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Feature Article

Mizoribine treatment for childhood IgA nephropathy

RIEKO NAGAOKA, KAZUNARI KANEKO, YOSHIYUKI OHTOMO AND YUICHIRO YAMASHIRO

Department of Pediatrics, Juntendo University School of Medicine, Tokyo, Japan

Abstract

Background: There is currently no established therapy for childhood IgA nephropathy (IgAN). Mizoribine, a newly developed immunosuppressive agent characterized as a safe and well-tolerated drug, has been widely used in diverse conditions. Our preliminary study demonstrated that mizoribine could reduce the amount of proteinuria in children with IgAN. The present study was conducted to confirm this finding.

Methods: Ten children with IgAN (median age 13.5 years) of moderate histological severity were enrolled. None of them had been previously treated by immunosuppressants. Mizoribine was administered orally for a median period of 20.5 months. We compared the urinary protein excretion expressed as the ratio of urinary protein to urinary creatinine (UP/UC) and the hematuria evaluated as the level of occult blood by dip-stick (OB score). Renal histology was also examined in three patients using paired biopsy specimens obtained both before and after treatment. We performed blood examinations regularly to monitor the toxicity and plasma concentration of mizoribine.

Results: The median observation period was 44.5 months, consisting of a median 13.0 months before therapy, 20.5 months during therapy and 12.0 months after therapy. Significant reductions in both UP/UC and OB score were induced by mizoribine ($P < 0.05$). Renal mesangial proliferation was also improved. Plasma peak levels of mizoribine varied from 0.30 μg/mL to 1.23 μg/mL and were not associated with its effectiveness. No adverse effects were observed during the therapy, although a slight decrease in leukocyte count was noted.

Conclusion: Mizoribine can be an alternative drug for childhood IgAN with moderate severity because it results in a significant reduction of proteinuria and hematuria with histological improvement and causes far fewer complications compared to the conventional immunosuppressants.

Key words child, glomerulonephritis, IgA nephropathy, immunosuppressant, mizoribine.

IgA nephropathy (IgAN) is currently the most common form of glomerulonephritis in many parts of the world, including Japan.[1–2] The prognosis of IgAN is not as benign as initially thought, and approximately 10–30% of children with IgAN will eventually suffer from end-stage renal disease (ESRD).[3–5]

Although the precise pathogenesis remains unknown, it has been postulated that the glomerular damage of IgAN might be related to deposits of IgA-containing immune complexes,[6,7] resulting from an uncontrolled mucosal immune response to chronic exposure to environmental antigens or from an anomaly of the medullary IgA system, which is thought to be a second line of defense against foreign antigens.[8] Based on these findings, immunosuppressive therapy such as prednisolone and/or azathioprine has been tried in children with progressive IgAN, although there is currently no fully evidence-based treatment.[2] Given the diverse clinical manifestations and variable laboratory and histological features of children with IgAN, it is unlikely that one therapy suits all patients.

Mizoribine (MZB) (p-INN: 4-carbamoyl-1-β-D-ribofuranosyl imidazolium-5-olate), formerly known as bredinin, is an antibiotic agent produced by the soil fungus *Eupenicilium brefeldianum*.[9] As MZB has been shown to prevent the proliferation of lymphocytes *in vitro*, it has been used for immunosuppression after organ transplantation.[10,11] It is noteworthy that MZB causes far fewer complications in patients with renal transplants than does azathioprine and does not appear to be significantly myelosuppressive, hepatotoxic, or nephrotoxic.[10] Because of this lowered toxicity and potential for good tolerance, this drug has been recently applied for the treatment of children with steroid-dependent nephrotic syndrome[12] and frequently relapsing nephrotic syndrome.[13]

Correspondence: Kazunari Kaneko MD, Department of Pediatrics, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. Email: kkaneko@med.juntendo.ac.jp

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Table 1 Summary of the observation period

Patient No.	Age (years)	Sex	Before mizoribine† (months)	During mizoribine‡ (months)	After mizoribine§ (months)	Total observation period
1	6	M	1	12	26	39
2	9.2	M	26	24	12	62
3	10.3	M	14	22	9	45
4	11.2	F	1	24	19	44
5	13.1	F	21	12	12	45
6	13.9	F	7	25	4	36
7	15	M	15	12	30	57
8	15.5	F	7	29	3	39
9	16.1	F	26	19	0	45
10	16.5	F	12	19	12	43
Median	13.5		13.0	20.5	12.0	44.5
Minimum	6.0		1.0	12.0	0.0	36.0
Maximum	16.5		26.0	29.0	30.0	62.0

†Before mizoribine, duration before mizoribine, treatment.‡During mizoribine, duration of mizoribine treatment. §After mizoribine, duration after cessation of mizoribine treatment.

We first studied the efficacy of MZB for IgAN of moderate severity, and the result showed that MZB reduced the amount of proteinuria.[14] We then conducted the current study to assess the efficacy of MZB in childhood IgAN for a longer period of observation.

Methods

Patients

Ten children (four males, six females, median age 13.5 years, range 6.0–16.5 years) who had been diagnosed with moderate IgAN between 1997 and 1999 at our department were enrolled in this study. Nine children were found to have hematuria and/or proteinuria by an annual screening program for renal disease in school children. One child was discovered to have persistent proteinuria with hematuria by urinalysis after group A streptococcal pharyngitis.

All children were enrolled into this study within 3 years of the onset of hematuria and/or proteinuria. Inclusion criteria were as follows: children without clinical symptoms due to disturbed renal function, such as oliguria or edema, without hypertension (< 130/80 mmHg), with normal creatinine clearance (CCr. > 80 mL/min per 1.73m^2), and with renal histology showing moderate severity (diffuse mesangial proliferation, i.e. > 80% out of all glomeruli with significant IgA deposition, but no significant cresentic or sclerotic lesions, i.e. < 10% out of all glomeruli). Informed consent was obtained from the parents before entry to this study.

Methods

Treatment protocol by MZB

The observation period was divided into three clinical stages: (i) the baseline period (BP) prior to MZB treatment; (ii) the treatment period (TP); and (iii) the post-treatment period (PP). Table 1 shows the duration of each period, summarized as follows: BP, median 13.0 months (range 1.0–26.0 months); TP, median 20.5 months (range 12.0–29.0 months) and PP, median 12.0 months (range 0.0–30.0 months).

The TP and PP were each subdivided into two groups, the early period of MZB treatment (0–6 months after the institution of MZB: TP1), the late period of MZB treatment (6–12 months after the institution of MZB: TP2), the early period of post-treatment (0–12 months since stopping MZB: PP1), and the late period of post-treatment (more than 12 months since stopping MZB: PP2).

Although an antiplatelet agent (dipyridamole, 3–5 mg/kg per day) was administered orally to all children during BP, none were on angiotensin-converting enzyme inhibitors or non-steroidal anti-inflammatory drugs and none had past histories of steroids or immunosuppressive treatment. The subjects were treated orally with 3 mg/kg bodyweight per day (t.i.d., max. 200 mg/day) of MZB (Bredinin, Asahi Chemical Industry, Tokyo, Japan) with dipyridamole at the same dose as previously described during TP. The TP was initially set at either 12 months or 24 months, depending on its efficacy: if the proteinuria disappeared (urinary protein concentration of the morning urine < 20 mg/dL) within the first 12 months, it was discontinued; if the proteinuria persisted after 12 months of TP, it was continued for an additional 12 months.

Effect of MZB on proteinuria and hematuria

Urinalysis using morning urine was performed monthly in order to evaluate the changes in proteinuria and/or hematuria. We used the ratio of urinary protein to creatinine (UP/UC, mg/mg[15]) to assess the amount of proteinuria and evaluated

Table 2 Summary of the results: changes in proteinuria and hematuria

	Before mizoribine	During mizoribine (0–6 months)	During mizoribine (6–12 months)	After mizoribine (0–12 months)	After mizoribine (12 months–)
Proteinuria					
UP/UC (M ± SD)	0.71 ± 1.10	0.23 ± 0.25	0.12 ± 0.20	0.06 ± 0.12	0.14 ± 0.18
P value* (*vs* before mizoribine)	$P < 0.05$	$P < 0.01$	$P < 0.01$	$P < 0.01$	
Hematuria					
OB score†(M ± SD)	2.90 ± 0.23	1.85 ± 0.97	1.30 ± 1.25	1.00 ± 1.41	0.80 ± 1.23
P-value* (*vs* before mizoribine)	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	

**P*-value by Bonferroni test. OB, occult blood; UP/UC, Urinary protein per creatinine ratio (mg/mg).†Reported as urinary dipstick (0 for negative to 3 for 3+).

hematuria semiquantitatively as the degree of occult blood (OB), scoring 0–3 corresponding to negative to 3+ by dipstick test.

We compared the mean UP/UC and the mean OB score of TP and PP with those of BP.

Renal histology before and after MZB treatment

Paired renal biopsy specimens, that is, materials obtained at both BP and TP, were available from three patients. These materials were evaluated using light microscopy and immunofluorescent microscopy by an independent pathologist.

Adverse effects of MZB

To monitor the toxicity of MZB, we took blood measurements such as blood cell count, levels of asparate transaminase, alanine transaminase, serum creatinine, blood urea nitrogen, and uric acid monthly during the first 3 months of TP and then every 3 months.

If abnormal values presumed to be caused by MZB, such as leukocytopenia (leukocyte count $< 3.0 \times 10^9$/L), anemia (hemoglobin level < 10.0 g/dL), thrombocytopenia (platelet count $< 100 \times 10^9$/L), elevated levels of asparate transaminase (AST > 40 U/L), alanine transaminase (ALT > 40 U/L), serum creatinine (> 1.2 mg/dL), or uric acid (> 6.5 mg/dL) were detected, it was planned to discontinue MZB. Physical examinations including the measurement of blood pressure were also performed at the same time.

Peak blood levels of MZB were also measured between 1 and 12 months after the institution of MZB treatment, according to the method described previously.[16] Peak levels were defined as the concentration of MZB in the blood obtained at 2–3 h after taking the drug. We statistically analyzed the dose-dependent efficacy of MZB in terms of the correlation with the peak serum concentration and the degree of decrease in the amount of urinary protein (rate of decrease: UP/UC at BP divided by UP/UC at PP).

Statistical analysis

For statistical analysis, as the data showed non-parametric distribution, we used the Mann–Whitney *U*-test for the unpaired data and the Wilcoxon rank sum test for the paired data. In addition, we used Friedman's test (two-tailed analysis) and the Bonferroni test to compare more than two different clinical stages. The Spearman rank correlation test was applied for the correlation study. A probability level of less than 0.05 was considered significant. The data are expressed in mean values ± standard deviation (M ± SD) throughout the paper.

Results

Changes in proteinuria and hematuria

Our study results are summarized in Table 2 and demonstrated in Figs 1 and 2. Briefly, both proteinuria and hematuria were significantly reduced after the institution of MZB ($P < 0.05$ and $P < 0.01$, respectively, by Friedman's test), and the efficacy continued throughout the PP: the mean UP/UC was reduced from BP (0.71 ± 1.10) to TP1 (0.23 ± 0.25, $P < 0.05$), TP2 (0.12 ± 0.20, $P < 0.01$), PP1 (0.06 ± 0.12, $P < 0.01$), and PP2 (0.14 ± 0.18, $P < 0.01$), and the mean OB score was reduced significantly from BP (2.90 ± 0.23) to TP1 (1.85 ± 0.97, $P < 0.01$), TP2 (1.30 ± 1.25, $P < 0.01$), PP1 (1.00 ± 1.41, $P < 0.01$) and PP2 (0.80 ± 1.23, $P < 0.01$).

Alteration of renal histology before and after MZB treatment

In three cases, paired renal biopsy specimens were available for histological comparison. The renal specimens obtained at TP or PP revealed the amelioration of mesangial cell proliferation compared with those obtained at BP in all three pairs, while the deposition of IgA in these areas were unchanged. Figure 3 demonstrates the improvement of the mesangial proliferation of the renal glomerulus obtained from patient no. 6 in Table 1.

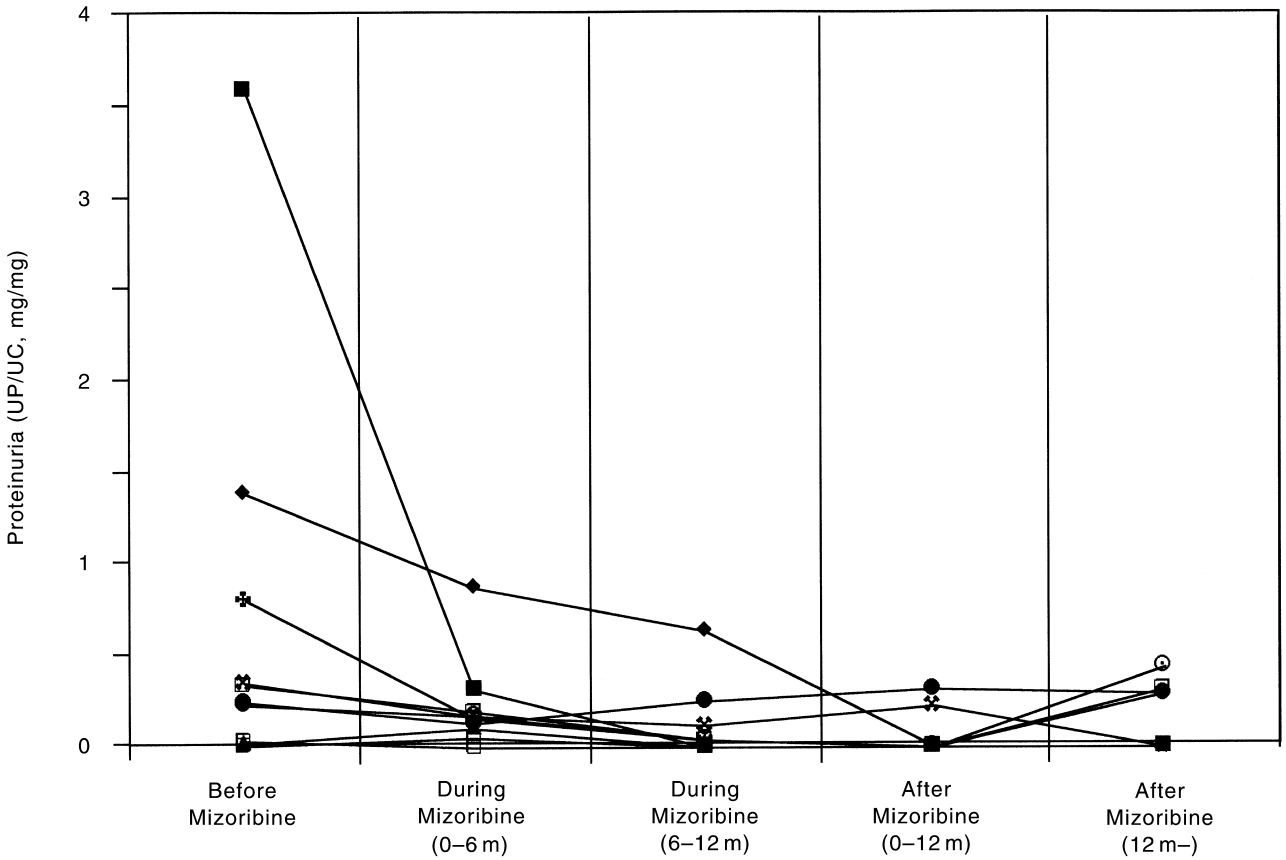

Fig. 1 Changes in proteinuria by mizoribine treatment ($n = 10$). The amount of proteinuria was assessed by urinary protein to creatinine ratio (UP/UC, mg/mg).

Serum levels of MZB during treatment

Peak blood levels of MZB were 0.62 ± 0.34 μg/mL, and no dose-dependent efficacy of MZB on the amount of proteinuria was demonstrated: there was no significant correlation with the peak MZB concentration and the degree of decrease in the amount of urinary protein excretion ($P > 0.05$).

Adverse effects of MZB

None of our patients had indications of MZB toxicity, such as leukocytopenia, gastrointestinal symptoms, alopecia, hepatotoxicity, or nephrotoxicity, as assessed by regular examinations. However, the white blood cell count was significantly reduced from $6.63 \pm 1.26 \times 10^9$/L at BP to $5.60 \pm 1.26 \times 10^9$/L at TP, although no patient demonstrated leukocytopenia, that is, $< 3.0 \times 10^9$/L. These results are summarized in Table 3. Hypertension (> 130/80 mmHg) was not noted in any of the patients during the observation period.

Discussion

Although most early studies concluded that childhood IgAN was a benign disorder,[1,2] some recent pediatric series have included a higher percentage of patients with progression to ESRD.[3–5] Data from three pediatric studies of kidney survival showed the survival at 20 years to be only 70% in the USA study as compared to 82 and 89% in two studies from Japan.[3–5]

It is therefore evident that IgAN in childhood is not always benign. Therapies for IgAN are urgently needed, as there is currently no established therapy. Most studies of immunosuppressive therapy in the past decade have demonstrated a beneficial response.[1,2] Some have reported the efficacy of multiple combined therapy including prednisolone and azathioprine to treat children with severe IgAN.[17] However, because therapies involving prednisolone and conventional immunosuppressive agents have potent serious complications for children, an application of this strategy to all children with IgAN seems not to be justified.

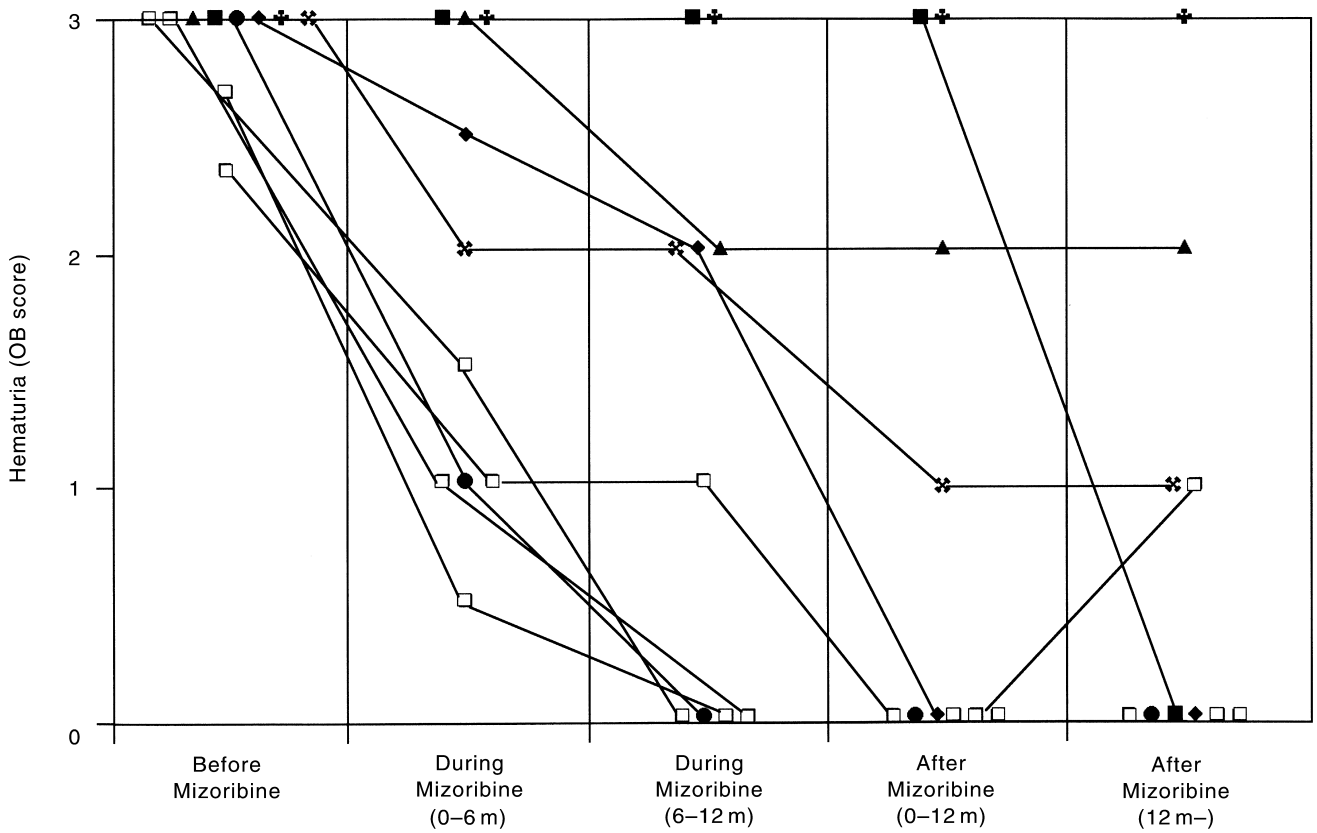

Fig. 2 Changes in proteinuria by mizoribine treatment (n = 10). The amount of hematuria was evaluated semiquantitatively as the degree of occult blood scoring 0–3 corresponding to negative to 3+ by dip-stick test (OB score).

Mizoribine is the first imidazole nucleoside with demonstrated biologic activity. It was initially found to inhibit the growth of *Candida albicans*, vaccinia virus and mouse L5178Y malignant lymphoma cells *in vitro* and to suppress hemolysin production effectively after the injection of sheep red blood cells in mice.[10] In the early 1980s, Japanese studies demonstrating the inhibitory effects of MZB on T- and B-lymphocyte activity *in vitro* and examining the pharmacokinetics and immunosuppressive effects of MZB *in vivo* began to be reported.[10,11] In view of its inhibition of purine synthesis and its relative lack of toxicity, MZB has been used increasingly in Japan during the last decade instead of azathioprine as part of immunosuppressive drug regimens: it was first approved by the Ministry of Health and Welfare of Japan as a drug indicated for the prevention of rejection in renal transplantation in 1984, and since then the indication has been extended to 'lupus nephritis' in 1990, 'rheumatoid arthritis' in 1992, and 'primary nephritic syndrome' in 1995.[11] In addition, Shimizu *et al*. reported that MZB could ameliorate the mesangial cell proliferation with the reduction of proteinuria in animal models of IgAN, that is, ddY mice.[18]

Based on these findings, we and others have recently reported preliminary results confirming the short-term efficacy of this drug for the treatment of patients with IgAN in children and adults, respectively.[14,19] Continuing our research of this drug, we further studied the long-term efficacy of MZB for childhood IgAN of moderate severity. Our results showed that the median duration of 20.5 months of MZB administration significantly improved both proteinuria and hematuria without evident adverse reactions.

Histological improvements, such as amelioration of mesangial proliferation, were also noted in paired renal biopsy specimens obtained from three patients. Furthermore, improved findings in urinalyses have continued at least 12.0 months (median duration, range 0–30 months) after cessation of this drug.

In terms of *in vivo* metabolism of MZB, it has been reported that peak drug concentrations occurred 2–3 h after oral administration, most of the drug was gone by 12 h, and levels were not measurable at 24 h.[20] Oral administration to healthy subjects yielded mean $t_{1/2}$ values of 2.2 h.[21]

We measured the peak blood levels of MZB in order to investigate the dose-dependency in its clinical efficacy.

However, we found no significant correlation with the peak mizoribine concentration and the amount of decrease in UP/UC ($P > 0.05$), while peak blood levels were 0.62 ± 0.34 μg/mL. These findings agreed well with the results of Hamasaki *et al.*, who measured the peak levels of MZB in steroid-dependent nephrotic children.[12] They demonstrated that there was no significant difference in the peak levels between the children with response to MZB and those without response (mean peak values of MZB: 0.44–0.55 μg/mL in responding children and 0.22–0.51 μg/mL in non-responding children, respectively).

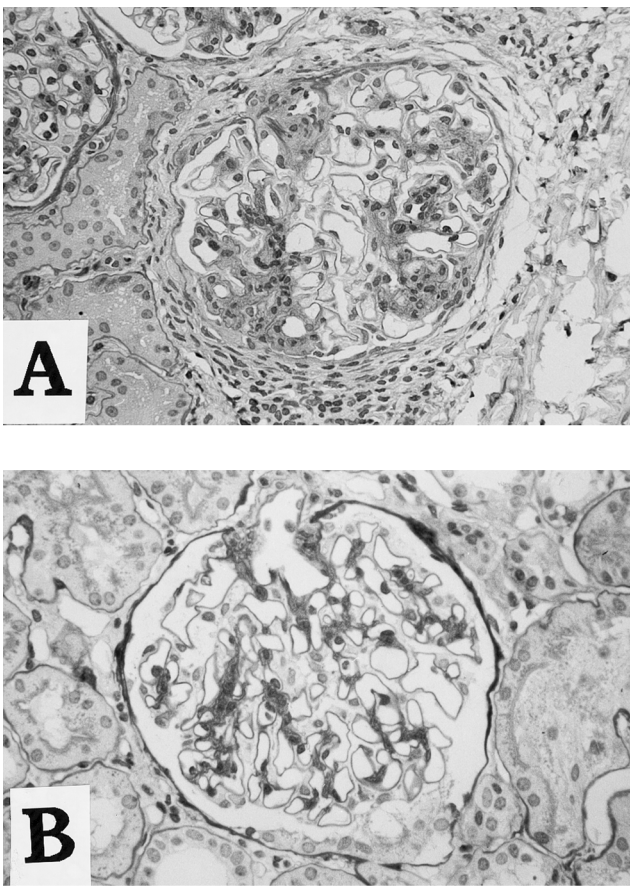

Fig. 3 Change in renal histology by mizoribine (MZB) treatment. Renal biopsy specimen obtained from the patient no. 6 in Table 1 (light microscopy, Periodic acid Schiff stain, × 400). (a), Glomerulus before MZB treatment showing mesangial cell proliferation; (b) glomerulus after 14 months of MZB treatment showing amelioration of mesangial cell proliferation.

Mizoribine has been characterized as a safe and well-tolerated drug because even minor gastrointestinal symptoms, such as anorexia and gastroenteritis, are not clinically significant problems at immunosuppressive doses unless renal function is impaired. In fact, none of our patients developed leukocytopenia, gastrointestinal synptoms, alopecia, hepatotoxicity, or nephrotoxicity, as assessed by regular examinations.

Although the mechanism(s) of action of MZB on IgAN is currently uncertain, it appears to be mediated via inhibition of interleukin-6 (IL-6) from lymphocytes. It has been postulated that numerous cytokines are up-regulated in IgAN, including IL-2, IL-4, IL-6, and transforming growth factor-β.[22] Among them, special attention has been paid to IL-6, because it is produced by human mesangial and tubular cells and is thought to play an important role in mesangial cell proliferation and tubulointerstitial damage.[23–25]

We recently demonstrated that MZB significantly suppressed the IL-6 release from peripheral blood mononuclear cells *in vitro* and suggested that this action played some role in the clinical efficacy of MZB on IgAN.[26]

Mizoribine might also be associated with reduced antibody production resulting in the decreased formation of IgA immune complexes (IgA-IC) and the improvement of histological damage. Recent studies using mice demonstrated that MZB had an inhibitory effect on the antibody production of B lymphocytes stimulated with lipopolysaccharide, as well as on T cell proliferation.[27] In fact, we measured preliminarily the levels of IgA-IC using paired sera obtained both before and after MZB treatment, and the result revealed that levels of IgA-IC decreased after MZB treatment in five out of seven patients enrolled in the present study (data not shown).

In conclusion, MZB can be the choice of treatment for childhood IgAN with moderate severity because of its relatively long-term efficacy with less toxicity compared to conventional immunosuppressants.

Table 3 Changes in laboratory data during mizoribine treatment

	Before mizoribine treatment	During mizoribine treatment	*P*-value (before *vs* during)
WBC count ($\times 10^9$/L)	6.63 ± 1.26	5.60 ± 1.26	< 0.01
Hb (g/dL)	12.87 ± 1.03	13.20 ± 0.80	> 0.05
Platelet count ($\times 10^9$/L)	254.2 ± 52.2	249.1 ± 34.7	> 0.05
AST (U/L)	19.5 ± 6.2	20.8 ± 4.0	> 0.05
ALT (U/L)	11.9 ± 4.8	14.5 ± 7.5	> 0.05
Serum creatinine (mg/dL)	0.56 ± 0.13	0.58 ± 0.14	> 0.05
Serum uric acid (mg/dL)	4.69 ± 1.47	4.52 ± 1.23	> 0.05

*Interval between the 1st and the 2nd sampling: 12.90 ± 3.41 months (mean ± SD). ALT, alanine aminotransferase; AST, asparate aminotransferase; Hb, hemoglobin; WBC, white blood cell.

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