treatment, the follow-up treatment with cyclosporine should be a dose producing a whole-blood trough level between 60 and 80 ng/ml. This treatment was given from month 13 to month 24.

Registration

This study has been registered in a public trials registry, UMIN (the University Hospital Medical Information Network, ID C000000009 http://www.umin.ac.jp/ctr/index.htm.)

Results

Patient characteristics

This prospective study was conducted by Japanese Study Group of Renal Disease in Children. Between January 2001 and December 2007, a total of 35 children (21 male and 14 female) were enrolled at 14 centers. The patients' characteristics are shown in Table 1. At the start of the protocol treatment, the median age of the patients was 2.7 years (range 1.4–15.0 years); 20 of the 35 patients (57.1%) were <3 years. The mean duration from the onset of nephrotic syndrome to the start of the protocol treatment was 3.4 months (range 1.0–25.0 months). Twenty-six patients had an initial non-response to steroids, while nine had a late non-response to steroids. The mean serum total protein level and albumin level at the start of treatment were 4.1 and 1.7 g/dl, respectively.

Pathological examination (initial biopsy for all patients) at study entry revealed that 23 patients had MC, five had DMP, and seven had FSGS.

Cyclosporine dosage and trough level

The mean trough level and mean dose of cyclosporine during months 1–3 of treatment were 110.2 ng/ml (range 71.0–159.7 ng/ml) and 6.0 mg/kg per day (range 3.1–10.4 mg/dl), respectively. During months 4–12, the mean trough level and the mean dose of cyclosporine were 88.6 ng/ml (range 61.0–136.5 ng/ml) and 5.1 mg/kg per day (range 3.0–8.1 mg/dl), respectively.

Response to treatment

A flow diagram of the patients, summarizing the numbers of patients enrolled, followed up, and included in the analyses, is shown in Fig. 2. The response to treatment was analyzed separately in patients with MC/DMP and in those with FSGS on renal biopsy. Thirty-five patients were enrolled: 28 patients in the MC/DMP group and seven in the FSGS group.

The response to treatment within 4 months after initiation of the protocol is shown in Table 2. Remission (including complete remission and partial remission) was achieved during the first month of treatment in 60.7% (17/28) of the patients in the MC/DMP group and 71.4% (5/7) of those in the FSGS group. The remission rate at the end of month 4 was 92.9% (26/28) in the patients with MC/DMP, with 23 patients having complete remission and three having partial remission; two had non-remission. In contrast, the remission rate was 85.7% (6/7) in the patients with FSGS, with five patients having complete remission and one having partial remission; one patient had non-remission. Two patients with MC/DMP who had non-remission received the regimen for the FSGS group. One patient with FSGS who had non-remission received off-protocol treatment.

The results of the evaluation at month 12 are shown in Table 3. Twenty-three patients completed the 12-month course of protocol treatment in the MC/DMP group, with 22 of these achieving complete remission and one achieving partial remission. Five patients received off-protocol treatment during months 5–12. The remission rate at month 12 was thus 82.1% [23/28; 95% confidence interval (CI) 0.63–0.93]. Of the 22 patients who had complete remission, two received treatment that violated the protocol: one patient received mizoribine and the other received MPT at the first relapse after achieving remission. If these patients are excluded from analysis, the remission rate was 80.8% (21/

Table 1 Characteristics of the patients

Characteristic	Level	MC/DMP (n=28) n (%)	FSGS (n=7) n (%)
Age at entry (years)	0 to <3	15 (53.5)	5 (71.4)
	≥3 to <7	5 (17.9)	1 (14.3)
	≥7 to <11	4 (14.3)	1 (14.3)
	≥11 to <15	3 (10.7)	0 (0.0)
	≥15	1 (3.6)	0 (0.0)
Sex	Male	17 (60.7)	4 (57.1)
	Female	11 (39.3)	3 (42.9)

MC, Minimal change; DMP, diffuse mesangial proliferation; FSGS, focal segmental glomerulosclerosis

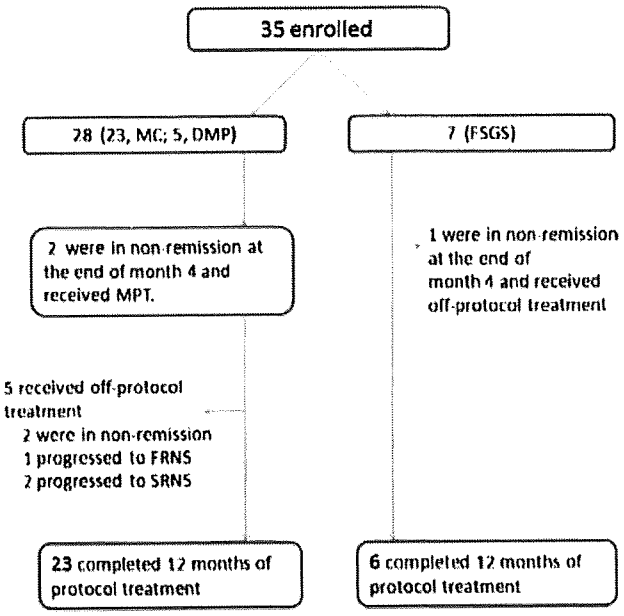

Fig. 2 Flow diagram of patients. *MC* Minimal change, *DMP* diffuse mesangial proliferation, *FRNS* frequently relapsing nephrotic syndrome, *SRNS* steroid-resistant nephrotic syndrome, *FSGS* focal segmental glumerulosclerosis

26; 95% CI 0.60–0.93). Six patients completed the 12-month protocol treatment in the FSGS group, with five achieving complete remission and one achieving partial remission. The remission rate was 85.7% (6/7; 95% CI 0.42–0.99).

Among the 22 patients with complete remission in the MC/DMP group at month 12, 15 patients continued to show complete remission during months 5–12, and relapse occurred during this period in seven patients, but was steroid-sensitive. Among the five patients with complete remission in the FSGS group at month 12, three patients continued to show complete remission during months 5–12 and relapse involving steroid-sensitive nephrotic syndrome occurred in two patients during the same period. The status at month 12 of the patients who received off-protocol treatment was as follows: two patients had complete remission, three patients in the MC/DMP group had nephrotic syndrome, and one patient in the FSGS group had partial remission.

Adverse events

Follow-up renal biopsies were performed in 26 patients (nine at month 12 and 17 at month 24). Mild nephrotoxicity attributable to cyclosporine occurred in one patient (3.8%) who had mild arteriolar hyalinosis and mild interstitial fibrosis with mild tubular atrophy. No patient in this series had striped interstitial fibrosis. Four patients had mild tubular atrophy without interstitial fibrosis, and four had mild tubular atrophy with mild interstitial fibrosis. These findings were considered to reflect the natural course of SRNS rather than an adverse effect of cyclosporine.

Other adverse events are summarized in Table 4. Severe adverse events occurred in three patients with MC/DMP: one patient had bacterial peritonitis, one had sepsis with disseminated intravascular coagulation and multiorgan failure, and one patient had posterior reversible encephalopathy syndrome (PRES). The two patients with infections received antibiotics and supportive therapy. The infections resolved immediately and uneventfully, and treatment according to the protocol was resumed. The patient with PRES was in complete remission when the event occurred at the end of the protocol treatment. Cyclosporine was discontinued after the development of PRES, and the patient completely recovered after receiving antihypertensive and supportive therapy. This patient did not receive cyclosporine again. Hypertension was present in ten of 35 patients (28.6%), but blood pressure was easily controlled with antihypertensive therapy. Transient arrhythmias (sinus bradycardia) associated with MPT were observed in two patients. No patient had elevated serum creatinine levels during cyclosporine treatment. The mean creatinine clearance was similar at the start of cyclosporine treatment (119.9 ml/min per 1.73 m^2) and at month 12 (117.7 ml/min per 1.73 m^2). The mean standard deviation (SD) scores for height at the start of the protocol treatment and at month 12 were −0.38 and −0.08, respectively. The mean difference in the SD scores for height was 0.30 (95% CI 0.10–0.50). Other complications, such as aseptic necrosis of the femoral head, diabetes, and pancreatitis, were not observed.

Table 2 Response to treatment within 4 months after the initiation of protocol treatment

Pathology	Patients (*n*) who went into remission at:					Patients with non-remission[a] (*n*)	Total (*n*)
	0–1 months	1–2 months	2–3 months	3–4 months	Subtotal		
MC/DMP	17	4	3	2	26	2	28
FSGS	5	1	0	0	6	1	7

Values are given as the number of patients

[a] Patients with persistent nephrosis at the end of month 4

Table 3 Evaluation of patients with steroid-resistant nephrotic syndrome at month 12

Pathology	Patients who completed 12-month protocol treatment (*n*)		Patients who received off-protocol treatment[a] (*n*)	Total (*n*)
	Complete remission	Partial remission		
MC/DMP	22[b]	1	5	28
FSGS	5	1	1	7

NS, Nephrotic syndrome; FRNS, frequently relapsing nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome; MPT, methylprednisolone pulse therapy

[a] Includes patients with persistent nephrosis at month 4 and those who progressed to FRNS or SRNS during months 5–12

[b] Two patients achieved complete remission with additive immunosuppressive agents (MPT or mizoribine) at the first relapse

Clinical course during months 13–24

After 12 months of treatment, cyclosporine was discontinued in four patients with FSGS in 2003. SRNS recurred immediately in all patients. There was no relapse of SRNS in the MC/DMP group; however, progression to frequently relapsing nephrotic syndrome occurred in four (80%) of the five patients. In May 2003, the Safety Committee therefore recommended that patients who completed the 12 months of protocol treatment should receive an additional 12 months of treatment with cyclosporine.

The status of the patients at month 24 is shown in Table 5. Seventeen patients with MC/DMP received the recommended treatment; of these, 11 patients continued to have complete remission, and six had relapses with steroid-sensitive nephrotic syndrome between months 13 and 24. Two patients with FSGS received the recommended treatment; remission (complete remission or partial remission) continued in both patients from months 13 to 24.

One patient with MC/DMP who received off-protocol treatment had progression to end-stage renal failure at month 24. The patient had persistent nephrotic syndrome, with no response to treatment, including to cyclosporine and prednisolone plus MPT.

Discussion

This prospective, multicenter trial was conducted in children with SRNS with the aim of evaluating the safety and effectiveness of a 12-month course of cyclosporine and prednisolone in children with MC/DMP and a 12-month course of cyclosporine and prednisolone plus MPT in children with FSGS. Both groups of patients had high remission rates, and end-stage renal failure developed in only one of 35 patients during the 2 years of follow-up. Renal biopsy at the end of treatment showed that the protocol treatment was safe in terms of nephrotoxicity.

In our trial, all patients received prednisolone combined with cyclosporine based on the hypothesis that prednisolone improves the effectiveness of cyclosporine in patients with SRNS. The 12-month protocol treatment was com-

Table 4 Adverse events

Adverse events	Total (*n*=35)	MC/DMP (*n*=28)	FSGS (*n*=7)
Peritonitis	1 (2.9)	1 (3.6)	0 (0.0)
Sepsis	1 (2.9)	1 (3.6)	0 (0.0)
PRES	1 (2.9)	1 (3.6)	0 (0.0)
Hypertrichosis	18 (51.4)	13 (46.4)	5 (71.4)
Hypertension	10 (28.6)	9 (32.1)	1 (14.3)
Hyperlipidemia	5 (14.3)	3 (10.7)	2 (28.6)
Obesity	3 (8.6)	2 (7.1)	1 (14.3)
Gastric pain	3 (8.6)	3 (10.7)	0 (0.0)
Gingival hypertrophy	2 (5.7)	1 (3.6)	1 (14.3)
Alopecia	2 (5.7)	2 (7.1)	0 (0.0)
Sinus bradycardia	2 (5.7)	0 (0.0)	2 (28.6)
Glaucoma	1 (2.9)	1 (3.6)	0 (0.0)
Acne	1 (2.9)	1 (3.6)	0 (0.0)
Hyperuricemia (>8 mg/dl)	1 (2.9)	1 (3.6)	0 (0.0)

Values are given as the number of patients, with the percentage in parenthesis

PRES, Posterior reversible encephalopathy syndrome

Table 5 Status of patients with steroid-resistant nephrotic syndrome at month 24

Status of patients	Patients who completed 12-month protocol treatment (*n*)				Patients who received off-protocol treatment[b]		Total
	Recommended treatment (+)		Recommended treatment (-)[a]				
	MC/DMP	FSGS	MC/DMP	FSGS	MC/DMP	FSGS	
CR	16[c]	1	6	4[c]	2[c]	1	30
PR	0	1	0	0	0	0	1
NS	0	0	0	0	2	0	2
ESRF	0	0	0	0	1	0	1
Unknown	1[d]	0	0	0	0	0	1
Total	17	2	6	4	5	1	35

CR, Complete remission; PR, partial remission; ESRF, end-stage renal failure

[a] Patients in whom treatment was left to the discretion of their physicians after 12 months

[b] Includes patients with persistent nephrosis at month 4 and those who had FRNS or SRNS during months 5–12

[c] Includes one patient each with FRNS at month 24

[d] Patients who were lost to follow-up; data were unavailable

pleted in 23 of 28 patients in the MC/DMP group and six of seven patients in the FSGS group. High remission rates were obtained at month 12: 82.1% (80.8% after excluding the two patients with protocol violations) in the MC/DMP group and 85.7% in the FSGS group. Previous studies have shown that remission is generally achieved in 20–50% of patients with SRNS who receive cyclosporine monotherapy [7, 8, 13]. A multicenter trial of cyclosporine with low-dose prednisolone in children with SRNS, conducted by the French Society of Pediatric Nephrology, reported that remission was achieved in 23 (51.1%) of 45 patients with MC and eight (40.0%) of 20 with FSGS, suggesting that prednisolone enhanced the remission rate [5]. Several other studies also have provided evidence that combining prednisolone with cyclosporine considerably improves outcomes in comparison to cyclosporine monotherapy [10, 14, 15, 21]. These results are supported by our findings.

The patients with FSGS received MPT in addition to cyclosporine and prednisolone; to the best of our knowledge, this is the first prospective, multicenter trial to evaluate combined therapy with MPT and cyclosporine in children with FSGS. An excellent remission rate (85.7% at month 12) was obtained. Several retrospective studies have reported that a combination of MPT with cyclosporine and prednisolone produces better outcomes than those previously obtained in patients with FSGS, with remission rates ranging from 84 to 90% [20–22]. Other studies have shown that MPT alone is an effective treatment in children with SRNS [17, 18]. These results suggest that MPT combined with cyclosporine and prednisolone may improve the remission rate in children with FSGS. However, randomized controlled trials are needed to confirm these findings.

Cyclosporine-related nephrotoxicity, which is characterized by arteriolopathy (arteriolar hyalinosis and hyperplasia), with or without striped interstitial fibrosis and tubular atrophy [23, 24], is the most important factor limiting the long-term or high-dose use of cyclosporine [25–29]. One study reported that 2 years of treatment with cyclosporine in a dose that maintained the trough level at 100 ng/ml caused tubulointerstitial changes in seven of 13 patients with steroid-dependent nephrotic syndrome [29]. Only a few studies have evaluated nephrotoxicity in children with SRNS. We therefore performed renal biopsy at month 12 or 24 to evaluate the safety of treatment with cyclosporine in 26 patients and found that only one patient showed mild signs of cyclosporine-related nephrotoxicity. This low frequency of nephrotoxicity may be attributable to the management and adjustment of the cyclosporine dosage by trough-level monitoring. As mentioned above, we believe that our protocol treatment did not affect long-term cyclosporine-related nephrotoxicity in most of the patients.

Other serious adverse events were infections and PRES. There were two episodes of severe bacterial infections (sepsis and peritonitis) in the MC/DMP group, both of which responded to treatment with antibiotics. Nephrosis predisposes patients to bacterial infections [30], and cyclosporine treatment may increase the risk. Therefore, patients who receive cyclosporine should be closely monitored for bacterial infections. PRES is a distinct and potentially serious complication of cyclosporine treatment or hypertension [31] that may develop in children, including those with nephrotic syndrome [32, 33]. In our trial, PRES developed in one patient at the end of 12 months of the protocol treatment; this patient fully recovered in response to antihypertensive treatment and the withdrawal

of cyclosporine. Meticulous control of blood pressure is required to prevent PRES, particularly in patients given cyclosporine.

The optimal duration of cyclosporine treatment in children with SRNS remains unclear. In our trial, an excellent remission rate was achieved with 12 months of treatment; however, after the withdrawal of cyclosporine, most children had severe relapses, with SRNS developing in the FSGS group and frequently relapsing nephrotic syndrome developing in the MC/DMP group. In May 2003, the Safety Committee therefore proposed that patients should receive an additional 12 months of treatment with cyclosporine in a dose producing a whole-blood trough level between 60 and 80 ng/ml after the initial 12 months of protocol treatment. The trough level was based on the results of a previous study showing that this level was effective and relatively safe in children with frequently relapsing nephrotic syndrome [34]. Although even 2 years of treatment with cyclosporine may not be long enough to prevent relapses after the discontinuation of this agent, more than 2 years of treatment has been shown to be an independent risk factor for cyclosporine-related nephrotoxicity [35]. A total cyclosporine treatment period of 2 years may therefore be reasonable.

During the 12 months of treatment, five of 28 patients in the MC/DMP group and one of seven patients in the FSGS group received off-protocol treatment. Most of these patients were resistant to the protocol treatment, and end-stage renal failure finally developed in one patient at 2 years following treatment initiation. Renal function in the other patients may have been maintained by concurrent treatments, such as cyclophosphamide, plasma exchange, frequent MPT, and mizoribine combined with cyclosporine (data not shown). The establishment of new strategies for patients who do not respond to treatment is awaited.

In addition to the remission rate after 12 months of the protocol treatment, outcomes were also evaluated 24 months after the start of treatment. Similar to the results at 12 months, remission rates remained high in both groups, and most relapses of nephrosis were steroid-sensitive. Although 24 months of follow-up may not be adequate, our treatment protocol may result in long-term remission and prevent the development of end-stage renal failure in children with SRNS. To evaluate long-term outcomes of treatment, a 5-year follow-up study is currently being conducted.

An important limitation of our trial was the lack of a control group. The need for MPT in children with SRNS and the associations between pathological diagnosis (i.e. MC/DMP and FSGS) and outcomes have to be confirmed in future studies. Another limitation is that renal biopsy was not performed after treatment in nine patients. In six patients, the attending physicians decided not to perform follow-up renal biopsies because of associated risks; two patients received short-term cyclosporine before discontinuing the protocol treatment, and one patient was lost to follow-up. Because these reasons did not indicate a general trend, we believe that the incidence of cyclosporine-related nephrotoxicity was not affected by the lack of follow-up biopsy data in some patients.

In conclusion, this prospective, multicenter trial in children with SRNS showed that high remission rates were obtained after 12 months of treatment with cyclosporine and prednisolone in patients with MC/DMP and after 12 months of treatment with cyclosporine and prednisolone plus MPT in patients with FSGS. Maintenance cyclosporine treatment may be required to prevent relapses after the initial 12 months of treatment. Renal biopsy performed after treatment according to the protocol showed that cyclosporine was safe in terms of nephrotoxicity. Results from randomized controlled trials are necessary to confirm the need for MPT.

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