Aggressive, Long-Term Cyclosporine Therapy for Steroid-Resistant Focal Segmental Glomerulosclerosis

Elizabeth Ingulli, Anup Singh, Noosha Baqi, Hadi Ahmad, Shohreh Moazami, and Amir Tejani

ABSTRACT
Short-term cyclosporine (CsA) has been shown to reduce the proteinuria in refractory nephrotic syndrome, but the effect on disease progression has not been evaluated. This study was undertaken to evaluate whether maintenance CsA therapy in steroid-resistant focal segmental glomerulosclerosis (FSGS) will prevent progression to ESRD. Twenty-one black and Hispanic children (mean age, 8.4 ± 4.5 yr) with biopsy-proven, steroid/cyclophosphamide-resistant FSGS were treated with CsA (initiated at 6 mg/kg per day and titrated to the serum cholesterol level to achieve a response). The mean CsA dose was 7 (4 to 20) mg/kg per day, the duration of CsA therapy was 27.5 (3 to 97) months, and the duration of follow-up was 8.5 ± 4.7 yr. At the end of CsA therapy, the mean (± SE) proteinuria fell from 6.2 ± 0.2 to 2.0 ± 0.1 g/24 h (P < 0.001), the mean albumin rose from 1.95 ± 0.04 to 3.41 ± 0.04 g/dL (P < 0.001), the mean cholesterol decreased from 472 ± 12.7 to 257 ± 5.3 mg/dL (P < 0.005), and the mean creatinine rose from 0.79 ± 0.02 to 1.16 ± 0.03 mg/dL (P < 0.005). Seven children continue to receive maintenance CsA therapy, and 14 patients have had CsA stopped: 6 for an increase in serum creatinine and/or continued proteinuria, 5 for sustained remission, 2 for noncompliance, and 1 for pregnancy. Five (24%) of the 21 patients progressed to ESRD. This ESRD rate was compared with a historical population (12%) of ESRD using long-term CsA therapy (5 of 21 [24%] versus 42 of 54 [78%]; P < 0.05). Long-term CsA therapy reduces the proteinuria and blunts the progression of FSGS to ESRD in black and Hispanic children.

Key Words: Cyclosporine, nephrotic syndrome, focal sclerosis

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Focal segmental glomerulosclerosis (FSGS) is the most common acquired renal disease leading to either dialysis or transplantation among North American children (1). We have previously reported that black and Hispanic children demonstrate a more virulent form of FSGS, resulting in a more rapid progression to ESRD compared with white children (2). It has been suggested that the proteinuria contributes to the progression of disease and, when massive, can accelerate the disease process (3). The treatment of proteinuria in patients with FSGS is difficult because many are resistant to corticosteroid and alkylating therapy (4,5). Short-term cyclosporine (CsA), a potent immunosuppressive, has been shown to reduce the massive proteinuria in instances where corticosteroids and alkylating agents have failed; however, discontinuation of the drug often leads to a relapse of proteinuria (6–11). We have shown improved remission rates in resistant patients using an alternative dosing regimen of CsA (12). To date, there are no studies addressing whether a reduction in the proteinuria induced with CsA in this lesion affects the devolution of renal function. In this study, we test the hypothesis that maintenance CsA therapy will reduce the proteinuria and blunt the progression to ESRD among black and Hispanic patients with FSGS.

MATERIALS AND METHODS

Patients were included in this study if they (1) had biopsy-proven FSGS and proteinuria ≥ 40 mg/m² per hour or 3 g/day; (2) were younger than 18 yr of age; (3) were black or Hispanic; (4) were corticosteroid resistant, which was defined as a failure to respond to the International Study of Kidney Disease in Children protocol of prednisone, 60 mg/m² per day, for the first 4 wk, followed by 40 mg/m² every other day for 4 wk; and (5) received at least one course of cyclophosphamide (2.5 to 3.4 mg/kg per day for 60 days). Additionally, parents and patients were required to consent to percutaneous renal biopsies at 12- to 18-month intervals after the initiation of CsA therapy.

The protocol for treating patients with CsA has varied through the years. Previously, patients received CsA at an initial daily dose of 7 mg/kg. The dose was titrated to maintain a whole blood trough level measured by high-pressure liquid chromatography between 100 and 200 ng/mL. The dose was reduced if the level was more than 200 ng/mL, but the dose was not increased above 7 mg/kg per day if the level was below 100 ng/mL (11). More recently, in the setting of severe hypercholesterolemia, the dose of CsA is titrated to the serum cholesterol level to achieve a response, regardless of blood level. Patients are started with 10 mg/kg of CsA, and the dose is gradually increased in a stepwise manner every 2 wk. In the presence of severe hypercholesterolemia, this stepwise increase in CsA dose is carried on up to a maximum of 32 mg/kg unless signs of nephrotoxicity are seen. Nephrotoxicity was defined as a rise of serum creati-
TABLE 1. The mean (± SD) proteinuria, serum albumin, serum cholesterol, and serum creatinine in the 21 patients before the initiation of CsA (PRE) and at the end of CsA therapy (POST).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PRE CSA</th>
<th>POST CSA</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria (g/24 h)</td>
<td>0.34 ± 0.02</td>
<td>0.51 ± 0.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>1.95 ± 0.73</td>
<td>3.41 ± 0.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>0.79 ± 0.14</td>
<td>1.16 ± 0.63</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The mean (± SD) proteinuria, serum albumin, and serum cholesterol at the end of CsA therapy were significantly higher than those at the initiation of CsA therapy. The mean serum creatinine at the end of CsA therapy was also higher than that at the initiation of CsA therapy.

RESULTS

Twenty-one children (13 boys) met inclusion criteria and formed the study population. Thirteen patients were black, and eight were Hispanic. All patients had biopsy-proven FSGS, and their proteinuria was resistant to both corticosteroid and cyclophosphamide therapy. The mean age of the patients at the time of diagnosis was 8.4 ± 4.5 yr. The mean duration of follow-up was 8.5 ± 4.7 yr.

The mean duration of CsA therapy was 27.5 ± 22 months, and it ranged from 3 to 97 months. Table 1 shows the mean pretherapy and posttherapy laboratory values for all patients at the end of CsA therapy. There was a significant reduction in the mean 24-h proteinuria, serum albumin, and serum cholesterol at the end of the study period. There was also a significant elevation in the serum creatinine level at the end of the study period.

At the most recent follow-up (April 1994), 7 of the 21 patients continue on maintenance CsA therapy. The current status of these patients is shown in Table 2. CsA was discontinued in the remaining 14 patients, in 5 because of sustained remission, in 5 because of rising creatinine, and in 2 because of noncompliance. Persistent proteinuria (N = 1) and pregnancy (N = 1) necessitated withdrawal in two cases. Table 3 depicts the current status of the five patients who continue to be in remission without CsA or prednisone therapy. In two patients, the drug was discontinued because the patients did not comply with the frequent clinic visits and blood tests required. Both patients were in a partial remission of their nephrotic syndrome (normal serum albumin, no edema, and proteinuria of 1.1 and

TABLE 2. The proteinuria, serum albumin, and serum creatinine before CsA treatment (PRE) and at most recent follow-up (POST), the serum cholesterol at the most recent follow-up, the duration of CsA therapy in months, and the most recent dose for the patients continuing on CSA.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Proteinuria (g/24 h)</th>
<th>Albumin (g/dL)</th>
<th>Creatinine (mg/dL)</th>
<th>Cholesterol (mg/dL)</th>
<th>Duration of CsA Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRE/POST</td>
<td>PRE/POST</td>
<td>PRE/POST</td>
<td>PRE/POST</td>
<td>CSA (months)</td>
</tr>
<tr>
<td>1</td>
<td>7.2/0.2</td>
<td>2.0/4.3</td>
<td>0.5/0.7</td>
<td>191</td>
<td>101</td>
</tr>
<tr>
<td>2</td>
<td>2.5/0.2</td>
<td>4.2/4.3</td>
<td>1.0/1.6</td>
<td>196</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>3.0/0.2</td>
<td>1.4/4.0</td>
<td>1.0/1.7</td>
<td>150</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>3.0/0.4</td>
<td>2.4/4.4</td>
<td>0.9/0.7</td>
<td>200</td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td>3.0/0.2</td>
<td>1.3/4.0</td>
<td>1.0/1.0</td>
<td>140</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>5.1/1.0</td>
<td>2.5/3.9</td>
<td>0.9/1.2</td>
<td>240</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>8.0/0.1</td>
<td>1.9/3.3</td>
<td>0.5/0.5</td>
<td>290</td>
<td>15</td>
</tr>
</tbody>
</table>

The mean duration of CsA therapy was 27.5 ± 22 months, and it ranged from 3 to 97 months. Table 1 shows the mean pretherapy and posttherapy laboratory values for all patients at the end of CsA therapy. There was a significant reduction in the mean 24-h proteinuria, serum albumin, and serum cholesterol at the end of the study period. There was also a significant elevation in the serum creatinine level at the end of the study period.
1.0 g/24 h) at the time CsA was stopped. The patients were treated with CsA for 28 and 30 months, respectively. In one of the patients, CsA was discontinued at 6.5 yr of age (serum creatinine, 0.8 mg/dL). After CsA was stopped, a relapse of the nephrotic syndrome resulted in massive proteinuria, and in 8 months, the patient progressed to ESRD. The course of this patient, plotted as 1 /cr, is shown in Figure 1. For the other patient, no follow-up was available. CsA was stopped, a relapse of the nephrotic syndrome resulted, and the patient reached ESRD in 4 months.

Five (24%) of the 21 patients have reached ESRD over the study period. The time to reach ESRD from the time of the diagnosis of FSGS in the 5 patients was 30, 43, 44, 47, and 63 months. We reviewed histology to determine if globally prominent collapse of the glomerular tuft (14) could identify progression to ESRD. Of our 21 patients, only 4 had the collapsing variant of FSGS. One of these patients has a sustained remission, one went into ESRD, one dropped out because of noncompliance, and one continues to receive maintenance CsA. In order to determine whether prolonged maintenance CsA therapy prevents the progression to ESRD, we compared the renal outcome of this study group with our historical controls previously reported (2). Despite similar racial distributions of patients in the two groups, the mean age at diagnosis, and the duration of follow-up, the renal outcome was significantly better in CsA-treated patients (6 of 21 [24%] versus 42 of 54 [78%]; P < 0.05; Table 4). An actuarial renal survival comparing this CsA-treated population with our historical controls is depicted in Figure 3.

There was no clear histologic evidence for CsA nephrotoxicity in any of the biopsy specimens; however, in all of the biopsy specimens, the lesion of FSGS persisted. Side effects included gingival hyperplasia (N = 6), hypertrichosis (N = 8), coarse facies (N = 4), and hypertension (N = 21); however, they did not necessitate the discontinuation of CsA.

**DISCUSSION**

On the basis of clinical correlations and in vitro studies, it has been suggested that the proteinuria of the nephrotic syndrome is the result of a circulating substance produced from an abnormal cellular immune response (15–20). With the improved understanding of the mechanisms of the immune response, it is now believed that the circulating substance is a cytokine, produced by T lymphocytes, that injures the glomerular basement membrane and/or the epithelial cell, resulting in the leakage of protein in the urine (21–23). Administration of interleukin-2 (IL-2) to hu-
**Figure 2.** The course of renal function, plotted as 1/cre, in Patient A.K. during CsA therapy and after the discontinuation (D/C) of CsA.

**TABLE 4.** Comparison of this study with our historical controls (2)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Historical Controls</th>
<th>This Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black, N (%)</td>
<td>38/57 (70)</td>
<td>13/21 (62)</td>
</tr>
<tr>
<td>Age at diagnosis (yr)</td>
<td>7.3 ± 4.6</td>
<td>8.4 ± 4.5</td>
</tr>
<tr>
<td>Follow-up (yr)</td>
<td>8.3 ± 4.3</td>
<td>8.5 ± 4.7</td>
</tr>
<tr>
<td>ESRD, N (%)</td>
<td>42/54 (78)</td>
<td>5/21 (24)a</td>
</tr>
</tbody>
</table>

a P < 0.05.

**Figure 3.** Actuarial renal survival for patients with steroid/cyclophosphamide-resistant FSGS treated with CsA in this study (dotted line) and historical controls (solid line).

mals has been associated with the development of nephrotic syndrome (24). Studies have shown a correlation between elevated IL-2 levels *in vitro* and its receptor, IL-2R, *in vivo* in nephrotic syndrome patients (11,25–28). CsA, a potent immunosuppressive agent, has been shown to inhibit the production of various cytokines, especially IL-2 (29). Remission of the proteinuria in patients with the nephrotic syndrome after the addition of CsA correlates with a decrease in IL-2 levels (11,25,28).

In patients with FSGS, an inverse relationship with the degree of proteinuria and time to renal failure has been reported (3). Thus, shutting off the proteinuria and remitting the nephrotic state should, theoretically, prevent renal insufficiency. Our population of predominantly black and Hispanic patients with FSGS usually demonstrated a virulent course of disease, with half predicted to reach ESRD within 3 yr (2). This time course is three to six times faster than the time course reported in the literature for predominantly white populations (30–32). The North American Pediatric Renal Cooperative Study supports the notion that the disease is more severe among black and Hispanic children and has reported that black and Hispanic children comprise 44% of renal transplants for FSGS but only 32% of the entire transplant population (33). On the basis of this, we feel that intervention in our population to prevent or slow the development of ESRD is necessary.

Many uncontrolled studies have shown CsA to be highly effective in reducing the proteinuria in steroid-dependent or frequently relapsing nephrotic syndrome (33–40). The ability of CsA to completely remit the proteinuria in cases of steroid resistance is variable (7,8,10–12,35–37,41–43). Recently, two controlled studies have shown a significant reduction in proteinuria associated with a 6-month course of CsA in steroid-resistant patients (44,45). Our current dosing of CsA is unconventional and is based on our previous observations that, in the setting of severe hypercholesterolemia, higher doses of CsA are necessary to achieve a clinical response in both idiopathic FSGS and recurrent proteinuria after renal transplantation (12,46). The need for higher doses is thought to be based on the erratic absorption of CsA, the in-
creased metabolism of the drug in children, and the amount of drug bound to serum lipids (47).

After the discontinuation of CsA, a sustained remission is variable, often necessitating the reinstitution of CsA (11,41). We, therefore, have treated patients with long-term CsA therapy to maintain the reduction in proteinuria. For this study, we evaluated the efficacy of maintenance CsA therapy in a group of patients with a high likelihood of a poor outcome due to their persistent proteinuria. The comparison of the outcome of these patients with a historical control group is not ideal, but a controlled trial using a conventional or supportive therapy arm for comparison would be redundant, because this patient group was refractory to conventional modes of therapy.

Despite similar demographics and duration of follow-up, the renal outcome between these two populations is significantly different. Fewer patients in this study have progressed to ESRD than in our historical population (2). With our aggressive dosing of CsA, we were able to maintain a sustained reduction in proteinuria in seven patients (33%) continuing on CsA and in five patients (24%) remaining off CsA for 8 to 105 months. In the remaining patients, CsA was discontinued for various reasons and more than half (five of nine) have progressed to ESRD.

It has been suggested that the antiproteinuric effect of CsA is due to its vasoconstrictive properties (47). Zeitse and colleagues have shown that CsA reduces proteinuria, independent of its effect on GFR (48). Long-term treatment with CsA is cautioned by its nephrotoxic effect. We have not been able to differentiate the histologic markers of CsA toxicity from the lesion of FSGS, despite surveillance renal biopsies in patients in remission maintained on CsA. Renal biopsies in these patients were difficult to interpret because many of the patients had interstitial changes at baseline. The persistence of the histologic lesion while in remission on CsA is concerning but not surprising because it is unlikely that the drug will reverse the damage already done. Because the incidence of ESRD is reduced and the time to reach ESRD is prolonged in these patients compared with our historical population, it appears that the nephrotoxic effect of CsA did not accelerate the disease process. Longer follow-up of these patients in remission will be necessary to see if the lesion progresses even though the proteinuria has remitted.

In summary, long-term CsA therapy successfully reduces the proteinuria in black and Hispanic children with steroid-resistant FSGS and blunts the progression to renal failure. Close monitoring of these patients is essential.

REFERENCES
