Modulating the Progression in IgA Nephropathy

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Key Words

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Abstract

IgA nephropathy affects almost 1% of the population and yet the diagnosis is often missed. This significant kidney disease is often progressive with 25% of the patients going on to end-stage kidney disease over the course of 25 years. This minireview describes the clinical presentations in children and young adults. Therapeutic options are discussed including angiotensin-converting enzyme blockade, steroids, cytotoxics, tonsillectomy, fish oil, vitamin E, singly or in combination, in order to modulate the rate of progression.

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Introduction

Immunoglobulin A (IgA) nephropathy, first described in 1968, was originally called Berger's disease [1]. The index cases were children in France presenting with asymptomatic, macroscopic hematuria a few days following an acute upper respiratory tract infection [2]. The kidney biopsies showed markedly expanded mesangium filled with IgA, hence the name IgA nephropathy. By the 1980s, it was recognized as the most common primary

form of glomerulonephritis worldwide [2]. Julian [3] and others [4–7] suggested that it affects more than 1% of the general population.

Variations in Clinical Presentation

The peak incidence of IgA nephropathy in children occurs between 9 and 10 years of age [7]. It is more common in males with a ratio of male to female ranging from 2:1 to 6:1. Asymptomatic microscopic hematuria at any time point can be found in 60% of subjects. Recurrent macroscopic hematuria continues to occur in 20–80% of the patients. Usually the painless, gross hematuria occurs 1–2 days after an upper respiratory or gastrointestinal infection. Hypertension is infrequently present at the onset of the disease and is usually mild to moderate in severity and relatively easy to control. Sixty percent of the patients have proteinuria at any time point. Thirty percent of the patients have urine findings of active nephritis and/or nephrotic range proteinuria. Acute kidney failure is extremely rare. The serum IgA concentration is elevated in only 10–15% of children in contrast to 30–50% of adults with IgA nephropathy [6, 7]. For these reasons, serum IgA concentration cannot be used as a diagnostic test in place of a kidney biopsy. The serum concentration of C3 is usually normal; ASO titers are negative and serum creatinine is normal in the early stages of disease [7].

Racial and Regional Differences

In all kidney biopsies performed for primary glomerulonephritis, IgA nephropathy accounts for 50% of the histologic findings in countries around the western shores of the Pacific: Japan, Singapore, Australia, and New Zealand [7]. In Europe, the incidence of the disease is lower, with this pathology found in 20–30% and in North America it is present in 2–10% of biopsies performed for primary glomerulonephritis. The reasons for these differences between various regions of the world are not yet known. One possible explanation is that in Japan and South Korea, children between 6 and 18 years of age undergo mandatory urinary screening in their school annual checkup. Accordingly, 30–40% of the biopsies for persistent microscopic and macroscopic hematuria and proteinuria reveal IgA nephropathy [7, 8]. Such routine urinalysis is absent in North American schoolchildren, and the prevailing practice of not performing biopsies for repeated gross hematuria unless it is accompanied by proteinuria or family history may account for the lower prevalence rates.

Predisposing Factors

Macroscopic hematuria in IgA nephropathy may follow various infectious events: herpes simplex virus, cytomegalovirus, Epstein-Barr virus, hepatitis B, adenovirus, and H influenza [2–4]. When there is familial predisposition to the disease [9], the prognosis is less favorable, especially in kidney transplantation recipients [5]. Other predisposing factors include linkages to 6q22-23 and CD14/-159 polymorphism [10–12]. Finally, downregulation of podocyte nephrin may contribute to the development or progression of IgA nephropathy [13].

Histopathologic Features and Other Markers of Progression

A number of studies have demonstrated that a variety of glomerular, interstitial, or vascular alterations may predict renal outcome in patients with IgA nephropathy [14, 15]. Glomerular or interstitial proliferation, as assessed by MIB-1 immunostaining, correlated with progressive renal disease in a group of patients with IgA nephropathy [16]. However, as in other glomerular diseases, the extent of interstitial fibrosis appears to most accurately predict the subsequent clinical course of patients

with IgA nephropathy [14, 17]. Recent studies have indicated that TGF- β induces interstitial fibrosis by promoting epithelial to mesenchymal transformation [18]. Whether fibroblasts arise from proliferation of resident cells, from bone marrow-derived stem cells, or from epithelial to mesenchymal transformation, α -smooth muscle actin has been employed as a marker of an ‘activated’ phenotype that is involved in production of extracellular matrix. Interstitial inflammation may also contribute to the development of progressive renal disease. Markers of this process including glomerular or interstitial accumulation of CD68-positive macrophages predict decreased renal function.

In the last few years, the new tools of molecular biology have been used to delineate new prognostic indicators in IgA nephropathy. Haraka et al. [19] demonstrated a worsening prognosis if urinary IL-6 excretion exceeds 2.5 ng/day. Yoon et al. [10] evaluated the association of CD14-159C polymorphism with a deteriorating prognosis. Florquin et al. [20] demonstrated that CD44 expression was associated with poor prognosis. Ishiguro et al. [21] demonstrated that patients with a ratio of serum IgA to complement C3 in excess of 3.01 suffer a higher risk of progression. Lemley et al. [22] demonstrated that podocytopenia is related to disease severity in IgA nephropathy associated with a poor prognosis. Podocyturia, indicated by abnormal urinary nephrin mRNA, may be an early marker of susceptibility for damage to the podocytes. Its value in IgA nephropathy may be similar to that documented by Nakamura et al. [23] in patients with lupus nephritis and in diabetic nephropathy [24] by Meyer et al. [25]. These investigators used podocyte number to predict long-term urinary albumin excretion and microalbuminuria in diabetic nephropathy.

Pathogenesis

Although the pathogenesis of IgA nephropathy is unknown, it is most likely an autoimmune complex disease, based on the following observations: (1) the presence of circulating IgA immune complexes, (2) recurrence in allografts, and (3) the production of experimental IgA nephropathy by active immunization with bovine γ -globulin or with passive preformed IgA immunocomplexes.

Although IgA immune complexes are not directly cytotoxic, the interaction of IgA immune complexes with glomerular mesangial cells results in the local production of free radicals and cytokines [26, 27]. In addition, polymeric IgA and monomeric IgA from patients with IgA

nephropathy induce an upregulation of TGF- β in cultured human mesangial cells via the renin-angiotensin system [28, 29]. This deleterious interaction could account for the renal protective effect of angiotensin-converting enzyme (ACE) inhibitors in IgA nephropathy by reducing TGF- β . In addition, there is significant superoxide production by peripheral blood polymorphonuclear leukocytes in patients with IgA nephropathy, and the amount of free radical production correlates positively with the degree of proteinuria [27]. Thus proliferation of human mesangial cells and production of immune/chemical mediators and superoxide anions may be amplified by nephritogenic IgA-IC, resulting in kidney lesions commonly seen in IgA nephropathy [26]. The increased production of superoxide anions by kidney mesangial cells [27] and polymorphonuclear leukocytes [26] support a novel direction in the treatment of IgA nephropathy, namely the use of an antioxidant, such as vitamin E, to prevent mesangial cell proliferation and attenuate growth-factor-mediated kidney injury [30, 31]. In parallel with enhanced superoxide production, aggregated IgA induces Fc α receptor expression in leukocytes [27, 32]. These findings correlated with the severity of proteinuria in patients with IgA nephropathy [27, 32].

Isolated glomeruli, when appropriately stimulated *in vitro*, have the capacity to produce oxygen-free radicals such as superoxide, hydroxyl radical, and hydrogen peroxide [33]. Production of oxygen-free radicals contributes to organ dysfunction in ischemic acute kidney failure in rats [34] and experimental models of glomerulonephritis [35]. Weanling rats subjected to 6 weeks of selenium and vitamin E deficiency showed reduction in glomerular filtration rate, kidney plasma flow, and enhanced lipid peroxidation following ischemia-reperfusion injury [36]. Dietary reduction of the antioxidant for 9 weeks induced spontaneous kidney injury associated with increased antibody production [37]. Furthermore, vitamin E prevented radical-induced inactivation of kidney Na-K-ATPase [38]. Oxygen-free radicals generated by neutrophils cause acute glomerular injury with resulting proteinuria [39]. Reactive oxygen molecules contribute to the initial development of chronic kidney failure [40] and play important roles [41–51] in the progression of kidney disease. In the remnant kidney model, tubular hypermetabolism results in increased oxygen consumption and generation of free radicals [52], leading to lipid peroxidation of the kidney parenchyma, evidenced by increased malondialdehyde content per unit tubular mass [53].

Trachtman et al. [54, 55] found that antioxidants, specifically vitamin E [56] and taurine [57], are renoprotec-

tive and are effective in attenuating the development of glomerulosclerosis in the puromycin-induced nephrotic rat model. Hahn et al. [56] demonstrated that the glomerulosclerotic index and the tubulointerstitial index were significantly reduced with vitamin E treatment. The use of vitamin E also markedly reduced kidney TGF- β mRNA expression. In addition, even after glomerulosclerosis and tubulointerstitial injury have been well established, administration of vitamin E can reverse the process [56], akin to the clinical situation of therapy after presentation of symptomatic kidney disease. These findings support a new approach, namely long-term administration of antioxidants, to prevent glomerulosclerosis [55] or at least slow the rate of progression of chronic kidney diseases.

Tubulointerstitial damage and kidney failure are encountered in approximately 30% of patients, but IgA depositions are not detected in the tubules [57]. Exactly how glomerular IgA depositions lead to tubulointerstitial fibrosis and kidney failure is an intriguing issue and the subject of ongoing research. New evidence suggests that IgA depositions in human mesangial cells trigger release of TNF- α , and this glomerulotubular communication plays an important role in the pathogenesis of tubulointerstitial injury in IgA nephropathy [57].

Increased renal expression of TGF- β 1 has been associated with severity of kidney disease in models of IgA nephropathy in rats [30]. The finding of elevated intrarenal levels of glomerular TGF- β 1 mRNA has been reported in patients with IgA nephropathy [58]. The progression of IgA nephropathy may result from overexpression of TGF- β 1 leading to mesangial matrix expansion, interstitial fibrosis, and glomerulosclerosis [58]. There is evidence linking oxidant stress within the kidney to enhanced renal expression of TGF- β . Therefore, interception of autocrine activation of TGF- β 1 by the natural antioxidant, vitamin E, may check disease progression in experimental IgA nephropathy [30].

Clinical Studies in Prevention of Progression in IgA Nephropathy

We conducted a review of clinical studies published in the last 3 years using a Medline search. The paucity of well-controlled, randomized clinical trials, especially in children, is apparent. The medications and procedures (table 1) used in these clinical studies can be divided into four major categories: (1) ACE inhibitors and angiotensin receptor blockers, (2) corticosteroids with or without cy-

Table 1. Medications for IgA nephropathy

Drug	Mechanism	Current use	Dosage	Potential complications
Vitamin E	Antioxidant	Mild, early IgA nephropathy GFR >60 ml/min/1.73 m ² NKF stage 1 and 2	400–800 IU/day	Nose bleeds
Lisinopril and losartan	ACE inhibition and blockade	Moderate renal impairment GFR 30–59 ml/min/1.73 m ² NKF stage 3	Lisinopril, up to 0.4 mg/kg/day Losartan, 50 mg/day	Coughing, hypotension
PAHwD	Combined immunosuppressive	Moderate renal impairment GFR 30–59 ml/min/1.73 m ² NKF stage 3	Center dependent	Leukopenia, bleeding diathesis, allergic reactions
Methylprednisolone and tonsillectomy	Immunosuppression	Moderate renal impairment GFR 30–59 ml/min/1.73 m ² NKF stage 3	Methylprednisolone, 30 mg/day, max 1 g/day	Cushingoid features, hypertension, bleeding and surgical complications of tonsillectomy
Methylprednisolone and cytotoxics	Immunosuppression	Moderate renal impairment GFR 30–59 ml/min/1.73 m ² NKF stage 3	Center dependent	Cushingoid features, leukopenia
Fish oil	Anti-inflammation	GFR >60 ml/min/1.73 m ²	Center dependent	Nose bleed, fishy breath
Mycophenolate	Immunosuppression	Moderate to severe renal impairment and heavy proteinuria >2 g/day	600 mg/m ² b.i.d. Max dose based on patient safety and tolerance	Leukopenia, liver damage, intestinal symptoms

totoxic agents, (3) n-3 polyunsaturated fatty acid (fish oil), (4) tonsillectomy and (5) other forms of immunosuppressive therapy, plasmapheresis, and mycophenolate mofetil (CellCept).

ACE Inhibitors and Angiotensin Receptor Blockers

Yoshida et al. [59] demonstrated that the use of ACE inhibitors reduced proteinuria. In addition, Perico et al. [60] and Praga et al. [61] demonstrated that glomerular filtration rate is better preserved with ACE inhibitors. In addition, in adult patients with biopsy-proven IgA nephropathy randomized to enalapril or control (i.e., not on ACE inhibitors), there was a reduced rate of doubling of serum creatinine at follow-up of over 70 months in the former group [61]. Moreover, the kidney survival at 4 years was 100% with enalapril but only 70% in the control group ($p < 0.05$). At 7 years, this dropped to 92 and 55%, respectively ($p < 0.05$). In the enalapril-treated group, proteinuria decreased significantly, whereas in the control group, proteinuria increased ($p < 0.01$).

In a study by Park et al. [62] comparing losartan to amlodipine, after 12 weeks of therapy, blood pressure was

effectively controlled in both groups. The proteinuria in the losartan group dropped to 1.2 ± 1.5 g/day compared to the baseline value of 2.3 ± 1.5 g/day, whereas there was no change in the amlodipine group. Finally, urinary TGF- β excretion, decreased in the losartan group compared to the baseline value, whereas there was no change in the amlodipine group. With the exception of Praga et al. [61], these were case studies involving adult patients. There have been few studies in children with IgA nephropathy, except Tanaka et al. [63] and Bhattacharjee and Filler [64], who demonstrated the combination ACE inhibitor and losartan to ameliorate progression. But these were also case series and neither was a double-blinded, randomized, controlled trial.

Corticosteroids Alone or in Combination with Cytotoxics

The use of intravenous methylprednisolone may slow the rate of progression to end-stage kidney disease [6, 65, 66]. Repeat biopsies in the steroid-treated group showed a decreased matrix crescent formation and time until doubling of serum creatinine was lengthened. In 16 adult

patients with advanced IgA nephropathy, Kuriki et al. [67] administered a loading dose of methylprednisolone followed by 10–15 mg prednisolone per day. The urinary protein before treatment was 1.6 ± 1.7 g/day and dropped to 0.4 ± 0.2 g/day after therapy ($p < 0.005$). The mesangial matrix index was 14.5 ± 5.2 before treatment dropping to 9.5 ± 3.6 after treatment ($p < 0.001$). Suzuki and Joh [65] and Hotta [66] confirmed and advocated this use of steroid therapy. Thus, the efficacy of corticosteroids in patients with advanced IgA nephropathy is encouraging. But the issues of long-term steroid side effects continue to be unsettling, especially side effects of growth retardation in children.

Evidence that pulse steroid plus intravenous cyclophosphamide slow the rate of progression was provided by Tumlin et al. [68] and Rasche et al. [69]. In the Tumlin study [68], the serum creatinine before this combined therapy was 2.7 ± 0.4 mg/dl, which fell to 1.5 ± 0.1 mg/dl after three doses of methylprednisolone at 15 mg/kg/day, followed by intravenous cyclophosphamide at 0.5 g/month for 6 months. The proteinuria decreased from 4 to 1.3 g/day after treatment ($p < 0.01$). In addition, using the plot of the reciprocal of the serum creatinine versus time as an index of the rate of progression, there was a minus value of 0.039 before therapy, which slowed to a positive value of 0.0076 after therapy ($p < 0.08$). Repeat kidney biopsies showed decreased endocapillary proliferation, crescents and karyorrhexis. Using 12 historical controls with the same period of follow-up, 5 out of the 12 historical control patients developed end-stage kidney disease, whereas with combination treatment, only 1 out of 12 progressed to end-stage kidney disease. Combining prednisone and cytotoxics (cyclophosphamide and azathioprine) slowed the rate of progression with follow-up to a maximum of 10 years in adult patients. No pediatric subjects were included in these studies.

Fish Oil

In 1994, Donadio et al. [70] demonstrated that 2 years of treatment with fish oil in adults with IgA nephropathy slowed the rate of progression. However, Dillon [71] in a meta-analysis of all published studies up to 1997 came to the conclusion that fish oil is of minimal benefit. In addition, the adult patients complained of excessive belching and the onerous fishy taste of the medicine [72], which may decrease compliance especially in children. In addition, children treated with fish oil for other conditions encounter an increased incidence of epistaxis [73]. A recent study performed by the Southwest Pediatric Nephrology Study group failed to demonstrate therapeutic

efficacy of fish oil supplementation in children and young adults with IgA nephropathy [74]. However, when the body weight was factored in, there appeared to be a dose-related effect [74]. More recently, Branten et al. [75] demonstrated no difference between fish oil-treated and untreated controls with IgA nephropathy. It is important to note that the beneficial effects of fish oil may be a consequence of the vitamin E in the fish oil preparation, as shown in experimental IgA nephropathy [76]. These unresolved issues about the use of fish oils demand a careful re-appraisal of its long-term efficacy [77, 78]. The extended observations on the Mayo study cohort of 106 patients in the first fish oil study [79] plus the second fish trial [80] suggest the advantage of fish oil treatment may be related to the initial fatty acid status of the patients (who were previously on fish oil) and the benefit continues in an extended off-study follow-up of over 6 years.

Tonsillectomy Alone or in Combination with Steroids

In Japan, tonsillectomy is widely used in patients with IgA nephropathy, based on the assumption that tonsillectomy changes mucosal immunity to prevent uncharacterized antigenic deposition in the kidneys [81]. However, its applicability has not been accepted in other parts of the world. Recent evidence from Xie et al. [82] compels a re-examination of this issue. In 118 patients followed for 193 ± 75 months, in the tonsillectomy group, only 10.4% progressed to end-stage kidney disease compared to 63.7% in the nontonsillectomy group ($p < 0.03$).

A recent study of Sato et al. [83] provided further evidence on the efficacy of tonsillectomy. Seventy adult patients with moderate IgA nephropathy characterized by serum creatinine in excess of 1.5 mg/dl were divided into three treatment groups: (1) steroid plus tonsillectomy, (2) steroid alone, and (3) supportive therapy only. At follow-up of 17 months, in the steroid plus tonsillectomy group, end-stage kidney disease was 13% compared to 56% in the conventional steroid-treated group and 73% in the group under supportive strategy only. Doubling of serum creatinine occurred in 16% of patients in the steroid plus tonsillectomy group compared to 64% in a conventional steroid group and 73% in the supportive group. Hotta et al. [84] studied 35 adult patients with IgA nephropathy who underwent repeat kidney biopsy after an average of 70 months of follow-up. They demonstrated that high-dose methylprednisolone plus tonsillectomy is associated with a mesangial proliferation score of 2.49 ± 0.73 in the first biopsy with a significant drop to 0.91 ± 0.89 in the second kidney biopsy ($p < 0.001$). The interstitial fibrosis

index was $98.6 \pm 81.7\%$ in the first biopsy compared to $21.40 \pm 20.3\%$ in the second biopsy ($p < 0.01$).

However, these studies on the efficacy of such interventions remain observational and not mechanistic. This treatment option stays contentious partly because 'blinding' cannot be done for a surgical procedure such as tonsillectomy. In addition, the side effects of long-term, high-dose steroids and the complications of the tonsillectomy procedure continue to limit wider acceptability.

Other Combined Therapies in IgA Nephropathy

For moderately severe IgA nephropathy, Yoshikawa and Ito [85] demonstrated that after 2 years of combined therapy with prednisolone, azathioprine, heparin, warfarin, dipyridamole (PAHwD), patients randomized to this regime showed better outcome compared to patients randomized to heparin-warfarin, dipyridamole (HwD) therapy. The evidence showed that with PAHwD therapy, proteinuria decreased. The progression to end-stage kidney was reduced. The glomerulosclerosis showed no change with the PAHwD group compared to an increased glomerulosclerosis in the HwD group. In the kidney biopsies, there was decrease of IgA-1 complex in the PAHwD group with no change in the HwD group. The authors reported few side effects for both groups, although the repeated blood tests for clotting profile may limit wide acceptability.

Tacrolimus and mycophenolate mofetil [86, 87] have undergone clinical trials in patients with IgA nephropathy. The efficacies of these medications are encouraging. Plasmapheresis [88] has been used to remove circulating immune complexes, immediately before and after kidney transplantation. Prophylactic antibodies [89] and Chinese herb medicines [90], including *Cordyceps sinensis* [90], show promise but long-term effects are still under study. Urokinase [91] is reported to be effective in advanced IgA nephropathy but its long-term effect is uncertain.

Controlled, Clinical Studies in Children with IgA Nephropathy

Thirty children with IgA nephropathy [92] who demonstrated moderate mesangial proliferation and proteinuria were given 1 year of combined fluvastatin (29 mg/day) plus dipyridamole (5 mg/kg/day). They showed a decrease in proteinuria, blood urea nitrogen, creatinine, and cholesterol/triglyceride/low-density lipoprotein. The glomerular filtration rate increased. The long-term efficacy beyond 1 year of treatment is not known.

The Southwest Pediatric Nephrology Study group is testing mycophenolate mofetil in children and young adults with IgA nephropathy, with preliminary data showing benefits in slowing the rate of progression [93].

Finally, in a randomized, double-blinded study in children with biopsy-proven IgA nephropathy, Chan et al. [31] demonstrated that vitamin E significantly reduced proteinuria. While there was a trend to stabilization of glomerular filtration rate in the vitamin E-treated patients, long-term treatment and follow-up are needed to determine whether antioxidant therapy is associated with preservation of renal function.

Recommendations

Available evidence would suggest that for patients with mild proteinuria of less than 1 g/day, nephrologists could consider vitamin E either alone or combined with an ACE inhibitor as a treatment option. With moderate proteinuria of more than 1 g/day, steroid therapy with or without tonsillectomy may ameliorate progression. Administration of an ACE inhibitor or angiotensin receptor-blocking agent has proven to be of value with its mechanistic rationale. In severe proteinuria exceeding 2 g/day, mycophenolate mofetil has shown promise in adult patients in slowing progression. Finally, in severe cases of IgA nephropathy, prednisone plus cytotoxics as combined therapy have shown improved kidney survival and repeat biopsies have shown decreased endocapillary proliferation and crescent formation. However, the series describing these treatment regimens are too small to justify a recommendation and should be considered as another treatment option instead.

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