Chapter 11
Differences in Etiology and Treatment in Japan

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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.

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