Pediatr Nephrol (1998) 12:737–743

Pediatric Nephrology

Original article

Quantitative morphometry of renal biopsies prior to cyclosporine in nephrotic syndrome

William E. Smoyer[1], Melissa J. Gregory[3], Ravinder S. Bajwa[2], Kent J. Johnson[2], and Timothy E. Bunchman[1]

[1] Department of Pediatrics, University of Michigan, Ann Arbor, Michigan, USA
[2] Department of Pathology, University of Michigan, Ann Arbor, Michigan, USA
[3] Department of Pediatrics, University of Rochester, New York, USA

Received June 9, 1997; received in revised form October 14, 1997; accepted January 13, 1998

Abstract. Use of cyclosporine (CsA) in the management of children with steroid-resistant (SRNS) and steroid-dependent (SDNS) nephrotic syndrome has become increasingly popular in recent years. Although most children receive a renal biopsy prior to initiation of CsA, the relationship between initial renal histology and the subsequent clinical response to CsA is not known. We analyzed the correlation between pre-CsA segmental and global glomerular scarring and interstitial fibrosis and the subsequent response to CsA in 23 children (5.6±1.0 years, Mean±SEM) with SDNS (n=8) and SRNS (n=15) treated with CsA for 24.2±3.8 months and followed for 28.0±4.1 months. Complete remission was obtained in 78% of patients within 67.6±16 days, while 18% had a partial response and 4% no response. Quantitative histological analysis revealed a trend toward partial rather than complete response with increasing segmental glomerular (P=0.13), global glomerular (P=0.05), and interstitial (P=0.08) scarring, and among patients with minimal change nephrotic syndrome versus IgM nephropathy versus focal segmental glomerulosclerosis. Among complete responders, linear regression analyses revealed no correlation between time to response and pre-CsA glomerular or interstitial scarring. We conclude that increased glomerular or interstitial scarring on a pre-CsA renal biopsy tends to correlate with a partial, rather than complete, response to CsA in childhood nephrotic syndrome.

Key words: Interstitial fibrosis – Glomerulosclerosis – Focal segmental glomerulosclerosis – IgM nephropathy

Introduction

The use of cyclosporine A (CsA) in the management of childhood nephrotic syndrome has become increasingly popular in the last several years. It has been reported to be highly effective in the management of patients with steroid-dependent nephrotic syndrome (70%–100% response rate), but somewhat less effective in those with steroid-resistant nephrotic syndrome (0%–100% response rate) [1–10]. The response to CsA in both adult and pediatric studies has also been reported to correlate with initial renal histology, with patients with minimal change nephrotic syndrome (MCNS) on renal biopsy having a better response than those with focal segmental glomerulosclerosis (FSGS) [11–17].

Despite its effectiveness, many concerns remain regarding the long-term use of CsA for childhood nephrotic syndrome. The most-serious concern stems from the risk of CsA nephrotoxicity, characterized by the development of irreversible interstitial fibrosis [18]. The reported incidence of CsA nephrotoxicity among patients with nephrotic syndrome ranges from 0%–100%, with some reports noting a higher incidence of nephrotoxicity among patients with steroid-resistant compared with steroid-dependent nephrotic syndrome [1, 4, 5, 19–22]. Because of these concerns, most patients receive a renal biopsy prior to the introduction of CsA to document the extent of pre-existing interstitial fibrosis and to establish a baseline histological diagnosis. The ability to identify on initial renal biopsy those patients who would be least likely to benefit from CsA therapy would permit nephrologists to avoid subjecting those patients to the risks associated with CsA use. Unfortunately, no data correlating the extent of pre-existing glomerular or interstitial scarring with the clinical response to CsA have previously been reported.

We recently reported a high CsA response rate among patients who fell into groups with historically poor CsA response rates: (1) steroid-resistant patients [complete response in 13/15 (87%) patients], (2) African-American patients [complete response in 4/5 (80%) patients], and (3) patients with FSGS on pre-CsA renal biopsy [complete response in 5/5 (100%) patients] [10]. This good CsA response rate even among patients with FSGS led us to hypothesize that a pre-CsA renal biopsy may be of little value in predicting the clinical response to CsA in

Correspondence to: T.E. Buchman, Department of Pediatric Nephrology, University of Michigan Medical Center, F6865 Mott, Box 0297, 1505 Simpson Road East, Ann Arbor, MI 48109-0297, USA

childhood nephrotic syndrome. In an attempt to test this hypothesis, the present report describes a detailed analysis of pre-CsA renal biopsies from 23 children with steroid-dependent or steroid-resistant nephrotic syndrome, and correlates these findings with the subsequent clinical response of these children to CsA over 1–3 years.

Patients and methods

Patients

All patients included in this study had one of the following clinical indications for the introduction of CsA therapy: (1) steroid-dependent nephrotic syndrome (*n*=8), defined as complete remission following 4–8 weeks of daily steroids, with relapse soon after transition to alternate-day therapy and evidence of steroid toxicity or (2) steroid-resistant nephrotic syndrome (*n*=15), defined as absence of a partial or complete remission following an initial course of at least 4–8 weeks of daily steroids. Of the 15 patients in the latter group, 12 received 8 weeks of daily steroids. The remaining 3 patients had received 4–6 weeks of daily steroids with the development of severe complications of nephrotic syndrome, e.g, thrombosis, when CsA therapy was begun.

Written consent for renal biopsy was obtained from all patients or their parents prior to introduction of CsA. Each patient was monitored closely throughout the study period, with frequent measurements of blood pressure, serum creatinine, and CsA levels.

Clinical management

Initial therapy for all patients included daily prednisone at 2 mg/kg per day divided twice daily, with a maximal dose of 80 mg/day. Following induction of complete remission for 5–7 days, the total daily dose was administered in the morning, followed by gradual tapering. If remission had not been achieved after 8 weeks of therapy, patients were considered steroid resistant, and transferred to alternate-day steroids at 2 mg/kg per 48 h. This dose was continued while CsA was introduced, and tapered only after complete remission was induced. A slow prednisone taper was then initiated over 3–6 months.

Relapses were managed with prednisone at 2 mg/kg per day divided twice daily, followed again by slow taper over 2–3 months after remission was induced. Among patients receiving CsA who had previously been successfully tapered completely off steroids, prednisone was restarted and again tapered completely, and the patients maintained in remission on CsA alone. No changes in target CsA levels were made.

Complete response was defined as disappearance of proteinuria for at least 7 consecutive days [urine protein negative or trace by dipstick (or urine protein/creatinine ratio <0.5 in 1 patient)], in addition to normalization of serum albumin level, and resolution of edema. Among steroid-dependent patients, complete response was further defined as maintenance of remission when the steroid dosage was decreased to levels which had previously resulted in relapse. Partial response was defined as significant and sustained improvement in serum albumin, edema, and proteinuria, but without complete normalization.

Many patients had received cytotoxic therapy prior to the introduction of CsA. Among those patients, therapy included a 12-week course of either cyclophosphamide (2 mg/kg per day) or chlorambucil (0.2 mg/kg per day). Among steroid-resistant patients, cytotoxic agents were introduced after at least 8 weeks of steroid therapy, and the time between the end of the cytotoxic therapy and introduction of CsA was variable. White blood cell counts were monitored weekly and dosage adjustments made for neutropenia.

CsA therapy

Prior to the introduction of CsA, all patients whose serum albumin levels were less than 2.0 g/dl were treated with intravenous albumin (25%, 1–2 g/kg per day) to minimize intravascular volume depletion that often is present in this setting. Loop diuretics were also frequently administered during or following the albumin infusions to induce diuresis. Cyclosporine therapy (Sandimmune) was initiated at approximately 5–8 mg/kg per day, and doses adjusted to aim for target whole blood high-performance liquid chromatography trough levels of 70–120 ng/ml. Levels were followed at 2 to 4-week intervals. Following induction of remission, dosage adjustments were made only for trough levels above 120 ng/ml. Patients who had repeated relapses were maintained at slightly higher target CsA trough levels (100–120 ng/ml).

Routine histological evaluation

Renal biopsies were performed under ultrasound guidance using either a 16- or 18-gauge biopsy needle (Bard, Covington, Ga., USA). Biopsy samples were evaluated by light microscopy (using hematoxylin and eosin, periodic acid-Schiff, trichrome, and Jones stains), immunofluorescence (IF) microscopy, and electron microscopy. Each biopsy was reviewed by both a renal pathologist and pediatric nephrologist. Diagnoses were assigned using standard histological classifications.

MCNS was defined as minimal or no histological abnormalities on either light or IF microscopy and only diffuse foot process effacement on electron microscopy.

IgM nephropathy was defined as diffusely increased mesangial hypercellularity, often with diffusely increased mesangial matrix, but with minimal or no segmental glomerular sclerosis on light microscopy, mesangial IgM deposition on IF microscopy, and diffuse foot process effacement with mesangial immune deposits on electron microscopy.

FSGS was defined as focal glomerular abnormalities with segmental areas of sclerosis on light microscopy, deposition of C3 and IgM on IF microscopy, and diffuse foot process effacement with mesangial immune deposits on electron microscopy.

The extent of segmental and global glomerular scarring was determined by a renal pathologist, who analyzed the number of segmentally and globally scarred glomeruli and the total number of glomeruli in each biopsy. Values for percentage glomerular scarring were determined by calculating the percentage of total glomeruli in each biopsy which had either segmental or global scarring.

Quantitative digital morphometric histological analysis

Quantitative morphometric analysis of all biopsy tissues was performed to determine the extent of interstitial fibrosis present at the time of CsA initiation. For this analysis, interstitial areas of trichrome-stained biopsy slides were scanned with a video imaging system (Olympus BX40 microscope connected to a Sony CCD/RGB color video camera) at 40× magnification using IP Lab Spectrum software (Signal Analytic, Vienna, Va., USA) and a MacIntosh IIfx computer. Scanning windows were set for each specimen to quantify blue staining representing interstitial fibrosis. All available fields were scanned for each biopsy, providing an average of 23 fields (range 7–62) per biopsy. This quantitative approach for the measurement of interstitial fibrosis has been reported previously, and has proven highly accurate in the analysis of the extent of renal scarring [23].

Statistical analyses

Linear regression analyses were used to compare the correlation between the extent of renal scarring and the subsequent time to complete response to CsA using Cricket Graph computer graphics software. A correlation coefficient (*r*) less than 0.25 was interpreted to indicate little or no relationship between the variables. Comparisons between groups was made using unpaired, two-tailed *t*-tests.

Results

A total of 23 patients (aged 1.5–15.5 years) were included in the study. Of the 23 patients, 11 (48%) were female and 4 (17%) were African American. The mean age at the time of diagnosis was 5.6±1.0 (±SEM) years and the mean age at initiation of CsA was 6.7±1.0 years, resulting in a mean duration of nephrotic syndrome prior to CsA of 1.1±0.4 years. At the time of CsA introduction, 15 of 23 patients (65%) were steroid resistant, while 8 of 23 (35%) were steroid dependent. Twenty patients (87%) had previously received treatment with cytotoxic agents, including 13 of 15 (87%) steroid-resistant patients and 7 of 8 (88%) steroid-dependent patients. Renal biopsies performed prior to introduction of CsA revealed MCNS in 1 patient (4%), IgM nephropathy in 15 patients (65%), and FSGS in 7 patients (31%).

Table 1 shows the details of CsA usage, clinical response, and duration of follow-up for the study patients. The CsA dosages required to maintain trough CsA levels within the target range were similar over the course of the study. For the study population as a whole, 22 of 23 patients (96%) had at least a partial response to CsA, when treated with CsA combined with high-dose alternate-day steroids. These findings are consistent with our previously reported results in a similar, but not identical, group of patients (19 of the 23 patients common to both groups) [10]. Among the 4 patients (18%) who had only partial responses to CsA, the mean serum albumin increased from 2.8 to 3.7 g/dl and the mean urinary protein to creatinine ratio decreased from 4.92 to 1.91.

Following the introduction of CsA, serum creatinine values were monitored at 1 to 3-month intervals. Comparison of the mean serum creatinine values prior to CsA (0.45±0.04 mg/dl, ±SEM), after 6 months of CsA therapy (0.51±0.05 mg/dl), and after 12 months of CsA therapy (0.49±0.05 mg/dl) revealed no apparent significant effect of CsA on renal function.

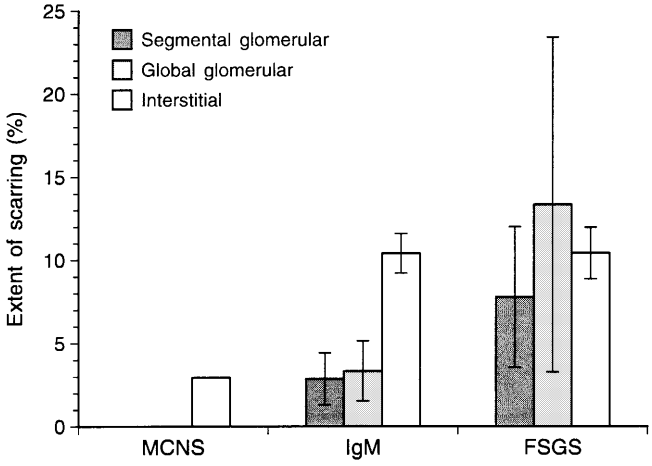

Fig. 1. Comparison of renal scarring based on pre-cyclosporine (CsA) renal histological diagnosis. The relationship between pre-CsA renal histology minimal charge nephrotic syndrome (*MCNS*), IgM nephropathy (*IgM*), [or focal segmental glomerlosclerosis (*FSGS*)] and the extend of segmental and global glomerular scarring (% of glomeruli involved), and interstitial fibrosis (as analyzed using digital morphometric quantitation of the entire interstitium of each biopsy specimen) is shown. A trend toward increased segmental and global glomerular and interstitial scarring was noted in patients with MCNS vs. IgM vs. FSGS. *P*=NS for FSGS vs. IgM for all types of scarring; *n*=1 patient with MCNS, 15 with IgM, and 7 with FSGS

Both glomerular and interstitial histological characteristics of the pre-CsA renal biopsies were determined for the entire study group. The average number of glomeruli per biopsy was 18.2±2.4, which confirms that the biopsy specimens were adequate for analysis. The mean number of glomeruli per biopsy with segmental scarring was 0.83±0.3 (4.3%±1.6%), while the mean number of glomeruli per biopsy with global scarring was 1.0±0.6 (6.2%±3.3%). Quantitative digital morphometric analysis of the entire interstitium in each biopsy specimen revealed that the mean percentage of the interstitium per biopsy with interstitial fibrosis was 10.1%±0.9%.

Table 1. Cyclosporine (CsA) usage, clinical response, and follow-up (*n*=23 patients)

Starting CsA dosage	7.2±0.6 mg/kg per day
Final CsA dosage	7.4±0.7 mg/kg per day
Average trough HPLC CsA level	90.7±3.8 ng/ml
Response to CsA	Complete or partial remission [22 patients (96%)]
	Complete remission [18 patients (78%)]
	Partial remission [4 patients (18%)]
	No response [1 patient (4%)]
Time to CsA response	67.6±16 days
Maintenance in remission on CsA monotherapy (prednisone stopped)	22%
Total time on CsA	24.2±3.8 months
Duration of follow-up	28.0±4.1 months

HPLC, High-performance liquid chromatography

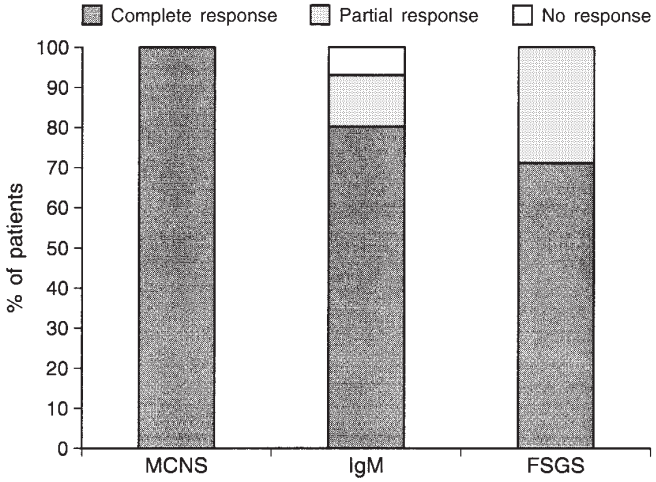

Fig. 2. Comparison of the clinical response to CsA based on pre-CsA renal histological diagnosis. The relationship between the Pre-CsA renal histological diagnosis (MCNS, IgM, and FSGS) and the percentage of patients who had a complete, partial, or no response to CsA is shown. The majority of patients in each group had a complete response to CsA, although a trend toward partial rather than complete response was seen among patients with MCNS vs. IgM vs. FSGS. Despite this, 100% of patients with FSGS (and the patient with MCNS) had at least a partial response, compared with 93% of those with IgM. *n*=1 patient with MCNS, 15 with IgM, and 7 with FSGS

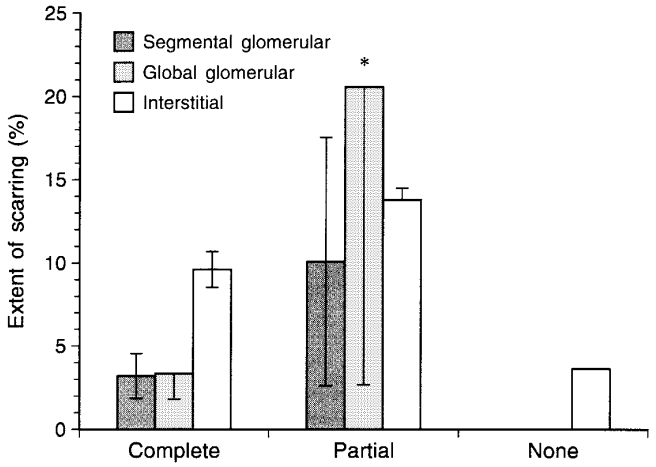

Fig. 3. Relationship between the type and extent of renal scarring and the clinical response to CsA. A comparison of the relationship between the extent of segmental glomerular scarring, global glomerular scarring, and interstitial fibrosis on pre-CsA renal biopsy, and the subsequent clinical response to CsA is shown. A trend toward a partial rather than a complete response to CsA was seen with more-extensive scarring of each of the three types. The only patient who had no response to CsA, however, had no segmental or global glomerular scarring, and less interstitial fibrosis (3.8%) than those patients with either a complete (9.6%) or partial (13.8%) response. The findings suggest that moderately increased scarring of any type may be predictive of a partial, rather than complete, clinical response to CsA, but not resistance to CsA. **P*=0.05 vs. complete response, *n*=18 patients with complete, 4 with partial, and 1 with no response

In contrast to the above data for the entire study population, Fig. 1 displays a comparison between the extent of renal scarring in each of the three pre-CsA renal histological groups. Consistent with the histological definitions, no glomerular scarring was present in the patient with MCNS. Minimal segmental glomerular scarring was noted in 3% of glomeruli from patients with IgM nephropathy compared with 7.8% of glomeruli from those with FSGS (*P*=NS for FSGS vs. IgM). Global glomerular scarring was seen in 3.4% of glomeruli from patients with IgM nephropathy, while it was found in 13% of glomeruli from patients with FSGS (*P*=NS for FSGS vs. IgM). Quantitative digital morphometric analysis of the entire interstitium from each biopsy revealed 3.0% interstitital fibrosis in the patient with MCNS, 10.4% in those with IgM nephropathy, and 10.5% in those with FSGS (*P*=NS for FSGS vs. IgM).

Following the introduction of CsA, a detailed analysis was performed of the relationship between several pre-CsA renal biopsy parameters (histological diagnosis, segmental and global glomerular scarring, and interstitial fibrosis) and the subsequent response to CsA. The clinical response to CsA therapy for each of the three histological groups is shown in Fig. 2. Although the majority of patients in each group had a complete response to CsA, a trend toward a partial rather than complete response was seen among patients with MCNS versus IgM nephropathy versus FSGS. Despite this, a partial or complete response was seen in 100% of those with FSGS or MCNS, compared with 93% of patients with IgM nephropathy. Among patients who had a complete response to CsA, the mean time to response was 60 days for the patient with MCNS (*n*=1), 61±18.5 days for those with IgM nephropathy (*n*=12), and 86±36.5 days for those with FSGS (*n*=5) (*P*=NS for FSGS vs. IgM).

Figure 3 shows the overall relationship between the type and extent of renal scarring and the clinical response to CsA for all 23 patients. A trend toward a partial rather than a complete response to CsA was seen with more-extensive segmental glomerular scarring (*P*=0.13), global glomerular scarring (*P*=0.05), and interstitial scarring (*P*=0.08). Despite this, the only patient who had no response to CsA had no segmental or global glomerular scarring, and markedly less interstitial fibrosis (3.8%) than those patients with either a partial (13.8%) or complete (9.6%) response. Thus, increased glomerular (segmental or global) or interstitial scarring correlated with a partial rather than complete clinical response to CsA, but not with CsA resistance.

For the 18 patients (78%) in the study who had a complete response to CsA, linear regression analyses were used to determine the correlation between each of the types of renal scarring and the time to complete response to CsA (Fig. 4). Figure 4a shows the correlation between segmental glomerular scarring and the time to complete response, while Fig. 4b shows the correlation between global glomerular scarring and complete response, and Fig. 4c the correlation between interstitial fibrosis and complete response. These analyses revealed essentially no correlation between the extent of segmental glomerular scarring (*r*=0.08) or interstitial fibrosis (*r*=0.15) and the time to complete clinical response to CsA. Interestingly, a weak negative correlation (*r*=0.25) was seen between the extent of global glomerular scarring and the time to complete CsA response.

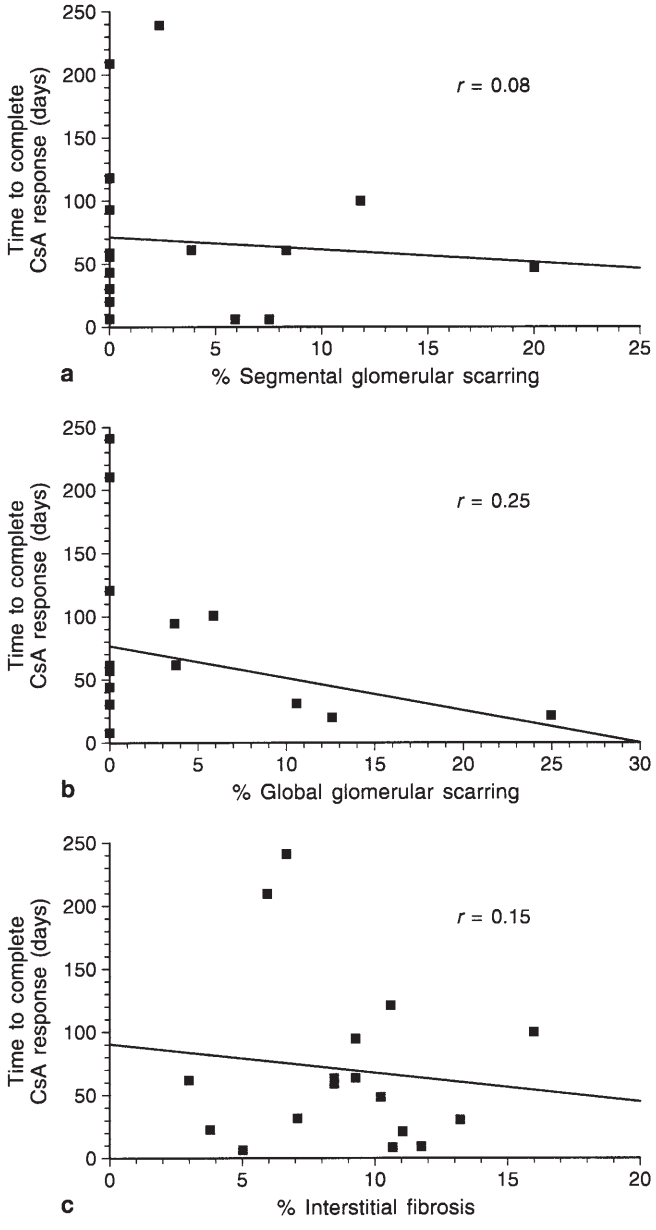

Fig. 4. Relationship between renal scarring and complete clinical response to CsA. **a** shows the correlation between pre-CsA segmental glomerular scarring and the time to complete clinical response to CsA among the 18 patients who had a complete response; **b** shows the correlation between pre-CsA global glomerular scarring and the time to complete clinical response to CsA; **c** shows the correlation between pre-CsA interstitial fibrosis and the time to complete clinical response to CsA. No correlation was seen between segmental glomerular scarring or interstitial fibrosis and the time to complete response to CsA, and only a weak negative correlation between global glomerular scarring and the time to CsA response. These findings suggest that increased glomerular or interstitial scarring on a pre-CsA renal biopsy does not prolong the time to clinical response among patients who have complete responses to CsA

Discussion

Because of the clinical efficacy of CsA in the management of children with steroid-dependent and steroid-resistant nephrotic syndrome, its use will almost certainly continue to increase in the future. Since there are potentially serious risks associated with its use, identification of specific situations in which it would be unlikely to be effective could provide important guidelines for directing therapy in these patients. Although the majority of nephrotic patients who are begun on CsA receive a renal biopsy prior to the introduction of CsA, the value of the biopsy in predicting the subsequent clinical response to CsA has not been clearly defined.

Several poor prognostic indicators for the response to CsA in nephrotic syndrome have previously been reported. These include African-American race [24], steroid resistance [4, 18], and the presence of FSGS on renal biopsy [8, 11]. The relationship between mesangial hypercellularity and IgM deposits (IgM nephropathy) and the response to CsA has not been often reported, but in our experience this group of patients was highly responsive to CsA (93% complete remission) [10]. This histological lesion, including increased mesangial hypercellularity and matrix with mesangial IgM deposition, has been referred to as IgM nephropathy, although some pathologists do not recognize it as a specific pathological lesion.

The present study attempted to identify what pre-CsA renal biopsy parameters, if any, could aid the clinician in estimating a nephrotic child's likelihood of responding to CsA. Our findings represent a comprehensive, quantitative analysis of the relationship between the clinical response to CsA and several important pre-CsA renal biopsy parameters, including: (1) histological diagnosis, (2) segmental glomerular scarring, (3) global glomerular scarring, and (4) interstitital fibrosis. To our knowledge, no similar analysis of this relationship has previously been reported.

Our results revealed a trend toward a partial, rather than complete response to CsA among patients with MCNS versus IgM nephropathy versus FSGS, consistent with previous reports [8, 12, 15]. Although too few patients were analyzed to permit a meaningful statistical comparison between the groups, clearly a majority of patients with both IgM nephropathy and FSGS had a complete response to CsA, and 100% of patients with FSGS had at least a partial response compared with 93% of those with IgM nephropathy. Although these response rates compare favorably with other reports [8, 11], a more-important observation was that no specific renal histological diagnosis was clearly associated with a poor response to CsA (i.e., CsA resistance).

Comparison of the extent of each of the three types of renal scarring with the response to CsA also revealed a trend toward a partial, rather than complete, response to CsA among patients with increased segmental glomerular, global glomerular, or interstitial scarring. Among the three types of scarring, increased global glomerular scarring revealed the strongest trend (P=0.05) toward predicting a partial response, and would likely gain statistical significance in a larger patient population. Despite this trend, the single patient who had no response to CsA had no glomerular scarring and less interstitial scarring than patients with either a complete (n=18) or partial (n=4) response. The present findings thus suggest that moderately increased renal scarring of any type may be predictive of a partial, rather than complete, clinical response to CsA, but not resistance to CsA.

Identification of only 1 patient who failed to respond to CsA clearly limits the ability of this study to rigorously quantitate the predictive value of a pre-CsA renal biopsy. This point is far overshadowed, however, by the observation that pre-CsA renal biopsies in a group of patients with IgM nephropathy and FSGS, and variable extents of glomerular and interstitital scarring, did not distinguish any subset of patients unlikely to respond to CsA (i.e., CsA-resistant patients). Indeed, this excellent response rate is perhaps the most compelling indicator of the potential effectiveness of CsA in patients with nephrotic syndrome, regardless of the underlying histological findings.

In the absence of evidence to suggest that a pre-CsA renal biopsy could identify patients who would be CsA resistant, we sought to determine if it could predict the time to response among those patients with a complete response. Linear regression analyses of the correlation between the extent of glomerular and interstitial scarring and the time to complete CsA response revealed that no correlation was present. These findings suggest that increased glomerular or interstitial scarring on a pre-CsA renal biopsy does not prolong the time to clinical response among patients who subsequently have a complete response to CsA.

The lack of a clear correlation between pre-CsA renal biopsy findings and the subsequent clinical response to CsA in this study raises some potentially important issues in this era of increasing cost containment. Historically, the standard of care at most institutions has been to perform a renal biopsy prior to the introduction of CsA for the management of children with nephrotic syndrome. The rationale for this has usually been that having a histological diagnosis would be helpful in guiding management decisions, and that establishing a baseline level of interstitial fibrosis was critical to monitor potential development of CsA nephrotoxicity. The present findings suggest that a renal biopsy may not be helpful in predicting whether a given patient will respond to CsA, and that an empirical trial of CsA could be considered. We belive that such an approach would be unwise in that it would preclude the nephrologist from being able to distinguish progressive interstitial fibrosis (CsA nephrotoxicity) from pre-existing scarring in those patients who subsequently develop renal insufficiency while receiving CsA. Despite this very serious risk, if the findings in this study prove to be true in larger groups of patients, it is possible that increasing pressure will be placed on nephrologists in the future for the standard of care to shift away from the use of pre-CsA renal biopsies. Finally, it is important to point out that the patients evaluated in this study all had essentially normal age-adjusted serum creatinine values. Extrapolation of these results to patients with moderate, or even mild, renal insufficiency would clearly be inappropriate.

In summary, the present study represents a comprehensive, quantitative analysis of the relationship between the clinical response to CsA and several important pre-CsA renal biopsy parameters, including: (1) histological diagnosis, (2) segmental glomerular scarring, (3) global glomerular glomerular or interstitial scarring, and (4) interstitial fibrosis. Our findings revealed a trend toward a partial rather than complete response to CsA, but not CsA resistance, among patients with increasing glomerular and interstitial scarring, and among patients with MCNS versus IgM nephropathy versus FSGS. Among those patients who had a complete response, no correlation was found between the time to complete response and the extent of pre-CsA glomerular or interstitial scarring. We conclude that increased segmental glomerular, global glomerular, or interstitial scarring on a pre-CsA renal biopsy tends to correlate with a partial, rather than complete, response to CsA in childhood nephrotic syndrome.

References

1. Capodicasa G, De Santo NG, Nuzzi F, Giordano C (1986) Cyclosporine A in nephrotic syndrome of childhood – a 14 month experience. Int J Pediatr Nephrol 7:69–72
2. Tejani A, Butt K, Trachtman H, Suthanthiran M, Rosenthal CJ, Khawar MR (1988) Cyclosporine A induced remission of relapsing nephrotic syndrome in children. Kidney Int 33: 729–734
3. Niaudet P, Habib R, Tete M-J, Hinglais N, Broyer M (1987) Cyclosporine in the treatment of idiopathic nephrotic syndrome in children. Pediatr Nephrol 1:566–573
4. Niaudet P, Broyer M, Habib R (1991) Treatment of idiopathic nephrotic syndrome with cyclosporine A in children. Clin Nephrol 35:S31–S35
5. Neuhaus TJ, Burger HR, Klingler M, Fanconi A, Leumann EP (1992) Long-term low-dose cyclosporin A in steroid dependent nephrotic syndrome of childhood. Eur J Pediatr 151: 775–778
6. Tanaka R, Yoshikawa N, Kitano Y, Ito H, Nakamura H (1993) Long-term ciclosporin treatment in children with steroid-dependent nephrotic syndrome. Pediatr Nephrol 7:249–252
7. Ponticelli C, Rizzoni G, Edefonti A, Altieri P, Rivolta E, Rinaldi S, Ghio L, Lusvarghi E, Gusmano R, Locatelli F, Pasquali S, Castellani A, Della Casa-Alberighi O (1993) A randomized trial of cyclosporine in steroid-resistant idiopathic nephrotic syndrome. Kidney Int 43:1377–1384
8. Niaudet P, French Society of Pediatric Nephrology (1994) Treatment of childhood steroid-resistant idiopathic nephrosis with a combination of cyclosporine and prednisone. J Pediatr 125:981–986
9. Lee HY, Kim HS, Kang CM, Kim SG, Kim SJ (1995) The efficacy of cyclosporine A in adult nephrotic syndrome with minimal change disease and focal-segmental glomerulosclerosis: a multicenter study in Korea. Clin Nephrol 43:375–381
10. Gregory MJ, Smoyer WE, Sedman AS, Kershaw DB, Valentini RP, Johnson K, Bunchman TE (1996) Long-term cyclosporine therapy for pediatric nephrotic syndrome: a clinical and histologic analysis. J Am Soc Nephrol 7:543–549
11. Meyrier A, Condamin M-C, Broneer D, The Collaborative Group of the French Society of Nephrology (1991) Treatment of adult idiopathic nephrotic syndrome with cyclosporin A: minimal-change disease and focal-segmental glomerulosclerosis. Clin Nephrol 35:S37–S42
12. Ittel TH, Clasen W, Fuhs M, Kindler J, Mihatsch MJ, Sieberth HG (1995) Long-term ciclosporine A treatment in adults with minimal change nephrotic syndrome or focal segmental glomerulosclerosis. Clin Nephrol 44:156–162
13. Ponticelli C (1992) Treatment of the nephrotic syndrome with cyclosporin A. J Autoimmun 5 [Suppl A]: 315–324

14. Meyrier A, Noel L-H, Auriche P, Callard P, Collaborative group of the Societe de Nephrologie (1994) Long-term renal tolerance of cyclosporin A in adult idiopathic nephrotic syndrome. Kidney Int 45:1446–1456
15. Hymes LC (1995) Steroid-resistant, cyclosporine-responsive, relapsing nephrotic syndrome. Pediatr Nephrol 9:137–139
16. Walker RG, Kincaid-Smith P (1990) The effect of treatment of corticosteroid-resistant idiopathic (primary) focal aand segmental hyalinosis and sclerosis (focal glomerulosclerosis) with ciclosporin. Nephron 54:117–121
17. Brodehl J, Brandis M, Helmchen U, Hoyer PF, Burghard R, Ehrich JH, Zimmerhackl RB, Klein W, Wonigeit K (1988) Cyclosporin A treatment in children with minimal change nephrotic syndrome and focal segmental glomerulosclerosis. Klin Wochenschr 66:1126–1137
18. Niaudet P, Habib R (1994) Cyclosporine in the treatment of idiopathic nephrosis. J Am Soc Nephrol 5:1049–1056
19. Sieberth H-G, Clasen W, Fuhs M, Ittel T, Kindler J, Mihatsch MJ (1992) Serial kidney biopsies in patients with nephrotic syndrome treated with cyclosporin. J Autoimmun 5 [Suppl A]:355–361
20. Ingulli E, Singh A, Baqi N, Ahmad H, Moazami S, Tejani A (1995) Aggressive, long-term cyclosporine therapy for steroid-resistant focal segmental glomerulosclerosis. J Am Soc Nephrol 5:1820–1825
21. Melocoton TL, Kamil ES, Cohen AH, Fine RN (1991) Long-term cyclosporine A treatment of steroid-resistant and steroid-dependent nephrotic syndrome. Am J Kidney Dis 18:583–588
22. Habib R, Niaudet P (1994) Comparison between pre- and posttreatment renal biopsies in children receiving ciclosporine for idiopathic nephrosis. Clin Nephrol 42:141–146
23. Young EW, Ellis CN, Messana JM, Johnson KJ, Leichtman AB, Mihatsch MJ, Hamilton TA, Groisser DS, Fradin MS, Voorhees JJ (1994) A prospective study of renal structure and function in psoriasis patients treated with cyclosporin. Kidney Int 46:1216–1222
24. Ingulli E, Tejani A (1991) Racial differences in the incidence and renal outcome of idiopathic focal segmental glomerulosclerosis in children. Pediatr Nephrol 5:393–397