early pregnancy and delivery outcome, notably the presence of congenital heart defects in the infants. Eur J Clin Pharmacol. 2009;65:615–25.
50. Caton AR, Bell EM, Druschel CM, Werler MM, Lin AE, Browne ML, et al. Antihypertensive medication use during pregnancy and the risk of cardiovascular malformations. Hypertension. 2009;54:63–70.
51. Li DK, Yang C, Andrade S, Tavares V, Ferber JR. Maternal exposure to angiotensin converting enzyme inhibitors in the first trimester and risk of malformations in offspring: a retrospective cohort study. BMJ. 2011;343:d5931.
52. Walfisch A, Al-maawali A, Moretti ME, Nickel C, Koren G. Teratogenicity of angiotensin converting enzyme inhibitors or receptor blockers. J Obstet Gynaecol. 2011;31:465–72.
53. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013;31:1281–357.
54. The Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2014): chapter 10. Hypertension in women. Hypertens Res. 2014;37:334–8.
55. NICE. Hypertension in pregnancy. 2010. Available from: https://www.nice.org.uk/guidance/cg107. Accessed 12 May 2014.
56. Kimura K. Preface: evidence-based clinical practice guidelines for CKD – an abridged English version. Clin Exp Nephrol. 2014;18:339–40.
57. Haas M. Histologic subclassification of IgA nephropathy: a clinicopathologic study of 244 cases. Am J Kidney Dis. 1997;29:829–42.
58. To KF, Choi PC, Szeto CC, Li PK, Tang NL, Leung CB, et al. Outcome of IgA nephropathy in adults graded by chronic histological lesions. Am J Kidney Dis. 2000;35:392–400.
59. Katafuchi R, Kiyoshi Y, Oh Y, Uesugi N, Ikeda K, Yanase T, et al. Glomerular score as a prognosticator in IgA nephropathy: its usefulness and limitation. Clin Nephrol. 1998;49:1–8.
60. Taneda S, Honda K, Nitta K, Kobayashi H, Uchida K, Yumura W, et al. Clinicopathological study of IgA nephropathy in adults: the influence of onset age on clinical and renal histological findings and on the effect of steroid therapy. Clin Exp Nephrol. 1999;3:96–103.
61. Nieuwhof C, Kruytzer M, Frederiks P, van Breda Vriesman PJ. Chronicity index and mesangial IgG deposition are risk factors for hypertension and renal failure in early IgA nephropathy. Am J Kidney Dis. 1998;31:962–70.

Chapter 17
What Is the Goal for Proteinuria in IgA Nephropathy?

Kyoko Watanabe and Keita Hirano

Abstract IgA nephropathy is not a one-shot disease, but follows a unique repetitive course from disease onset to progression, remission, and relapse. In order to determine appropriate management strategy for IgA nephropathy, target proteinuria needs to be defined. In two cohort studies examining at time-average proteinuria over the whole follow-up, proteinuria associated with decent renal survival was 1.0 g/day and less than 0.5 g/day. This category of proteinuria is referred to as partial remission. By contrast, a view that clinical remission with complete disappearance of both proteinuria and hematuria at final observation is required for better renal survival is widely common in Japan. However, by strict definition, time-average proteinuria during follow-up and urinary abnormalities at the end of observation period are not predictors of subsequent prognosis. Because of this, the more solid finding of the close association between proteinuria after 1–2 years of intervention and subsequent prognosis is explored to seek target proteinuria in management of IgA nephropathy.

Keywords Partial remission • Clinical remission • Time-average proteinuria

17.1 Why Is the Goal Necessary for Proteinuria in Treatment of IgA Nephropathy?

An important aspect in management of glomerular disease is to improve renal survival. For glomerular diseases, namely, minimal change nephrotic syndrome, membranous nephropathy, focal segmental glomerulosclerosis, and IgA nephropathy, proteinuria is the most reliable and independent predictor of renal survival [1–6]. Furthermore, clarifications of specific questions such as degree of proteinuria associated with highest risk of developing end-stage renal disease and the timings at which proteinuria should be measured are necessary. For glomerular diseases except IgA nephropathy, this question is described in their guidelines. For example, in minimal change nephrotic syndrome, complete disappearance of proteinuria is

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favored, while in membranous nephropathy, two categories of less than 0.3 g/day and less than 3.5 g/day are acceptable [1–3]. There have been only a few studies specific for IgA nephropathy, which examined this question. From disease onset, clinical course of IgA nephropathy is not uniform in that it experiences progression, remission, and relapse in a repetitive manner. Therefore, in IgA nephropathy, proteinuria and other clinical factors should be reassessed at each clinical stage to determine treatment strategy with an ultimate goal of renal protection. Ultimately, treatment strategy is decided on a basis of balance between benefits and risks and should be tailored for each individual. For this reason, target proteinuria must be defined unique for IgA nephropathy.

17.2 Rational for the Concept of Partial Remission in IgA Nephropathy from the Analysis of Mean Proteinuria During the Whole Follow-Up and Renal Prognosis

As shown in Table 17.1, Reich et al. proposed the concept of partial remission in IgA nephropathy through an observational study of 542 cases of IgA nephropathy with a mean observation period of 6.5 years in 2007 [6]. They noted that time-average proteinuria, which refers to the mean value of proteinuria calculated from proteinuria taken at half-year intervals, was an independent indicator of subsequent end-stage renal disease. Of note, time-average proteinuria of more than 1.0 g/day was shown to be an independent prognostic factor in a volume-dependent manner. Risk of developing end-stage renal disease was increased by hazard ratios of approximately 3.5, 5, and 10 for proteinuria 1.0–2.0 g/day, 2.0–3.0 g/day, and more than 3.0 g/day, respectively. Simultaneously, patients who achieved absence of proteinuria (sustained level of <0.3 g/day) did not have a different rate of renal function decline compared to patients who achieved partial remission to <1.0 g/day. Their interpretation of the results was a novel concept in that proteinuria of 1.0 g/day was taken as a cutoff for good renal prognosis, and so was proposed as the target value for proteinuria in management of IgA nephropathy. Furthermore, Le et al. reported a cohort study of 1155 cases of Chinese IgA nephropathy patients with a median observation period of 5.4 years and outcome of end-stage renal disease in 2012 [7], (Table 17.1). Similar to Reich et al., they showed that patients with time-average proteinuria >1.0 g/day were associated with a 9.4-fold increased risk of developing end-stage renal disease than those with time-average proteinuria <1.0 g/day. They also demonstrated that patients with proteinuria <0.5 g/day was more beneficial than proteinuria between 0.5 and 1.0 g/day. In detail, patients with time-average proteinuria 0.5–1.0 g/day were associated with a 10.7-fold increased risk than those with time-average proteinuria <0.5 g/day. Therefore, for Le et al., proteinuria of less than 0.5 g/day was referred to as partial remission. The reason for such a discrepancy is unclear. This may be due to differences in racial groups, sample sizes, and their strict definitions of time-average proteinuria.

Table 17.1 Major studies describing target proteinuria for IgA nephropathy

Authors	Proposed target proteinuria			Study design and characteristics of the cohort						
							Type of treatment, %			
	Partial remission or clinical remission	Definition of proteinuria remission, g/day	Timing of proteinuria measurements taken as a surrogate marker	Prospective or retrospective study design	Number of patients	Follow-up, years[a]	RAS-I	Steroid	IS	Tonsillectomy
Reich et al. [6]	PR	<1.0	Whole follow-up	Prospective study	542	6.5 ± 4.9	53.0	12.5	15.7	ND
Le et al. [7]	PR	<0.5	Whole follow-up	Prospective study	1155	5.4 (4.1–7.2)	90.0	10.8	13.6	ND
Hotta et al. [9]	CR	<0.2[b]	Final observation	Retrospective study	329	6.9 ± 3.2	47.1	83.6[c]	28.9	76.0
Hwang et al. [11]	PR	<1.0	Within 2 years after starting anti-proteinuric treatment	Retrospective study	125	7.5 ± 3.3	100.0	20.0	14.4	ND
Hirano et al. [13]	PR	<0.4	One year after starting steroid pulse therapy	Retrospective study	141	3.8 (2.5–5.3)	44.0	100.0[d]	0.0	48.2
Tatematsu et al. [15]	CR	<0.2	Within 2 years of starting steroid pulse therapy	Retrospective study	109	3.3[e]	53.2	100.0[d]	0.0[b]	49.5

RAS-I renin angiotensin aldosterone system inhibitors, *IS* any immunosuppresion, *PR* partial remission, *CR* clinical remission defined by absence of proteinuria and hematuria, *ND* not determined

[a]Values are presented as mean ± standard deviation or median (interquartile range)

[b]Author's speculation

[c]It included 59.9 % of steroid pulse therapy and 23.7 % as conventional steroid therapy

[d]Steroid pulse therapy by Pozzi's regimen

[e]Shown as median and its range was from 0.7 to 9.4

17.3 Previous Proposal of Clinical Remission Defined by the Absence of Proteinuria and Hematuria at Final Observation as Treatment Goal

Kobayashi et al. reported effectiveness of steroids for IgA nephropathy in 1988 [8]. At that time, oral steroids were the mainstay of treatment, and less than 1.0 g/day was commonly accepted as target proteinuria. With advances in treatment, target proteinuria may undergo a paradigm shift. In 2001, Hotta et al. proposed the concept of clinical remission defined by complete disappearance of proteinuria and hematuria at final observation as opposed to partial remission, as the treatment goal [9]. They reported an observational study composed by 329 cases of IgA nephropathy with a mean observation period of 6.9 years (Table 17.1). In this cohort, 197 cases received steroid pulse therapy, 250 cases had tonsillectomy, and 95 cases had immunosuppressive therapy. At the end of the observation period, among 158 cases with clinical remission, no one had 1.5 times increase in serum creatinine concentration from baseline, making it a more favorable outcome compared to the 24 cases (14 %) among 172 cases with no clinical remission. Furthermore, by multivariate analysis, steroid pulse therapy and tonsillectomy were shown to have significantly contributed to the achievement of clinical remission. Taken altogether, they recommend combination of steroid pulse therapy and tonsillectomy, and hence their suggestion of clinical remission as the goal in management of IgA nephropathy.

17.4 Limitations in Clinical Implications for the Concept of Partial and Clinical Remissions Taken from Proteinuria at Different Times During the Follow-Up

Several limitations exist when applying time-average proteinuria and final urine analysis in clinical practice. Firstly, some important information acquired during the clinical course of the disease is missed when calculating time-average proteinuria and only considering urine analysis at the end of the follow-up. Clinical course of IgA nephropathy involves periods of progression, remission, and relapse. Each period has a differing disease activity. Therefore, consideration of only average values and urine analysis at the end of the follow-up does not truly reflect the course of the disease. In the studies where the concepts of partial and clinical remissions were first described, it is uncertain as to how much attention was paid to relapses when analyzing results. Secondly, variabilities of treatment protocols were not considered in detail through analysis. Supportive treatment such as RAS inhibitors (RAS-I) and more active interventions such as steroid pulse therapy did not have different weights in the analysis, and so the results from a mixture of treatment strategies might have been interpreted as one entity. Finally, time-average

proteinuria and proteinuria at the end of follow-up are measures calculated concurrently with disease progression. This means that these measures in themselves are the results of disease course and hence not strictly the indicators of prognosis.

17.5 Clinical Implications of Proteinuria Responded to Initial Treatment as a Predictor of Renal Prognosis

In a secondary study of the randomized controlled trial of omega-3 polyunsaturated fatty acids in IgA nephropathy, Donadio et al. demonstrated that proteinuria after 1 year of intervention correlated with renal prognosis in a volume-dependent manner [10]. This analysis shed new light on the link between proteinuria and renal prognosis. Nevertheless, they did not mention the threshold of proteinuria after 1 year of intervention. This was then examined by Hwang et al. in a study analyzing 125 cases of IgA nephropathy [11]. They demonstrated that those who reached proteinuria of less than 1.0 g/day 1 year after intervention had better renal prognosis (Table 17.1). However, the main problem in this study was that intervention was not standardized in that it also included RAS-I for all cases as well as a mixture of steroid and other immunosuppressive therapy for some cases.

For the first time in 2004, Pozzi et al. demonstrated benefits of steroid therapy in an 8-year randomized controlled trial [12]. They reported that three courses of steroid pulse therapy given in half a year period resulted in good renal prognosis over 8 years. Although there had been studies examining at the effects of steroid therapy, the study by Pozzi was the first randomized controlled trial in this field. With their protocol, proteinuria decreased most in the first year of intervention. Leading from this, Hirano et al. standardized steroid therapy to Pozzi protocol and analyzed target proteinuria for IgA nephropathy [13], (Table 17.1). Firstly, out of proteinuria measured at three intervals, namely, before intervention, after half a year, and 1 year of intervention, proteinuria measured 1 year after intervention was most associated with renal survival. Following this, proteinuria 1 year after intervention was taken as the primary assessment point, and analysis was performed to determine the value of proteinuria above which renal function was likely to deteriorate. Regardless of baseline renal function and pathological findings, proteinuria of more than 0.4 g/day 1 year after intervention was likely to result in 1.5 times increase in creatinine concentration. Furthermore, details of relapse of IgA nephropathy with proteinuria of more than 1.0 g/day were also analyzed [14]. Risk of relapse increases rapidly when proteinuria reaches above 0.4 g/day after 1 year. For the reasons stated above, Hirano et al. proposed proteinuria of less than 0.4 g/day as the criterion for partial remission after undergoing Pozzi steroid protocol. In contrast, Tatematsu et al. who analyzed the slope of eGFR progression as the outcome suggested a more strict criterion of clinical remission within 2 years of initiating treatment as a pointer toward good renal prognosis [15], (Table 17.1).

However, both studies lacked enough sample size for more solid multivariate analysis.

17.6 Future Directions of Target Proteinuria

In order to clarify target proteinuria, large prospective multicenter studies with more defined intervention protocols and specified timings of proteinuria measurements are warranted. Limitations exist in taking proteinuria as a sole indicator of prognosis in clinical practice. Therefore, in the future other markers may be used alongside proteinuria to better predict the future course of the disease. Furthermore, advances in analysis of specific subclasses of urinary protein associated with disease relapse or fibrosis may offer a new direction. An ongoing study by Suzuki et al. investigating specific serum markers for activity of IgA nephropathy may shed new light on the use of serum markers alongside proteinuria [16].

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. KDIGO board members. KDIGO clinical practice guideline-minimal change nephrotic syndrome. Kidney Int Suppl. 2012;2:177–180.
2. Cattran DC. Idiopathic membranous glomerulonephritis. Kidney Int. 2001;59:1983–94.
3. Cattran DC. Management of membranous nephropathy: when and what for treatment. J Am Soc Nephrol. 2005;16:1188–94.
4. Troyanov S, Wall CA, Miller JA, Scholey JW, Cattran DC, Toronto Glomerulonephritis Registry Group. Focal and segmental glomerulosclerosis: definition and relevance of a partial remission. J Am Soc Nephrol. 2005;16:1061–8.
5. De Nicola L, Provenzano M, Chiodini P, Borrelli S, Garofalo C, Pacilio M, et al. Independent role of underlying kidney disease on renal prognosis of patients with chronic kidney disease under nephrology care. PLoS One. 2015;10:e0127071.
6. Reich HN, Troyanov S, Scholey JW, Cattran DC, Toronto Glomerulonephritis Registry. Remission of proteinuria improves prognosis in IgA nephropathy. J Am Soc Nephrol. 2007;18:3177–83.
7. Le W, Liang S, Hu Y, Deng K, Bao H, Zeng C, et al. Long-term renal survival and related risk factors in patients with IgA nephropathy: results from a cohort of 1155 cases in a Chinese adult population. Nephrol Dial Transplant. 2012;27:1479–85.
8. Kobayashi Y, Fujii K, Hiki Y, Tateno S, Kurokawa A, Kamiyama M. Steroid therapy in IgA nephropathy: a retrospective study in heavy proteinuric cases. Nephron. 1988;48:12–7.
9. Hotta O, Miyazaki M, Furuta T, Tomioka S, Chiba S, Horigome I, et al. Tonsillectomy and steroid pulse therapy significantly impact on clinical remission in patients with IgA nephropathy. Am J Kidney Dis. 2001;38:736–43.
10. Donadio JV, Bergstralh EJ, Grande JP, Rademcher DM. Proteinuria patterns and their association with subsequent end-stage renal disease in IgA nephropathy. Nephrol Dial Transplant. 2002;17:1197–203.
11. Hwang HS, Kim BS, Shin YS, Yoon HE, Song JC, Choi BS, et al. Predictors for progression in immunoglobulin A nephropathy with significant proteinuria. Nephrology (Carlton). 2010;15:236–41.

12. Pozzi C, Andrulli S, Del Vecchio L, Melis P, Fogazzi GB, Altieri P, et al. Corticosteroid effectiveness in IgA nephropathy: long-term results of a randomized, controlled trial. J Am Soc Nephrol. 2004;15:157–63.
13. Hirano K, Kawamura T, Tsuboi N, Okonogi H, Miyazaki Y, Ikeda M, et al. The predictive value of attenuated proteinuria at 1 year after steroid therapy for renal survival in patients with IgA nephropathy. Clin Exp Nephrol. 2013;17:555–62.
14. Hirano K, Kawamura T, Tsuboi N, Okonogi H, Hanaoka K, Ogura M, et al. Clinical and histological parameters associated with the recurrence of proteinuria after steroid therapy in IgA nephropathy patients. J Am Soc Nephrol. 2013;24:817A.
15. Tatematsu M, Yasuda Y, Morita Y, Sakamoto I, Kurata K, Naruse T, et al. Complete remission within 2 years predicts a good prognosis after methylprednisolone pulse therapy in patients with IgA nephropathy. Clin Exp Nephrol. 2012;16:883–91.
16. Suzuki Y, Suzuki H, Yasutake J, Tomino Y. Paradigm shift in activity assessment of IgA nephropathy – optimizing the next generation of diagnostic and therapeutic maneuvers via glycan targeting. Expert Opin Biol Ther. 2015;15:583–93.

Chapter 18
Beyond the Differences in Tonsillectomy in IgA Nephropathy: From Rationale To Indications in Patients

Yusuke Suzuki, Rosanna Coppo, and Yasuhiko Tomino

Abstract In the special symposiums on IgA nephropathy (IgAN) (Symposium 3, IgAN Basic; Symposium 4, IgAN Clinical/KDIGO) at the last Asian Pacific Congress of Nephrology (APCN) 2014 in Tokyo, discussion by expert nephrologists from Asian and Western countries revealed how actual clinical practices in IgAN, including timing of renal biopsy and choices of treatments, are different, despite evidence-based guidelines. In particular, indication for tonsillectomy with or without steroid pulse therapy for IgAN patients is markedly different between Asian and European-American practices. The tonsillectomy is considered to be old-fashioned in Western countries, while it is still widely accepted in Asian countries such as Japan and China. The present chapter discusses rationale of tonsillectomy, with up-to-date understanding of IgAN pathogenesis, and summarizes the actual difference in the IgAN practice with respect to tonsillectomy with or without steroid pulse therapy, such as clinical stages at the intervention, based on some key papers from Asian and Western countries. In addition, we attempt to identify the medical and social causes behind these differences.

Keywords Tonsillectomy • Steroid pulse therapy • Mucosal immunity • Galactose-deficient IgA • Randomized clinical trial

18.1 Introduction

The hallmark of IgA nephropathy (IgAN), well known to every medical student, is macroscopic hematuria, which is coincident with or immediately following acute tonsillitis [1]. This presentation is very common; therefore, patients with recurrence

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of such episodes receive a likely diagnosis of IgAN even without a renal biopsy detecting IgA in the mesangial area. Tonsillectomy was traditionally considered the treatment of choice for patients with IgAN, and reduction in the frequency of episodes of macroscopic hematuria is commonly observed when recurrent bacterial tonsillitis is cured via tonsillectomy [2]. However, it became clear that repeated episodes of gross hematuria do not represent a sign of progression and not a risk factor of IgAN [3]. Relentless progression is frequently associated with persistent heavy hematuria, particularly proteinuria [4]. This finding suggests that less clinical benefit of tonsillectomy is observed in IgAN patients than that expected. On the other hand, in Japan, only 10 % of IgAN patients are detected by episodic macroscopic hematuria, while 70 % IgAN patients are detected by chance microscopic hematuria in annual screening via urinalysis. This clinical fact clearly indicates that hematuria is an initial and essential manifestation of IgAN. However, the degree of proteinuria presents a greater risk for progressive IgAN than that of hematuria [4, 5]. These observations are reasonable because glomerular injury events leading to hematuria may precede those leading to persistent proteinuria in IgAN. Previous epidemiological studies assessing risk factors for CKD [6, 7] further support the idea that hematuria precedes proteinuria. Therefore, it is not surprising that proteinuria is a stronger predictor of IgAN progression than episodic macroscopic hematuria [5].

In addition to causing a debate over the clinical outcome of tonsillectomy, these observations had different effects on clinical practice all over the world. In Western countries, such as Europe and the USA, tonsillectomy is considered to be old-fashioned, while it is still widely used in Japan and China.

18.2 Comparison of Different Clinical Practices for Tonsillectomy in IgA Nephropathy

In the special symposiums on IgAN at the last Asian Pacific Congress of Nephrology (APCN) 2014 in Tokyo (President: Prof. Yasuhiko Tomino), Asian and European nephrologists discussed the differences in clinical practice of IgAN treatment in their respective countries as well as up-to-date understanding of IgAN pathogenesis. This discussion revealed how actual clinical practices, including timing of renal biopsy and choices of treatments, are different, despite evidence-based guidelines. Indication for tonsillectomy [often associated with steroid pulse therapy] is markedly different between Asian and European-American practices. This debate was followed by a blog discussion launched by *NDT-Educational*. Here we summarize the actual difference in the IgAN practice with respect to tonsillectomy and attempt to identify the medical and social causes behind this difference.

18.3 The Rationale for Tonsillectomy in IgA Nephropathy Is Debated

One can speculate that tonsillectomy represents an easy means to eliminate a pathogen source. However, several studies suggest that abnormalities of the mucosal-associated lymphoid tissue (MALT) are critical for the development of IgAN, with infections representing the simple role of triggering an event [1]. Experimental IgAN can be produced in animals after abrogation of the natural process of mucosal tolerance, which favors the host defense against pathogens [8]. In this context, IgAN is likely to develop because of a failure of mucosal antigen elimination and altered IgA synthesis, leading to the production of nephritogenic IgA. On the other hand, studies with experimental IgAN also demonstrated that chronic mucosal infection is not required for nephritogenic IgA production [9]. Moreover, transient mucosal activation of a pattern recognition receptor (PRR), such as Toll-like receptor (TLR), by pathogen-associated molecular patterns in IgAN-prone mice is sufficient to exacerbate this disease with rapid serum elevation of IgA [9, 10]; this suggests that preexisting mucosal B-cell clones produce nephritogenic IgA. Palatine tonsils have a unique cellular composition in the reticulated subepithelium, which is ideal for productive antigen sampling. One of the most important characteristics of the palatine tonsils is that very rich B-cell lymphoid follicles at the subepithelial space foster the development of memory B cells and plasma cells. This is very different from other tonsils in Waldeyer's ring. Japanese nephrologists and otolaryngologists are aware that the beneficial effect of tonsillectomy in IgAN patients is independent of the size of the palatine tonsils and the presence of abscesses. Therefore, if the responsible B cells producing nephritogenic IgA are localized in the palatine tonsils, tonsillectomy may abrogate mucosal antigen encounters to such B cells, even if not chronic, leading to acute elevation of nephritogenic serum IgA [9, 10] and their clonal expansion [11].

It is now accepted that galactose-deficient IgA1 (GdIgA1) and GdIA1 and immune complexes (IC) with endogenous antiglycan antibodies are essential nephritogenic molecules initiating IgAN [12, 13]. Although there is no study clearly demonstrating the type of mucosal B cells involved, the recent studies revealed that the palatine tonsils are, at least in part, delivery sources of GdIgA1 under abnormal cytokine conditions [14–18]. Total IgA is decreased by 10 % on average after tonsillectomy alone in IgAN patients; because patients who showed tonsillar activation of innate immunity and a large decrease of serum IgA after the tonsillectomy had a better clinical outcome, it was thought that the palatine tonsils may be the major delivery source of nephritogenic IgA [19]. One recent study directly demonstrated that tonsillectomy alone rapidly decreased serum levels of GdIgA1 in patients who showed rapid improvement of hematuria after this therapy [20].

However, when considering tonsillectomy for reducing MALT surface, we should consider that tonsils represent only 0.5 m^2 of the entire 400 m^2 of the total mucosal surface in humans. In a recent study [21], IgAN patients who underwent tonsillectomy showed a long-term reduction, but not normalization, of GdIgA1,

signs of persistently activated MALT, ongoing oxidative stress, and increased expression of TLR4. The ligand of TLR4 is lipopolysaccharide (LPS), produced by gram-negative intestinal bacteria. Notably, a correlation was found between progressive cases of IgAN and genetic polymorphism of the membrane receptor for LPS (CD14–159). A renewed interest toward intestinal immunity has been recently raised by a genetic-wide association study (GWAS), showing a strong association between IgAN and genes of intestinal MALT response [22]. These recent data, together with past reports on the role of dietary antigens in IgAN [23], tend to limit the extent of the rationale for tonsillectomy in patients with IgAN.

In contrast, other studies further supported tonsillectomy in nephropathy because serum levels of IgA and GdIgA1 were found to be correlated with tonsillar TLR9 overexpression [19, 20], and the TLR9 genotype was strongly associated with histological severity of IgAN [9]. Patients who did not show a decrease in GdIgA1 after tonsillectomy did so after the first additional steroid pulse therapy with improvement of hematuria, indicating GdIgA1 production outside the tonsils [20]. This finding suggests that some parts of the responsible cells producing GdIgA1 in such patients may be disseminated to MALT other than the tonsils and other lymphoid organs such as the bone marrow or spleen [24, 25]. It is known that tonsillectomy with steroid pulse therapy (TSP) leads to a better clinical outcome than tonsillectomy alone [26]. These clinical and experimental findings suggest that additional steroid pulse therapy on tonsillectomy may target these disseminated extratonsillar responsible cells [27].

18.4 The Clinical Effects of Tonsillectomy in IgA Nephropathy Are Difficult to Assess Using Randomized Controlled Trials

In the absence of large series studies or randomized clinical trials (RCTs), nephrologists in Western countries tend to consider tonsillectomy in IgAN as a procedure to be performed only in patients with macroscopic hematuria and clinically evident recurrent tonsillitis. However, in eastern countries tonsillectomy continues to be regularly performed. In 2003, a breakthrough report by Xie et al. from Japan resurrected the interest for tonsillectomy in IgAN because for the first time, the procedure was associated with a better outcome at long-term follow-up [28]. A Japanese retrospective analysis of 118 patients reported a significant effect of tonsillectomy on survival from dialysis.

Here, the scientific conflict regarding the benefits of tonsillectomy between Western and Asian countries began. In Europe, retrospective analyses of single medical centers showed negative results in tonsillectomy [29, 30]. However, reports from Japan showed a benefit of tonsillectomy, particularly with steroid pulse therapy versus steroid therapy alone [31–33]. A benefit of tonsillectomy was also

shown in IgAN recurrent in grafted kidneys while receiving a standard immunosuppressive regimen [34].

A recent RCT including 72 cases of IgAN in Japan was conducted. The patients received methylprednisolone pulse alone or in combination with tonsillectomy; some positive effects in reducing proteinuria at 1-year follow-up were observed [35]. However, this RCT did not provide data on the benefits on renal function decline and a longer follow-up is needed.

Due to these conflicting reports, the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines did not recommend the tonsillectomy as a therapeutic approach for IgAN [36].

Conflicting research findings highlight the differences between the European and American perceptions of tonsillectomy as a treatment for IgAN. The European-American practice, which limits tonsillectomy to cases with an obvious focal infection, is in clear disagreement with the common indication in Asia to perform tonsillectomy upon diagnosis of IgAN.

Why is there an underlying regional scientific conflict regarding the benefits of tonsillectomy? Although this conflict is based on the discrepancy between the abovementioned two European retrospective studies [29, 30] and some Asian studies [28, 31, 32], the clinical stages of the IgAN patients in these studies appear to be different. Rasche et al. included patients with relatively advanced stages: 55 % of the participants had hypertension, 35 % had elevated serum creatinine (>150 mmol/L), 62 % had heavy proteinuria (>1.5 g/day), and 25 % of the participants reached ESRD within 2.3 years after tonsillectomy [29]. Although Piccoli et al. selected only CKD stage 1 and 2 patients with tonsillectomy, they analyzed the efficacy of the tonsillectomy in both IgAN and non-IgAN patients [30].

Meanwhile, Xie et al. examined 118 Japanese patients in a moderate stage: 38.1 % had <0.5 g/day proteinuria and the mean serum creatinine was 1.07 mg/dl; in addition, a better outcome for tonsillectomy during the long-term follow-up was observed [28]. A recent study by Maeda et al. included a relatively early stage of IgAN patients; they demonstrated the efficacy of tonsillectomy adjusted for the known risk factors including blood pressure, proteinuria, and histological findings [31]. Therefore, perceived discrepancies in efficacy between Europe and Asia may partly be because of the clinical stage of IgAN at the time of intervention [5].

18.5 Current Clinical Practice in Western and Eastern Worlds with Respect to Indication for Tonsillectomy

In Europe and the USA, the guidelines for tonsillectomy provided by Ears, Nose, and Throat (ENT) International Societies do not recommend tonsillectomy in patients who do not present with recurrent tonsillitis, including fever, pharyngeal or tonsillar erythema, enlarged tonsils, tonsillar exudate, cervical adenopathy, and

supportive microbiological test results. Moreover, watchful waiting is recommended for patients with recurrent throat infections if they have had fewer than seven episodes in the previous year. At least 12 months of observation is recommended before considering tonsillectomy. No specific benefit is supported by nephrology guidelines; therefore, tonsillectomy in a patient with IgAN without clinical signs could be questionable in case of complications, even malpractice.

Following Hotta's 2001 report [32], tonsillectomy in Japan is frequently performed in combination with steroid pulse therapy. According to a nationwide survey in more than 350 Japanese teaching hospitals, TSP is now performed in approximately 65 % of the center hospitals [37], with remission of hematuria or proteinuria in more than 50 % patients. These uncontrolled clinical data represent the basis for TSP as the standard therapy for IgAN in Japan.

The majority of Japanese IgAN patients are less than 40 years old. 70 % of the patients were diagnosed at early stage of this disease [38] through chance hematuria in screening urinalysis. Although the KDIGO guidelines recommend renin-angiotensin system blockade (RASB) agents as the first choice of treatment for IgAN patients [39], Japanese medical guidelines do not permit the use of RASB in IgAN patients without hypertension. These guidelines in addition to teratogenic side effects further nourish a hesitation for RASB usage in normotensive young females with IgAN in common Japanese medical practice.

The difficultly in prescribing RASB along with well-demonstrated benefits of TSP are factors that favor tonsillectomy in early phases of IgAN in Japan, making it difficult to justify multicenter RCTs. However, a large, nationwide prospective cohort study in Japan began in 2008 and will provide some much needed clarity to this matter.

18.6 Conclusion

Tonsillectomy as monotherapy in IgAN has only a small possibility to be proven beneficial by RCT. It would not be feasible for opposite reasons in the two parts of the world.

In Europe and Asia, no ethical committee would permit a potentially invasive surgical intervention, which is not recommended by ENT or nephrology guidelines. No ENT specialist could be convinced to participate without a strong, evidence-based recommendation.

On the opposite side, in Japan, social medicine does not support RASB in normotensive young IgAN patients. Medical practitioners and patients generally believe that tonsillectomy and TSP are safe and beneficial. Tonsillectomy/TSP is the standard of practice; therefore, it would be not easy to conduct an RCT.

The abovementioned differences in clinical practice of tonsillectomy in IgAN provoke a still-passionate discussion at international meetings about this procedure in patients with IgAN. The interest remains strong and we do not abandon the hope to find a scientific solution.

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Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Schena FP, Coppo R. IgA nephropathies. In: Davison AM, Ritz E, Cameron JS, Winearls C, editors. Oxford textbook of clinical nephrology. 3rd ed. Oxford: Oxford University Press; 2005.
2. Béné MC, Hurault de Ligny B, Kessler M, Foliguet B, Faure GC. Tonsils in IgA nephropathy. Contrib Nephrol. 1993;104:153–61.
3. Coppo R, D'Amico G. Factors predicting progression of IgA nephropathies. J Nephrol. 2005;18:503–12.
4. Barbour SJ, Reich HN. Risk stratification of patients with IgA nephropathy. Am J Kidney Dis. 2012;59:865–73.
5. Suzuki Y, Suzuki H, Yasutake J, Tomino Y. Paradigm shift in activity assessment of IgA nephropathy – optimizing the next generation of diagnostic and therapeutic maneuvers via glycan-targeting. Expert Opin Biol Ther. 2015;20:1–11.
6. Yamagata K, Ishida K, Sairenchi T, Takahashi H, Ohba S, Shiigai T, et al. Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. Kidney Int. 2007;71:159–66.
7. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. Kidney Int. 2003;63:1468–74.
8. Amore A, Coppo R, Nedrud JG, Sigmund N, Lamm ME, Emancipator SN. The role of nasal tolerance in a model of IgA nephropathy induced in mice by Sendai virus. Clin Immunol. 2004;113:101–8.
9. Suzuki H, Suzuki Y, Narita I, Aizawa M, Kihara M, Yamanaka T, et al. Toll-like receptor 9 affects severity of IgA nephropathy. J Am Soc Nephrol. 2008;19:2384–95.
10. Kajiyama T, Suzuki Y, Kihara M, Suzuki H, Horikoshi S, Tomino Y. Different pathological roles of toll-like receptor 9 on mucosal B cells and dendritic cells in murine IgA nephropathy. Clin Dev Immunol. 2011;2011:819646.
11. Wu G, Peng YM, Liu FY, Xu D, Liu C. The role of memory B cell in tonsil and peripheral blood in the clinical progression of IgA nephropathy. Hum Immunol. 2013;74:708–12.
12. Novak J, Moldoveanu Z, Julian BA, Raska M, Wyatt RJ, Suzuki Y, et al. Aberrant glycosylation of IgA1 and anti-glycan antibodies in IgA nephropathy: role of mucosal immune system. Adv Otorhinolaryngol. 2011;72:60–3.
13. Suzuki H, Kiryluk K, Novak J, Moldoveanu Z, Herr AB, Renfrow MB, et al. The pathophysiology of IgA nephropathy. J Am Soc Nephrol. 2011;22(10):1795–803.
14. Horie A, Hiki Y, Odani H, Yasuda Y, Takahashi M, Kato M, et al. IgA1 molecules produced by tonsillar lymphocytes are under-O-glycosylated in IgA nephropathy. Am J Kidney Dis. 2003;42:486–96.
15. Inoue T, Sugiyama H, Hiki Y, Takiue K, Morinaga H, Kitagawa M, et al. Differential expression of glycogenes in tonsillar B lymphocytes in association with proteinuria and renal dysfunction in IgA nephropathy. Clin Immunol. 2010;136:447–55.

16. Chen X, Liu H, Peng Y, He L, Zhang Y, Xie Y, et al. Expression and correlation analysis of IL-4, IFN-γ and FcαRI in tonsillar mononuclear cells in patients with IgA nephropathy. Cell Immunol. 2014;289(1–2):70–5.
17. He L, Peng Y, Liu H, Yin W, Chen X, Peng X, et al. Activation of the interleukin-4/signal transducer and activator of transcription 6 signaling pathway and homeodomain-interacting protein kinase 2 production by tonsillar mononuclear cells in IgA nephropathy. Am J Nephrol. 2013;38(4):321–32.
18. Suzuki H, Raska M, Yamada K, Moldoveanu Z, Julian BA, Wyatt RJ, et al. Cytokines alter IgA1 O-glycosylation by dysregulating C1GalT1 and ST6GalNAc-II enzymes. J Biol Chem. 2014;289:5330–9.
19. Sato D, Suzuki Y, Kano T, Suzuki H, Matsuoka J, Yokoi H, et al. Tonsillar TLR9 expression and efficacy of tonsillectomy with steroid pulse therapy in IgA nephropathy patients. Nephrol Dial Transplant. 2012;27(3):1090–7.
20. Nakata J, Suzuki Y, Suzuki H, Sato D, Kano T, Yanagawa H, et al. Changes in nephritogenic serum galactose-deficient IgA1 in IgA nephropathy following tonsillectomy and steroid therapy. PLoS One. 2014;21:9.
21. Vergano L, Loiacono E, Albera R, Coppo R, Camilla R, Peruzzi L, et al. Can tonsillectomy modify the innate and adaptive immunity pathways involved in IgA nephropathy? J Nephrol. 2015;28(1):51–8.
22. Kiryluk K, Li Y, Scolari F, Sanna-Cherchi S, Choi M, Verbitsky M, et al. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. Nat Genet. 2014;46:1187–96.
23. Coppo R. The intestine-renal connection in IgA nephropathy. Nephrol Dial Transplant. 2015;30:360–6.
24. Suzuki Y, Tomino Y. The mucosa-bone-marrow axis in IgA nephropathy. Contrib Nephrol. 2007;157:70–9.
25. Nakata J, Suzuki Y, Suzuki H, Sato D, Kano T, Horikoshi S, et al. Experimental evidence of cell dissemination playing a role in pathogenesis of IgA nephropathy in multiple lymphoid organs. Nephrol Dial Transplant. 2013;28:320–6.
26. Kawaguchi T, Ieiri N, Yamazaki S, Hayashino Y, Gillespie B, Miyazaki M, et al. Clinical effectiveness of steroid pulse therapy combined with tonsillectomy in patients with immunoglobulin A nephropathy presenting glomerular haematuria and minimal proteinuria. Nephrology. 2010;15:116–23.
27. Suzuki Y, Suzuki H, Nakata J, Sato D, Kajiyama T, Watanabe T, et al. Pathological role of tonsillar B cells in IgA nephropathy. Clin Dev Immunol. 2011;2011:639074.
28. Xie Y, Nishi S, Ueno M, Imai N, Sakatsume M, Narita I, et al. The efficacy of tonsillectomy on long-term renal survival in patients with IgA nephropathy. Kidney Int. 2003;63:1861–7.
29. Rasche FM, Schwarz A, Keller F. Tonsillectomy does not prevent a progressive course in IgA nephropathy. Clin Nephrol. 1999;51:147–52.
30. Piccoli A, Codognotto M, Tabbi MG, Favaro E, Rossi B. Influence of tonsillectomy on the progression of mesangioproliferative glomerulonephritis. Nephrol Dial Transplant. 2010;25:2583–9.
31. Chen Y, Tang Z, Wang Q, Yu Y, Zeng C, Chen H, et al. Long-term efficacy of tonsillectomy in Chinese patients with IgA nephropathy. Am J Nephrol. 2007;27:170–5.
32. Hotta O, Miyazaki M, Furuta T, Tomioka S, Chiba S, Horigome I, et al. Tonsillectomy and steroid pulse therapy significantly impact on clinical remission in patients with IgA nephropathy. Am J Kidney Dis. 2001;38:736–43.
33. Miura N, Imai H, Kikuchi S, Hayashi S, Endoh M, Kawamura T, et al. Tonsillectomy and steroid pulse (TSP) therapy for patients with IgA nephropathy: a nationwide survey of TSP therapy in Japan and an analysis of the predictive factors for resistance to TSP therapy. Clin Exp Nephrol. 2009;13:460–6.
34. Sakai K, Saneshige M, Takasu J, Yanagisawa T, Aoki Y, Kawamura T, et al. Clinical remission and pathological progression after tonsillectomy in a renal transplant patient with recurrent IgA nephropathy. Clin Transplant. 2009;23:44–8.

35. Kawamura T, Yoshimura M, Miyazaki Y, Okamoto H, Kimura K, Hirano K, et al. A multi-center randomized controlled trial of tonsillectomy combined with steroid pulse therapy in patients with immunoglobulin A nephropathy. Nephrol Dial Transplant. 2014;29(8):1546–53.
36. KDIGO clinical practice guideline for glomerulonephritis. Kidney Int Suppl 2012;2:218–20.
37. Matsuzaki K, Suzuki Y, Nakata J, Sakamoto N, Horikoshi S, Kawamura T, et al. Nationwide survey on current treatments for IgA nephropathy in Japan. Clin Exp Nephrol. 2013;17:827–33.
38. Sugiyama H, Yokoyama H, Sato H, Saito T, Kohda Y, Nishi S, et al. Japan Renal Biopsy Registry and Japan Kidney Disease Registry: committee report for 2009 and 2010. Clin Exp Nephrol. 2013;17:155–73.
39. Radhakrishnan J, Cattran DC. The KDIGO practice guideline on glomerulonephritis: reading between the (guide) lines – application to the individual patient. Kidney Int. 2012;82:840–56.

Chapter 19
Is Tonsillectomy a Possible Treatment for IgA Nephropathy from Randomized Controlled Trial (RCT)?

Tetsuya Kawamura

Abstract Tonsillectomy combined with steroid pulses has become one of the most widely used therapy protocols in the treatment of active IgA nephropathy (IgAN) in Japan. However, the role of tonsillectomy in the long-term prognosis of IgAN remains unclear, because it has not yet been tested in a randomized controlled trial (RCT). Thus, we conducted a multicenter RCT of tonsillectomy combined with steroid pulse therapy in patients with IgAN. Patients with biopsy-proven IgAN, moderate proteinuria ranging from 1.0 to 3.5 g/day, and serum creatinine of $\leq$1.5 mg/dL were randomly allocated to receive tonsillectomy combined with steroid pulses (Group A; $n = 33$) or steroid pulses alone (Group B; $n = 39$). The primary end points were the percentage decrease in urinary protein excretion from baseline and the frequency of the disappearance of proteinuria and/or hematuria. During 12 months from baseline, the percentage decrease in urinary protein excretion was significantly larger in Group A than that in Group B ($P < 0.05$). However, the frequency of the disappearance of proteinuria, hematuria, or both (clinical remission) at 12 months was not statistically different between the groups. Logistic regression analyses revealed the assigned treatment was a significant, independent factor contributing to the disappearance of proteinuria. The results indicate the antiproteinuric effect was significantly greater in combined therapy, whereas it has no beneficial effect over steroid pulses alone to attenuate hematuria and to increase the incidence of clinical remission. Nonetheless, the role of tonsillectomy on the renal functional outcome remains to be clarified.

Keywords Antiproteinuric effect • Disappearance of proteinuria • Clinical remission • IgA nephropathy prospective cohort study

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19.1 Background

There has been an ample of evidence suggesting pathogenic role of tonsils in IgA nephropathy (IgAN). Clinically, macroscopic hematuria often occurs in patients with IgAN after acute pharyngitis, and in those patients, acute glomerular lesions such as cellular crescents or capillary necrosis are frequently observed. Previous experimental studies demonstrated that J chain mRNA-positive IgA-bearing cells were increased in tonsils of IgAN patients, suggesting increased dimeric IgA production. There is now convincing evidence that IgA1 molecules produced by tonsillar lymphocytes from patients with IgAN are under-O-glycosylated as well as those in serum or elution from glomeruli of IgAN patients [1–3]. As a result, glycan-containing epitopes on an aberrantly glycosylated serum IgA1 are exposed and recognized by IgG or IgA autoantibodies, leading to formation of IgG-IgA or IgA-IgA immune complexes and their deposition in the mesangium and subsequent renal injury.

On the other hand, several previous clinical studies have examined the effect of tonsillectomy on clinical remission and renal survival of patients with IgAN. In a retrospective study, Hotta et al. [4] found that tonsillectomy was an independent predictor of the remission of urine abnormalities and a lack of progression in renal injury. Xie et al. [5] followed up 118 patients for an average of 20 years and found that renal survival was better in the group with prior tonsillectomy than in the one without tonsillectomy at 240 months. Moreover, in a non-randomized prospective study, Komatsu et al. [6] found that tonsillectomy combined with steroid pulse treatment had a significant impact on the disappearance of both proteinuria and hematuria, when compared with steroid pulse treatment alone.

On the basis of these findings, increasing attention has been drawn to the role of tonsillectomy in the long-term prognosis of IgAN. In fact, tonsillectomy combined with steroid pulses has become one of the most widely used therapy protocols in the treatment of active IgAN and is now being performed in ∼50 % of the institutions in Japan [7].

However, the role of tonsillectomy in the long-term prognosis of IgAN remains unclear, because it has not yet been tested in a randomized controlled trial (RCT). Previous reviews of the Japanese studies about the effects of tonsillectomy in IgAN insist that tonsillectomy cannot be recommended for widespread use, or there is insufficient data to recommend tonsillectomy for IgAN patients [8, 9]. Importantly, the recent Kidney Disease: Improving Global Outcomes clinical guideline for glomerulonephritis suggests that tonsillectomy not be performed for IgAN, because no RCT of tonsillectomy has been performed [10]. In this regard, we conducted a multicenter RCT of tonsillectomy combined with steroid pulse therapy in Japanese patients with IgAN and reported the results of the RCT in Nephrology Dialysis Transplantation 2014 [11].

In this review, we consider whether tonsillectomy is a promising treatment for IgAN from the results of the RCT.

19.2 Outline of the RCT

19.2.1 Materials and Methods

The inclusion criteria were established primarily according to the previous trial by Pozzi et al. [12, 13] and were biopsy-proven IgAN, an age ranging from 10 to 69 years, urinary protein excretion ranging from 1.0 to 3.5 g/day, serum creatinine of $\leq$1.5 mg/dL, a histological grade diagnosed as a relatively good prognosis, a relatively poor prognosis or a poor prognosis in the classification proposed in 2004 [14], and systolic and diastolic blood pressures of $<$140 and $<$90 mmHg, respectively, regardless of the use or nonuse of antihypertensive drugs. We estimated the frequency of the disappearance of proteinuria at 12 months after the initiation of the treatment to be 40 % in patients treated with tonsillectomy plus steroid pulses [7, 15] and 10 % in those with steroid pulses alone [12, 13]. Based on the power of 80 % for detecting a significant difference ($P < 0.05$, two sided), 38 patients were required for each study group. To compensate for non-evaluable patients, we planned to enroll 40 patients per group.

Randomization was done in the registration center using a computer-based allocation program with the minimization method. Immediately after the input of patients' information, including the date of enrollment, gender, histological grade, the severity of proteinuria ($<$2.0 g/day or $\geq$2.0 g/day), serum creatinine (male, $<$1.2 mg/dl or $\geq$1.2 mg/dl; female, $<$0.9 mg/dl or $\geq$0.9 mg/dl), and the use or nonuse of RAS inhibitors (RAS-I), the participants were automatically assigned to Group A (tonsillectomy plus steroid pulses) or Group B (steroid pulses alone). The patients assigned to Group A underwent tonsillectomy and subsequently received 0.5 g/day of methylprednisolone intravenously for three consecutive days at 1–3 weeks later and then at 2 and 4 months later. They were also given oral prednisolone at a dose of 0.5 mg/kg every other day for 6 months. The patients assigned to Group B received only the steroid pulse therapy and were also given oral prednisolone in a manner identical to that in Group A. The protocol of steroid pulse therapy was essentially the same as the one in the trial by Pozzi et al. [12, 13], with the exception that a half dose of intravenous methylprednisolone was provided in the current study. The entire trial period (treatment + follow-up) was 12 months.

The primary end points were the percentage decrease in urinary protein excretion from baseline and the frequency of the disappearance of proteinuria and/or hematuria, which were defined as less than 0.3 g/day and urinary RBC less than 5/HPF at 12 months after the initial treatment, respectively. The secondary end points were a change in eGFR from baseline, the frequencies of a 100 % increase in serum creatinine from baseline, a 50 % decrease in eGFR from baseline, indications for renal replacement therapy, and adverse effects.

Data were subjected to intention-to-treat analysis. The percent reduction of proteinuria from baseline was compared between Groups A and B by analyzing the values from six fixed time points (2, 4, 6, 8, 10, and 12 months after randomization) using a mixed-effects model. For comparing the parameters between the

two groups, the unpaired t-test and non-parametric Wilcoxon rank-sum test were used for normally and non-normally distributed variables, respectively. The difference in frequency between the two groups was evaluated using Pearson's chi-square test. Logistic regression analysis was used to evaluate the impact of tonsillectomy, eGFR, mean arterial pressure, urinary protein excretion, and the use of RAS-I at baseline on the disappearance of proteinuria, hematuria, or both after adjusting for the other covariates.

19.2.2 Results

Eighty eligible patients were enrolled from 18 universities or community hospitals all over Japan and randomly allocated to receive tonsillectomy with steroid pulses (Group A) or steroid pulses alone (Group B) (Fig. 19.1). Of 40 patients in Group A, three were found not to meet the inclusion criteria and four withdrew the consent. Of 40 patients in Group B, one withdrew the consent. One patient in Group A who did not undergo tonsillectomy after randomization was analyzed as Group A according to the policy of intention-to-treat analysis. Likewise, two patients in Group B who underwent tonsillectomy after randomization were analyzed as Group B. We therefore analyzed 33 and 39 patients in Group A and Group B, respectively.

The two groups did not differ in age, gender distribution, eGFR, urinary protein excretion, blood pressure, the proportion of patients' given renin-angiotensin system (RAS) inhibitors, and histological grades (Table 19.1).

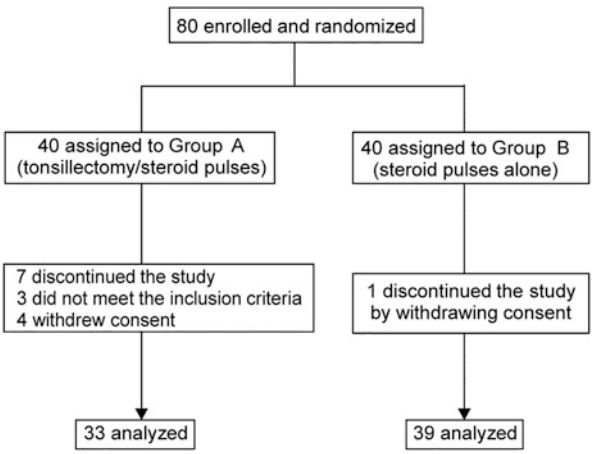

Fig. 19.1 Trial profile

Table 19.1 Baseline patient characteristics

	Group A	Group B
	Tonsillectomy/steroid pulse therapy	Steroid pulse therapy alone
	($n = 33$)	($n = 39$)
Age (years)	36 (13)	40 (13)
Gender		
Male	17* (52)	18* (46)
Female	16* (48)	21* (54)
eGFR (ml/min/1·73 m^2)	75 (24)	69 (22)
Proteinuria (g/day)	1.6 (0.5)	1.6 (0.6)
Proteinuria (g/g creatinine)	1.7 (1.0)	1.7 (1.0)
Systolic blood pressure (mmHg)	117 (12)	121 (10)
Diastolic blood pressure (mmHg)	69 (9)	73 (8)
Mean arterial pressure (mmHg)	85 (9)	89 (8)
Patients receiving RAS-I (%)	16* (48)	18* (46)
Histological grade		
Good prognosis	0*	0*
Relatively good prognosis	2* (6)	3* (8)
Relatively poor prognosis	20* (61)	23* (59)
Poor prognosis	11* (33)	13* (33)

Data are mean (SD) or *number of patients (%). Histological grade was assessed by the classification proposed by the Special IgAN Study Group in 2004 [14]
eGFR estimated glomerular filtration rate, *RAS-I* renin-angiotensin system inhibitors

19.2.2.1 Impact of Steroid Pulses and Tonsillectomy on Proteinuria

Figure 19.2 shows the percent changes in urinary protein excretion from baseline during the trial period. As revealed by a mixed effect model employing six fixed effects (group allocation, eGFR, mean arterial pressure, the use of RAS-I at baseline, time, and the interaction of group and time), the percentage decrease in urinary protein excretion during the 12 months from baseline was significantly larger in Group A than that in Group B (coefficient estimate −1.316, 95 % CI −2.617 to −0.015, $P = 0.047$). The percentage of patients with the disappearance of proteinuria (<0.3 g/gCr) was significantly higher in Group A than in Group B after 10 months ($P = 0.029$; Fig. 19.2). However, at 12 months, the difference was not statistically significant (Group A, 63 %; Group B, 39 %; $P = 0.052$).

19.2.2.2 Impact of Steroid Pulses and Tonsillectomy on Hematuria

The severity of microscopic hematuria gradually decreased following the initiation of therapy in both groups. However, the proportion of patients with the

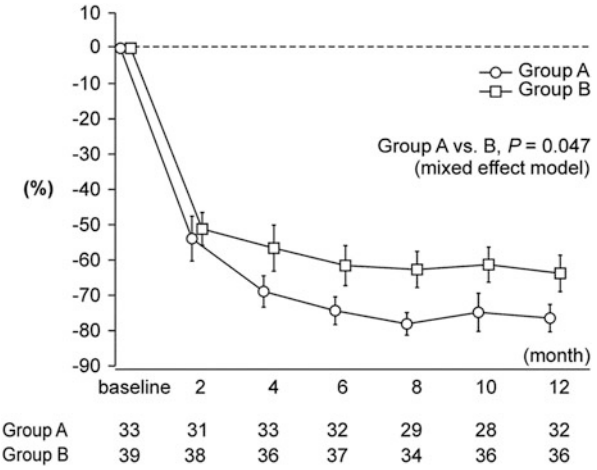

Fig. 19.2 Urinary protein excretion during the trial period. Mean values and standard errors are presented

disappearance of hematuria was not different between the two groups at any time point (e.g., at 12 months, Group A, 68 %; Group B, 64 %, $P = 0.672$).

19.2.2.3 Impact of Steroid Pulses and Tonsillectomy on Clinical Remission

The disappearance of both proteinuria and hematuria (i.e., clinical remission) did not occur at a higher rate in Group A than in Group B at any time point ($P = 0.160$ at 10 months, $P = 0.103$ at 12 months).

19.2.2.4 Impact of Steroid Pulses and Tonsillectomy on Renal Function

eGFR remained stable throughout the trial period and was comparable between the two groups at 12 months (Group A, 75 mL/min/1.73 m^2; Group B, 69 mL/min/1.73 m^2). No patient in either group showed a 100 % increase in serum creatinine from baseline or a 50 % decrease in eGFR from baseline or had indications for renal replacement therapy.

No adverse effect related to tonsillectomy or general anesthesia was reported. One patient in Group A and three in Group B developed diabetes during the trial period, with one of these Group B patients requiring insulin therapy during the treatment with corticosteroid. At the end of the study, blood sugar levels of all four patients were restored to the normal range.

19.2.2.5 Logistic Regression Analysis

Logistic regression analysis was performed to evaluate the impact of multiple covariates on the disappearance of proteinuria or hematuria and the occurrence of clinical remission. Independent variables included the allocated treatment, eGFR, mean blood pressure, urinary protein excretion, and the use of RAS-I at baseline (Table 19.2). Only the allocated treatment had a significant and independent impact on the disappearance of proteinuria (hazard ratio, 2.98; 95 % confidence interval, 1.01–8.83; $P = 0.049$). No independent factors were identified as achieving the disappearance of hematuria or clinical remission.

Table 19.2 Logistic regression analysis of the impact of tonsillectomy, renal function, blood pressure, and urinary protein excretion at baseline and after disappearance of proteinuria, hematuria, or both at study completion

	Odds ratio	95 % CI	*P* value
Disappearance of proteinuria			
Assigned treatment	2.98	1.01–8.83	0.049
eGFR (baseline)	0.99	0.97–1.02	0.560
Mean blood pressure (baseline)	1.04	0.97–1.11	0.297
Proteinuria (baseline)	0.61	0.33–1.13	0.115
RAS-I (baseline)	0.51	0.16–1.68	0.270
Disappearance of hematuria			
Assigned treatment	1.23	0.43–3.55	0.697
eGFR (baseline)	0.99	0.97–1.01	0.304
Mean blood pressure (baseline)	0.97	0.91–1.04	0.450
Proteinuria (baseline)	0.91	0.54–1.54	0.737
RAS-I (baseline)	0.95	0.29–3.13	0.930
Clinical remission			
Assigned treatment	2.24	0.77–6.51	0.140
eGFR (baseline)	0.99	0.97–1.02	0.554
Mean blood pressure (baseline)	1.01	0.94–1.08	0.858
Proteinuria (baseline)	0.75	0.41–1.38	0.348
RAS-I (baseline)	0.63	0.19–2.06	0.445

Logistic regression analysis was used to determine the association of assigned treatment, eGFR, mean blood pressure, or urinary protein excretion at baseline with the disappearance of proteinuria, hematuria, or both (clinical remission) after 12 months of treatment with tonsillectomy plus steroid pulse therapy or steroid pulse therapy alone after adjusting for the other covariates
CI confidence interval, *eGFR* estimated glomerular filtration rate, *RAS-I* renin-angiotensin system inhibitors

19.2.3 Discussion

For the first time, we performed a multicenter RCT of tonsillectomy combined with steroid pulse therapy in patients with IgAN. The findings of the present study indicated that the decrease in urinary protein excretion during follow-up was significantly greater in patients receiving tonsillectomy combined with steroid pulse therapy than in those receiving steroid pulse therapy alone, as shown by a mixed effect model and logistic regression analysis. However, 12 months after the initial treatment, the frequency of the disappearance of microscopic hematuria and clinical remission was comparable between the two groups. Thus, we conclude that tonsillectomy has no impact on the disappearance of hematuria but can have a beneficial effect on the decrease in proteinuria of IgAN patients, at least for those clinically comparable to the present patients. However, whether this subtle antiproteinuric effect by tonsillectomy indeed leads to better renal outcome remains to be elucidated.

This study had several limitations. First, the frequency of the disappearance of proteinuria at 12 months after the initiation of the treatment was 39 % in Group B, which was much higher than the value we expected (10 %). This unexpectedly high incidence may have resulted in the failure to find statistical difference between the two groups in comparison with 63 % in Group A ($p = 0.052$). More patients should be included for a more definitive conclusion. In addition, the unexpectedly higher number of excluded patients in Group A lessened the power of this RCT.

Second, the follow-up period was too short to be able to assess long-term renal survival, such as the progression of renal disease or the development of ESRD. Indeed, none of the patients were found to reach the secondary end points. Although the primary end points used in this study (e.g., the disappearance of proteinuria and/or hematuria after 12 months) were surrogate markers, many previous studies indicate that a marked reduction of proteinuria as an early response to the initial treatment ensures stable renal function after the cessation of treatment [4, 12, 13, 16, 17]. In addition to those studies that examined the relationship between the level of proteinuria after 12 months and the final renal outcome, Hirano et al. reported that, in the IgAN patients receiving 6 months of steroid therapy (Pozzi's protocol), the achievement of proteinuria <0.4 g/day after 12 months could be a therapeutic indicator for a favorable renal outcome [18]. Therefore, a superior antiproteinuric effect of tonsillectomy plus steroid pulses compared with steroid pulses alone could lead to better preservation of renal function in the long term.

Third, RAS-I was administered only in nearly half of the patients in both groups at baseline. If all the patients were given RAS-I prior to the trial, some patients could show proteinuria <1 g/day at baseline. The differential use of RAS-I by different investigators could have potentially biased the results. Moreover, the impact of RAS-I on patients who started RAS-I during the trial was not clear.

In conclusion, the results indicate that the antiproteinuric effect was significantly greater in tonsillectomy combined with steroid pulse therapy, whereas it has no beneficial effect over steroid pulses alone to attenuate hematuria and to increase the incidence of clinical remission. Since the difference in the antiproteinuric effect

was marginal (~10–15 % between the two groups), whether it improves long-term renal outcome remains to be clarified.

19.3 Perspectives of Tonsillectomy in IgA Nephropathy

From the baseline characteristics of the patients (urinary protein excretion ranging from 1.0 to 3.5 g/day and moderate to severe histological damage), the present RCT excluded patients with mild IgAN. In view of the possible effectiveness of steroid pulses alone, as revealed in the present and previous studies [12, 13], a question remains as to whether the advantage of tonsillectomy seen in the present study is relevant to patients with severer or milder IgAN than those in the present patients. Concerning this issue, tonsillectomy combined with steroid pulse therapy might be more effective in patients with advanced IgAN, as suggested by a previous report [19], which found that renal outcome was better with tonsillectomy plus steroid pulses in IgAN patients, particularly in patients with serum creatinine of 1.5–2.0 mg/dL. Further studies are necessary to clarify the profiles of IgAN patients suited for treatment with tonsillectomy plus steroid pulses.

The renoprotective effect of tonsillectomy itself remains unclear, since it was used in the combination with steroid therapy in the present RCT and previous studies [4, 6]. The results of the RCT simply suggest the need for a larger RCT to clarify whether tonsillectomy can protect IgAN patients from the progressive deterioration of renal function or the relapse/recurrence of proteinuria during a long-term follow-up. In this regard, we are now in the process of a study to follow-up the present patients for 3 years. In addition, it is possible to examine the GFR-preserving effect of tonsillectomy plus steroid pulses in an ongoing prospective Japanese IgA nephropathy cohort study (J-IGACS). J-IGACS started from 2005, and now, 1064 patients were enrolled by May 13th in 2015. Clinical data sets were obtained at the time of renal biopsy and every 6 months during the follow-up. The biopsy specimens were circulated to five renal pathologists, and both Oxford classification [20] and Japanese histological grading [21] were determined by the consensus of those renal pathologists. Since each of tonsillectomy plus steroid pulses or steroid pulses alone was performed in 30–40 % of the whole patients recruited in J-IGACS, this prospective cohort study may clarify whether this surgical procedure has a role in IgAN in the future.

Conflict of Interest The author declares that he has no conflict of interest.

References

1. Hiki Y, Iwase H, Kokubo T, Horii A, Tanaka A, Nishikido J, et al. Association of asialo-galactosyl beta 1-3N-acetylgalactosamine on the hinge with a conformational instability of Jacalin-reactive immunoglobulin A1 in immunoglobulin A nephropathy. J Am Soc Nephrol. 1996;7:955–60.

2. Hiki Y, Odani H, Takahashi M, Yasuda Y, Nishimoto A, Iwase H, et al. Mass spectrometry proves under-O-glycosylation of glomerular IgA1 in IgA nephropathy. Kidney Int. 2001;59:1077–85.
3. Allen AC, Bailey EM, Brenchley PE, Buck KS, Barratt J, Feehally J. Mesangial IgA1 in IgA nephropathy exhibits aberrant O-glycosylation: observations in three patients. Kidney Int. 2001;60:969–73.
4. Hotta O, Miyazaki M, Furuta T, Tomioka S, Chiba S, Horigome I, et al. Tonsillectomy and steroid pulse therapy significantly impact on clinical remission in patients with IgA nephropathy. Am J Kidney Dis. 2001;38:736–43.
5. Xie Y, Nishi S, Ueno M, Imai N, Sakatsume M, Narita I, et al. The efficacy of tonsillectomy on long-term renal survival in patients with IgA nephropathy. Kidney Int. 2003;63:1861–7.
6. Komatsu H, Fujimoto S, Hara S, Sato Y, Yamada K, Kitamura K. Effect of tonsillectomy plus steroid pulse therapy on clinical remission of IgA nephropathy: a controlled study. Clin J Am Soc Nephrol. 2008;3:1301–7.
7. Miura N, Imai H, Kikuchi S, Hayashi S, Endoh M, Kawamura T, et al. Tonsillectomy and steroid pulse (TSP) therapy for patients with IgA nephropathy: a nationwide survey of TSP therapy in Japan and an analysis of the predictive factors for resistance to TSP therapy. Clin Exp Nephrol. 2009;13:460–6.
8. Appel GB, Waldman M. The IgA nephropathy treatment dilemma. Kidney Int. 2006;69:1939–44.
9. Locatelli F, Vecchio LD, Pozzi C. IgA glomerulonephritis: beyond angiotensin- converting enzyme inhibitors. Nat Clin Pract Nephrol. 2006;2:24–31.
10. KDIGO Clinical Practice Guideline for Glomerulonephritis. Chapter 10: immunoglobulin A nephropathy. Kidney Int Suppl. 2012;2:209–17.
11. Kawamura T, Yoshimura M, Miyazaki Y, Okamoto H, Kimura K, Hirano K, et al. A multicenter randomized controlled trial of tonsillectomy combined with steroid pulse therapy in patients with immunoglobulin A nephropathy. Nephrol Dial Transplant. 2014;29:1546–53.
12. Pozzi C, Bolasco PG, Fogazzi GB, Andrulli S, Altieri P, Ponticelli C, et al. Corticosteroids in IgA nephropathy: a randomised controlled trial. Lancet. 1999;353:883–7.
13. Pozzi C, Andrulli S, Del Vecchio L, Melis P, Fogazzi GB, Altieri P, et al. Corticosteroid effectiveness in IgA nephropathy: long-term results of a randomized, controlled trial. J Am Soc Nephrol. 2004;15:157–63.
14. Tomino Y, Sakai H. Clinical guidelines for immunoglobulin A (IgA) nephropathy in Japan, second version. Clin Exp Nephrol. 2003;7:93–7.
15. Hotta O. Use of corticosteroids, other immunosuppressive therapies, and tonsillectomy in the treatment of IgA nephropathy. Semin Nephrol. 2004;24:244–55.
16. Reich HN, Troyanov S, Scholey JW, Cattran DC; Toronto Glomerulonephritis Registry. Remission of proteinuria improves prognosis in IgA nephropathy. J Am Soc Nephrol. 2007;18:3177–83.
17. Tatematsu M, Yasuda Y, Morita Y, Sakamoto I, Kurata K, Naruse T, et al. Complete remission within 2 years predicts a good prognosis after methylprednisolone pulse therapy in patients with IgA nephropathy. Clin Exp Nephrol. 2012;16:883–91.
18. Hirano K, Kawamura T, Tsuboi N, Okonogi H, Miyazaki Y, Ikeda M, et al. The predictive value of attenuated proteinuria at 1 year after steroid therapy for renal survival in patients with IgA nephropathy. Clin Exp Nephrol. 2012;17:555–62.
19. Sato M, Hotta O, Tomioka S, Horigome I, Chiba S, Miyazaki M, et al. Cohort study of advanced IgA nephropathy: efficacy and limitations of corticosteroids with tonsillectomy. Nephron Clin Pract. 2003;93:c137–45.
20. Working Group of the International IgA Nephropathy Network and the Renal Pathology Society, Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS. et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney Int. 2009;76:534–45.
21. Kawamura T, Joh K, Okonogi H, Koike K, Utsunomiya Y, Miyazaki Y, et al. A histological classification of IgA nephropathy for predicting long-term prognosis: emphasis on end-stage renal disease. J Nephrol. 2013;26:350–7.

Chapter 20
Validity of the Japanese Clinical Grade Criteria: Results from the Nationwide Retrospective Cohort Study in IgA Nephropathy

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Abstract In 2011, Japanese Society of Nephrology determined the clinical and histological grading criteria of IgA nephropathy (IgAN). In this study, we verify the validity of these clinical grading criteria to predict the renal outcome using the cohort of the Nationwide Retrospective Cohort Study in IgAN. Renal outcomes according to this clinical grading criteria and also additional subgrading by estimated glomerular filtration rate (eGFR) 60 ml/min/1.73 m^2 in patients with urinary protein (U-Prot) <0.5 g/day were analyzed in this cohort using 1055 adult patients who was diagnosed with IgAN by the first renal biopsy between 2002 and 2004. The primary end point was an increase of more than 50 % in serum creatinine levels from the baseline value or end-stage renal disease. The number of patients were 401 in C-Grade I (U-Prot <0.5), 406 in C-Grade II (eGFR ≥60 and U-Prot ≥0.5), and 248 in C-Grade III (eGFR <60 and U-Prot ≥0.5). There were significant differences of the incidence of renal outcome between each group. Hazard ratio to C-Grade I was 2.66 in C-Grade II and 11.7 in C-Grade III. In further subgrading, the number of patients with C-Grade Ia (eGFR ≧60 and U-Prot <0.5) was 336 and C-Grade Ib (eGFR <60 and U-Prot <0.5) was 65. Kaplan-Meier curve revealed significant less incidence of renal outcome in C-Grade Ia, and the hazard ratio to C-Grade I was 9.90 in C-Grade Ib, 6.63 in C-Grade II, and 29.2 in C-Grade III.

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Thus, C-Grade Ia seems to reflect far more benign prognosis grade compared with C-Grade I. In conclusion, this study verified the validity of Japanese clinical grading criteria to predict the renal outcome and also suggests that dividing the patients with C-Grade I into two groups by eGFR 60 seems to predict renal prognosis more precisely.

Keywords IgA nephropathy • Clinical grading criteria • Renal prognosis • The Nationwide Retrospective Cohort Study in IgAN in Japan

20.1 Introduction

Immunoglobulin A (IgA) nephropathy is the most common form of primary glomerular disease [1, 2]. Although IgAN was initially believed to represent a benign condition, subsequent studies showed that the long-term renal prognosis was relatively poor, and 30–40 % of patients progress to end-stage renal disease (ESRD) within 20 years [3, 4].

Several clinical and pathological characteristics are known to determine the progression to ESRD [5–7]. Japanese Society of Nephrology determined the clinical and histological grading criteria in the "Clinical guides for immunoglobulin A (IgA) nephropathy in Japan, third version" [8, 9]. In this criteria, the clinical grade was classified into three gradings according to the level of urinary protein (U-Prot) and estimated glomerular filtration rate (eGFR) at the time of renal biopsy: C-Grade I, U-Prot $<$0.5 g/day; C-Grade II, eGFR $\geq$60 ml/min and U-Prot $\geq$0.5 g/day; and C-Grade III, eGFR $<$60 ml/min and U-Prot $\geq$0.5 g/day. And the combination of clinical and histological grade determined the risk for progression to ESRD. These criteria were developed from 287 patients in a multicenter case-control study on IgA nephropathy. Therefore, it is necessary to verify its validity. Especially, difference of renal prognosis between the patients with eGFR $\geq$60 ml/min and eGFR $<$60 ml/min among C-Grade I (U-Prot $<$0.5 g/day) is still in question at state.

Until now, several treatments have been attempted to improve the prognosis of IgAN. However, disease-specific therapy for the patients with IgAN to improve renal prognosis has not been fully elucidated. In Japan, a combination of tonsillectomy and steroid pulse therapy has been widely performed and recognized as an effective strategy to achieve clinical remission [10, 11]. Although a recent multicenter randomized controlled trial of tonsillectomy combined with pulse steroids in treatment of patients with IgAN revealed benefit of decreasing proteinuria at 12 months in a significant manner compared with the patients treated with steroid pulses alone, there was not statistical difference between the groups regarding the frequency of the disappearance of proteinuria, hematuria, or both (clinical remission) [12]. Therefore, the effects of a combination of tonsillectomy and steroid pulse therapy on the renal functional outcome remain to be clarified. To clarify the effect of various treatments including a combination of tonsillectomy and steroid pulse therapy on renal outcome, we have conducted the Nationwide Retrospective

Cohort Study in IgAN in Japan from August 2012 and collected the data from 1171 patients with IgAN.

In this study, we verify the validity of Japanese clinical grading criteria to predict the renal outcome using the cohort of the Nationwide Retrospective Cohort Study in IgAN.

20.2 Materials and Methods

20.2.1 Participant Population and Measurements

In the Nationwide Retrospective Cohort Study in IgAN, we collected retrospectively the data of the adult patients who was diagnosed with IgAN by the first renal biopsy between 2002 and 2004. The time frame for registration was August 2012 to April 2013, and various clinical data at the time of renal biopsy and every 3 months of follow-up period were collected.

20.2.2 End Points

The primary end point in this study was an increase of more than 50 % in serum creatinine levels from the baseline value or ESRD, which was defined by the initiation of maintenance dialysis, renal transplantation, or uremic death.

20.2.3 Clinical Grading Criteria

In this study, we adopt two clinical grading criteria at the time of renal biopsy. One of which, grading 1, was the clinical grade defined in the Japanese Society of Nephrology and was classified into three gradings according to the level of U-Prot and eGFR: C-Grade I, U-Prot <0.5 g/day; C-Grade II, eGFR ≥ 60 ml/min and U-Prot ≥ 0.5 g/day; and C-Grade III, eGFR <60 ml/min and U-Prot ≥ 0.5 g/day. In another clinical grading criteria, grading 2, we further divided C-Grade I (U-Prot <0.5 g/day) into two grades according to the eGFR: C-Grade Ia, eGFR ≥ 60 ml/min, and C-Grade Ib, eGFR <60 ml/min. We calculated survival time from the time of renal biopsy (baseline) until occurrence of first event or end of follow-up through August 1, 2013 in each clinical grading criteria.

20.2.4 Statistical Analysis

The Kruskal-Wallis test and the chi-square test were used for variation analyses, as appropriate. We calculated the cumulative probability of study end points using Kaplan-Meier estimates and the log-rank test. Univariate Cox regression analyses were used to investigate whether clinical grading criteria were associated with our end points and to estimate the hazard ratios (HRs) and 95 % confidence intervals (CIs) for clinical grading criteria. For all analyses, we considered a two-tailed P-value <0.05 to be statistically significant. All statistical analyses were performed using SPSS software (version 22.0, IBM Inc., Chicago, USA). The Committee on Human Research at the St. Marianna University School of Medicine and also each institute approved the study protocol.

20.3 Results

20.3.1 Patient Characteristics

A total of 1171 patients with IgAN were registered in the Nationwide Retrospective Cohort Study in IgAN from 42 institutes all over Japan. In this study we selected 1055 patients with sufficient data and observation period.

In grading 1, the number of patients was 401 in C-Grade I, 406 in C-Grade II, and 248 in C-Grade III. The age was older and their blood pressure was higher in patients with C-Grade III compared with those with other C-Grades. The observation period was the longest in patients with C-Grade II (Table 20.1).

In grading 2, which further divided the patients with C-Grade I by the level of eGFR 60 ml/min/1.73 m^2, the number of patients with C-Grade Ia (eGFR ≧60 ml/min/1.73 m^2) was 336 and C-Grade Ib (eGFR <60 ml/min/1.73 m^2) was 65. The age was older and their blood pressure was higher in patients with C-Grade Ib compared with those with C-Grade Ia (Table 20.2).

20.3.2 Progression to the Primary End Point

Primary end point was observed in 131 (12.4 %) patients: 12 (3.0 %) in C-Grade I, 37 (9.1 %) in C-Grade II, and 82 (33.1 %) in C-Grade III. Kaplan-Meier curve in grading 1 group was shown in Fig. 20.1. There were significant differences of the incidence of renal outcome between each group (log-rank test $p < 0.001$ between C-Grade I and C-Grade III and between C-Grade II and C-Grade III, and $P = 0.002$ between C-Grade I and C-Grade II). Hazard ratio to C-Grade I was 2.66 (95 % CI: 1.39–5.10) in C-Grade II and 11.7 (95 % CI: 6.39–21.5) in C-Grade III.

Table 20.1 Patients characteristics according to the clinical grading 1

	C-Grade I	C-Grade II	C-Grade III	P
Number of patients	401	406	248	
Male/female	195:206	192:214	143:105	0.026
Age	30	31	51	<0.0001
SBP (mmHg)	120	120	136	<0.0001
DBP (mmHg)	71	72	80	<0.0001
U-Prot (g/day)	0.20	1.00	1.31	<0.0001
eGFR (ml/min)	87.8	83.7	45.4	<0.0001
Observation period (years)	5.7	7.1	4.7	0.005

In clinical grading 1, Grade I, U-Prot<0.5 g/day; Grade II, eGFR≥60 ml/min and U-Prot≥0.5 g/day; Grade III, eGFR <60 ml/min and U-Prot≥0.5 g/day
Data of age, SBP, DBP, U-Prot, eGFR, and observation period are shown as median
SBP systolic blood pressure, *DBP* diastolic blood pressure, *U-Prot*, urinary protein, *eGFR*, estimated glomerular filtration rate

Table 20.2 Patients characteristics according to the clinical grading 2

	C-Grade Ia	C-Grade Ib	C-Grade II	C-Grade III	P
Number of patients	336	65	406	248	
Male/female	156:180	39:26	192:214	143:105	0.010
Age	29	56	31	51	<0.0001
SBP (mmHg)	118	130	120	136	<0.0001
DBP (mmHg)	70	79	72	80	<0.0001
U-Prot (g/day)	0.20	0.26	1.00	1.31	<0.0001
eGFR (ml/min)	92.7	49.4	83.7	45.4	<0.0001
Observation period (years)	5.6	5.7	7.1	4.7	0.013

In clinical grading 2, Grade Ia, eGFR≥60 and U-Prot<0.5 g/day; Grade Ib, eGFR<60 and U-Prot<0.5 g/day; Grade II, eGFR≥60 ml/min and U-Prot≥0.5 g/day; Grade III, eGFR <60 ml/min and U-Prot≥0.5 g/day
Data of age, SBP, DBP, U-Prot, eGFR, and observation period are shown as median
SBP systolic blood pressure, *DBP* diastolic blood pressure, *U-Prot* urinary protein, *eGFR* estimated glomerular filtration rate

Difference of the incidence of renal outcome was more prominent between grading 2 groups (Fig. 20.2). Kaplan-Meier curve revealed significant less incidence of renal outcome in C-Grade Ia compared with other C-Grades (log-rank test $p < 0.001$). Cox regression analysis showed that the hazard ratio to C-Grade I was 9.90 (95 % CI: 2.98–32.9) in C-Grade Ib, 6.63 (95 % CI: 2.36–18.9) in C-Grade II, and 29.2 (95 % CI: 10.7–79.8) in C-Grade III. There was no difference of the incidence of renal outcome between C-Grade Ib and C-Grade II (log-rank test $p = 0.996$).

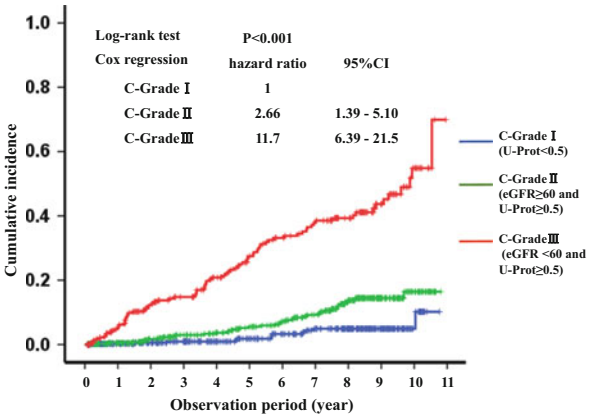

Fig. 20.1 Cumulative incidence of renal outcome according to the clinical grading 1

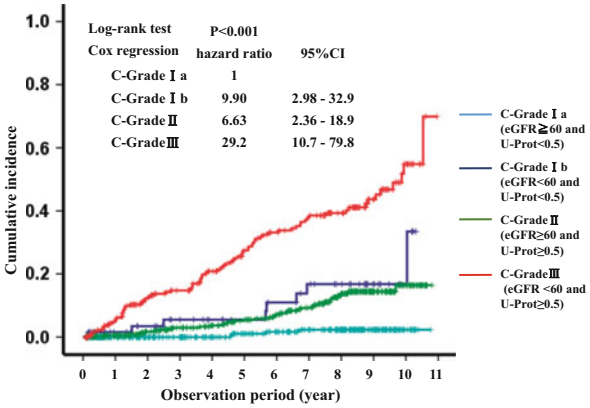

Fig. 20.2 Cumulative incidence of renal outcome according to the clinical grading 2

20.4 Discussion

There are many studies addressing the renal prognostic factors in IgAN, and an impaired GFR, hypertension, substantial proteinuria, and scarring on renal biopsy specimens are well-known predictive factors [5–7, 13–15]. In 2011, the Japanese Society of Nephrology determined the clinical and histological grading criteria in the "Clinical guides for immunoglobulin A (IgA) nephropathy in Japan, third version," putting the emphasis on simplicity and convenient. In this study, there were significant differences of the incidence of renal outcome between three groups according to these clinical grading criteria. Thus, this study confirmed the validity of these simple clinical grading criteria.

We further divided C-Grade I (U-Prot <0.5 g/day) into two groups by eGFR: C-Grade Ia and C-Grade Ib (eGFR ≧60 and <60 ml/min/1.73 m^2, respectively). Although the number of patients with C-Grade Ib was quite small, they were older and had higher blood pressure compared with the patients with C-Grade

Ia. Furthermore, the renal prognosis was significantly poorer in patients with C-Grade Ib compared with those with C-Grade Ia. The incidence of renal outcome in the patients with C-Grade Ib was comparable with those with C-Grade II. Therefore, it seems likely that C-Grade Ia and C-Grade Ib were quite different stages of IgAN. In addition, hazard ratios for the incidence of renal outcome in patients with C-Grade II and C-Grade III to the patients with C-Grade Ia were quite higher compared with to the patients with C-Grade I. Thus, C-Grade Ia seems to reflect far more benign prognosis grade compared with C-Grade I.

There are several limitations in this study. First, since the study design was retrograde approach, there is a possibility of having many biases. Especially, the observation period of the patients with C-Grade I was shorter than those with C-Grade II, although the incidence of renal outcome was smaller in patients with C-Grade I than those with C-Grade II. This fact seems to suggest that the follow-up periods of the patients with benign clinical course were shorter than those with worse clinical course. This results in follow-up bias. Second, many factors including a wide variety of treatments, such as oral corticosteroid, steroid pulse therapy, tonsillectomy and steroid pulse therapy, and antihypertensive agents, especially renin-angiotensin system inhibitors after renal biopsy, modify the renal prognosis. We excluded these factors in this study to clarify the prognosis at the time of renal biopsy. In order to elucidate the effects of various treatments, further analysis using this cohort is necessary.

By using the Nationwide Retrospective Cohort Study in IgAN, this study verified the validity of Japanese clinical grading criteria to predict the renal outcome and also suggests that dividing the patients with C-Grade I (U-Prot <0.5 g/day) into two groups by eGFR 60 ml/min/1.73 m^2 seems to predict renal prognosis more precisely.

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Conflict of Interest The authors declare that they have no conflict of interest.

References

1. D'Amico G. The commonest glomerulonephritis in the world: IgA nephropathy. Q J Med. 1987;245:709–27.
2. Barratt J, Feehally J. IgA nephropathy. J Am Soc Nephrol. 2005;16:2088–97.
3. Koyama A, Igarashi M, Kobayashi M. Coworkers of the research group on progressive renal disease. Natural history and risk factors for immunoglobulin A nephropathy in Japan. Am J Kidney Dis. 1997;29:526–32.
4. D'Amico G. Natural history of idiopathic IgA nephropathy and factors predictive of disease outcome. Semin Nephrol. 2004;24:179–96.
5. Reich HN, Troyanov S, Scholey JW, Cattran DC, Toronto Glomerulonephritis Registry. Remission of proteinuria improves prognosis in IgA nephropathy. J Am Soc Nephrol. 2007;18:3177–83.

6. Frimat L, Briançon S, Hestin D, Aymard B, Renoult E, Huu TC, et al. IgA nephropathy: prognostic classification of end-stage renal failure. L'Association des Néphrologues de l'Est. Nephrol Dial Transplant. 1997;12:2569–75.
7. Barratt J, Feehally J. Treatment of IgA nephropathy. Kidney Int. 2006;69:1934–8.
8. Matsuo S, Kawamura T, Joh K, Utsunomiya Y, Okonogi H, Miyazaki Y, et al. Clinical guides for immunoglobulin A (IgA) nephropathy in Japan, third version. Jpn J Nephrol. 2011;53:123–35.
9. Kawamura T, Joh K, Okonogi H, Koike K, Utsunomiya Y, Miyazaki Y, et al. A histologic classification of IgA nephropathy for predicting long-term prognosis: emphasis on end stage renal disease. J Nephrol. 2013;26:350–7.
10. Hotta O, Miyazaki M, Furuta T, Tomioka S, Chiba S, Horigome I, et al. Tonsillectomy and steroid pulse therapy significantly impact on clinical remission in patients with IgA nephropathy. Am J Kidney Dis. 2001;38:736–43.
11. Matsuzaki K, Suzuki Y, Nakata J, Sakamoto N, Horikoshi S, Kawamura T, et al. Nationwide survey on current treatments for IgA nephropathy in Japan. Clin Exp Nephrol. 2013;17:827–33.
12. Kawamura T, Yoshimura M, Miyazaki Y, Okamoto H, Kimura K, Hirano K, Special IgA Nephropathy Study Group, et al. A multicenter randomized controlled trial of tonsillectomy combined with steroid pulse therapy in patients with immunoglobulin A nephropathy. Nephrol Dial Transplant. 2014;29:1546–53.
13. Radford MG, Donadio JV, Bergstralh EJ, Grande JP. Predicting renal outcome in IgA nephropathy. J Am Soc Nephrol. 1997;8:199–207.
14. D'Amico G, Minetti L, Ponticelli C, Fellin G, Ferrario F, Di Belgioioso GB, et al. Prognostic indicators in idiopathic IgA mesangial nephropathy. Q J Med. 1986;59:363–78.
15. Berthoux F, Mohey H, Laurent B, Mariat C, Afiani A, Thibaudin L. Predicting the risk for dialysis or death in IgA nephropathy. J Am Soc Nephrol. 2011;22:752–61.

Column 1: Spontaneous Animal Model

Hitoshi Suzuki

Despite the more than 40 years that have passed since IgA nephropathy (IgAN) was first described, the mechanisms underlying the disease development are not fully understood. Small-animal experimental models of IgAN can be very helpful in studies of the disease, but the development of these models has been hindered by the fact that only humans and hominoid primates have the IgA1 subclass. In spite of these obstacles, several different models have been developed that may be helpful in the study of various specific aspects of primary IgAN.

The ddY mouse strain is a model of spontaneous IgAN that develops glomerulonephritis with a striking deposition of IgA in the mesangium, as well as co-deposits of IgG, IgM, and C3 [1]. A major disadvantage of the ddY mouse model is the high degree of variability in the age of onset and severity of the disease, due to the strain being maintained as an outbred stock. The high-IgA (HIGA) mouse strain was established by the interbreeding of ddY strains with high serum levels of IgA to assess the possible correlation of serum IgA levels with the development of IgAN [2]. These models have revealed that although HIGA mice have high IgA levels, serum IgA levels are not associated with the severity of glomerular injury and incidence of the disease [3]. We previously reported that ddY mice could be classified into the early-onset, late-onset, and quiescent groups, based on analyses of serial renal biopsies [3]. A genome-wide association study identified several genetic loci linked with the early-onset phenotype [3]. One of the candidate loci lies within a region of synteny with human 6q22–23 containing *IGAN1*, which is implicated in familial IgAN [4]. These results suggest that IgAN in ddY mice and in humans may be, at least partly, affected by the same susceptibility genes.

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To overcome the high degree of variability in the age of onset and severity of the disease in the ddY mouse model, we inter-crossed early-onset ddY mice. After selective intercrossing for >20 generations, we established a novel 100 % early-onset grouped ddY mice model [5]. All grouped ddY mice develop proteinuria within 8 weeks of birth. The grouped ddY mice show severe glomerular and tubulointerstitial lesions, characterized by mesangial proliferation, mesangial matrix expansion, and tubulointerstitial infiltrations. Glomerular cell numbers and glomerular sclerosis scores at 8 and 24 weeks of age in female grouped ddY mice are significantly higher than those in HIGA mice [5]. Electron microscopy showed electron-dense deposits mainly in the paramesangial area similar to those found in human IgAN. Immunofluorescence staining revealed glomerular deposits of IgA with IgG and C3 co-deposits in grouped ddY mice [5].

IgAN is a polygenic disease and the clinical and histopathologic findings of IgAN patients are heterogeneous. Moreover, molecular features of human IgA1, the autoantigen that plays a key role in the pathogenesis of human IgAN, are different from rodent IgA. However, it is possible to analyze selected phenotypes and pathological pathways that are common for both the animal model and human disease or to delineate the differences between the two. Even though murine IgA is different from human IgA1, aberrant glycosylation of IgA tends to enhance production of polymeric IgA and the formation of immune complexes with autoantibodies in both human and murine IgAN [5, 6]. Furthermore, genetic factors, the dysregulation of mucosal immunity, and complement factors are important for the initiation and progression of IgAN in animal models and human disease. The grouped ddY mouse model may be a useful tool for studies of many of these aspects.

Column 2: Bone Marrow Transplantation (BMT) Using an Animal Model

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Excess amounts of poorly glycosylated serum IgA1 appear to be the trigger for the generation of glycan-specific IgG and IgA autoantibodies, resulting in the formation of circulating IgA immune complexes, which have a pivotal role in the development of nephritis. It remains unclear where the major site of production of poorly glycosylated IgA is. One intriguing possibility is that this IgA is derived from displaced mucosal B cells, which have mis-homed from their mucosal induction sites to systemic sites, where they secrete polymeric, poorly glycosylated IgA directly into circulation rather than onto mucosal surfaces. IgA plasma cells primed in mucosal sites, such as salivary glands and tonsils, routinely traffic to the bone marrow and back to the site of antigen encounter [7]. There is increasing evidence for the presence of a mucosa–bone marrow axis in humans, and abnormalities in this axis may play an important role in the development of IgA nephropathy (IgAN) [8, 9].

Previous clinical studies indicated that the presence of large numbers of IgA1 plasma cells produced polymeric IgA in the bone marrow of IgAN patients [8, 10]. Moreover, bone marrow transplantation (BMT) and peripheral blood stem cell transplantation in patients with leukemia and IgAN is associated with the cure of both leukemia and IgAN [11, 12]. These data suggest that mucosa polymeric IgA1 may be derived from bone marrow. Imasawa et al. reported that BMT from wild-type mice attenuated glomerular injuries in the high-IgA (HIGA) mouse, and conversely, BMT from HIGA mice developed mesangial IgA deposition in wild-type mice [13]. The ddY mouse is a spontaneous model of IgAN, described in my previous column (Column 1). This model was divided into three groups by serial

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renal biopsies: early onset (~20 weeks of age), late onset (~40 weeks of age), and quiescent groups [3]. We have confirmed that BMT from the early onset mice to the quiescent mice resulted in the development of IgAN [6]. The early onset ddY mice showed mesangial co-deposition of IgA and IgG and increased levels of serum IgA-IgG2a immune complexes. Similar findings are seen in the recipient mice. On the other hand, BMT from the quiescent mice to the early onset ddY mice improved glomerular injuries with mesangial deposition of IgA and IgG [6].

These findings suggest that bone marrow may be a reservoir of memory cells that produce nephritogenic IgA. These cells homed in bone marrow appear to be essential for the continuous delivery of pathogenic IgA.

References

1. Imai H, Nakamoto Y, Asakura K, Miki K, Yasuda T, Miura AB. Spontaneous glomerular IgA deposition in ddY mice: an animal model of IgA nephritis. Kidney Int. 1985;27:756–61.
2. Muso E, Yoshida H, Takeuchi E, Yashiro M, Matsushima H, Oyama A, et al. Enhanced production of glomerular extracellular matrix in a new mouse strain of high serum IgA ddY mice. Kidney Int. 1996;50:1946–57.
3. Suzuki H, Suzuki Y, Yamanaka T, Hirose S, Nishimura H, Toei J, et al. Genome-wide scan in a novel IgA nephropathy model identifies a susceptibility locus on murine chromosome 10, in a region syntenic to human IGAN1 on chromosome 6q22-23. J Am Soc Nephrol. 2005;16:1289–99.
4. Gharavi AG, Yan Y, Scolari F, Schena FP, Frasca GM, Ghiggeri GM, et al. IgA nephropathy, the most common cause of glomerulonephritis, is linked to 6q22-23. Nat Genet. 2000;26:354–7.
5. Okazaki K, Suzuki Y, Otsuji M, Suzuki H, Kihara M, Kajiyama T, et al. Development of a model of early-onset IgA nephropathy. J Am Soc Nephrol. 2012;23:1364–74.
6. Suzuki H, Suzuki Y, Aizawa M, Yamanaka T, Kihara M, Pang H, et al. Th1 polarization in murine IgA nephropathy directed by bone marrow-derived cells. Kidney Int. 2007;72:319–27.
7. Kunkel EJ, Butcher EC. Plasma-cell homing. Nat Rev Immunol. 2003;3:822–9.
8. van den Wall Bake AW, Daha MR, Evers-Schouten J, van Es LA. Serum IgA and the production of IgA by peripheral blood and bone marrow lymphocytes in patients with primary IgA nephropathy: evidence for the bone marrow as the source of mesangial IgA. Am J Kidney Dis. 1988;12:410–4.
9. Suzuki Y, Tomino Y. Potential immunopathogenic role of the mucosa-bone marrow axis in IgA nephropathy: insights from animal models. Semin Nephrol. 2008;28:66–77. doi:10.1016/j.semnephrol.2007.10.008.
10. Harper SJ, Allen AC, Pringle JH, Feehally J. Increased dimeric IgA producing B cells in the bone marrow in IgA nephropathy determined by in situ hybridisation for J chain mRNA. J Clin Pathol. 1996;49:38–42.
11. Sakai O. IgA nephropathy: current concepts and future trends. Nephrology. 1997;3:2–3.
12. Iwata Y, Wada T, Uchiyama A, Miwa A, Nakaya I, Tohyama T, et al. Remission of IgA nephropathy after allogeneic peripheral blood stem cell transplantation followed by immunosuppression for acute lymphocytic leukemia. Intern Med. 2006;45:1291–5.
13. Imasawa T, Nagasawa R, Utsunomiya Y, Kawamura T, Zhong Y, Makita N, et al. Bone marrow transplantation attenuates murine IgA nephropathy: role of a stem cell disorder. Kidney Int. 1999;56:1809–17.