Long-Term Treatment of Focal Segmental Glomerulosclerosis in Children With Cyclosporine Given as a Single Daily Dose

Aftab S. Chishti, MD, Jonathan M. Sorof, MD, Eileen D. Brewer, MD, and Arundhati S. Kale, MD

• **Cyclosporine (CsA) has been successfully used for treatment of children with focal segmental glomerulosclerosis (FSGS) and nephrotic syndrome (NS) for the last decade. Response rates of 50% to 100% have been reported using twice-daily dosing of 5 to 32 mg/kg/d, achieving trough blood levels of 70 to 500 ng/mL. Treatment has been associated with a high incidence of side effects, including nephrotoxicity, hypertension, gingival hyperplasia, and hirsutism. To determine whether once-daily low-dose CsA could minimize side effects and still induce remission, 21 children with biopsy-proven FSGS and NS, each treated with CsA, 4.6 ± 0.8 mg/kg/d, with no predetermined target trough blood levels, were studied. Eleven of 21 children (52%) attained complete remission and 5 of 21 children (24%) attained partial remission, for a total response rate of 76%. Mean time to response was 2.8 ± 0.8 months, and mean duration of therapy was 20.6 ± 13.7 months. CsA dosage was tapered or stopped in 9 responders; 3 of these patients maintained remission at last follow-up 6 to 13 months later, and 6 patients relapsed at 1.5 to 18.7 months (mean, 8.7 months). Five of these 6 patients responded again when CsA therapy was restarted or the dosage was increased. Twelve of 16 responders were still being administered CsA at last follow-up 11 to 60 months (mean, 24.6 months) later. Five of 21 patients (24%) had no response to CsA during 2 to 27 months of therapy; 4 of these 5 patients developed end-stage renal disease after CsA therapy was stopped. Side effects of CsA therapy were minimal: 1 patient each developed new-onset hypertension or gingival hyperplasia, and no patient had hirsutism or nephrotoxicity. Single daily low-dose CsA appears to be effective for long-term treatment of children with FSGS and NS, with fewer side effects than twice-daily dosing.**

INDEX WORDS: Nephrotic syndrome (NS); focal segmental glomerulosclerosis (FSGS); cyclosporine (CsA); pediatric; treatment.

FOCAL SEGMENTAL glomerulosclerosis (FSGS) is the second most common cause of end-stage renal disease (ESRD) in North American children.[1] The usual presentation is proteinuria and nephrotic syndrome (NS), and standard initial treatment is high-dose steroids. Because renal biopsy is usually reserved for patients with steroid-dependent or steroid-resistant NS, the true incidence of steroid-responsive FSGS is not known. The reported rate of complete remission for histologically documented FSGS treated with high-dose prednisone ranges from 0% to 50%, with an average of 20%.[2-5] Treatment with alkylating agents such as cyclophosphamide or chlorambucil has had little efficacy in the treatment of children or adults with FSGS.[6,7] The most recent International Study of Kidney Diseases in Children report on the treatment of FSGS with alkylating agents showed complete remission in only 25% of patients and no response in 57%.[6] Remission rates up to 60% have been noted with a combination of high-dose intravenous steroids and alkylating agents.[8-10]

In the last decade, cyclosporine (CsA), a lipophilic endecapeptide, has emerged as a new immunosuppressive agent for the treatment of FSGS.[11-13] Several mechanisms have been proposed to explain the CsA-induced reduction in proteinuria in NS, including changes in properties of the glomerular barrier, resulting in increased charge and size selectivity[14]; reduction in glomerular plasma flow or ultrafiltration pressure, which reduces proteinuria on a hemodynamic basis[14]; and inhibition of interleukin-2 production.[15] CsA has shown promise in inducing remission in both steroid-dependent and steroid-resistant NS, including that caused by FSGS. Remission rates of 30% to 70% have been reported,[11,13,16-22] but some patients have developed chronic renal failure (CRF) or CsA toxicity as a result of therapy. The major concern with the use of CsA therapy has been its potential for nephrotoxicity, reported to occur in 17% to 60% of patients.[13,23-25] Most studies reporting the effec-

From the Department of Pediatrics, Renal Section, Baylor College of Medicine and Texas Children's Hospital, Houston, TX.

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Address reprint requests to Arundhati S. Kale, MD, Renal Section, MC 3-2482, Texas Children's Hospital, 6621 Fannin, Houston TX 77030. E-mail: akale@bcm.tmc.edu

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tiveness of CsA for treatment of NS have included patients with a variety of pathological diagnoses underlying NS, and only one study was restricted to patients with biopsy-proven FSGS.[19] In all previous studies, CsA was administered orally daily in two divided doses. Because NS associated with FSGS has a particularly worse prognosis, we restricted our study population to include only those patients with biopsy-proven primary FSGS. We now report our experience with the long-term use of CsA administered as a single daily dose in a pediatric population with biopsy-proven FSGS.

MATERIALS AND METHODS

We reviewed outpatient records of all patients in whom NS was diagnosed at Texas Children's Hospital (Houston, TX) for the 10-year period from 1988 to 1997. Patients with steroid-dependent or steroid-resistant NS and biopsy-proven FSGS who were subsequently treated with CsA were identified. All renal biopsy specimens had been evaluated by light, electron, and immunofluorescence microscopy using standard methods. Twenty-one patients met the criteria and were included in this study. Their medical records were examined in detail for clinical parameters that included assessment of proteinuria; serum albumin, serum creatinine, and serum cholesterol levels; presence of hypertension; use of adjunctive therapy with angiotensin-converting enzyme (ACE) inhibitors; duration of CsA therapy; and occurrence of side effects of CsA.

All patients were administered prednisone, 2 mg/kg/d orally, for at least 6 weeks. Sixteen patients were resistant to this therapy, and five patients were partially responsive but steroid dependent. Five patients were treated unsuccessfully with cytotoxic therapy, which was discontinued before starting CsA therapy. None of the patients was treated by the Tune-Mendoza protocol of combination high-dose pulse steroids and alkylating agents.[8-10]

Nineteen patients were administered CsA in the form of Sandimmune (Novartis, East Hanover, NJ) and two patients were administered Sandimmune and Neoral (Novartis), either liquid or capsules, as a single daily dose, starting at a convenient dosage near 5 mg/kg. Actual CsA dosage was 4.6 ± 0.8 mg/kg/d. No target blood levels were set, and CsA dosages were not modified by blood levels. When measured for this study and historically in other patients treated with single daily low-dose CsA at our center, 24-hour trough blood CsA levels have been less than 50 ng/mL, so routine monitoring was not considered cost effective.

Response of NS to CsA therapy was categorized as complete remission, partial remission, or no response. Complete remission was defined as the absence of proteinuria, serum albumin level greater than 3.5 g/dL, and resolution of edema. Partial remission was defined as 1 to 2+ proteinuria by dipstick associated with a serum albumin level of 2.5 to 3.5 g/dL and the absence of edema. No response was defined as 3+ or greater proteinuria by dipstick and a serum albumin level less than 2.5 g/dL.

Statistical analysis of means was performed using unpaired *t*-test or chi-square analysis when appropriate.

RESULTS

Patient demographics and outcomes are listed in Table 1. Patients ranged in age from 1.5 to 16 years (8.8 ± 6.1 years); 9 patients (43%) were aged younger than 5 years at the start of the study period. There were 9 boys (43%) and 12 girls (57%). Ethnic distribution was 10 blacks (48%), 6 whites (28%), and 5 Hispanics (24%). Patients were followed up for a mean duration of 32 months (range, 12 to 72 months), with a mean duration of therapy of 20.6 ± 13.7 months (range, 1.6 to 61.2 months). Nonresponders were administered CsA for the shortest times (Table 1). Hypertension was diagnosed in 4 patients before starting CsA therapy. Pretreatment serum creatinine concentration was 0.8 ± 0.4 mg/dL (range, 0.3 to 1.6 mg/dl). Pretreatment mean serum cholesterol level was 376 ± 148 mg/dL (range, 154-666 mg/dL).

Sixteen patients (76%) had a response to treatment: 11 patients (52%) had a complete remission and 5 patients (24%) had a partial remission (Fig 1). Five patients (24%) failed to respond. Among patients achieving a complete or partial remission, the mean duration of therapy to time of response was 2.8 ± 0.8 months (range, 0.3 to 13.3 months). Racial distribution by response is shown in Fig 2. Sixty-seven percent of white patients, 80% of black patients, and 80% of Hispanic patients showed a response to treatment (Fig 2). Partial response was more prevalent in black and Hispanic patients than in whites. There was no significant difference in nonresponsiveness among ethnic groups. Chi-square analysis of patients' responses to steroids versus CsA did not show a predilection toward steroid responsiveness being predictive of positive CsA response. Although all 5 CsA nonresponders were steroid resistant, 8 of 11 complete responders were also steroid resistant. Two of 5 steroid-dependent patients were partial responders, and the other 3 patients had a complete remission with CsA.

The mean serum cholesterol concentration measured at the initiation of CsA therapy tended to be greater, although not significantly, in the five patients who never achieved remission. Mean cholesterol level for patients with complete remission was 306 ± 138 mg/dL; for patients with

Table 1. Patient Characteristics and Response to CsA Treatment

Patient No.	Age at Diagnosis (y)	Sex	Ethnicity	Duration of NS Pre-CsA (mon)	Estimated GFR at Diagnosis (mL/min/1.73 m²)	Steroid Response	CsA Response	Duration of CsA Therapy (mon)	Estimated GFR at Last Follow-Up (mL/min/1.73 m²)	Outcome	ACE Inhibitor Therapy
1	1.5	M	W	152.0	101	Dependent	CR	12.7	105	NF	None
2	1.7	F	H	6.9	90	Dependent	CR	15.6	147	NF	Enalapril
3	2.1	M	B	64.5	125	Resistant	CR	35.1	130	NF	None
4*	3.6	F	H	38.0	108	Resistant	CR	34.2	115	NF	None
5	5.3	M	W	80.0	130	Resistant	CR	11.0	154	NF	Enalapril
6	9.1	F	B	4.0	125	Resistant	CR	17.4	120	NF	None
7	14.2	F	B	7.7	88	Resistant	CR	34.7	85	NF	None
8	15.0	F	B	2.1	157	Resistant	CR	31.4	124	NF	None
9	15.1	F	B	2.1	159	Resistant	CR	34.2	124	NF	None
10	15.8	F	W	5.3	114	Dependent	CR	61.2	115	NF	None
11	2.5	F	W	4.7	198	Resistant	CR/NR	10.3	<10	ESRD	Enalapril
12	2.2	M	H	15.6	170	Resistant	PR	26.5	212	NF	None
13	2.6	M	H	35.1	149	Dependent	PR	25.8	111	NF	None
14*	10.2	M	B	2.2	83	Dependent	PR	15.0	86	NF	Enalapril
15	14.3	F	B	7.0	76	Resistant	PR	12.7	77	NF	Enalapril
16	14.7	F	B	4.5	91	Resistant	PR	14.6	93	NF	Captopril
17	2.8	F	W	5.8	127	Resistant	NR	13.3	38	CRF	Enalapril
18	4.1	F	W	62.8	116	Resistant	NR	27.8	<10	ESRD	Enalapril
19	15.3	M	H	2.1	83	Resistant	NR	7.3	<10	ESRD	Enalapril
20	16.0	M	B	2.9	63	Resistant	NR	3.7	<10	ESRD	Enalapril
21	16.1	M	B	6.5	61	Resistant	NR	1.6	<10	ESRD	None

Abbreviations: M, male; F, female; W, white; B, black; H, Hispanic; CR, complete remission; PR, partial remission; NR, no response; GFR, glomerular filtration rate; NF, normal function; CRF, chronic renal failure (<75 mL/min/1.73 m²).

*Administered both Sandimmune and Neoral; all others were administered only the Sandimmune preparation of CsA.

partial remission, 382 ± 158 mg/dL; but for patients with no response, 467 ± 88 mg/dL.

CsA dosage was tapered or stopped in 9 of the 16 complete responders. Three patients remained in remission at follow-up 6 to 13 months later. Six patients who had been in complete remission after 16.4 ± 10.7 months of treatment relapsed 8.7 ± 7.4 months (range, 1.5 to 18.7 months) after tapering CsA dosage or stopping CsA therapy. Five of these 6 patients responded again with complete remission when CsA dosage was increased or CsA therapy was restarted at the same dosage. One of these patients was administered concomitant daily oral steroids in addition to CsA. The patient who did not respond to a second course of CsA progressed to ESRD within 36 months. Twelve of the 16 responders were still being administered CsA at last follow-up, 11 to 60 months (mean, 24.6 months) after initiation of CsA therapy. In the 5 patients unresponsive to therapy, CsA therapy was stopped after 2 to 27 months. Four of these patients progressed to ESRD, and the other patient had CRF (Table 1).

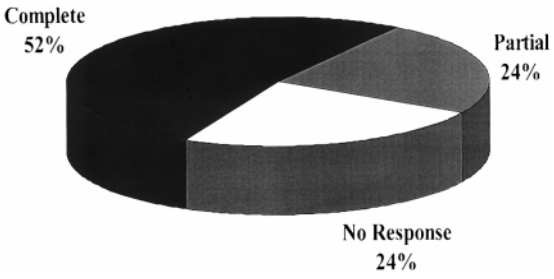

Fig 1. Response rates of NS to single daily low-dose CsA, 5 mg/kg, among 21 pediatric patients with biopsy-proven FSGS.

Ten patients (48%) were administered concomitant treatment with ACE inhibitors, usually enalapril. ACE inhibitor therapy was initiated pre–CsA treatment for control of hypertension in four patients and for proteinuria in one patient. ACE inhibitor therapy was initiated during CsA treatment for control of hypertension in one patient and for proteinuria in four patients; three

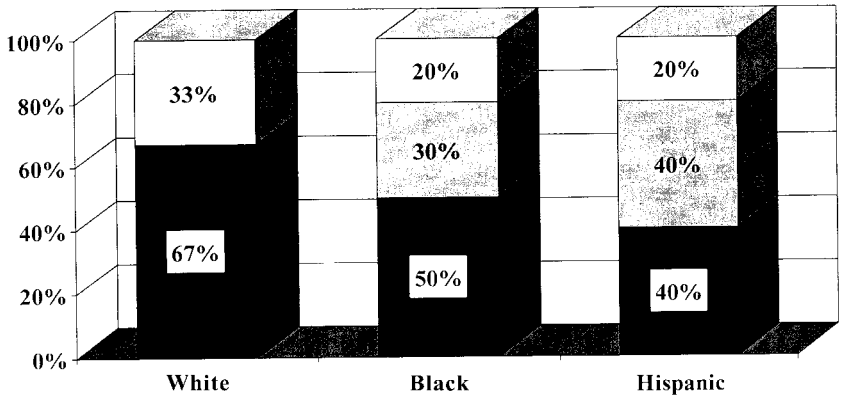

Fig 2. Ethnic distribution of response of NS to single daily low-dose CsA, 5 mg/kg, among 21 pediatric patients with biopsy-proven FSGS. (■) Complete remission; (▩) partial remission; (□) no response.

of these patients had no response to CsA, and one patient only achieved a partial remission.

Fifteen patients (71%) had no change in serum creatinine levels during CsA therapy, three patients (14%) had CRF before starting CsA therapy but had no change in their estimated glomerular filtration rate at last follow-up, one patient developed CRF after starting CsA therapy, and five patients (24%) developed ESRD. All patients who developed ESRD were nonresponders to either a first or second course of CsA, and two of these patients had CRF before starting CsA treatment. None of the patients developed hirsutism. Only one patient developed gingival hypertrophy by the end of the study period.

DISCUSSION

In this study, the response rate was 76% to treatment with single daily-dose CsA, 5 mg/kg/d, in 21 pediatric patients with steroid-resistant or steroid-dependent NS and biopsy-proven FSGS. Other studies have shown similar response rates, using 5 to 32 mg/kg/d of CsA in two divided doses and aiming for 12-hour target blood CsA levels of 70 to 500 ng/mL (Table 2).[13,16,19,21-23,26-31] We are the first to show better results using only single daily low-dose CsA resulting in 24-hour trough CsA blood levels less than 50 ng/mL when measured and little evidence of CsA toxicity. Therapeutic trough CsA blood levels at which control of proteinuria occurs are unknown for patients with NS. Our high response rate suggests that remission of NS is possible at much lower trough CsA levels than previously reported. Response may be based on peak CsA blood level or total area under the curve after a given CsA dose. Neither our study nor others have addressed this question. The majority of our patients were administered the Sandimmune brand of CsA, and only 2 patients were adminis-

Table 2. Review of Previous Studies

Reference	Diagnosis	CsA Dose (mg/kg/d)	CsA Response	Duration of Follow-Up (mon)	Side Effects	Incidence of ESRD (%)
Lieberman and Tejani[16]	FSGS (n = 12)	≥6 (target, 300-500 ng/mL)	33% Complete 67% Partial	6	17% HTN, 17% gingival hyperplasia	0
Ingulli et al[19]	FSGS (n = 21)	4-32 (target, 100-200 ng/mL)	57% Remission 19% No response	18	100% HTN, 28% gingival hyperplasia, 38% hirsutism	24
Gregory et al[13]	MCD, IgMN, FSGS (n = 22)	5-10 (target, 70-100 ng/mL)	87% Complete 13% Partial	41	14% HTN, 17% nephrotoxicity (Bx)	0
Melocoton et al[23]	MCD, IgMN, FSGS (n = 18)	≥6 (target, 100-200 ng/mL)	50% Remission	29	52% Gingival hyperplasia, 70% hirsutism, 39% nephrotoxicity (Bx)	0

Abbreviations: MCD, minimal change disease; IgMN, immunoglobulin M nephropathy; HTN, hypertension; B_x, biopsy.

tered Neoral; 1 of these patients did not respond and the other patient had complete remission. Because pharmacokinetics of the two compounds are completely different, it is possible that the type of drug preparation may influence response in nephrotic patients.

Most previous studies of the efficacy of CsA in steroid-resistant or steroid-dependent NS have included patients with a variety of underlying renal biopsy pathologies or no renal biopsy to distinguish the underlying disease process. We limited our study to pediatric patients with biopsy-proven FSGS to have a more homogenous population from which to draw conclusions. In our region, pediatric patients with FSGS have a particularly poor prognosis, accounting for approximately 35% of our ESRD population at the time of this review. Ingulli et al,[19] who also limited their study population to 21 black and Hispanic children with FSGS, but used CsA dosages up to 32 mg/kg/d divided twice daily, reported a 57% response rate, a figure somewhat lower but similar to our data. We found a high prevalence of response (67%) among whites, as well as blacks and Hispanics, in our study population, suggesting no specific racial predilection for CsA response. In both our study and that of Ingulli et al,[19] the rate of progression to ESRD was 24%, and patients who progressed to ESRD were both steroid resistant and nonresponsive to CsA therapy.

Ingulli et al[19] escalated CsA dosages up to 32 mg/kg/d based on serum cholesterol levels. Their hypothesis was that greater CsA dosages may be necessary to counteract the effect of hyperlipidemia to achieve the desired therapeutic trough CsA blood levels. Repeat renal biopsies performed at 12 to 18 months of therapy did not show CsA nephrotoxicity with the use of such high dosages of CsA, but other side effects occurred among their patients: 100% developed hypertension, 38% had hypertrichosis, and 28% had gingival hyperplasia. In a more recent adult study by the North American Nephrotic Syndrome Study Group,[22] a 70% response rate was seen with CsA dosages starting at less than 5 mg/kg/d administered in two divided doses, but with dose escalation to achieve trough blood levels of 125 to 225 μg/L. These patients also were administered daily oral prednisone. A third of the patients administered CsA developed worsening of hypertension on this study. In our study, only one patient developed hypertension (5%), none had hypertrichosis (0%), and only one patient had gingival hyperplasia (5%). We conclude that a similar to somewhat better effectiveness of CsA therapy can be achieved at lower CsA doses associated with fewer side effects.

The mean serum cholesterol concentration at the initiation of CsA therapy in our 21 patients was 376 $\pm$ 148 mg/dL. Mean serum cholesterol levels tended to be greater for our 5 nonresponders (467 $\pm$ 88 mg/dL), but was not significantly different from values for our complete- or partial-responder groups, possibly because of the small number of patients per group. We acknowledge that a subclass of patients, especially those with very high cholesterol levels, may require greater dosages of CsA than we used to achieve a response. Whether our nonresponders may have benefited from greater CsA dosages cannot be determined by the current study, but warrants further investigation.

Lieberman and Tejani[16] performed a double-blind placebo-controlled trial of CsA therapy in 24 children with FSGS and NS and showed a 100% response rate. However, only a third of the patients achieved a complete remission in the 6 months of study. Their starting dosage was 6 mg/kg/d in two divided doses, with stepwise escalation to achieve a 12-hour trough CsA level in the targeted range of 300 to 500 ng/ml. At the end of the 6-month trial, there was no difference in measured glomerular filtration rate between the treatment and control groups. A correlation was noted between prestudy serum cholesterol level and response to CsA. In our study population with a similar number of patients, but a much lower single daily CsA dose and no dose escalation to achieve targeted CsA blood levels, the response rate was 76%. Only 3 patients required more than 6 months to show a response. Our study shows that similar results may be achieved using smaller doses of the drug with fewer side effects. Administering the dose as a single daily dose may have led to greater peak CsA levels, which may account for the difference in response.

In a small study by Waldo et al,[32] a combination of pulse intravenous methylprednisolone followed by CsA and alternate-day prednisone was used in patients with steroid-resistant FSGS,

and an 80% remission rate was reported. One patient developed Hodgkin's lymphoma after 10 months of treatment, but none developed hypertension or worsening of renal function. Our remission rates are similar without the need for intravenous methylprednisolone.

Some earlier studies[23,25] also suggested that response to CsA is limited in steroid-resistant patients (0% to 36%) compared with steroid-dependent patients (80% to 100%). Other studies that included only patients with steroid-resistant FSGS have shown a 57% to 100% response rate to CsA therapy.[16,19] In our study population, the response rate was 100% in the steroid-dependent group and 69% in the steroid-resistant group. Moreover, 50% of steroid-resistant patients achieved complete remission of NS. The 5 steroid-resistant patients who reached ESRD were also CsA resistant, but even 1 of those patients had an initial complete remission that was lost when the dosage was tapered (Table 1, patient 11).

We conclude that CsA is an effective medication for the treatment of children with steroid-resistant FSGS, and treatment success can be achieved with a low dosage of oral CsA, 5 mg/kg/d, administered once daily to minimize side effects of CsA therapy. Because most patients treated with CsA for steroid-resistant FSGS remain CsA dependent, the lowest effective CsA dose should be used to avoid side effects of long-term use. Single daily dose administration may also improve patient and/or parent compliance and lead to more successful treatment outcomes with CsA.

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