Controversial Management Strategies for IgA Nephropathy

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When Professor Jean Berger *et al.* first reported on “Nephropathy with mesangial IgA-IgG deposits,” namely, IgA nephropathy, in 1968, the prognosis of this disease was generally considered to be benign¹⁾. Since then, however, patients with IgA nephropathy have been shown to have microscopic and macroscopic hematuria and/or proteinuria. Macroscopic hematuria is occasionally observed after upper respiratory infections, including acute tonsillitis and/or pharyngitis. The occurrence of nephrotic syndrome is rare. About 30% of IgA nephropathy patients develop end stage kidney disease (ESKD) within 15–20 years, and 5–10% within 5 years, in Japan. The progression to ESKD in patients with this disease is not as rare as originally thought. Basically, a low-salt diet is usually recommended to control blood pressure, as high salt intake is a major cause of blood pressure increases. Long-term dietary protein restriction is generally considered to reduce the levels of urinary protein excretion and ameliorate glomerular injuries in patients with IgA nephropathy. There are many reports, such as those regarding kidney disease with improving global outcomes (KDIGO) and those from the Japanese guidelines, with respect to medications for IgA nephropathy patients^{2) 3)}. KDIGO clinical practice guidelines were published in *Kidney International* in 2012²⁾. Within each recommendation, the strength of recommendation is indicated as Level 1, Level 2, or not graded, and the quality of the support is shown as A, B, C, or D. In this plenary session, I would like to review controversial management strategies for IgA nephropathy patients using several drugs.

Keywords : therapy, kidney disease improving global outcomes (KDIGO), guideline, IgA nephropathy

Controversial management strategies for IgA nephropathy

1. Renin-angiotensin system (RAS) inhibitor and/ or calcium channel blocker (CCB)

Angiotensin-converting enzyme (ACE) inhibitor and/or angiotensin II receptor blocker (ARB) induce a marked renoprotective effect in patients with IgA nephropathy. Therapy with an ACE inhibitor and/or ARB was reported to produce a more marked decrease in proteinuria and progression to ESKD in normotensive patients with IgA nephropathy. Antiproteinuric and antihypertensive therapy using ACE inhibitor or ARB was recommended in the KDIGO guideline sponsored by the National Kidney Foundation (Recommendation 1B to 2D)²⁾. However, in Japan, ACE inhibitor and/or ARB are not used in normotensive patients under the national insurance system. We reported the

anti-proteinuric effect of olmesartan, one of the ARBs, in normotensive patients with IgA nephropathy in a multicenter controlled trial financially supported by the Daiichi-Sankyo Company, Tokyo, Japan⁴⁾. The change in urinary protein to creatinine ratio (UP/Cr) was –56.2%. Creatinine clearance (CCr) showed no changes throughout the study period. There was no relationship between the decrease of urinary protein excretion and that of blood pressure. It appears that olmesartan monotherapy showed a robust reduction of urinary protein in normotensive IgA nephropathy patients, suggesting that this effect is independent of its blood pressure-lowering properties.

The long-term anti-proteinuric effects of benidipine, a calcium channel blocker (CCB), have been evaluated in detail in 65 hypertensive patients with chronic kidney disease (CKD) including IgA nephropathy⁵⁾. Benidipine (4 mg/day or 8 mg/day)

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was administered to previously untreated hypertensive patients with CKD, or hypertensive patients with CKD not achieving target blood pressure (BP) despite taking an ARB. BP (systolic/diastolic) decreased from $154 \pm 19/91 \pm 12$ mmHg before treatment to $134 \pm 16/78 \pm 10$ mmHg at one year after treatment ($p < 0.001$). The UP/Cr ratio decreased significantly 2.21 ± 2.47 g/gCr before treatment to 1.43 ± 2.21 g/gCr after treatment ($p < 0.001$). Especially, the percentage decrease of the UP/Cr ratio was greater in elderly patients. It is suggested that benidipine may have more potent antiproteinuric effects in elderly hypertensive patients with CKD including IgA nephropathy⁵⁾.

2. Fish oil

Omega-3 polyunsaturated fatty acids (n-3 PUFA) have gained wide attention in medical literature⁶⁾. Favorable effects of n-3 PUFA in a variety of cardiovascular and autoimmune diseases are supported by an impressive number of previous studies. In 2006, Hagiwara *et al.*⁷⁾, my colleagues, reported that eicosapentaenoic acid (EPA) ameliorates diabetic nephropathy of type 2 diabetic KKA^y/Ta Mice. We proposed that the observed down-regulation of monocyte chemoattractant protein-1 (MCP-1), a regulating macrophage recruitment protein, is critically involved in the beneficial effect of EPA, probably in concert with the improvement of other clinical markers⁷⁾. In IgA nephropathy, only fish oil supplementation was used in the reported clinical studies. Some studies of fish oil reduced renal disease progression in high-risk IgA

nephropathy. KDIGO suggested that using fish oil in the treatment of IgA nephropathy with persistent proteinuria of more than 1g/day, despite 3-6 months of optimized supportive care (including ACE inhibitors or ARBs and blood pressure control (Recommendation 2D). However, there have been some controversial previous results due to different dosages of EPA and DHA in patients with IgA nephropathy as shown in Table-1. It will be necessary to determine the efficacy of using fish oil (EPA and/or DHA) in treating this disease in the future.

3. Corticosteroid and Anti-platelet therapy

In 1983, Mustonen *et al.*¹⁴⁾ reported that patients with mild renal histological findings of IgA nephropathy seem to respond to corticosteroids, whereas those with more advanced changes do not. They also indicated that the treatment with corticosteroids is justified when the nephrotic syndrome is due to IgA nephropathy with minor glomerular changes. KDIGO suggested that patients with persistent proteinuria of more than 1.0 g/day, despite 3-6 months of optimal supportive care (including ACE inhibitor or ARB and blood pressure control), and glomerular filtration rate (GFR) of more than 50 ml/min per 1.73m^2 , receive a 6-month course of corticosteroid therapy (Recommendation 2C). In IgA nephropathy, KDIGO recommended the use of blood pressure treatment goals of less than 130/80 mmHg in patients with proteinuria of less than 1 g/day, and less than 125/75 mmHg when initial proteinuria is more than

Table-1 Controversial clinical outcome of Fish oil treatment in IgA nephropathy patients

Study	Year	Design	Patient	Age	Proteinuria	sCr	Medication	Period (M)	Results
Hamazaki ⁸⁾	1984	RCT	20			1.7	EPA-DHA 1.6g-1.0g	12	Improved renal function
Alexopoulos ⁹⁾	2004	RCT	29	41	2.0	2.2	EPA-DHA 0.85g-0.57g	24	Stable renal function Lower urinary protein
Ferraro ¹⁰⁾	2008	RCT	30	40	1.3		EPA-DHA 2.55g-0.45g	6	Stable renal function Lower urinary protein
Bennet ¹¹⁾	1989	RCT	37	39	2.0	2.3 1.0	EPA-DHA 1.8g-1.2g	24	Decline in renal function
Petterson ¹²⁾	1994	RCT	32	41	1.9	1.1	EPA-DHA 3.3g-1.8g	6	Decline in renal function, No change in proteinuria
Cheng ¹³⁾	1990	before and after study	11	39	2.5	2.8	EPA-DHA 1.8g-1.2g	10	No effect in the maintenance of renal function

Figure-1 Effect of dilazep hydrochloride in IgA nephropathy patients

1 g/day (not graded)²⁾. However, Kobayashi *et al.*¹⁵⁾ studied the effect of steroids in a 10-year follow-up of the early stage (proteinuria of 1-2 g/day, CCr of more than 70 ml/min and a histological severity score of more than seven) of progressive IgA nephropathy. Twenty patients received corticosteroid and anti-platelet drug treatment for an average period of 18 months, and another 26 patients received an anti-platelet drug without corticosteroid treatment. The renal survival rate was significantly different between the two groups (corticosteroid 100% vs. non-steroid anti-platelet drug 84% at 5 years after the start of therapy and 80% vs. 34% at 10 years; $p < 0.01$). The final CCr values differed significantly between the two groups (54 ± 35 ml/min vs. 20 ± 29 ml/min; $p < 0.05$). On the other hand, the patient groups with mild histological changes or decreased renal function due to moderate proteinuria showed no significant differences in the final outcome. They concluded that corticosteroids are beneficial in stabilizing renal function over the long term during the early stage of progressive IgA nephropathy¹⁵⁾. Since anti-platelet drugs, such as dilazep hydrochloride or dipyridamole, show multifunctional pharmacological effects, as shown in Figure-1, we have usually used these drugs for mild stages of IgA

nephropathy in Japan. Although KDIGO suggested not using only anti-platelet agents to treat IgA nephropathy (Recommendation 2C), those agents are considered for use as fundamental drugs for mild stage of this disease and combination therapy with corticosteroids.

4. Tonsillectomy with steroid pulse therapy

The tonsils are mucosa in very close contact with extrinsic antigens, especially infectious antigens, and are the site of the initiation of immune responses. In recent years, focus has been centered on the tonsils, a part of the immune system, as a site of infections. Patients with IgA nephropathy often show aggravation of renal injury with macroscopic hematuria after mucosal infections, especially tonsillitis. Clinical effects of a tonsillectomy with steroid pulse therapy on the treatment of proteinuria and hematuria in patients with IgA nephropathy have been reported mainly from Japan.

Toll-like receptors (TLR) are a family of pathogen pattern recognition receptors that have several different classes of pathogen-related structures and active defense mechanisms, particularly in innate immunity. We previously demonstrated the important role of mucosal Toll-like receptor 9 (TLR9) activation in the pathogenesis in spontaneous

murine model of IgA nephropathy¹⁶⁾. Moreover, a single nucleotide polymorphism (SNP) in TLR9 was significantly associated with pathological severity in human IgA nephropathy¹⁶⁾. Recently, we investigated correlations between tonsillar TLR9 messenger RNA expression, TLR SNP genotypes and clinical outcomes following tonsillectomy with steroid pulse therapy in patients with IgA nephropathy. Tonsillar TLR9 expression was examined in 49 patients with IgA nephropathy and 15 controls without kidney diseases. High expressions of tonsillar TLR9 were observed in about 23% of IgA nephropathy¹⁷⁾. These patients showed stronger and earlier remission of hematuria and proteinuria than those with low TLR9 expression. Patients with the TT genotype SNP (rs352140) had more severe renal injury than those with other genotypes. The patients whose serum IgA level decreased more than average after the tonsillectomy (large Δ IgA) showed higher cumulative remission rates of proteinuria than patients with a smaller decreases in these levels (small Δ IgA). CT/CC genotypes were more dominant and tonsillar expressions significantly higher large Δ IgA patients than in small Δ IgA patients. It was reported that tonsillar TLR9 expression was correlated with the therapeutic efficacy of a tonsillectomy followed by steroid pulse therapy¹⁷⁾. Recently, Ohya *et al.*¹⁸⁾ have reported that tonsillectomy was associated with a reduction in the relapse rate from clinical remission, i.e. disappearance of urinalysis abnormalities (proteinuria and hematuria). The relapse of clinical remission was the re-appearance of proteinuria or hematuria defined by dipstick test and an erythrocyte count > 5–9 cells/HPF on 3 consecutive visits. It appears that the tonsillectomy was associated with a reduction in the relapse rate from clinical remission after steroid pulse therapy in IgA nephropathy patients¹⁸⁾.

Since the tonsillectomy with steroid pulse therapy have not been accepted by Nephrologists internationally, it is necessary to perform a randomized controlled trial (RCT) of this combination therapy. The results of a multicenter RCT on concomitant tonsillectomy and steroid pulse therapy in IgA nephropathy patients in Japan are now being submitted to an international journal. The percentage decrease in urinary protein excretion from baseline during 12 months was significantly

larger in Group A (tonsillectomy combined with steroid pulse group) than Group B (steroid pulse alone group) ($p < 0.05$). The results indicate that the tonsillectomy combined with steroid pulse therapy can be a superior treatment protocol to steroid pulse alone to attenuate of IgA nephropathy patients, but not to induce them to clinical remission (Kawamura *et al.* for The Special IgA nephropathy Study Group, in submitted, data not shown).

Conclusions

Long-term salt and dietary protein restriction is generally considered to reduce the levels of blood pressure and urinary protein, and ameliorate glomerular injuries in patients with IgA nephropathy. Since there are some controversial results of the treatments in the world, further clinical trials are needed to determine the ideal treatment for IgA nephropathy patients.

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