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# Efficacy of Steroid Pulse Therapy in Combination with Mizoribine Following Tonsillectomy for Immunoglobulin A Nephropathy in Renally Impaired Patients

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**Abstract**

**Background:** The long-term prognosis of immunoglobulin A nephropathy is poor. Treatment is intended to achieve complete remission in the early stage or to preserve renal function in the advanced stages. In Japan, aggressive steroid pulse therapy following tonsillectomy (tonsillectomy-pulse therapy) has recently been used to treat early IgA nephropathy and has achieved favorable outcomes. However, steroid doses are sometimes limited because of adverse reactions s and the efficacy of tonsillectomy-steroid pulse therapy has not been established in patients with renal dysfunction. In our current treatment protocol, the total steroid dose has been significantly reduced through the use of the immunosuppressant mizoribine in combination with tonsillectomy-steroid pulse therapy for the treatment of active IgA nephropathy in patients with renal impairment.

**Methods:** The subjects were 18 patients with active IgA nephropathy who were younger than 70 years and had an estimated glomerular filtration rate ≥20 and <60 mL/min/1.73 $m^2$. After giving informed consent, the patients underwent bilateral tonsillectomy. One week later, intravenous methylprednisolone pulse therapy (500 mg/day) was administered for 3 days, followed by oral prednisolone in combination with mizoribine (100 to 150 mg/day). A renin-angiotensin system inhibitor was used before tonsillectomy in all cases. One year after tonsillectomy, the safety of this protocol and its effects on hematuria, proteinuria, and the progression of renal dysfunction were assessed.

**Results:** The mean patient age was 48.4 years, and the mean time from disease onset to tonsillectomy was 8.4 years. After 1 year, urinary protein had decreased (1.80 ± 1.36 to 0.47 ± 0.75 g/g・Cr) in all cases but 1 and had resolved completely in 38.9% of cases. Hematuria had decreased in all cases and had resolved completely in 61.1% of cases. The estimated glomerular filtration rate also improved in all cases and the mean increased significantly from 42.4 ± 11.9 to 50.1 ± 15.9 mL/min/1.73 $m^2$. No serious complications were found during follow-up. Steroid acne that required treatment occurred in 2 cases (11.1%) but was transient and mild.

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**Conclusion:** Steroid pulse therapy in combination with mizoribine following tonsillectomy is effective in improving urinary findings and preserving renal function in the treatment of IgA nephropathy, which remained active in patients with renal impairment (estimated glomerular filtration rate ≥20 and <60 mL/min/1.73 $m^2$).
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**Key words:** immunoglobulin A nephropathy, tonsillectomy, mizoribine, renal impairment

## Introduction

Immunoglobulin A (IgA) nephropathy was first reported by Berger and Hinglais in 1968[1], and many articles investigating the cause and pathology or establishing treatment have been published[2–4]. The clinical picture varies, ranging from spontaneous remission to gradual progression to end-stage renal failure or the sudden deterioration of renal function. The establishment of specific therapies has been hampered by the varied clinical picture.

In about half of patients with IgA nephropathy who receive a kidney transplant because of end-stage renal failure, IgA nephropathy develops again in the transplanted kidney[5]; in contrast, when the kidneys of patients who had IgA nephropathy are transplanted to patients with renal failure due to other diseases, IgA is no longer deposited in the transplanted kidney[6,7]. Such cases suggest that the cause of IgA nephropathy is nonrenal. The development of focal infection in the palatine tonsils or other mucosal sites can result in immune disorders and the overproduction of abnormally glycosylated IgA1[8,9]. Either IgG or IgA antibodies that specifically recognize abnormally glycosylated IgA1 are also present in the blood of patients with IgA nephropathy, and the resulting increase in glomerular deposition of abnormally glycosylated IgA1 immune complexes is assumed to be the mechanism by which this disease develops[10]. Treatment strategies for IgA nephropathy, in light of the mechanism involved in the progression of nephritis following glomerular deposition of immune complexes, are shown in **Figure 1**. Treatment with steroids, including steroid pulse therapy, is needed to reset the immune response and to inhibit glomerular inflammation, but a high rate of remission has been achieved in patients with early IgA nephropathy treated with steroid pulse therapy following bilateral palatine tonsillectomy (tonsillectomy-pulse therapy) in Japan[11–14].

These treatments involve the use of moderately high doses of steroids, including 3 courses of pulse therapy, and adverse reactions are often a problem. Steroid use is also associated with increases in sclerotic glomeruli and interstitial fibrosis in patients with low glomerular filtration rates (GFRs). Treatment for chronic kidney disease with grade 3 or greater IgA nephropathy is, therefore, based on renin-angiotensin system (RAS) inhibitors, but outcomes have not been satisfactory.

Use of the immunosuppressant mizoribine in an animal model of IgA nephropathy has been associated with decreases in IgA staining intensity in the glomerular mesangium and lower B cell counts and IgA-bearing B cell counts in spleen cells[15]. A recent study of steroid pulse therapy in combination with mizoribine in 34 children with diffuse IgA nephropathy showed significant decreases in tissue damage, IgA deposition, macrophage infiltration, and α-smooth muscle actin (SMA)-positive cells[16]. Mizoribine has also been reported to suppress glomerular sclerosis and interstitial fibrosis[17].

We have devised a treatment protocol in which 1 course, rather than 3 courses, of steroid pulse therapy was administered after tonsillectomy and was followed by the concomitant use of mizoribine (tonsillectomy-pulse therapy + mizoribine combination therapy)[18]. In the present study, we investigated the safety of this protocol and its effects on hematuria, proteinuria, and the progression of renal dysfunction in 18 patients with chronic kidney

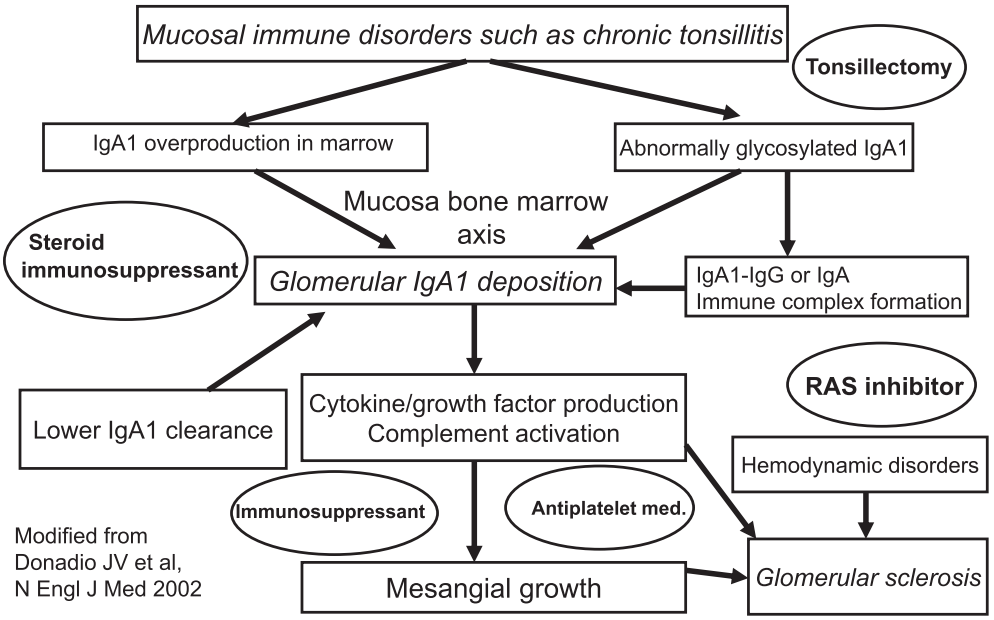


Fig. 1 Treatment strategies for IgA nephropathy

disease and active IgA nephropathy of grade 3 or greater who were followed up for at least 1 year after the start of treatment.

## Patients and Methods

### Patients

We retrospectively analyzed 18 patients who had been examined by our department since 2005, met all of the following conditions, and were followed up for at least 1 year after the start of this treatment: (1) IgA nephropathy confirmed with renal biopsy, (2) persistent microscopic hematuria and proteinuria, (3) estimated GFR (eGFR) ≥20 and <60 mL/min/1.73 m$^2$, (4) age <70 years, and (5) personal or familial informed consent.

Patients who were 70 years or older, were steroid-contraindicated, or had renal pathology associated with systemic lupus erythematosis or other systemic diseases were excluded.

### Treatment

After informed consent had been obtained from the patient or the patient's family, bilateral palatine tonsillectomy was performed by the Department of Otorhinolaryngology. One week later, methylprednisolone pulse therapy (500 mg) was performed for 3 days. Patients were also given an antiplatelet medication, an antiulcer medication, sulfamethoxazole-trimethoprim, and a bisphosphonate. After methylprednisolone pulse therapy, patients were given oral prednisolone, 30 mg/day once daily. After 4 weeks, the dosage was changed to 30 mg every 2 days, and treatment was started with mizoribine, 150 mg/day once daily. The prednisolone dose was then decreased by 5 mg every 4 weeks and was discontinued at 7 months. The sulfamethoxazole-trimethoprim and antiulcer medication were discontinued when the prednisolone dosage reached 20 mg every 2 days. The mizoribine and antiplatelet medication were continued for 1 year. An RAS inhibitor was used in all cases from before the start of this treatment.

### Efficacy Assessment

Proteinuria was assessed with quantitative urinalysis of casually obtained urine samples, corrected for urinary creatinine. Remission was defined as a decrease in urinary protein concentration to <0.2 g/g・Cr. Remission of hematuria was defined as a decrease in the red blood cell count to <5 per high-power field on urine microscopy. Hematuria severity was scored with urinary dipstick tests. Renal function was assessed on the basis of calculations obtained with the following equation by the Japanese Society of

Table 1 Baseline characteristics of subjects

| | |
|---|---|
| Sex | 8 men and 10 women |
| Mean age (years) | 48.4 ± 13.9 |
| Mean duration of illness (years) | 8.39 ± 7.50 |
| Hematuria score | 2.44 ± 0.62 |
| Proteinuria (g/g Cr) | 1.80 ± 1.36 |
| Serum creatinine (mg/dL) | 1.38 ± 0.48 |
| eGFR (mL/min/1.73 $m^2$) | 42.4 ± 11.9 |
| Serum IgA (mg/dL) | 403.9 ± 147.2 |
| Histological grade (patients) | IA: 1, IC: 3, IIC: 4, IIIA/C: 3, IIIC: 3, IVA/C: 1, IVC: 1, unknown: 2 |
| Clinical severity (patients) | I: 2, III: 16 |
| Risk of dialysis (patients) | Moderate: 1; high: 8; very high: 7; unknown: 2 |

Nephrology for the eGFR in Japanese patients: eGFR = 194 × (serum creatinine)$^{-1.094}$ × (age)$^{-0.287}$ × (0.739 if female). We also checked for adverse events through regular blood pressure measurements, general hematology, blood biochemistry, urinalysis, and infection marker tests during follow-up.

### Statistics

Statistical analysis was performed with tests of normality and comparison based on the Wilcoxon rank-sum test. The homogeneity of demographic variables was analyzed with the chi-square test, and numerical variables were analyzed with repeated measures analysis of variance for reference. The significance level was set at $P<0.05$ (two-sided). The statistical software package SPSS for Microsoft Windows version 11.0 (IBM Corp., Armonk, NY, USA) was used for the analyses. Data are expressed as means ± standard deviation (SD).

## Results

**Table 1** shows the baseline characteristics of patients at the start of treatment. The mean patient age was 48.4 ± 13.9 years, which is higher than the age at which IgA nephropathy commonly develops, and the average interval from disease onset to the start of treatment was a relatively long 8.4 ± 7.5 years. The interval varied greatly among patients. All patients had been treated with an RAS inhibitor more than 4 weeks before tonsillectomy and had never previously been treated with steroids or immunosuppressants. Analysis of patients at risk of requiring dialysis, as grouped by histological grade and clinical grade (**Table 2**)[19], showed 1 patient in the moderate-risk category, 8 patients in the high-risk category, 7 patients in the very high risk category, and 2 patients with unknown risk (histological grade could not be determined because fewer than 10 glomeruli were available on renal biopsy).

**Figure 2** shows the changes over time in proteinuria from before treatment to 1 year after the start of treatment. Urinary protein decreased in all cases except 1, from a mean of 1.80 ± 1.36 to 0.47 ± 0.75 g/g・Cr. Remission of proteinuria was achieved in 38.9% of cases. Hematuria decreased in all cases and resolved completely in 61.1% of cases (**Fig. 3**). The complete remission rate, as assessed with urinalysis showing resolution of hematuria and proteinuria, was 22.2%. The eGFR also improved in all cases, and the mean eGFR increased significantly from 42.4 ± 11.9 to 50.1 ± 15.9 mL/min/1.73 $m^2$ (**Fig. 4**). The IgA levels in blood decreased compared with baseline in all cases (mean of 403.9 ± 147.2 to 275.4 ± 107.7 mg/dL) (data not shown).

No serious complications occurred. Steroid acne required treatment in 2 cases (11.1%) but was transient and mild. There were no tonsillectomy-related complications except for postoperative pain. There were no cases of severe immunosuppression (CD4 <400%; IgG <600 mg/dL) or other severe adverse reactions, such as infection, diabetes, aggravated hypertension, psychiatric symptoms,

Table 2 Dialysis Risk Classification (Clinical Guideline for IgA Nephropathy: Ver. 3)

a: Histological grade classification

| Histological grade | Percentage of glomeruli with lesions* related to renal prognosis | Acute lesions only | Acute lesions and chronic lesions | Chronic lesions only |
|---|---|---|---|---|
| H-Grade Ⅰ | 0% to 24.9% | A | A/C | C |
| H-Grade Ⅱ | 25% to 49.9% | A | A/C | C |
| H-Grade Ⅲ | 50% to 74.9% | A | A/C | C |
| H-Grade Ⅳ | ≥75% | A | A/C | C |

Acute lesions (A): cellular crescent (including tuft necrosis), fibrocellular cresent
Chronic lesions (C): global sclerosis, segmental sclerosis, fibrous cresent

b: Clinical severity classification

| Clinical severity | Urine protein (g/day) | eGFR (mL/min/1.73 m$^2$) |
|---|---|---|
| C-GradeⅠ | <0.5 | - |
| C-Grade Ⅱ | ≥0.5 | ≥60 |
| C-Grade Ⅲ | ≥0.5 | <60 |

c: Dialysis risk groups for patients with IgA nephropathy

| | H-Grade Ⅰ | H-Grade Ⅱ | H-Grade Ⅲ |
|---|---|---|---|
| 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 |

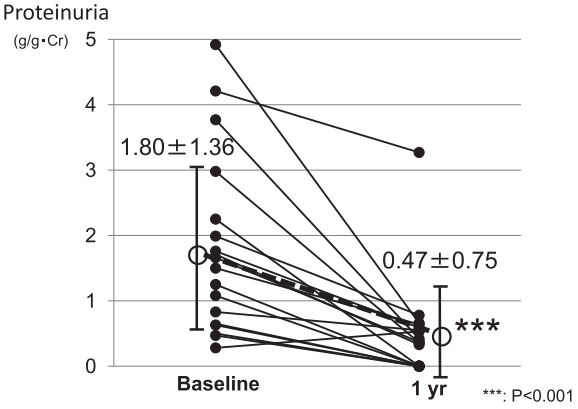


Fig. 2 Time course of changes in proteinuria
The mean level of proteinuria had significantly decreased by 1 year after the start of treatment. Data are expressed as the means ± S.D.

hyperuricemia, or other abnormal laboratory results or bone complications (data not shown).

## Discussion

Patients with active IgA nephropathy who had renal impairment (eGFR ≥20 and <60 mL/min/1.73 m$^2$) underwent tonsillectomy-steroid pulse therapy in combination with mizoribine. This treatment resulted in decreases in proteinuria in all cases but 1 and to improvement in the GFR in all cases. Hematuria, which is a marker of active disease, also decreased in all cases. The efficacy of tonsillectomy-steroid pulse therapy in patients with IgA nephropathy is reportedly affected by the GFR and the interval from disease onset to the start of treatment. At many facilities, tonsillectomy-steroid pulse therapy is indicated for blood creatinine levels less than 1.5 mg/dL, but the subjects in the present study included 5 patients with creatinine levels ≥1.5 mg/dL and 2 patients with creatinine levels ≥2.0 mg/dL. In addition, the interval from disease onset to the start of treatment was more than 10 years in 28.6% of cases, and 43.8% of patients were at a very high risk of requiring dialysis. The total steroid dose was far lower and the duration of treatment was far shorter than in conventional tonsillectomy-steroid pulse therapy, but these decreases appear to be due to the addition of mizoribine to the treatment regimen.

Like that of mycophenolate mofetil, the immunosuppressant effect of mizoribine occurs through the specific inhibition of inosine

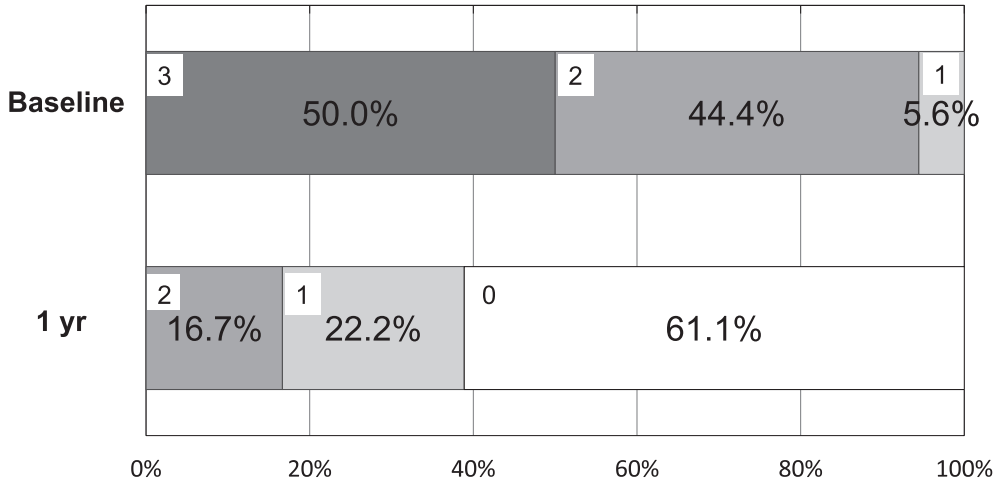


Fig. 3 Rate of negative tests for hematuria
The severity of hematuria was scored with urinary dipstick tests. The numbers 0, 1, 2, and 3 indicate (−) or (±), (1+), (2+), and (3+).
Hematuria had improved in all cases by 1 year after the start of treatment.

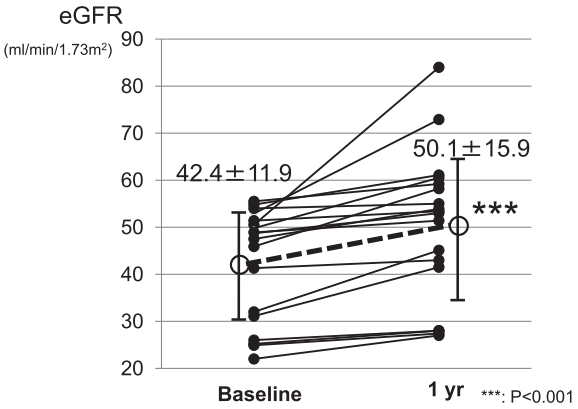


Fig. 4 Time course of changes in eGFR
The eGFR improved in all cases, and the mean eGFR had increased significantly by 1 year after the start of treatment.
Data are expressed as the means±S.D.

monophosphate dehydrogenase, a key rate-limiting enzyme in the pathway of de novo guanosine monophosphate synthesis, and through the selective inhibition of lymphocyte proliferation. Mizoribine is now known to act on inosine monophosphate dehydrogenase by a different enzymatic mechanism than that for mycophenolate mofetil. In addition to selectively inhibiting lymphocyte proliferation, mizoribine was recently shown to have many unique pharmacological properties. The 14-3-3 protein and heat shock protein (HSP) 60 are expressed in the glomerular cells of patients with IgA nephropathy, but mizoribine binds to the 14-3-3 protein and HSP60 to enhance the transcriptional activity of the glucocorticoid receptor and to potentiate steroid efficacy[20,21]. Studies comparing steroid monotherapy and steroid + mizoribine combination therapy in patients with IgA nephropathy have found that steroid monotherapy is associated with decreases in proteinuria but also with increases in sclerotic glomeruli, whereas mizoribine combination therapy have been found to reduce proteinuria and prevent increases in sclerotic glomeruli[22]. It thus appears that through the use of mizoribine in our study, the immediate effect of steroids on glomerular cells in patients with IgA nephropathy was maintained, despite lower steroid doses.

We then looked at improvements in patients with renal dysfunction. Mizoribine suppresses renal interstitial macrophage infiltration and inhibits α-SMA expression in myofibroblasts[23]. Furthermore, through the reaction with HSP60 noted above, mizoribine inhibits the action of α3β1 integrin and decreases the motility of fibroblast-specific protein 1-positive fibroblasts, which are involved in the progression of interstitial fibrosis in IgA nephropathy[24]. Activated macrophages have recently been found to play an important role in IgA nephropathy[25,26]. In cases of IgA nephropathy with an abundance of activated macrophages on renal biopsy, extensive tissue infiltration with α-SMA-positive cells is involved in the exacerbation of

nephritis and sclerosis. In the chronic stage, when renal function is already compromised, macrophages have spread to the interstitium, which shows advanced fibrosis, and are decreased in sclerotic glomeruli. Mizoribine dose-dependently suppresses nitric oxide synthase, interleukin-1β, and tumor necrosis factor-α, which are produced by activated macrophages. Steroid-induced increases in transforming growth factor β production by macrophages are suppressed by the concomitant use of mizoribine. Mizoribine not only potentiates steroidal anti-inflammatory action but may also prevent the progression of chronic lesions, such as tissue fibrosis and sclerosis, through its inhibition of activated macrophages.

These effects of mizoribine may be responsible for the improvement in renal function which was observed even in patients with moderate renal dysfunction, a condition that does not respond to conventional tonsillectomy-steroid pulse therapy. Inhibitors of RAS, which have a similar effect on the preservation of renal function, were used in all cases but had already been used before the start of this therapy, which supports the claim postulated above. Another possible factor in the improved renal function is that the reduced steroid dosage permitted the treatment of acute lesions while helping to control increases in sclerotic glomeruli and in interstitial fibrosis to a certain extent. To clarify this point, a study should compare tonsillectomy-steroid pulse therapy and tonsillectomy-steroid pulse therapy in combination with mizoribine.

Mizoribine is often administered at a dosage of 50 mg 3 times daily, but we administered mizoribine at a dosage of 150 mg once daily. This latter dosage was used because a mizoribine concentration of 1 μg/mL effectively inhibits lymphocyte proliferation[27,28] and because a peak blood concentration of 1 μg/mL can be achieved in humans. Mizoribine is renally eliminated, with 81% eliminated unchanged in the urine; therefore, the dose should be adjusted when renal function is compromised. In patients with an eGFR <30 mL/min/1.73 $m^2$, a peak mizoribine concentration greater than 3 μg/mL may result in problems, such as hyperuricemia and bone marrow depression. We therefore monitored blood concentrations and adjusted the mizoribine dose to avoid peak concentrations greater than 3 μg/mL. These precautions allowed mizoribine to be safely used.

Two adverse events, both of which were mild, occurred during follow-up. This method of treatment thus appears to be safer because of the characteristics of mizoribine, such as its selective inhibition of lymphocyte proliferation, the absence of hepatic metabolism, and the lack of uptake into high molecular weight nucleic acids, thereby resulting in a lower incidence of adverse reactions compared with other immunosuppressants. With the combined use of mizoribine, patients could be adequately treated with just a single course of methylprednisolone pulse therapy, and the total steroid dose could be markedly reduced. As a result, the adverse events associated with long-term steroid treatment can be avoided. We will continue to investigate long-term outcomes in the future.

## Conclusions

Tonsillectomy-steroid pulse therapy in combination with mizoribine appears to be safer than conventional tonsillectomy-steroid pulse therapy for the treatment of IgA nephropathy and can be recommended for patients who wish to reduce the total steroid dose and patients with predominantly chronic lesions who already have renal impairment.

**Conflict of Interest:** The authors have no financial conflicts of interest to declare with regard to the publication of this article.

## References

1. Berger J, Hinglais N: Les dépôts intercapillaires d'IgA-IgG. J Urol Nephrol (Paris) 1968; 74: 694–695.
2. Julian BA, Waldo FB, Rifai A, Mestecky J: IgA nephropathy, the most common glomerulonephritis worldwide. A neglected disease in the United States? Am J Med 1988; 84: 129–132.
3. Barratt J, Feehally J, Smith AC: Pathogenesis of IgA nephropathy. Semin Nephrol 2004; 24: 197–217.
4. Pozzi C, Andrulli S, Del Vecchio L, et al.: Corticosteroid effectiveness in IgA nephropathy:

long-term results of a randomized, controlled trial. J Am Soc Nephrol 2004; 15: 157–163.
5. Floege J, Burg M, Kliem V: Recurrent IgA nephropathy after kidney transplantation: not a benign condition. Nephrol Dial Transplant 1998; 13: 1933–1935.
6. Cuevas X, Lloveras J, Mir M, et al.: Disappearance of mesangial IgA deposits from the kidneys of two donors after transplantation. Transplant Proc 1987; 19: 2208–2209.
7. Sanfilippo F, Croker BP, Bollinger RR: Fate of four cadaveric donor renal allografts with mesangial IgA deposits. Transplantation 1982; 33: 370–376.
8. Hiki Y, Odani H, Takahashi M, et al.: Mass spectrometry proves under-O-glycosylation of glomerular IgA1 in IgA nephropathy. Kidney Int 2001; 59: 1077–1085.
9. Horie A, Hiki Y, Odani H, et al.: IgA1 molecules produced by tonsillar lymphocytes are under-O-glycosylated in IgA nephropathy. Am J Kidney Dis 2003; 42: 486–496.
10. Suzuki H, Fan R, Zhang Z, et al.: Aberrantly glycosylated IgA1 in IgA nephropathy patients is recognized by IgG antibodies with restricted heterogeneity. J Clin Invest 2009; 119: 1668–1677.
11. Hotta O, Miyazaki M, Furuta T, et al.: Tonsillectomy and steroid pulse therapy significantly impact on clinical remission in patients with IgA nephropathy. Am J Kidney Dis 2001; 38: 736–743.
12. Xie Y, Nishi S, Ueno M, et al.: The efficacy of tonsillectomy on long-term renal survival in patients with IgA nephropathy. Kidney Int 2003; 63: 1861–1867.
13. Komatsu H, Fujimoto S, Hara S, Sato Y, Yamada K, Kitamura K: Effect of tonsillectomy plus steroid pulse therapy on clinical remission of IgA nephropathy: a controlled study. Clin J Am Soc Nephrol 2008; 3: 1301–1307.
14. Miyazaki M, Hotta O, Komatsuda A, et al.: Japanese Multicenter Study Group on Treatment of IgA Nephropathy (JST-IgAN): A multicenter prospective cohort study of tonsillectomy and steroid therapy in Japanese patients with IgA nephropathy: a 5-year report. Contrib Nephrol 2007; 157: 94–98.
15. Shimizu M, Shou I, Tsuge T, Abe M, Tomino Y: Effect of mizoribine on glomerulonephritis of early-stage IgA nephropathy in ddY mice. Nephron 1998; 79: 67–72.
16. Kawasaki Y, Suzuki J, Sakai N, et al.: Efficacy of prednisolone and mizoribine therapy for diffuse IgA nephropathy. Am J Nephrol 2004; 24: 147–153.
17. Sato N, Shiraiwa K, Kai K, et al.: Mizoribine ameliorates the tubulointerstitial fibrosis of obstructive nephropathy. Nephron 2001; 89: 177–185.
18. Kaneko T, Hirama A, Ueda K, et al.: Methylprednisolone pulse therapy combined with mizoribine following tonsillectomy for immunoglobulin A nephropathy: clinical remission rate, steroid sparing effect, and maintenance of renal function. Clin Exp Nephrol 2011; 15: 73–78.
19. Matsuo S, Kawamura T, Joh K, et al.: Clinical guides for immunoglobulin A (IgA) nephropathy in Japan, third version. Jpn J Nephrol 2011; 53: 123–135.
20. Takahashi S, Wakui H, Gustafsson JA, Zilliacus J, Itoh H: Functional interaction of the immunosuppressant mizoribine with the 14-3-3 protein. Biochem Biophys Res Commun 2000; 274: 87–92.
21. Itoh H, Komatsuda A, Wakui H, Miura AB, Tashima Y: Mammalian HSP60 is a major target for an immunosuppressant mizoribine. J Biol Chem 1999; 274: 35147–35151.
22. Kawasaki Y, Hosoya M, Suzuki J, et al.: Efficacy of multidrug therapy combined with mizoribine in children with diffuse IgA nephropathy in comparison with multidrug therapy without mizoribine and with methylprednisolone pulse therapy. Am J Nephrol 2004; 24: 576–581.
23. Sakai T, Kawamura T, Shirasawa T: Mizoribine improves renal tubulointerstitial fibrosis in unilateral ureteral obstruction (UUO)-treated rat by inhibiting the infiltration of macrophages and the expression of α-smooth muscle actin. J Urol 1997; 158: 2316–2322.
24. Nishitani Y, Iwano M, Yamaguchi Y, et al.: Fibroblast-specific protein 1 is a specific prognostic marker for renal survival in patients with IgAN. Kidney Int 2005; 68: 1078–1085.
25. Ikezumi Y, Suzuki T, Karasawa T, et al.: Use of mizoribine as a rescue drug for steroid-resistant pediatric IgA nephropathy. Pediatr Nephrol 2008; 23: 645–650.
26. Ikezumi Y, Suzuki T, Karasawa T, et al.: Contrasting Effects of Steroids and Mizoribine on Macrophage Activation and Glomerular Lesions in Rat Thy-1 Messangial Proliferative Glomerulonephritis. Am J Nephrol 2010; 31: 273–282.
27. Sonda K, Takahashi K, Tanabe K, et al.: Clinical pharmacokinetic study of mizoribine in renal transplantation patients. Transplant Proc 1996; 28: 3643–3648.
28. Stypinski D, Obaidi M, Combs M, Weber M, Stewart AJ, Ishikawa H: Safety, tolerability and pharmacokinetics of higher-dose mizoribine in healthy male volunteers. Br J Clin Pharmacol 2006; 63: 459–468.

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