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INVITED REVIEW ARTICLE

Clinical and histological features and therapeutic strategies for IgA nephropathy

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Abstract

Chronic glomerulonephritis is the second most common reason, after diabetic nephropathy, for initiation of dialysis in Japan and IgA nephropathy (IgAN) is the most prevalent form of chronic glomerulonephritis. In the half century since IgAN was initially reported, our understanding of the long-term prognosis, clinical and histological features, pathogenesis of onset and progression, risk factors for progression, and appropriate treatment under different clinical and histological conditions, has steadily increased. Strong experimental and clinical evidence, *the Clinical Practice Guidelines for IgA Nephropathy* in Japan, the Oxford Classification, and the Kidney Disease Improving Global Outcomes guidelines have all contributed to the appropriate treatment of IgAN. Several intensive therapies, such as tonsillectomy, steroid therapy, and their combinations, can result in clinical remission, and prevent the progression to end stage renal disease (ESRD). However, some IgAN patients still progress to ESRD even when treated with intensive therapies. In this review, we discuss the clinical and histological features of IgAN, focusing primarily on our previous reports, and our opinions on therapeutic strategies for IgAN.

Keywords IgA nephropathy · Prognosis · Risk factors · Guidelines · Treatments

Introduction

Half a century has passed since Berger et al. first described IgA nephropathy (IgAN) in 1968 [1]. Initially, IgAN was considered a benign disease because of its clinical and histological features of being associated with few cases of nephrotic syndrome, rapidly progressive glomerulonephritis, and crescentic glomerulonephritis. In the 1970s, intensive treatments, such as steroids, tonsillectomy, and immunosuppressive agents, were not provided to patients with IgAN. However, in the 1980s and 1990s, long-term survival analyses over 10–20 years revealed that the disease was not so benign, as 40% of IgAN patients had progressed to end-stage renal disease (ESRD) within 20 years [2–4]. Subsequently, several studies were performed to identify risk factors and appropriate treatments to prevent progression to ESRD.

Several investigators have identified risk factors associated with progression to ESRD (Table 1). In Japan, *the Clinical Practice Guidelines for IgA Nephropathy* were first reported in 1995 [5] and subsequently underwent minor revision in 2002 [6]. As per these guidelines, prognosis was divided into four groups according to histological features: good, relatively good, relatively poor, and poor. In contrast, clinical parameters such as creatinine (Cr), Cr clearance, the level of urinary protein excretion (U-Prot), and blood pressure were recognized only as supplementary parameters. However, the relative importance of these clinical parameters was re-evaluated, and the guidelines underwent major revision in 2011 (third edition) [7, 8]. In the third edition, U-Prot and estimated glomerular filtration rate (eGFR) were selected as clinical risk factors, while crescents, segmental sclerosis, and global sclerosis were selected as histological risk factors. In 2009, the first international histological classification, the Oxford Classification, was reported [9, 10] from a working group of the international IgA Nephropathy Network and the Renal Pathology Society. Mesangial hypercellularity, endothelial hypercellularity, segmental sclerosis

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Table 1 The risk factors of IgA nephropathy

Clinical findings
Deteriorated renal function [3, 7, 8, 20–26, 50, 57]
Higher amount of urinary protein excretion [2, 3, 7, 8, 20, 22–26, 32, 33, 35, 36, 41, 48, 50, 53, 57]
Hypertension [2, 21, 24–26, 48, 50, 57]
Sex (male) [24, 25, 50]
Age (older [20, 50, 56], younger [24–26])
Hematuria (mild [24–26, 42], severe [37–39, 41, 50], without macrohematuria [2, 21, 50])
Higher uric acid [20, 48, 52, 53]
Lower serum albumin [21, 24–26] or total protein [3]
Dyslipidemia (higher total cholesterol, LDL-cholesterol, and triglyceride [48])
Obesity [49]
Higher serum IgA or IgA/C3
Anemia
Histological findings [3, 5–11, 22, 24–26, 58–60]
Active lesions
Cellular and fibrocellular crescent [11], endothelial hyper cellularity [9, 10], mesangial hyper cellularity [9, 10]
Tuft necrosis
Chronic lesions
Global sclerosis, segmental sclerosis [9, 10, 21], fibrous crescent, glomerular tuft adhesion to Bowman's capsule [9, 10]
Mesangial matrix increase, interstitial fibrosis and tubular atrophy [9, 10]
Depositions
IgG [63, 64], IgA, IgM, C3, C4d

or adhesion, and interstitial fibrosis/tubular atrophy were selected as risk factors. In 2016, the Oxford Classification was revised to include cellular and fibrocellular crescents [11].

Regarding treatment, the beneficial effects of corticosteroid therapy were first described by Kobayashi et al. in 1996 [12, 13], although this was in a retrospective cohort analysis. In 1999, Pozzi et al. [14] reported the results of a randomized controlled trial (RCT) to demonstrate the effects of intermittent steroid pulse (SP) therapy. The long-term follow-up results of this RCT were also reported in 2004 [15]. This form of SP therapy is one of the strongest evidence-based treatments in the world. In Japan, Hotta et al. [16] reported that combined tonsillectomy and corticosteroid therapy was the most effective treatment regimen to achieve clinical remission of IgAN, and those who achieved remission did not progress to ESRD. Following the report by Hotta et al., the number of IgAN patients who underwent tonsillectomy combined with SP (TSP) therapy [17] and the number of institutions that performed TSP therapy [18] increased dramatically in Japan. Moreover, a Japanese multicenter RCT that compared TSP and SP according to Pozzi's regimen was undertaken, and its results indicated that TSP had a beneficial effect in decreasing U-Prot compared with SP [19].

In summary, the risk factors, guidelines, and treatments for IgAN have changed dramatically over the last half century. In this review, we discuss the clinical and histological features of IgAN, and share our opinions on therapeutic strategies for IgAN described in our previous reports.

Long-term prognosis of IgAN

According to reports from the 1990s, roughly 40% of patients with a 20 year natural history of IgAN progressed to ESRD [3, 4]. In our total cohort from 1974 to 2011, renal survival rate was 84.3% over 10 years, 66.6% over 20 years, 50.5% over 30 years, and 46.6% over 35 years [20]. These results were similar to previous observations, and the 35 year prognosis represents the longest analysis to date. A single group from Korea reported the 30 year prognosis, and found that the composite outcome of mortality and renal survival rates over 10, 20, and 30 years was 79.8, 66.9, and 62.5%, respectively [21]. According to these results, IgAN appears to be associated with poor prognosis. However, recent therapeutic strategies, such as oral prednisolone (oPSL), SP therapy, TSP therapy, renin-angiotensin system inhibitors (RASIs), and other supportive therapies, such as fish oil, statins, and antiplatelet agents, have improved prognosis [20, 22]. In our previous reports, mean arterial pressure, eGFR, serum albumin, serum uric acid (UA), total cholesterol (T-Cho), U-Prot, IgA/C3 ratio, and T lesions as per the Oxford Classification of histology were identified as risk factors by univariate Cox regression analysis. Among these risk factors, multivariate analysis showed that eGFR, U-Prot,

and UA were associated with renal prognosis. The eGFR and U-Prot results were consistent with clinical guidelines in Japan [7, 8].

Deteriorated renal function as a risk factor for IgAN

The deterioration of renal function is a severe risk factor for progression to ESRD in IgAN. In our previous reports, a 20 ml/min/1.73 m^2 decline in eGFR increased the risk of progression to ESRD by 1.93 times [95% confidence interval (CI) 1.47–2.56, $P < 0.0001$] according to multivariate Cox regression analysis [20]. According to *the Clinical Practice Guidelines for IgA Nephropathy* in Japan [7, 8], the risk of progressing to ESRD in patients with C-grade III (defined as eGFR < 60 ml/min/1.73 m^2 and U-Prot ≥ 0.5 g/day) is 42.5 times higher than in patients with C-grade I (defined as U-Prot < 0.5 g/day), although the risk of progression to ESRD in patients with C-Grade II (defined as eGFR ≥ 60 ml/min/1.73 m^2 and U-Prot ≥ 0.5 g/day) is 6.4 times higher than that in patients with C-grade I [23]. In a nationwide prospective cohort study of 2,269 IgAN patients in 97 centers in Japan, Cr was reported as the severest and most important risk factor compared with others such as sex, age, blood pressure, proteinuria, hematuria, serum albumin, and histological findings [24, 25]. This study was validated in 633 Caucasians in a Norwegian cohort study, which used eGFR instead of Cr. In multivariate analysis, risk of progression to ESRD was 3.1 times higher for chronic kidney disease (CKD) grade 3, 10.1 times higher for CKD grade 4, and 31.2 times higher for CKD grade 5 in comparison with CKD grade 1 [26].

As described above, it is disputable whether deteriorated renal function is a risk factor for progression, and prevention of progression to ESRD in advanced IgAN remains challenging. In advanced IgAN patients with deterioration of renal function, histological features are important factors in determining method of treatment. If active lesions such as mesangial hypercellularity, endothelial hypercellularity, and cellular and fibrocellular crescents are still present, corticosteroid therapy has the potential to prevent progression to ESRD, or at least delay it. In our previous study [27], oPSL decreased U-Prot and delayed the increase in Cr. We used oPSL because the mean ratio of cellular and fibrocellular crescents was high (17.2%), as was that of global sclerosis (23.9%). Corticosteroid therapy appeared to be effective for active lesions, and decreased U-Prot and delayed progression to ESRD. Notably, a significant amount of glomerular hyperfiltration in the remaining glomeruli is observed in advanced IgAN patients because of global sclerosis. RASIs, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone blockers, and direct renin inhibitors, are effective for these patients by decreasing glomerular hypertension and hyperfiltration through dilatation of the efferent arteriole of glomeruli. RASIs are more beneficial for long-term renal survival compared with antiplatelet agents [28], and have effects similar to oPSL [29, 30], SP therapy [31], and TSP therapy [31] in IgAN patients with eGFR < 60 ml/min/1.73 m^2. It is important to select appropriate treatments according to histological features in patients with advanced IgAN with deterioration of renal function. At minimum, administration of treatment with RASIs according to the physiological state of glomeruli might be considered.

Proteinuria in IgAN

Proteinuria is the best evaluable marker of treatment response and the best surrogate marker for predicting prognosis. High level of U-Prot is a risk factor for progression to ESRD. Our previous multivariate analysis showed that an increase of U-Prot by 1.0 g/day increased the risk of progression to ESRD by 1.34 times (95% CI 1.07–1.69, $P = 0.0116$) [20]. We found similar results in a nationwide multicenter retrospective cohort study to establish the *Clinical Practice Guideline for IgA Nephropathy* in Japan [23]. In that study, risk of progression to ESRD was increased 1.69 times by a 1.0 g/day increase in U-Prot in multivariate analysis adjusted by clinical findings and 1.61 times when adjusted for clinical findings and treatment [23]. In the above-described nationwide survey in Japan [24, 25], U-Prot was recognized as the second most common risk factor after renal function. Recently, the importance of mean U-Prot of follow-up (time-average proteinuria: TAp) has been reported [32, 33]. Of course, it is important to predict outcome from clinical findings at the time of renal biopsy. Several treatments have been reported to decrease U-Prot during follow-up, and in Japan the first goal of treatment is to achieve remission of U-Prot and hematuria [34]. Therefore, consideration of changes in U-Prot is also important in analyzing treatment response and predicting prognosis.

Although IgAN with nephrotic syndrome is rare and occurs only in 5–10% of IgAN patients [35], it seems to be important because of its severe prognosis and lack of appropriate treatment. In our previous report [35], 42 cases of IgAN with nephrotic syndrome were identified among 954 IgA patients (4.4%), and had severe renal function impairment (mean eGFR: 51.1 ml/min/1.73 m^2), high level of U-Prot (mean 5.76 g/day), and urinary red blood cells (U-RBC) (mean 50/HPF). As per the Oxford Classification, M1: 60.0%, E1: 32.9%, S1: 82.9%, T1: 40.0%, T2: 25.7%, C1: 54.3%, and C2: 17.1% were observed, and were more severe than in non-nephrotic IgAN. The cumulative 15-year renal survival rate was only 25.3%, and 74.5% in

non-nephrotic IgAN. Lower eGFR, Oxford T lesions, and no steroid treatment were independent risk factors for progression to ESRD by multivariate Cox regression analysis. In the Korean cohort, renal survival rate was also poor. The results over 8 years showed that renal survival was about 40% in IgAN patients with nephrotic syndrome and about 75% in those with non-nephrotic IgAN [36].

To prevent progression to ESRD, decreasing the level of U-Prot is important [36]. In this regard, analysis of TAp might be important, and appropriate treatment to decrease TAp is required.

Hematuria in IgAN

In recent years, hematuria has been recognized as a consequence of inflammation of glomerular capillaries, which is related to active glomerular lesions such as tuft necrosis, endothelial hypercellularity, and cellular and fibrocellular crescents. In several Asian studies of IgAN patients with mild proteinuria, hematuria was one of the risk factors for progression to hypertension, increase of proteinuria and progression to ESRD [37–39]. On the contrary, a Spanish study showed that few Caucasian patients had increased proteinuria and progression to ESRD [40]. However, another Spanish study showed that persistent hematuria was an independent risk factor for progression to ESRD [41], similar to TAp. In our cohort of 1,012 IgAN patients [20], U-RBC was not a risk factor for progression by univariate analysis (HR: 1.02, 95% CI 0.92–1.13, $P=0.6851$). In Japan, U-RBC is not recognized as a risk factor of progression to ESRD in the *Clinical Practice Guidelines for IgA Nephropathy* [7, 23]. A nationwide survey in Japan also showed that mild hematuria (U-RBC $\leq$ 30/HPF) was an independent risk factor for progression, while severe hematuria was not [25, 42]. Hematuria is still seen as the most controversial risk factor for progression of IgAN. In our previous study, in IgAN patients with mild proteinuria ($\leq$0.5 g/day at the time of renal biopsy), a higher level of U-RBC did not affect renal prognosis [43]. Additionally, in IgAN patients with moderate-to-severe proteinuria ($\geq$1.0 g/day at the time of renal biopsy), a higher level of U-RBC did not affect the response to steroid treatment or outcome [44]. Moreover, there was no relationship between the level of U-RBC and the severity of active histological lesions [44]. In recent years, low vacuum-scanning electron microscopy has revealed the presence of large gaps, thinning, and alterations of the glomerular basement membrane (which are generally observed in patients with thin basement membrane disease) in IgAN patients in addition to active lesions [45]. These additional alterations may affect the indefinite relationship between the hematuria and outcome of IgAN, although hematuria is considered the primary result of active histological lesions. The clinical importance of hematuria is still unresolved in IgAN.

Other risk factors in IgA nephropathy

Uric acid and other metabolic factors

Recently, metabolic factors such as dyslipidemia, obesity, hypertension (HT), and impaired fasting glucose have been reported to relate to onset and progression of CKD [46, 47]. IgAN is also one of the CKDs, and the above factors are also reported to have a relationship with progression of IgAN [48–50]. Higher T-Cho, body mass index, and blood pressure are also independent factors for progression to ESRD in univariate analysis, and higher UA was an independent risk factor in both univariate and multivariate analysis in our previous study [20]. Hyperuricemia (HU) induces oxidative stress, which decreases endothelial nitric oxide expression and increases endothelial dysfunction, resulting in glomerular hypertension. HU also results in proliferation of vascular smooth muscle cells in preglomerular arteries with activation of the RAS [51]. In IgAN, a 1.0 mg/dl increase of UA increased the risk of progression to ESRD by 1.24 times (95% CI 1.04–1.48, $P=0.0176$) in our cohort [20] and 1.17 times (95% CI 1.08–1.27, $P<0.001$) in a large Chinese cohort ($n=1965$) by multivariate Cox regression analysis [52]. Until progression to CKD stage G3a without decreasing UA, global glomerular sclerosis due to HU was increased in addition to the histological features caused by IgAN. Furthermore, the risk of progression to ESRD was also increased compared with IgAN with normal UA [53]. Therefore, until progression to CKD stage G3a, controlling HU appears to be important.

Age

Given the current aging society in Japan, aging in IgAN patients is an important factor to consider, although IgAN frequently occurs in younger people. In our cohort, mean age at diagnosis was 32.9 years [20]. In a Japanese cohort from a nationwide survey, among 5679 patients with IgAN, only 497 (8.8%) patients were > 65 years old [54]. As renal function (eGFR) gradually decreases with age, histological findings also change. Global and focal segmental sclerosis, tubular atrophy and interstitial changes, and arterio- and arteriolosclerosis are increased, as shown by light microscopy [55]. In older IgAN patients ($\geq$60 years old) in our cohort [56], blood pressure, blood urea nitrogen, UA, T-Cho, U-Prot, and *N*-acetyl-β-D-glucosaminidase were significantly higher, while total protein, albumin, and eGFR were significantly lower than in middle-aged (40–59 years old), and/or younger (20–39 years old) patients. Older IgAN patients

were associated with higher numbers of T lesions as per the Oxford Classification compared with younger patients, although the number of active lesions, such as M1 and E1 was similar. The grade of arteriolosclerosis was significantly higher in older IgAN patients compared with middle-aged and younger patients. In total, 51.6% of older IgAN patients were treated with corticosteroids, and 67.7% of patients were treated with RASIs. However, cumulative renal survival rate was poor (22.9%/19 years), and was significantly lower than that of middle-aged (69.2%/20 years) and younger patients (84.9%/20 years) [56]. The most important factor for preventing progression to ESRD was reducing proteinuria by therapeutic intervention [57]. Older IgAN patients frequently have active and chronic histological lesions associated with IgAN, in addition to chronic lesions associated with aging, HT, HU, and dyslipidemia (DL). Therefore, careful treatment of IgAN and other risk factors is required.

Histopathological features and glomerular depositions

Histopathological features, such as mesangial hypercellularity, endocapillary proliferation, cellular and fibrocellular crescents as active lesions, global and segmental sclerosis, fibrous crescents, increased amounts of mesangial matrix, glomerular tuft adhesions to Bowman's capsule, and tubulointerstitial change as chronic lesions, are important factors for prognostic prediction of IgAN, as well as clinical findings, such as renal function and U-Prot (Table 1). Several histological grading systems for analyzing the above histological factors have been reported in the past half century [58–60]; however, no global consensus has been reached. The Oxford Classification has been used worldwide under global consensus since its introduction [9–11]. In Japan, the third edition of the *Clinical Practice Guidelines for IgA Nephropathy* has also been used to evaluate the histopathological findings [7, 8]. However, it has been controversial whether the glomerular immune deposits are predictive markers of prognosis. According to Suzuki, the pathogenesis of IgAN is considered a multi-hit process [61]. Hit 1 is the secretion of galactose-deficient (Gd) IgA1 into the circulation, Hit 2 is the production of IgG or IgA autoantibodies against the Gd-IgA1 hinge region, Hit 3 is the formation of immune complexes with Gd-IgA1, and Hit 4 is glomerular deposition of Gd-IgA1 and subsequent glomerular injury. From the perspective of a multi-hit pathogenesis, IgG deposition appears to be the critical event associated with pathogenesis, disease activity, and prognosis. In our cohort, IgG deposition was related to glomerular tuft adhesions to Bowman's capsule, although there was no correlation with other histological or clinical findings, or renal prognosis [62]. Other studies indicated that IgG deposition was related to U-Prot, eGFR, and T lesions as per the Oxford Classification, and was an independent risk factor for progression to ESRD (HR 2.9, 95% CI 1.6–5.3, $P=0.001$) by multivariate analysis [63]. It was also shown that IgG deposition was related to poor complete remission of urinary parameters by multivariate analysis (HR 0.31, 95% CI 0.12–0.77, $P=0.016$), and poor renal prognosis [64]. Recently, the deposition of Gd-IgA was detected by immunofluorescence analysis [65]. Therefore, further research will clarify the importance of the colocalization of IgG and Gd-IgA deposits with regard to the pathogenesis of IgAN.

Treatment of IgAN

TSP therapy

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend RASIs to reduce proteinuria in IgA patients with U-Prot > 1 g/day. In IgAN patients with persistent proteinuria, corticosteroid therapy is recommended instead of conservative therapies [66]. Combined corticosteroid therapy with RASIs was reported to reduce proteinuria and prevent progression to ESRD in several RCTs [67, 68]. SP therapy was also reported to have beneficial effects on IgAN by Pozzi et al. [14, 15]. However, in Japan, TSP therapy has become the primary treatment for IgAN, and many clinical studies have analyzed its beneficial effects since the report by Hotta et al. [16]. In IgAN patients with U-Prot ranging from 1.0 to 3.5 g/day, and Cr < 1.5 mg/dl according to inclusion criteria of Pozzi's RCT [14, 15], the decrease in U-Prot from baseline during the 12 months after TSP therapy was significantly higher than after SP therapy (coefficient estimate: −1.316, 95% CI −2.617 to −0.015, $P=0.047$) [19]. Additionally, multivariate logistic regression analysis showed that TSP therapy was an independent factor for the resolution of proteinuria (odds ratio: 2.98, 95% CI 1.01–8.83, $P=0.049$), although the effect on remission of U-RBC and both U-Prot and U-RBC was similar to that of SP therapy in a multicenter RCT [19]. Komatsu et al. performed a prospective controlled study that compared TSP and SP therapy. TSP therapy significantly decreased U-Prot and U-RBC, and multivariate analysis indicated that TSP therapy was an independent factor that contributed to remission of U-Prot (HR: 6.20, 95% CI 1.98–19.50, $P=0.002$) [69]. In our cohort, TSP therapy was associated with a significantly higher rate of remission of U-RBC and urinary abnormalities (clinical remission) compared with SP therapy [70], there was also a significantly higher rate of remission of U-RBC, U-Prot, and both, and the renal survival rate was significantly improved compared with oPSL therapy [71]. It was recently reported that the production of Gd-IgA1 is related to tonsillar Toll-like receptor (TLR)-9, a proliferation-inducing ligand (APRIL) in tonsillar B cells,

and B cell-activating factor belonging to TNF (BAFF) in tonsils [61, 72–75]. APRIL expression in tonsillar B cells was induced by TLR-9 and correlated with disease activity [75]. These results indicate that tonsillectomy is an appropriate treatment for IgAN. However, worldwide, it cannot be confirmed that tonsillectomy is a well-recognized treatment for IgAN, especially in Europe [76]. Tonsillectomy may be considered overtreatment and as such has not been recognized as an appropriate treatment in Europe, because there is a lack of an appropriate protocol that accommodates different IgAN patients. In reality, the protocol regarding the number of SP treatments in TSP therapy (three vs. one) is not related to the ratio of IgAN patients who achieved remission of U-Prot, U-RBC, and both [77]. Moreover, in IgAN patients with U-Prot < 1.0 g/g Cr or IgAN patients with CKD G3, there was no significant difference in 20-year renal survival rate among those treated with TSP, SP, oPSL, and RASI [31]. These results indicate that the protocol for TSP therapy should be adjusted according to disease activity in each IgAN patient. Short duration of nephropathy may have beneficial effects for achieving clinical remission [78]. However, there are some IgAN patients who will not progress to ESRD despite a lack of therapeutic intervention, such as TSP therapy, tonsillectomy, SP therapy, oPSL, RASIs, or even antiplatelet agents. We are currently facing a dilemma regarding the goal of treatment for IgAN [79].

Other supportive therapies

In this section, we describe the effects of fish oil and statins that are used to treat DL. There is insufficient evidence for these therapies because of a lack of large RCTs, and their effectiveness remains controversial for the treatment of IgAN. However, these therapies also have antiarteriosclerotic effects, and given that glomeruli are aggregations of arteries, they may have beneficial effects on the progression of glomerulosclerosis and diminished renal function. Moreover, during the long-term period from onset of IgAN to the end of life, cerebrocardiovascular events are risk factors for progression to ESRD or death, and these therapies may also have beneficial effects on such life-threatening events in IgAN patients.

Fish oil

Fish oil contains substantial amounts of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as polyunsaturated fatty acids (PUFAs). PUFAs have been reported to have anti-inflammatory effects that block several inflammatory cytokines/cascades, such as tumor necrosis factor-α [80], interleukin-6 [81], and cyclooxygenase-2 [81, 82]. Moreover, PUFAs have been shown to inhibit expression of profibrotic genes such as transforming growth factor-β, fibronectin, connective tissue growth factor, and type IV collagen [83] in mesangial cells and in a mouse model of IgAN [81, 84, 85]. In 1984, EPA and DHA therapy were first reported to improve renal function for 1 year compared with nonsupplemented control subjects [86]. Subsequently, several RCTs were performed and a meta-analysis of the results revealed beneficial effects in reducing U-Prot, but not in preserving renal function. In addition, their antiproteinuric effects were not dose-dependent [87]. In our previous study [88], 1 year treatment with EPA combined with RASIs decreased U-Prot when compared with dilazep combined with RASIs (median U-Prot: baseline: 0.80, after 1 year: 0.41 g/g Cr with EPA, $P < 0.001$; and baseline: 0.88, after 1 year: 0.60 g/g Cr with dilazep, not significant). In another study [89], additional treatment with DHA and EPA stabilized renal function (median %ΔeGFR: before addition of DHA: −7.35% for 6 months, and after addition of DHA: +1.26% for 6 months, $P = 0.0132$) in advanced IgAN with deterioration of renal function (mean eGFR 48.3 ml/min/1.73 m^2). Its pleiotropic effects were beyond the antiproteinuric, antihypertensive, and antidyslipidemic effects. Although these studies were small retrospective analyses, and the effects of PUFAs on IgAN remain controversial, PUFAs have potential for IgAN because of their pleiotropic effects and ease of use without severe adverse events. We believe PUFA may represent a therapeutic strategy for use in future large RCTs for the treatment of IgAN.

Statins

Recently, the evidence of beneficial effects of statins on cardiovascular events and progression to ESRD in CKD patients has dramatically increased [90], although there is a lack of strong evidence for their effect in IgAN. Following suppression of glomerular inflammation in IgAN by immunosuppressive therapies such as TSP, SP, or oPSL, the primary goal for the treatment of IgAN is changed to management of CKD to control and reduce risk factors such as HT, HU, DL, and obesity. Statins may have beneficial effects in IgAN that prevent progression to ESRD. In our previous study [91], in 24 patients with deterioration of renal function (mean eGFR: 55.8 ml/min/1.73 m^2), mean %ΔeGFR was −5.9% for 1 year before statin treatment was started, and was significantly increased to 2.4% for 1 year after statin treatment was started ($P = 0.0098$). In other studies, the beneficial effects of statins on IgAN, such as antiproteinuric effects [92, 93], anti-inflammatory effects [94, 95], and stabilization of renal function [92, 93] were described, although the evidence was weak. We anticipate that strong evidence for the use of statins in preventing progression to ESRD in IgAN will be reported in the future.

Therapeutic strategies for IgAN

A therapeutic strategy for IgAN is shown in Fig. 1. The initial step in the development of IgAN is a mucosal infection. Therefore, tonsillectomy is important for removing this trigger and to stop subsequent production of Gd-IgA1. Tonsillectomy also suppresses the relapse of nephropathy in IgAN patients after achieving clinical remission by reducing the risk of tonsillitis and mucosal infections in the future. Furthermore, epipharyngeal abrasive therapy and oral care may have beneficial effects on the treatment of IgAN, although there is no evidence supporting this. Corticosteroid therapy is the most effective method of suppressing Gd-IgA1, immune complexes with Gd-IgA1, and mesangial IgA deposition, owing to its immunosuppressive effects. Other immunosuppressive agents, such as cyclophosphamide, calcineurin inhibitors (tacrolimus and cyclosporin A), and antimetabolites (azathioprine, mycophenolate mofetil, and mizoribine) may affect these factors because of their mechanism of action. However, there is currently no strong supporting evidence, and recommendations in the KDIGO guidelines are relatively weak [66]. The anti-inflammatory effects of corticosteroid therapy suppress glomerular inflammation, such as mesangial hypercellularity, endothelial hypercellularity, tuft necrosis, and cellular and fibrocellular crescents. It is critical to suppress active lesions in IgAN as soon as possible, before glomerular inflammation spreads diffusely and globally to other glomeruli. If there are no active lesions in glomeruli, corticosteroid therapy should be carefully considered, referring to clinical findings and the patient's social background (age, sex, marital status, future pregnancy intentions, and occupation). After active lesions are suppressed, prognosis depends on the stress on the remaining glomeruli in the form of glomerular hyperfiltration and glomerular hypertension, as well as on CKD management. RASIs are most effective treatment to reduce glomerular hyperfiltration and hypertension. Once RASIs are started, they should be continued until progression to ESRD, because hyperfiltration and glomerular hypertension in the remaining glomeruli will become severe, along with the deterioration of renal function and the continuous decline in the number of remaining glomeruli. Importantly, hyperkalemia and teratogenicity must also be considered carefully. In CKD management, the risk factors for progression of CKD, such as HT, DL, HU, and obesity, should be well controlled. The onset of other diseases in the future, such as diabetes mellitus, cerebrocardiovascular disease, malignancy, systemic disease, and other visceral diseases represent a risk factor for the deterioration of renal function. Since the peak age at onset of IgAN is relatively young, IgAN patients must be treated with careful consideration of the need for long-term observation.

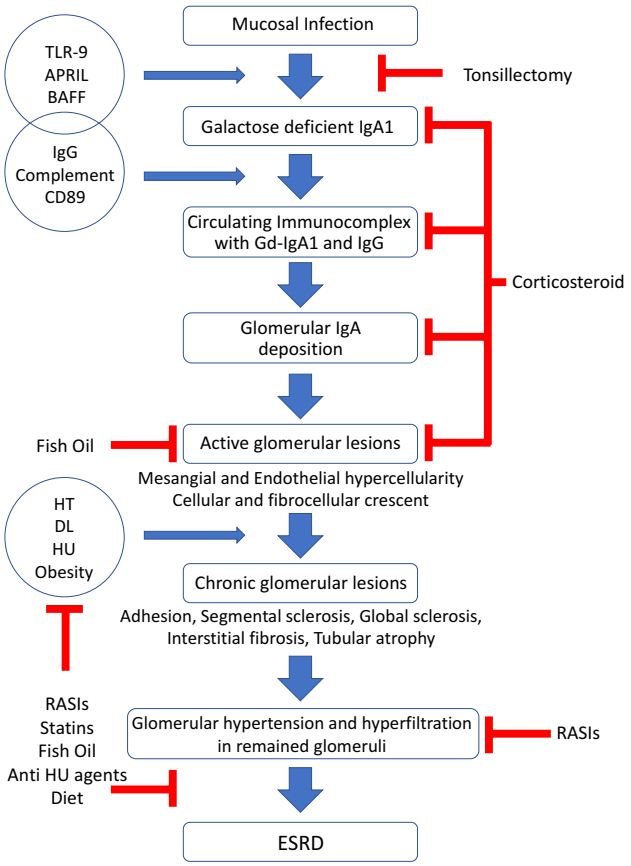

Fig. 1 Onset, progression, and treatment of IgA nephropathy. After mucosal infection, production of Gd-IgA1 and subsequent formation of immune complexes with Gd-IgA1 and IgG autoantibodies occur. They induce glomerular IgA deposition and subsequent glomerular injury. Glomerular active lesions progress to chronic lesions, and chronic lesions induce glomerular hypertension and hyperfiltration in the remaining glomeruli, culminating in ESRD. Tonsillectomy suppresses the production of Gd-IgA1, while corticosteroid therapy suppresses the circulation and deposition of Gd-IgA1 through immunosuppressive mechanisms and suppresses active glomerular lesions through anti-inflammatory mechanisms. Glomerular hypertension and hyperfiltration in the remaining glomeruli induced by chronic glomerular lesions are treated by RASIs. The control of other risk factors, such as HT, DL, HU, and obesity is also important for the progression of CKD in IgAN

Conclusions

In this review, clinical and pathological characteristics and therapeutic strategies for IgAN were discussed. IgAN is a slow but progressive disease with various active and chronic histological lesions, mild-to-moderate proteinuria, and several degrees of hematuria. Appropriate treatment to adjust for the different histological and clinical features should be provided. Fortunately, recent therapeutic interventions have improved prognosis of the disease. Moreover, along with furthering of our understanding of the pathogenesis of

IgAN, new treatments such as biologics and mucosa-related therapies have been trialed. In the future, we believe it will be possible to prevent the progression to ESRD in all IgAN patients.

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Compliance with ethical standards

Conflicts of interest The author declares there is no conflict of interest.

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