CASE REPORT

Favorable Renal Outcome of Japanese Children with Severe IgA Nephropathy With Nephrotic Syndrome

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Background: Nephrotic syndrome is a rare but severe feature of IgA nephropathy. **Case characteristics**: Nine Japanese children with severe IgA nephropathy with nephrotic syndrome. **Intervention:** All received low-dose intravenous methylprednisolone (IVMP) within five weeks after the disease onset. Eight out of nine patients achieved resolution of proteinuria without severe adverse events. **Message**: Early low-dose intravenous methylprednisolone may be safe and effective for children with severe IgA nephropathy with nephrotic syndrome.

Keyword: *Low-dose pulse methylprednisolone, Refractory, Resistant, Treatment*.

Nephrotic syndrome (NS) is an unusual presentation of IgA nephropathy (IgAN) occurring in approximately 5% of the patients. Patients with severe nephrotic IgAN have renal insufficiency and active histologic features such as endocapillary hypercellularity and crescentic formation. This nephrotic-range proteinuria is generally resistant to conventional steroid therapy, and the renal prognosis is poor unless resolution of proteinuria is achieved. Optimal treatment regimen for this rare condition remains unknown, particularly in children. We report the favorable renal outcomes in Japanese children with severe nephrotic IgAN who received early treatment with low-dose intravenous methylprednisolone.

CASE REPORT

Between November 2011 and December 2015, nine Japanese children (7 boys; median (range) age 6.8 (4.6, 13.3) years were newly diagnosed with nephrotic IgAN at Saitama Children's Medical Center. All patients were symptomatic at onset (gross hematuria and/or generalized edema), and renal biopsies were performed within 30 days after the appearance of the symptoms. At the time of renal biopsy, the median (range) serum albumin, urine protein-to-creatinine ratio (UP/C), and estimated glomerular filtration rate (eGFR) were 1.8 (1.1, 2.5) g/dL, 7.1 (2.0, 73.5) g/g, and 78.2 (32.1, 110.7) mL/min/1.73 m^2, respectively. Five of the nine patients had renal insufficiency (eGFR <90 mL/min/1.73 m^2). According to new Oxford MEST–C classification [1], M, E and C lesions were present in most children, whereas no patient had T lesion (***Table* I**). The treatment regimen consisted of low-dose intravenous methylprednisolone (IVMP; 15-20 mg/kg/day, maximum 600 mg/day) for three consecutive days weekly for three weeks, followed by oral prednisolone (1 mg/kg/day, maximum 30 mg/day) every alternate day [2]. The oral prednisolone dosages were tapered off within 12 months at a dose of 2.5-5 mg every 4-8 weeks on the basis of the reduction in urinary protein excretion. If patients had persistent NS after low-dose IVMP, treatment with angiotensin receptor blocker (ARB; telmisartan 0.5-1.0

TABLE I PATIENTS IN EACH OXFORD MEST–C SCORE CATEGORY

Mesangial hypercellularity	
≥50% (M0)	3
>50% (M1)	6
Endocapillary hypercellularity	
Absent (E0)	1
Present (E1)	8
Segmental glomerulosclerosis	
Absent (S0)	4
Present (S1)	5
Tubular atrophy/interstitial fibrosis	
≤25% (T0)	9
26-50% (T1)	0
>50% (T2)	0
Cellular/fibrocellular crescents	
Absent (C0)	3
≤25% (C1)	3
>25% (C2)	3

mg/kg/day, maximum 40 mg/day) and/or cyclosporine (CsA 3-5 mg/kg/day, maximum 150 mg/day) was introduced. Furthermore, tonsillectomy was performed within 3 months after the initiation of IVMP. Disappearance of proteinuria and hematuria was defined as a first morning UP/C of <0.15 g/g and a urinary sediment red blood cell count of <5 per high-power field, respectively. During the follow-up period of median (range) 3.2 (1.3, 5.4) years, although ARB and CsA were required in six and three patients, respectively, the remission of proteinuria was achieved in all but one patient at a median (range) of 91 (57, 255) days. The median (range) duration of treatment with ARB and CsA was 219 (120, 276) days, and 188 (168, 197) days, respectively. After the cessation of the treatment with ARB and CsA, no patient had a recurrence of proteinuria during the follow-up period. Disappearance of hematuria was also obtained in all patients at a median (range) of 397 (169, 1289) days. During IVMP, transient glycosuria and elevated intraocular pressure developed in eight and one patient, respectively. However, severe adverse events such as severe infection or clinical osteoporosis did not occur in any patient. At the latest follow-up (median (range) age 10.9 (5.9, 18.2) years), although only one patient received ARB because of mild proteinuria (UP/C 0.2 g/g), all patients discontinued to receive PSL and CsA without relapse of NS. At last visit, the median serum albumin, UP/C, and eGFR were 4.4 g/dL, 0.04 g/g, and 116 mL/min/1.73 m^2, respectively, and no patient developed chronic kidney disease (CKD) stage 3 or worse.

DISCUSSION

These cases suggest the efficacy and safety of low-dose IVMP followed by oral prednisolone and tonsillectomy for children with severe nephrotic IgAN as an early intervention. As IgAN often manifests clinically as episodes of gross hematuria during acute tonsillitis, chronic and recurrent tonsillitis may play an important role in the progression of the disease. Despite the fact that Kidney Disease Improving Global Outcomes (KDIGO) guideline suggest that tonsillectomy not be performed for IgAN [3], tonsillectomy is becoming a standard treatment for patients with IgAN, particular in Japan [4]. The discrepancy of the indication for tonsillectomy might be related to the racial differences of response to the treatment between Asians and Caucasians. Hirano, *et al*. [5] recently reported that Japanese adult patients with IgAN had a lower risk of recurrence after tonsillectomy plus IVMP than after IVMP alone. In addition, none of our patients experienced recurrence after the resolution of proteinuria with IVMP plus tonsillectomy during the follow-up periods. According to the original therapeutic protocol by Hotta, *et al*. [6], we performed a standard regimen of low-dose IVMP *viz.*, three consecutive days weekly for 3 weeks. At present, although optimal protocol, including doses of IVMP for patients with IgAN remains unclear, Watanabe, *et al*. [7] recently reported that the mean period from starting IVMP to remission of hematuria in patients with three courses of IVMP was shorter than that in patients with one course of IVMP, indicating that the patients with three courses of IVMP may have higher efficacy of suppression of glomerular inflammation.

Although KDIGO guideline recommend supportive therapy for IgAN patients with proteinuria – angiotensin-converting enzyme inhibitors (ACE-I) or ARB treatment [3] – in our study, ARB was only added if the patients had continued to NS after IVMP because the reduced proteinuria in the non-nephrotic range proteinuria may have been masked, presumably due to the administration of ACE-I or ARB, leading to delay of the true complete resolution of proteinuria, especially in children without chronic lesions.

In a retrospective study of 100 Korean adults with nephrotic IgAN, Kim, *et al*. [8] reported that 24 patients underwent spontaneous remission without the use of steroid therapy. However, patients showing minor glomerular abnormalities or only minimal mesangial hypercellularity, commonly known as minimal change disease with IgA deposition, were not excluded from their study. The authors also observed that 24 patients (24%) had a doubling of the baseline serum creatinine concentration and 11 of the 24 patients (11%) progressed to end stage renal disease (ESRD) during median follow-up of 45.2 months. On the other hands, despite the fact that patients with mild histological features were excluded from our study, no patient developed a doubling of the baseline serum creatinine concentration or ESRD. In a recent retrospective study of 30 Japanese children with nephrotic IgAN, Shima, *et al*. [9] observed that nine children (30%) did not show remission of proteinuria (UP/C <0.2 g/g) and three patients (10%) developed chronic kidney disease (CKD) stage 3 or worse after a median follow-up of 5 years. The authors opined that the renal outcomes in patients with nephrotic IgAN were clearly worse than in those with non-nephrotic IgAN. In an another recent retrospective study of 33 Chinese children with steroid-resistant nephrotic IgAN, Kang, *et al*. [10] showed that 12 patients (36%) were unable to achieve complete remission of proteinuria (UP/C <0.3 g/g) after 4 months of combined treatment with mycophenolate mofetil (MMF) and prednisolone. These studies indicate that early treatment with steroids and immuno-suppressive agents before the development of irreversible chronic pathological lesions may be crucial for preventing the progression of IgAN to

CKD. In our series, the shorter time between the initial presentation and the initiation of IVMP and the homogeneous treatment regimen may have contributed to the relatively favorable renal outcomes.

In conclusion, early intervention with low-dose IVMP followed by oral prednisolone and tonsillectomy may be a safe and effective treatment in children with severe nephrotic IgAN. Prospective studies and clinical trials from different settings are needed to confirm these findings.

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REFERENCES

1. Trimarchi H, Barratt J, Cattran DC, Cook HT, Coppo R, Haas M, *et al*; IgAN Classification Working Group of the International IgA Nephropathy Network and the Renal Pathology Society. Oxford Classification of IgA Nephropathy 2016: An update from the IgA Nephropathy Classification Working Group. Kidney Int. 2017;91: 1014-21.
2. Fujinaga S, Ohtomo Y, Hirano D, Nishizaki N, Someya T, Ohtsuka Y, *et al*. Low-dose pulse methylprednisolone followed by short-term combination therapy and tonsillectomy for childhood IgA nephropathy. Pediatr Nephrol. 2010;25:563-4.
3. KDIGO clinical practice guidelines for glomerulonephritis–chapter 10: immunoglobulin A nephropathy. Kidney Int Suppl. 2012;2:209-17.
4. Matsuzaki K, Suzuki Y, Nakata J, Sakamoto N, Horikoshi S, Kawamura T, *et al*. Nationwide survey on current treatments for IgA nephropathy in Japan. Clin Exp Nephrol. 2013;17:827-33.
5. Hirano K, Amano H, Kawamura T, Watanabe K, Koike K, Shimizu A, *et al*. Tonsillectomy reduces recurrence of IgA nephropathy in mesangial hypercellularity type categorized by the Oxford classification. Clin Exp Nephrol. 2016; 20:425-32.
6. Ieiri N, Hotta O, Sato T, Taguma Y. Significance of the duration of nephropathy for achieving clinical remission in patients with IgA nephropathy treated by tonsillectomy and steroid pulse therapy. Clin Exp Nephrol. 2012;16:122-9.
7. Watanabe H, Goto S, Kondo D, Takata T, Yamazaki H, Hosojima M, *et al*. Comparison of methods of steroid administration combined with tonsillectomy for IgA nephropathy patients. Clin Exp Nephrol. 2017; 21:257-65.
8. Kim JK, Kim JH, Lee SC, Kang EW, Chang TI, Moon SJ, *et al*. Clinical features and outcomes of IgA nephropathy with nephrotic syndrome. Clin J Am Soc Nephrol. 2012; 7:427-36.
9. Shima Y, Nakanishi K, Sato M, Hama T, Mukaiyama H, Togawa H, *et al*. IgA nephropathy with presentation of nephrotic syndrome at onset in children. Pediatr Nephrol. 2017;32:457-65.
10. Kang Z, Li Z, Duan C, Wu T, Xun M, Ding Y, *et al*. Mycophenolate mofetil therapy for steroid-resistant IgA nephropathy with the nephrotic syndrome in children. Pediatr Nephrol. 2015;30:1121-9.