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Therapy of focal and segmental glomerulosclerosis with methylprednisolone, cyclosporine A, and prednisone

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Abstract. Patients with steroid-resistant focal and segmental glomerulosclerosis (FSGS) have a poor prognosis but may benefit from high-dose methylprednisolone or cyclosporine A therapy. Ten patients were treated with a protocol of methylprednisolone infusions for 8 weeks followed by a combination of cyclosporine A and alternate-day prednisone for maintenance of remission for 2 weeks. Eight of ten patients remitted the nephrotic syndrome within 8 weeks of beginning treatment. One patient remitted edema but remained proteinuric, and one did not respond. After observation for 12–24 months, seven patients maintained remission with normal glomerular filtration rate. One non-responder had renal insufficiency and one patient had secondary non-response and end-stage renal disease. No patients developed hypertension. One patient had the diagnosis of Hodgkin disease made after 10 months of therapy. Follow-up renal biopsy in four patients showed no evidence of progressive interstitial disease. There were no other major side effects. Steroid-resistant FSGS may be successfully treated with the described protocol. Additional studies will be needed to determine if this approach prevents progression of renal disease.

Key words: Nephrotic syndrome – Focal segmental glomerulosclerosis – Treatment – Prednisone – Cyclosporine A

Introduction

Patients with the nephrotic syndrome and focal and segmental glomerulosclerosis (FSGS) on renal biopsy are resistant to standard oral prednisone therapy in 80% or more of cases. If the nephrotic syndrome does not remit, these patients often progress to end-stage renal disease (ESRD) [1–5]. This poor prognosis has provided a rationale for the use of several novel immunosuppressive protocols, including high-dose intravenous methylprednisolone in combination with cyclophosphamide [6, 7] and cyclosporine A in various dosage schedules with or without prednisone [8]. Mendoza et al. [7] have described excellent results with a combination of methylprednisolone infusions and cyclophosphamide. Remission was achieved in 66% of patients, with another 15% achieving a partial remission (urine protein creatinine 0.2–2.0). About 10% of these patients have developed ESRD during follow-up and 15% have renal insufficiency. We have previously reported our experience with a slightly modified version of this protocol [9]; we were able to achieve a remission of the nephrotic syndrome in up to 80% of patients. However, many patients, particularly African Americans, relapsed when the frequency of methylprednisolone infusions was reduced from weekly to alternate weeks or monthly.

Cyclosporine A in conventional dosage will induce remission in 30%–60% of patients with steroid-resistant FSGS. Ingulli et al. [10] were able to achieve >80% response rate by the use of very high-dose cyclosporine A. In this protocol if a patient remains edematous with hypercholesterolemia, the cyclosporine A dose is gradually increased until either remission or toxicity occurs. Despite its efficacy in inducing remission, almost all patients will relapse if cyclosporine A is stopped.

We have designed a treatment protocol that utilizes solumedrol for induction and relatively low-dose cyclosporine A in combination with alternate-day prednisone for maintenance in the treatment of steroid-resistant FSGS. We hoped to maximize our induction rate, minimize relapses, and minimize the toxic effects of either prednisone or cyclosporineA with this approach.

Patients and methods

Patients. To be eligible for enrollment patients had to have the nephrotic syndrome as defined by the presence of generalized edema, a serum albumin <2.5 g/dl, a urine protein/creatinine ratio >3, and a renal biopsy showing FSGS. FSGS was defined by the presence of at

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least one glomerulus demonstrating a segmental area of loop collapse and sclerosis. Finally, the patient had to fail to remit the nephrotic syndrome after 6 weeks of daily divided prednisone at a dose of 2 mg/kg per day. Response to or failure of cyclophosphamide therapy was not a criterion for entry. Two patients (nos. 1 and 2) had received 84 mg/kg cyclophosphamide over 6 weeks without benefit.

Treatment regimen. Methylprednisolone (30 mg/kg per dose up to a maximum of 1 g) was given by intravenous infusion over 1 h, 3 days a week for 2 weeks, and the once weekly for 6 weeks. At the start of week 3, when weekly methylprednisolone infusions were begun, oral prednisone at a dose of 2 mg/kg every other morning (maximum dose of 80 mg) and cyclosporine A at a dose of 6 mg/kg per day (maximum dose of 300 mg) were begun.

After 8 weeks of treatment, methylprednisolone infusions were stopped and prednisone dosage reduced to 1 mg/kg on alternate mornings for 5 months (maximum dose of 40 mg), 0.5 mg/kg every other day for 6 months (maximum dose of 20 mg), and prednisone was then discontinued. After 8 weeks of treatment, the cyclosporine A dosage was reduced to 3 mg/kg daily for the duration of the study (maximum dose of 150 mg).

Remission was defined as the loss of all proteinuria, as demonstrated by a urinalysis showing negative or trace proteinuria for 3 consecutive days. Partial remission was defined as loss of edema but persistent proteinuria by urinalysis, and a urine protein/creatinine ratio >0.2 and <3.0 and a serum albumin >2.5 g/dl. Relapse was defined as either a complete or partial remission followed by redevelopment of the nephrotic syndrome.

Results

Ten patients have been treated to date. Their data are presented in Table 1. They ranged in age at presentation from 2 to 14 years (mean 6.9 years). There were seven females and three males. Four of the patients were African American and seven were Caucasian. This distribution occurred by chance alone. All patients who developed steroid-resistant FSGS during this time period were offered this treatment protocol. All patients had the nephrotic syndrome which failed to respond to 6 weeks of oral prednisone therapy and had a renal biopsy showing FSGS. Two patients (nos. 1 and 2) had received a course of Cytoxan (cyclophosphamide) (2 mg/kg per day for 6 weeks) without clinical benefit. The patients received intravenous methylprednisolone infusions as outlined above, in combination with oral cyclosporine A and alternate-day oral prednisone.

Eight of the ten patients remitted the nephrotic syndrome within 8 weeks of beginning treatment. Two patients remitted during the 2 weeks of treatment, before cyclosporine was begun. The mean time to remit was 3.6 weeks. One patient had remission of edema but continued to have proteinuria (partial remission), and one patient failed to remit. She is discussed in detail below. Of the nine patients with complete or partial remission of the nephrotic syndrome, seven maintained a full remission and one a partial remission during 1–3 years of observation.

One patient has been treated twice (patient no. 1). She initially achieved a full remission and was successfully maintained for 2 years with cyclosporine and alternate-day prednisone therapy. A repeat renal biopsy showed minimal interstitial fibrosis and 1 of 16 glomeruli showed focal sclerosis. Therapy was discontinued. Six months later the nephrotic syndrome recurred and the patient was resistant to oral prednisone therapy. The protocol of methylprednisolone and cyclosporine was restarted. On this second course of therapy the patient had loss of edema but persistence of proteinuria at >3 g/day per 1.73 m^2. After 3 months of maintenance therapy, the patient again developed the nephrotic syndrome with a decline in glomerular filtration rate (GFR), and conservative therapy with diuretics and no immunosuppression was begun. At last follow-up this patient had an estimated GFR of <10 ml/min per 1.73 m^2 and was on hemodialysis with minimal residual edema but a urine protein/creatinine ratio of 8.3.

Patient no. 4 failed to achieve a remission of the nephrotic syndrome with the initial course of 8 weeks' induction with methylprednisolone and cyclosporine. This patient had a renal biopsy with fragmented basement membrane on electron microscopy, suggestive of hereditary nephritis. However, staining with monoclonal antibodies to the $\alpha1$, $\alpha3$, $\alpha4$, and $\alpha5$ chains of type IV collagen was normal. The patient was changed to conservative therapy with diuretics and no immunosuppressives. She continued with active nephrotic syndrome and has now had slow progression of renal insufficiency, with a most recent GFR of 72 ml/min per 1.73 m^2.

One patient (no. 7) initially had a prompt response to therapy, and was treated for 10 months with cyclosporine when she presented with cervical adenopathy and the diagnosis of Hodgkin disease was made. She was treated with nitrogen mustard, oncovin, prednisone, procarbazine and Adriamycin (doxorubicin hydrochloride), bleomycin, vinblastine, and dacarbazine. She has now been followed for 36 months and remains disease free, with no proteinuria and normal renal function.

On follow-up observation of the eight patients who initially had a complete response, seven have had a sustained remission of the nephrotic syndrome and maintained a normal GFR, with a range of 79–140 (mean 113) ml/min per 1.73 m^2 by the Schwartz formula [11]. None of these patients has hypertension or abnormal liver enzymes. Growth was well maintained in those who responded. There were no cataracts or clinically evident bone disease. Mild hypertrichosis occurred in all patients on cyclosporine, but did not lead to drug withdrawal in any. Follow-up has ranged from 12 to 42 months.

Cyclosporine has been discontinued in seven patients. These include the initial treatment failure (no. 4), the secondary failure (no. 1), and the patient with lymphoma (no. 7). The other four patients have successfully been withdrawn from cyclosporine. One of these patients has had a relapse of the nephrotic syndrome which responded to oral prednisone therapy in less than 4 weeks. The other three patients remain on cyclosporine because of parental choice and are in stable remission.

Follow-up renal biopsy after at least 2 years of therapy has been performed in four of the patients and the results are outlined in Table 2. Over the 2 years of cyclosporine therapy there was no increase in the percentage of globally or segmentally sclerosed glomeruli. Interstitial disease was present focally in all patients prior to cyclosporine therapy. There was no change in the degree of interstitial disease at follow-up. One patient (no. 1) who is now on dialysis had a dramatic decline in renal function over the 2 years since her

Table 1. Results of therapy

Patient no.	Race/ gender	Age onset (years)	Years illness prior to Rx	Urine Pr/Cr pre/post	HTN status pre/post	GFR (ml/ min per 1.73 m^2) Pre Rx	GFR (ml/ min per 1.73 m^2) Rx	Time to remit NS weeks	CyA Rx months final status	Urine Pr/Cr at last visit	GFR (ml/ min per 1.73 m^2) at last visit
1	W/F	3	5	12/5	Y/N	121	121	Failed	3 off	>10	<10
2	W/M	3	0.25	28/0.2	N/Y	40	65	3.5	34 on	5 No edema	91
3	B/F	13	0.15	8/0.2	N/N	139	145	1.5	24 off	0.2	122
4	M/F	2	0.5	6/9	Y/Y	65	65	Failed	3 off	5 Mild edema	72
5	B/M	14	0.15	12/0.2	N/N	139	117	1	36 off	Neg	120
6	W/F	8	0.5	14/0.2	N/N	102	80	4.5	24 off	Neg	79
7	W/F	10	0.15	13/0.2	N/N	147	147	3.7	10 off	Neg	134
8	B/F	11	4	12/0.2	N/N	107	99	5	24 off	Neg	108
9	W/F	2	1.5	16/0.2	Y/N	33	165	6	26	Neg	123
10	B/M	3	0.15	21/0.2	Y/N	114	144	4.2	21	Neg	132

Pr/Cr, Protein/creatinine ratio; HTN, hypertension; Neg, urine negative on dipstick analysis; GFR, glomerular filtration rate; CyA, cyclosporine A; NS, nephrotic syndrome; W, white; B, black; M, male; F, female; Rx, therapy; Y, yes; N, no

Table 2. Results of follow-up renal biopsies

Patient no.	Glomerular sclerosis prior to Rx	Glomerular sclerosis after Rx	Focal glomerular sclerosis prior to Rx	Focal glomerular sclerosis after Rx	Interstitial fibrosis prior to Rx	Interstitial fibrosis after Rx
6	Nil	Nil	1 of 17	Nil	Nil	Focal, mild
3	Nil	Nil	1 of 12	1 of 11	Focal, mild	Focal, mild
2	1 of 30	1 of 24	2 of 30	Nil	Focal, mild	Focal, mild
1	1 of 17	0 of 12	3 of 17	1 of 12	Focal, mild	Nil

second biopsy was performed. This occurred after cyclosporine A was stopped because of failure to respond.

Discussion

Patients with steroid-resistant FSGS present very challenging management problems. With no immunosuppressive therapy they usually have persistent nephrotic syndrome and progress slowly towards ESRD. In the past several years, more aggressive approaches to therapy have been attempted, with some success. The current study combines the use of short-term, high-dose intravenous methylprednisolone with oral cyclosporine A and alternate-day prednisone in the treatment of these patients. The results are very encouraging. Overall there was an 80% initial remission rate. If partial remission is included, the rate goes to 90%. This compares well with the response rate observed by Mendoza et al. [7] with a combination of methylprednisolone and cyclophosphamide and is significantly better than most series with cyclosporine alone [8–10]. It is also comparable with the response rate of Ingulli et al. [10] with accelerated dose cyclosporine A. The therapy was well tolerated by most patients and GFR was well maintained in eight of the ten patients.

Despite the apparent success of the current treatment approach, there are several concerns raised. First, one patient developed Hodgkin disease. It is well known that lymphoma may cause the nephrotic syndrome [12]. Alternatively, cyclosporine is known to induce an Epstein-Barr virus (EBV)-positive B cell lymphoproliferative syndrome in transplant patients. The lymphoma in our patient was EBV negative and appeared histologically to be a Hodgkin lymphoma. This would argue against cyclosporine A being the cause of the malignancy in this patient. However, there are other reported cases of lymphoma developing during the course of cyclosporine A therapy [13–15] and immunosuppression clearly increases the risk of malignancy. This must be included in the potential complications of any vigorous course of immunosuppression.

A second area of concern is the difficulty in withdrawal of cyclosporine A. Previous data have indicated that patients who require the use of cyclosporine A for control of the nephrotic syndrome will almost all relapse when the drug is stopped. Indeed, two of the five patients in the current series who discontinued cyclosporine relapsed. However, one of these was initially unresponsive and had an unusual biopsy. This patient met the entry criteria for the present study but may have a primary disorder which is distinct from typical FSGS. The difficulty in withdrawing cyclosporine raises the issue of total duration of therapy.

There has been significant concern about the long-term nephrotoxic effects of cyclosporine A, particularly on native kidneys. Data from patients with autoimmune disorders, such as uveitis, and non-renal transplant recipients have indicated that interstitial fibrosis will develop in most native kidneys after 2 years of cyclosporine A therapy at >5 mg/kg per day [16]. Most patients with FSGS have interstitial fibrosis at diagnosis and this progresses along with their glomerular disease. This makes it impossible to clearly distinguish cyclosporine A toxicity from disease progression in patients with FSGS. Our limited follow-up biopsy data show no clinically significant progression of interstitial disease after 2 years in patients who responded

and remained protein free. It is quite significant that one patient (no. 1) had very stable renal function and biopsy findings after 2 years of successful cyclosporine therapy. When the drug was stopped she developed drug-resistant relapse and then fairly rapidly developed renal insufficiency. This may have represented the natural history of her disease, since FSGS is well described with long periods of stability followed by rapid decline. However, the years of stability on cyclosporine, followed by a rapid decline off therapy, suggests that the effects of the underlying disease are far more important in mediating renal damage than any toxic effects of the cyclosporine. Data from Ingulli et al. [10] support this concept. Their data have shown remission of the nephrotic syndrome in 12 of 21 patients with steroid-resistant FSGS and significant reduction in the rate of renal failure in long-term-treated patients (24%) compared with untreated historical controls (78%).

A fundamental problem in interpretation of these data is the uncertain natural history of FSGS. There are approximately 10% of patients who will either remit the disease or have a prolonged period of clinical stability with minimal proteinuria and no progression. Although novel therapeutic approaches, such as that described here, can remit the nephrotic syndrome it remains to be shown that they can prevent progression of the underlying glomerular disease. Prospective studies are badly needed. Given our current knowledge it seems incumbent on the clinician to make an attempt to remit the nephrotic syndrome in patients with steroid-resistant nephrotic syndrome. The combination of methylprednisolone and cyclosporine outlined here appears to offer promise in minimizing the side effects of both agents, while achieving a high initial remission rate with excellent long-term maintenance.

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Literature abstract

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Management of hyperlipidemia in children with refractory nephrotic syndrome: the effect of statin therapy

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The efficacy and safety of hydroxymethylglutaric coenzyme. A reductase inhibitor (statins) in the treatment of hyperlipidemia were evaluated in 12 infants and children with steroid-resistant nephrotic syndrome followed prospectively for 1 to 5 years. All patients experienced a hypolipidemic response with a marked reduction in their total cholesterol (40%), low-density lipoprotein cholesterol (44%), and triglyceride levels (33%), but no appreciable change in high-density lipoprotein cholesterol. Statin therapy was well tolerated without clinical or laboratory adverse effects. In spite of a significant hypolipidemic response to statin therapy there were no changes observed in the degree of proteinuria, hypoalbuminemia, or in the rate of progression to chronic renal failure. Long-term controlled studies with statin therapy are needed to further document or negate their renoprotective role in refractory nephrotic syndrome.