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Feature Article

Nephrotic syndrome and mizoribine in children

MASATAKA HONDA

Department of Pediatric Nephrology, Tokyo Metropolitan Kiyose Children's Hospital, Tokyo, Japan

Abstract

Background: The treatment of nephrotic syndrome (NS) has recently made dramatic progress. The ultimate purpose of treatment is that patients can lead a normal, disease-free life with no adverse effects from treatment. However, clear treatment guidelines remain to be established in the children with frequent relapsing NS (FRNS) and steroid-resistant NS (SRNS). The frequent use or large dose of steroids may lead to a serious adverse effect. Immunosuppressive drugs including cyclophasphamide and cyclosporin have been used to induce lasting remission, thereby sparing patients from further exposure to steroids. However, these drugs have both acute and chronic side-effects. Mizoribine is a relatively safe and effective immunosuppressant. The report discusses the role of mizoribine in FRNS and SRNS in children.

Methods: The papers in experimental and clinical studies about mizoribine in NS were reviewed. Our experiences of mizoribine were also added.

Results: Mizoribine has been reported as an effective and safe drug for patients with FRNS. However, the efficacy of mizoribine has differed among various reports, depending on the dose given. There have yet to be any conclusive reports on the effects of mizoribine in SRNS in children.

Conclusions: Better results might be obtained if the doses of mizoribine increased in children with FRNS. When 5 mg/kg was used, no serious adverse effects were seen, therefore this dose may be safe and effective. An investigation of appropriate, effective and safe doses of mizoribine should be examined in the future. In patients with SRNS, large doses of mizoribine of more than 5 mg/kg might be effective, while the combined use of mizoribine and cyclosporin or methylpredonisolone pulse therapy might also be even more effective. Further studies are called for to examine the use of large doses of mizoribine.

Key words immunosuppressant children, mizoribine, nephrotic syndrome.

The treatment of nephrotic syndrome (NS) has recently made dramatic progress. The ultimate purpose of treatment is that patients can lead a normal, disease-free life with no adverse effects from treatment. However, clear treatment guidelines remain to be established.

Generally, when the children with NS are observed, predonsolone is started at a dose of 2 mg/kg or 60 mg/m^2 per day within 4 weeks. This treatment excludes patients who are suspected of having some type of glomerulonephritis such as hematuria, hypocomplementemia, true renal failure and hypertesion. About 90% of the patients show remission during steroid therapy under the above regimen and we define them as minimal change NS (MCNS), without a renal biopsy, whose renal prognosis is excellent.[1,2] However, 30 to 40% patients tend to frequently relapse after a remission of NS.[2–4]

Correspondence: Masataka Honda MD, Department of Pediatric Nephlorogy, Tokyo Metropolitan Kiyose Children's Hospital, 1-3-1, Umezono Kiyoseshi, Tokyo 204-8567, Japan.
Email: masahonda@amy.hi-ho.ne.jp

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In patients with frequent relapsing NS (FRNS), the toxicity of steroids may lead to serious problems, such as growth failure, cataracts or osteoporotic bone disease. However, most patients with steroid-sensitive NS have a good long-term prognosis: their renal functions are normal and relapses of NS either disappear or occur less frequently. It is therefore important to prevent the adverse effects of steroids, which may affect a patient's life in the future.

Immunosuppressive drugs including cyclophasphamide, chrolambucil and cyclosporin have been used to induce lasting remission, thereby sparing patients from further exposure to steroids. However, these drugs have both acute and chronic side-effects, such as leucopenia, infection, hemorrhagic cystitis, alopecia, infertility, central nervous disorders, malignancy and nephrotoxity. In addition, more than one-half of all such patients tend to demonstrate FRNS after discontinuing immunosuppressants.[3,5] Because the frequent or long-term use of these drugs creates a further

Table 1 Effect of mizoribine on clinical profiles in rats with puromycin aminonucleoside-induced nephrosis

	Days	PAN rats	PAN + mizoribine rats	Control rats
Bodyweight (%)	0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0
	5	– 16.9 ± 1.6	3.9 ± 2.3*	16.1 ± 2.7
	11	– 38.6 ± 3.4	11.4 ± 3.7*	13.0 ± 10.4
Urinary volume (mL/day)	0	6.3 ± 1.3	7.3 ± 1.2	13.7 ± 0.5
	5	6.2 ± 1.7	8.0 ± 2.5	7.6 ± 2.2
	11	7.5 ± 0.5	11.2 ± 4.2	12.5 ± 2.2
Urinary protein (g/day)	0	0.01 ± 0.01	0.02 ± 0.01	0.03 ± 0.05
	5	0.42 ± 0.01	0.07 ± 0.01	0.08 ± 0.04
	11	0.74 ± 0.05	0.21 ± 0.12*	0.07 ± 0.03
Serum protein (g/dL)	0	7.2 ± 0.03	7.6 ± 0.4	7.9 ± 0.3
	11	5.1 ± 0.3**	5.8 ± 0.3**	7.4 ± 0.4
Serum creatinine (μmol/L)	0	53.9 ± 8.8	53.9 ± 4.4	61.9 ± 17.7
	11	185.6 ± 17.7**	8 8.4 ± 3 5.4*	53.9 ± 8.8

The reduction of bodyweight in puromycin aminonucleoside (PAN) + mizoribine rats was less marked in comparison with PAN rats ($P < 0.01$). Serum total protein in PAN + mizoribine and PAN rats showed lower levels in comparison with control rats ($P < 0.01$). Serum creatinine level was lower in PAN + mizoribine rats than in PAN rats; *$P < 0.01$ compared with PAN rats; **$P < 0.0$l compared with control rats.

increased risk of adverse effects, we do not use these immunosuppressants on a long-term basis. New, effective and safe drugs are therefore needed for the treatment of FRNS.

About 10–20% of the patients with NS are steroid-resistant NS (SRNS). The prognosis is poor when focal segmental glomerular sclerosis (FSGS) is evident in a patient. Focal segmental glomerular sclerosis is found in approximately 50% of SRNS patients.[3] Approximately one-half of patients with FSGS develop end-stage renal disease within 10 years. Recently, high doses of cyclosporin[5,6] or the frequent use of methyl-predonisolone pulse therapy (MPT) with immunosuppressants[7] have been reported to be effective in patients with NS and FSGS. However, these treatment methods may cause significant adverse effects as mentioned above. From this point of view, we need to develop safe and effective drugs for SRNS patients.

Mizoribine blocks the purine biosynthesis pathways and inhibits mitogen-stimulated T- and B-cell proliferation. The clinical efficacy of mizoribine was first approved for renal transplantation. Controlled trials conducted in Japan demonstrated this drug to prolong graft survival without either myelosuppression or hepatotoxicity.[5,8]

Because mizolibine is relatively safe and effective, it has been recently used for a wide range of diseases besides NS including lupus nephritis, rheumatoid arthritis and renal transplantation.

The report discusses the role of mizoribine in FRNS and SRNS in children.

Experimental animal studies

Experimental studies showed that mizoribine favorably influenced the course of lupus nephritis in New Zealand black/white F1 mice, while antiglomerular basement membrane antibody, mediated nephritis and IgA nephropathy in ddy mice.[6,9]

Puromycin aminonucleoside (PAN) induced a nephrotic state resembling MCNS in rats. Shibasaki *et al*. investigated the effect of mizoribine (10 mg/kg) on nephrosis produced in rats given PAN.[10,11] The urinary protein level in rats injected with PAN and mizoribine was shown to significantly decrease in comparison to rats given only PAN (PAN + mizoribine *vs* PAN: 0.21 g *vs* 0.74 g/day) (Table 1). Although mild hypoproteinemia persisted during the experimental period in PAN + mizoribine rats (PAN + mizoribine *vs* PAN: 5.8 *vs* 5.1 g/dL), no loss of bodyweight or malnutrition was observed. The reduction in the serum IgG and C3 levels was reversed by the administration of mizoribine. Polyethyleinenemia staining of renal sections showed a greater number of anionic sites in PAN + mizoribine rats than in PAN rats, thus suggesting that mizoribine improved the permselectivity of glomerular basement membrane. No serious adverse effects related to mizoribine were observed after large doses of the agent.

The above data suggested that mizoribine may be an effective agent for the treatment of NS, while also being suitable for long-term use without any major side-effects.

Clinical studies

Mizoribine and FRNS

Three articles written in English have previously reported children with FRNS.

In 1994, Igarashi *et al*. reported the steroid-sparing effect of mizoribine in four children with FRNS.[8] Mizoribine was

started in children ranging in age from 4 to 12 years at a dose of 3.8 ± 0.8 mg/kg per day. The dose of predonisolone decreased from 146 ± 29 to 69 ± 22 mg/kg per year when comparing 1 year before and 1 year after the start of mizoribine therapy. The number of days with proteinuria exceeding 100 mg/dL decreased from 8.8 ± 3.8 to 6.2 ± 3.4 days/year. The rate of relapse 1 year before and after mizoribine was almost the same, but 2 years after the start of mizoribine therapy, three patients were free of relapse.

Hamasaki *et al*. evaluated the 1 year course of mizoribine (at a dosage of 3 mg/kg bodyweight per day), in nine children with steroid-dependent nephrotic syndrome.[12] As a result, steroid treatment could be discontinued in two patients and the maintenance dosage of steroids could be reduced to less than half of that given before mizoribine therapy in the third patient. There were no beneficial effects in the remaining six patients. No adverse effects of mizoribine were observed during the course of therapy. They examined the peak and trough blood levels at 3, 6, 9 and 12 months. The mean peak values of the three responding patients appeared to be higher than those of the six non-responding patients. They concluded the dose of 3 mg/kg bodyweight per day to be low in the non-responding patients.

There have also been two large unpublished studies.

In 1992, we reported the effect of mizoribine on the relapse rate in 32 patients with FRNS.[13]

The patients (22 males and 10 females) whose ages ranged from 3- to 26-years-old (a mean of 12 years), received mizoribine 5 mg/kg (maximum 300 mg) for 24 weeks. Their onsets of NS occurred from 1- to 13-years-old and the mean age was 6-years-old. We examined the rate of relapse before and during mizoribine therapy. Before mizoribine therapy, the relapse rate was 1.7 ± 0.5 times for 24 weeks and it significantly decreased to 0.4 ± 0.7 times for 24 weeks during mizoribine therapy. We next compared the rate of relapse 48 weeks before and 48 weeks after the start of the treatment: 2.4 ± 1.2 to 1.2 ± 1.2. The doses of prednisolone decreased in 53% of the patients, but the mean dose of prednisolone did not significantly change from 74 mg/kg to 62 mg/kg. Adverse effects were only seen in one patient with transient leucocytopenia.

The second study was a multicenter pilot study performed during 1989 to 1992. Two to five mg/kg of mizoribine for 24–48 weeks was administered in 34 (20 males and 14 females) patients with FRNS. Sixteen patients ranged from 3- to 10-years-old and 18 patients were between 11- and 26-years-old. The rate of relapse significantly decreased from 2.7 ± 0.9 times to 1.5 ± 2.0 times for 48 weeks. Fourteen patients had no relapse during mizoribine therapy. In the follow-up periods after the discontinuation of mizoribine, the relapse rate of 1.4 ± 1.5 times for 48 weeks continued to be a lower rate than before the treatment. The doses of prednisolone showed no significant change: 18.9 ± 8.9 mg/kg per day before mizoribine therapy and 17.7 ± 7.9 mg/kg per day during mizoribine therapy. The adverse effect showed increased serum uric acid levels in four patients.

A double-blind, placebo-controlled multicenter study was performed in 197 children with FRNS, from 2- to 19-years-old. Mizoribine at a daily dose of 4 mg/kg was given orally for 48 weeks.[14] The characteristics of the patients are shown in Table 2. A primary analysis was conducted on 99 mizoribine- and 98 placebo-treated patients. The relapse rate was lower in the mizoribine group than in the placebo group (1.85 *vs* 2.25 per 48 weeks; ratio, 0.81; 95% CI, 0.61–1.05; $P = 0.12$). The cumulative remission rate was calculated based on the period until the first relapse using the Kaplan-Meier method on a total of 197 patients (Fig. 1). In this analysis, the hazard ratio of remission between two groups was 0.79 ($P = 0.13$). In the subgroups consisting of patients aged 10 years or younger, the relapse rate was significantly lower in the mizoribine group than in the placebo group (1.74 *vs* 2.62 per 48 weeks; ratio, 0.66; 95% CI, 0.44–0.94; $P = 0.12$). The hazard ratio of the cumulative remission rate between the mizoribine and the placebo subgroups consisting of children aged 10 years or younger was 0.56 ($P = 0.007$) (Fig. 2). The author searched for risk factors associated with predisposition to future relapse using logistic regression techniques. To determine the reason that mizoribine showed a different efficacy according to patients' age, the prevalence of relapses was investigated. The relapses risk was greater in patients aged 10 years or yonger than in patients aged 11 years or older. Adverse effects were observed in 33 out of 99 patients in the mizoribine group and in 21 out of 98 patients in the placebo group (Table 3). No significant differences were noted in the prevalence of adverse events except for hyperuricemia, which occurred more frequently in the mizoribine group than in the placebo group. In the mizoribine group, hyperuricemia mostly occurred within 8 weeks after the start of the trial. The serum uric acid level gradually returned to the normal level in 15 out of 16 patients.

Mizoribine and SRNS

There have yet to be any conclusive reports on the effects of mizoribine in patients with SRNS in children.

In an adult report, from 1989 to 1991, Koshikawa *et al*. performed a 24-week, prospective, randomized, double-blind and placebo-controlled trial to evaluate the efficacy of mizoribine in adult patients with SRNS.[15] Efficacy was assessed in a total of 158 patients (80 in the mizoribine group and 78 in the placebo group). Urinary protein showed a significant reduction of 25.2% before mizoribine therapy in comparison to a 10.0% reduction in the placebo group (Fig. 3). However, the serum albumin and total protein levels

Table 2 Baseline characteristics of patients

	Mizoribine (n = 99)	Placebo (n = 98)	P-value
Sex			
Male	72	70	0.84†
Female	27	28	
Age†† (years)			
0–5	18	22	
6–10	36	35	0.46‡
11–15	35	33	
16+	10	8	
Duration of illness (years)			
< 1	19	21	
< 3	24	29	0.46‡
< 6	28	22	
≥ 6	28	26	
Disease type††			
Steroid-dependent	90	90	0.82†
Nonsteroid-dependent	9	8	
Renal biopsy			
Not performed	57	55	
Performed††			0.76†
Minimal change	39	38	
Others§	3	5	
Number of previous relapses††			
Two times/24 weeks	26	31	
Three times/48 weeks	39	35	0.70†
≥ Four times/48 weeks	34	32	
History of other immunosuppressants at least 6 months before the study¶ (some overlapped)			
Immunosuppressants††			
Yes	39	42	0.62†
No	60	56	
Cyclosporin††			
Yes	14	14	0.98†
No	85	84	
Cyclophosphamide			
Yes	34	38	0.52†
No	65	60	

†χ^2 test; ‡Wilcoxon test; §focal segmental glomerulosclerosis in two patients (one, mizoribine; one, placebo) and mesangial proliferative glomerulonephritis in six patients (two, mizoribine; four, placebo); ¶patients treated with immunosuppressants in the recent 6 months were excluded from the study; ††Used as balancing factors for allocation.

did not show any significant change in both groups. The incidences of side-effects in the mizoribine and placebo groups also did not differ significantly.

Discussion

The above data showed mizoribine to be an effective and safe drug for patients with FRNS. However, the efficacy of mizoribine has differed among various reports, depending on the doses given (Table 4). We used 5 mg/kg of mizoribine and the relapse rate was 0.4 episodes per 24 weeks,[13] but in a control study, they used 4 mg/kg and the relapse rate was 1.85 episodes per 48 weeks.[14] Recently, after renal transplantation in children, the use of mychophenolate mofetil (MMF) instead of azathiopurine has increased in children.[16] Both mizoribine and MMF are immunosuppressive agents that inhibit the proliferation of lymphocytes selectively, via the inhibition of inosine monophosphate dehydrogenase (IMPDH). The use of MMF significantly reduced acute rejection.[17,18] However, the rate of infection, especially tissue infiltrate cytomegalovirus infection and herpes zoster infection increased.[17–19] Based on the above findings, better results might be obtained if the doses of mizoribine increased, but the occurrence of a viral infection might be one serious side-effect. When we used 5 mg/kg, no serious viral infections were seen, therefore 5 mg/kg may be safe. We have to examine the appropriate effective and safe dose of mizoribine.

In patients with FRNS, cyclosporin is effective and the relapse rate was very low when they received 5 mg/kg of cyclosporin.[20,21] However, the effect was transient and if cyclosporin was discontinued, most patients tended to relapse. When 5 mg/kg of cyclosporin is used long-term, renal damage tends to be a serious problem.[22] Based on the

a Relapse rate

	n	Relapse rate	Relapse rate ratio	*P*-value
Mizoribine	97	0.0055	0.81	0.12
Placebo	96	0.0067		

b Kaplan-Meier plot

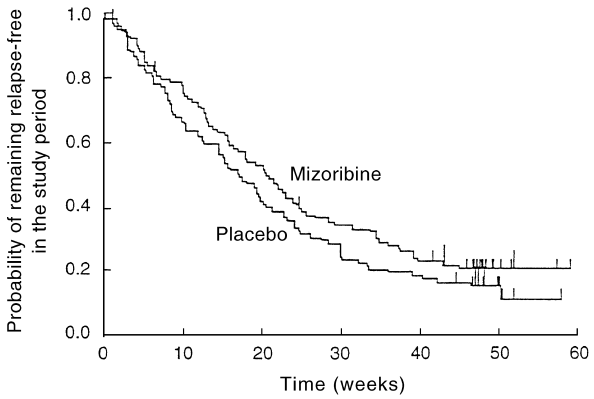

Fig. 1 (a) Relapse rate and (b) cumulative remission rate in mizoribine and placebo groups. Hazard ratio = 0.79, $P = 0.13$. Figure used from reference 14 with permission.

Table 3 Adverse events

	Mizoribine ($n = 99$)	Placebo ($n = 98$)
Hyperuricemia	16	4
Hepatic dysfunction	9	9
Alopecia	3	2
Leukocytopenia	2	1
Leukocytosis	1	2
Anemia	0	1
Hyperlipidemia	0	2
Headache	2	0
Hypertension	1	0
Aphthous stomatitis	1	1
Nausea	1	0
Chest discomfort	1	0
Finger tremor	1	0
BUN increased	1	0
Serum creatinine increased	1	0
Hypocomplemetemia	1	0
Edema	0	1
Urticaria	0	1
Tonsillitis	1	0
Varicella	0	1
Urinary tract infection	1	0
Ureteral calculus	1	0

The occurrence of adverse events was 33% (33/99) in the mizoribine group and 21% (21/98) in the placebo group. BUN, blood urea nitrogen.

findings of reports and our experience, mizoribine was less effective than cyclosporin, but mizoribine can be used long-term without serious adverse effects. When cyclosporin was

a Relapse rate

	n	Relapse rate	Relapse rate ratio	*P*-value
Mizoribine	54	0.0052	0.66	0.017
Placebo	57	0.0078		

b Kaplan-Meier plot

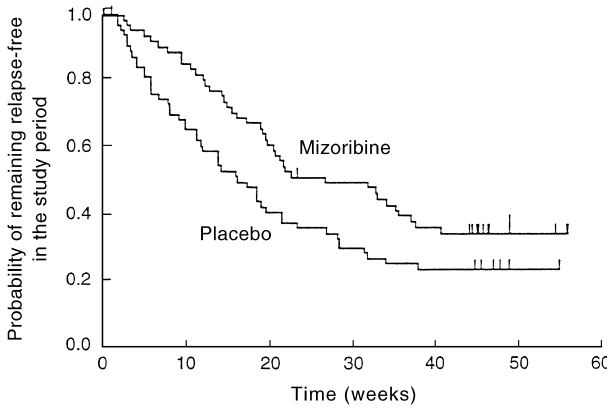

Fig. 2 (a) Relapse rate and (b) cumulative remission rate in the subgroup of patients aged 10 years or younger at the start of the trial. Hazard ratio = 0.56, $P = 0.007$. Figure used from reference 14 with permission.

discontinued and patients relapsed immediately, mizoribine could be used in this situation. In addition, the combined use of mizoribine and low dose cyclosporin (2–3 mg/kg) may reduce the cyclosporin toxicity and the number of relapses of steroid-dependent NS. Furthermore, if the patients have frequent relapses while receiving 5 mg/kg of cyclosporin therapy, the combined use of cyclosporin and mizoribine therapy as a renal transplant recipient might reduce the rate of relapse.

We recently started a multicenter study of mizoribine in patients with NS. When the patients have their first relapse within 6 months from the onset, half of them demonstrate FRNS. We use 5 mg/kg per day of mizoribine in these high-risk patients and the aim of this protocol is to reduce steroid toxicity and the use of immunosuppressive agents, except mizoribine, due to the reduced rate of relapse.

In a report of SRNS in adults, the effect of mizoribine was not sufficient.[15] This report did not induce a remission. In the children with FSGS, remission is an important indicator of the long-term prognosis. The dose of mizoribine was 150 mg in this report and this dose was low as mentioned above. For the above reasons we could not conclude the effect of mizoribine in SRNS.

Until now, no effective treatment by a controlled study was seen in the long-term prognosis of patients with FSGS and SRNS. About one-half of the patients showed end-stage renal disease. Recently, high doses of cyclosporin or the recurrent use of MPT with immunosuppressant was effective

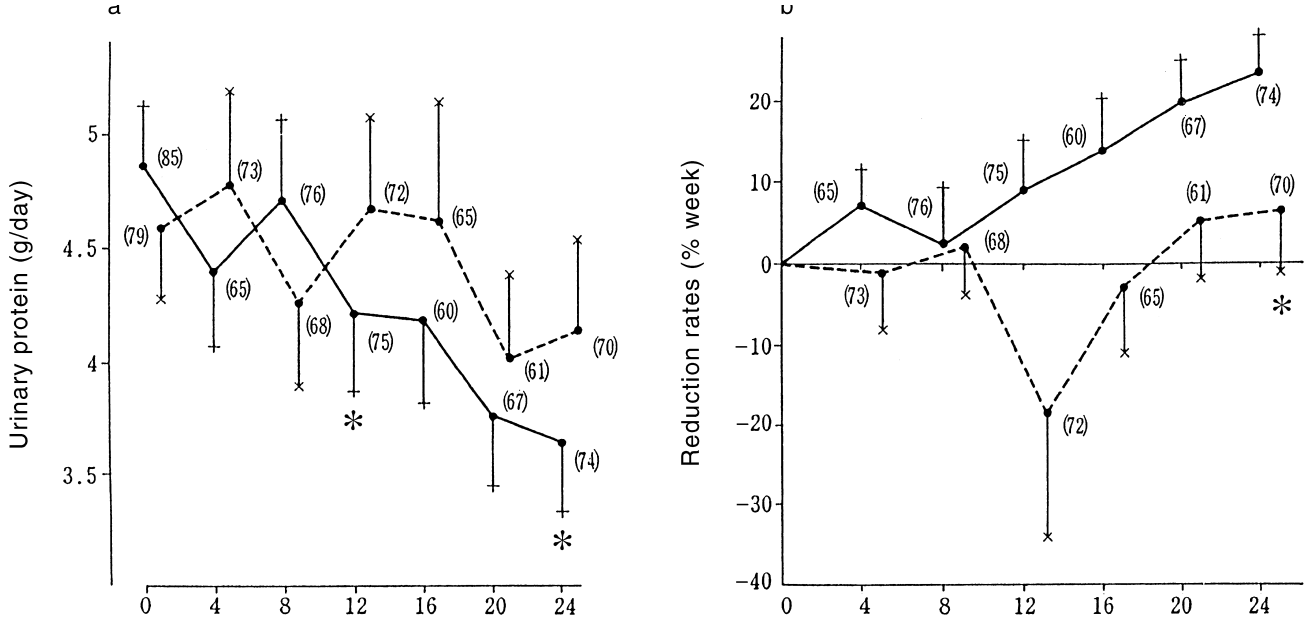

Fig. 3 Change in daily proteinuria in mizoribine group and placebo group. (a) Protein levels; (b) reduction rates; (—), mizoribine group; (- - -), placebo group; ( ), patient number. Figure used from reference 15 with permission.

Table 4 The relapse rate and mizoribin dose in patients with frequent recurring nephrotic syndrome

	Mizoribine dose (mg/kg per day)	Patient number	Relapse rate (before → during treatment)
Igarashi	3.8	4	2.0 → 1.5 (year)
TMCH	5	32	1.7 → 0.4 (24 weeks)
			2.4 → 1.2 (48 weeks)*
Multicenter study	2–5	34	2.7 → 1.5 (48 weeks)
Controlled study	4	99	2.3/1.9 (48 weeks) (placebo/mizoribine)
< 10-years-old			2.6/1.7 (48 weeks) (placebo/mizoribine)

*Mizoribine used for 24 weeks. TMCH, Tokyo Metropolitan Children's Hospital.

in children with FSGS, but not in a controlled study. According to Ingulli's report, the long-term use of high dose cyclosporin (more than 10 mg/kg) might be the cause of renal damage.[6] One-half of the remission cases in their reports had an increased serum creatinine level. Patients receiving MPT with immunosuppressant also had problems. In their report, one-third of all patients received clearly dangerous doses for aspermia because of the recurrent use of immunosuppressants.[7] Recently, we started a new treatment protocol in children with SRNS. We made two separate protocols in SRNS patients according to the findings of biopsy specimens. In patients with MCNS, based on the biopsy findings, cyclosporin was used for 12 months (trough level 120–150 ng/mL for 3 months and followed 80–100 ng/mL for 9 months). In patients with FSGS, MPT was used for 4 months (three consecutive days for a month) with cyclosporin used for 12 months as the same as MCNS. If the MCNS patients showed a resistance to the treatment, we changed to a FSGS protocol. We estimated that there were about 20% of the patients with resistant or recurring NS using the above protocol. Recently, we experienced two patients with SRNS who were resistant to cyclosporin, cyclophasphamide and the recurrent use of MPT, however, they achieved remission after the long-term use of cyclosporin (trough 80–100 ng/mL) and mizoribine (5 mg/kg). Mizoribine is thus considered to be a safe long-term treatment, but its effect may be weaker than other immunosuppressants. However, most immnosuppressants cannot be used long-term due to adverse effects. I recommend the long-term use of mizoribine in patients who are resistant or show recurrence after use of other immunosuppressants.

As I mentioned above, even in SRNS patients, large doses of mizoribine of more than 5 mg/kg might be effective, while the combined use of mizoribine and cyclosporin or MPT might also be even more effective. Further studies are called for to examine the use of large doses of mizoribine.

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