Effective and safe treatment with cyclosporine in nephrotic children: A prospective, randomized multicenter trial

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We conducted a prospective, open-label multicenter trial to evaluate the efficacy and safety of treating children with frequently relapsing nephrotic syndrome with cyclosporine. Patients were randomly divided into two groups with both initially receiving cyclosporine for 6 months to maintain a whole-blood trough level between 80 and 100 ng/ml. Over the next 18 months, the dose was adjusted to maintain a slightly lower (60–80 ng/ml) trough level in Group A, while Group B received a fixed dose of 2.5 mg/kg/day. The primary end point was the rate of sustained remission with analysis based on the intention-to-treat principle. After 2 years, the rate of sustained remission was significantly higher while the hazard ratio for relapse was significantly lower in Group A as compared with Group B. Mild arteriolar hyalinosis of the kidney was more frequently seen in Group A than in Group B, but no patient was diagnosed with striped interstitial fibrosis or tubular atrophy. We conclude that cyclosporine given to maintain targeted trough levels is an effective and relatively safe treatment for children with frequently relapsing nephrotic syndrome.

Kidney International (2008) **73,** 1167–1173; doi:10.1038/ki.2008.24; published online 27 February 2008

KEYWORDS: clinical trial; nephrotic syndrome; cyclosporine; pediatric nephrology

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The participants were listed at the end of the manuscript

Received 22 March 2007; revised 22 November 2007; accepted 12 December 2008; published online 27 February 2008

The establishment of effective and safe immunosuppressive therapies other than corticosteroids is urgently required for children with frequently relapsing nephrotic syndrome (FRNS). Although corticosteroids remain the first-line treatment for nephrotic syndrome and approximately 90% of patients have remission during treatment, a substantial proportion of these patients progress to FRNS.[1–4] Corticosteroid-related toxicity may lead to serious problems in these patients, such as growth failure, osteoporotic bone disease, cataract and glaucoma, and adrenal suppression.

Cyclosporine (CyA) is an immunosuppressive drug that has been used to sustain remission and decrease exposure to corticosteroids in children with steroid-sensitive nephrotic syndrome.[5–20] Although CyA has been shown to be as effective as other immunosuppressive drugs, such as cyclophosphamide and chlorambucil, in children with FRNS or steroid-dependent nephrotic syndrome, its general use remains controversial because of potentially serious adverse effects, including hypertension, infection, neurotoxicity, and nephrotoxicity.[2,5,6,12,21–24]

The optimal dosage and duration of treatment with CyA for these patients have yet to be determined. Short-term (6-month) courses of CyA are associated with frequent relapses of nephrotic syndrome just after the discontinuation of treatment.[11] Low-dose treatment with CyA for 18 months has also produced discouraging results.[10] On the other hand, 2 years of treatment with CyA in a dose producing a trough level of 100 ng/ml caused chronic CyA-induced nephrotoxicity in 7 of 13 patients.[8] To better define the optimal dosage and duration of treatment with CyA, we conducted a prospective, randomized, open-label multicenter trial to evaluate the efficacy and toxicity of a 2-year course of treatment with CyA (Sandimmune; Novartis, Basel, Switzerland) in children with FRNS.

RESULTS

Analysis set (data set)

Between January 1996 and January 2002, a total of 56 patients were registered at 23 centers and randomly assigned

to treatment group (Group A, 29; Group B, 27). One patient was later found to be ineligible, and another patient was lost to follow-up and had no data available. These two patients were excluded from all analyses. All 10 patients enrolled at three particular centers received the regimen for Group A regardless of the assigned treatment (three patients in Group A and seven in Group B); the steering committee decided to exclude these 10 patients from all analyses except for the analysis of adverse events because these three centers were considered to violate the guidelines for good clinical practice in Japan. Therefore, this report is based on 44 patients in the intention-to-treat analysis.

A flow diagram of the patients, summarizing the numbers of patients assigned to treatment, followed up, and included in analyses, is shown in Figure 1. Data from 3 of 17 patients who discontinued the allocated treatment regimen were used as censored observations in the survival analyses: 1 (Group B) because of progression to steroid resistance and 2 because of adverse events (Group A, 1 and Group B, 1).

Patient characteristics

The clinical characteristics of the patients were analyzed to confirm whether major prognostic factors were balanced between the treatment groups. The mean age of the patients was 8.5 years in Group A and 8.9 years in Group B. The demographic characteristics of the patients are shown in Table 1. Before study entry, the number of relapses/year was 3.1 in Group A and 3.6 in Group B (Table 2a, $P = 0.155$). The demographic characteristics of the 10 patients treated at the three excluded centers are also shown in Table 2b.

As for concomitant medications, angiotensin-converting enzyme inhibitors (lisinopril or enalapril) were used in four patients in Group A and one patient in Group B. Calcium channel blockers (nifedipine or amlodipine) were used in two

Table 1 | Patient demographics

Characteristics	Level	Group A (*N*=24) *N* (%)	Group B (*N*=20) *N* (%)
Age at entry (years)	0 to <3	1 (4.2)	4 (20.0)
	⩾3 to <6	6 (25.0)	3 (15.0)
	⩾6 to <11	9 (37.5)	5 (25.0)
	⩾11	8 (33.3)	8 (40.0)
Age at diagnosis (years)	0 to <3	3 (12.5)	5 (25.0)
	⩾3 to <6	13 (54.1)	9 (45.0)
	⩾6 to <11	4 (16.7)	3 (15.0)
	⩾11	4 (16.7)	2 (10.0)
Missing		0 (0.0)	1 (5.0)
Sex	Male	18 (75.0)	17 (85.0)
	Female	6 (25.0)	3 (15.0)

Table 2a | Relapse rate before entry

Treatment	*N*	Number of relapses before entry (per year) Missing	Mean	Median	s.d.	Min	Max
Group A	24	1	3.1	3	1.02	2	5
Group B	20	1	3.6	3	1.22	2	6

Table 2b | Relapse rate before entry in 10 patients at the three excluded institutions

Treatment	*N*	Number of relapses before entry (per year) Missing	Mean	Median	s.d.	Min	Max
Group A	3	1	3.0	3	1.41	2	4
Group B	7	2	3.6	3	0.89	3	5

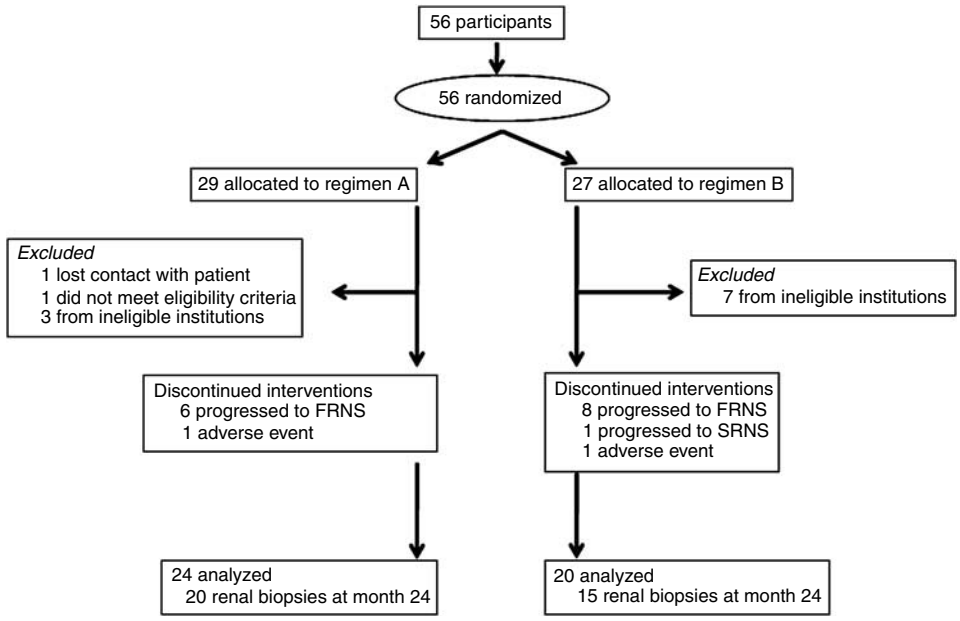

Figure 1 | Flow diagram of the patients. SRNS, steroid-resistant nephrotic syndrome; FRNS, frequently relapsing nephrotic syndrome.