

Cyclosporine in the Treatment of Idiopathic Focal Segmental Glomerulosclerosis

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Cyclosporine is a known powerful immunosuppressive medication and has been used in the treatment of focal segmental glomerulosclerosis (FSGS) for over a decade. Its precise mechanism of action in this disorder is still debated and is likely at more than one level related to the pathophysiology of the disease. Multiple studies have been performed but the numbers of randomized trials of this drug in this disease are very limited. However, both the best studies in children and adults indicate in the steroid-resistant patients that 50% to 70% will have a response in terms of a significant reduction in proteinuria. Provided the total dose is kept to 5 mg/kg or less and duration to less than 12 months, the drug is safe but careful monitoring is required to maintain the blood pressure at ideal levels and to avoid nephrotoxicity. Relapses are common, but rather than considering this a failure of therapy the drug should be reintroduced because in most cases it will reestablish control of the proteinuria. Although in the past cyclosporine has been considered a second-line agent in FSGS, emerging data would suggest in the high-risk patients related to corticosteroid toxicity it should be considered primary therapy.

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THE USE OF cyclosporine (csa) in the treatment of glomerular diseases began shortly after the introduction of this agent in the treatment of solid organ transplantation in 1976.^{1,2} This fungal peptide is a proven powerful immunosuppressant. Its effects are reversible and specific for the T lymphocyte. The hematopoietic tissue is not affected. The latter is particularly important and is in marked contrast to the cytotoxic agents commonly used in other types of renal disease. The precise molecular mechanisms of action of CSA and the effect on the immune response at the macrophages, monocyte, and T-cell level involves both the inhibition of interleukin 2 and cytokine production.³ Its mechanism of action in the glomerular diseases has been the subject of much debate over the past 2 decades. The original hypothesis formulated in 1986 suggested that CSA modified the vascular permeability factor thought to be of T-cell origin and important in the pathophysiology of both minimal change disease and focal segmental glomerulosclerosis (FSGS).⁴ The complete remission commonly observed with CSA treatment in patients with minimal change disease suggests that it reverses or interrupts the pathogenic process completely in this disease.^{2,5,6} In other forms of ne-

phropathy the CSA response often was not complete and this led to speculation that it was related to the hemodynamic effects of the agent rather than immune suppression.⁷ Zietse et al^{8,9} have examined the drug's effects on the glomerular filtration barrier by comparing the fractional clearances of endogenous proteins that vary in both size (eg, albumin versus immunoglobulins) and charge (eg, immunoglobulin (Ig)G versus IgG₄). The studies performed in minimal change disease indicated albumin excretion is the dominant protein lost compared with the larger immunoglobulins, resulting in a high selectivity index (ie, the sieving of small dextrans [$<50 \text{ \AA}$] is depressed), indicating a defect in the charge-selective properties of the GBM. Based on mathematic models, this is most compatible with a marked decrease in ultrafiltration coefficient (K_f) with only a slight increase in flow through the so-called nondiscriminatory shunt pathway. These investigators studied the changes with CSA treatment and concluded that the effect on glomerular barrier function was related to an increase in K_f (ie, results in an increase in filtration surface area), most probably through an improvement in the function of the glomerular epithelial cell. The investigators also were able to show the marked loss in glomerular charge activity was improved significantly with CSA, indicating the drug increased the negative charge content of the glomerular basement membrane. How this occurs and its relationship to the basic pathophysiology of the disease is unknown.

Recent work by Sharma et al^{10,11} on the effects of CSA on isolated glomeruli in vitro indicates, however, that the drug may work independently of

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the vascular permeability factor. In contrast, in membranous nephropathy a presumed immune complex disease in which no vascular permeability factor is felt to be relevant but, similar to FSGS proteinuria, is unselective, the effects of CSA are different. Fractional clearance of both albumin and the larger proteins such as IgG are increased in this disease. This is a result of a defect in the size-selective properties of the glomerular filtration barrier, indicating a significant increase of flow through the large unselective shunt pores. Zietse et al⁹ have shown CSA increased filtration fraction associated with altered glomerular permeability, indicating the effect in membranous nephropathy is independent of renal hemodynamics. These investigators suggest therefore that CSA may alter permselectivity in these cases via inhibition of transcriptions of various cytokines. In summary, the specific mechanism of action of CSA in FSGS still is unclear and may be at multiple levels.

Whether these actions of CSA or others are operative in FSGS remains a subject of debate. This is perhaps not surprising given the continuing changes that have been observed in the disease itself in terms of new etiologic agents implicated in causation of the FSGS lesion such as human immunodeficiency virus nephrotoxicity, additional histologic types such as the hilar variant, and recently described genetic abnormalities associated with the disease such as the α -actinin-4 defect. The specific relationship between drugs that modify T-cell response such as CSA and T-cell/monocyte production of vascular permeability factor and the idiopathic form of this disorder cannot truly be defined until we determine specific etiologic agents and perhaps common pathways related to disease progression.

Despite these limitations we review the best of the clinical studies in primary FSGS in relationship to CSA's emerging role in its treatment. Use of this agent in FSGS dates back to results published in abstract form at the American Society of Nephrology meeting in 1985.¹² Despite this long history, even today it must be recognized that the majority of the trials and studies published on the effects of CSA on both short- and long-term outcome in patients with this disorder have quite variable definitions in regards to the clinical state of the patient and treatment preceding their CSA exposure. These now are recognized as important factors that are likely to substantially alter the response to CSA

(eg, steroid responsive versus resistant cases and short prednisone treatment versus prolonged prednisone therapy before CSA therapy). The background in terms of steroid exposure and response in each patient is important and is underlined by our publication on the long-term outcome in children and adults with primary FSGS.¹³ Aside from a slightly higher percentage of nephrotic syndrome at presentation in children versus adults, the groups were equal at that time in terms of their creatinine clearance corrected for body size, incidence of hematuria, and hypertension. Outcome also was similar. Over an average observation period of 11 years, end-stage renal disease occurred in 34% of children versus 32% of adults, chronic renal insufficiency in 11% versus 13%, and low-grade persistent proteinuria in 13% versus 24%. Similarly, in the prednisone-treated patients, complete remission also was equal, 47% versus 44%. This emphasizes that within the defined classic FSGS pathology there is a variation of responsiveness with steroid-sensitive, steroid-dependent, and steroid-resistant cases and that much of the variance in terms of the percentage in each series labeled as steroid resistance appears to be related to the timing and duration of treatment.^{14,15} It is the highest, for example, when the diagnosis is made after a standard corticosteroid course is given and lowest when a higher dose and more prolonged prednisone course is administered. We therefore note the steroid-resistance definition in each CSA study reviewed, if given. Although recent reports have suggested a minimum duration of prednisone treatment of 6 months, this number actually is based on the maximum time to response.¹⁶ The increasing risk for drug toxicity often precludes this duration.^{16,17} Also, what constituted a response in terms of complete or partial remission of proteinuria varies considerably and markedly influences the percentage labeled steroid resistant before starting CSA therapy.^{15,16} Our review on CSA therapy in FSGS attempts to define these pretreatment variables, but we are somewhat limited by the information provided by the investigators.

We also focus on studies or parts of studies in which the specific lesions of FSGS have been found rather than attempt to review all studies in which CSA was given to patients with resistant nephrotic syndrome given the earlier variations. This was done to try and produce some homogeneity to the review. This disease still has a bad

Table 1. Levels of Evidence of Rating Studies of Treatment, Prevention, and Quality Assurance

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1. Randomized controlled trial that showed a statistically significant difference in at least one important outcome (eg, survival or major illness).
- OR
2. A randomized controlled trial that does not meet the level 1 criteria.
 3. A nonrandomized trial with contemporaneous controls selected by some systematic method (ie, not selected by perceived suitability for one of the treatment options for individual patients).
- OR
- Subgroup analysis of a randomized trial.
 4. A before-after study or case series (of at least 10 patients) with historic controls or controls drawn from other studies.
 5. Case series (of at least 10 patients) without controls.
 6. Case reports (<10 patients).
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prognosis. Progressive renal failure to end-stage disease, even with the new definition of steroid resistant (a minimum of 10-16 weeks of daily prednisone), occurs in 30% to 50% of patients, with resistance to corticosteroid treatment remaining the best guide to long-term prognosis.^{13,17,18}

We present the data in these selected studies of CSA with their level of evidence in support of efficacy. This plus their pre-CSA treatment time with corticosteroids is given so the readers are able to discern the rationale for our subsequent recommendations related to the use of CSA in this disease. Tables 1 and 2 outline the level of evidence for rating studies of treatment, prevention, and quality assurance that are used in this review.¹⁹

The major clinical studies of CSA chosen for review are listed in Tables 3 and 4. Virtually all of the patients in these tables had failed corticosteroid treatment and frequently had failed cytotoxic therapy as well. However, the course of steroids was quite variable. In the majority of studies in children the therapy was limited to 4 weeks of daily prednisone +/- 4 weeks of alternate-day prednisone,²⁰⁻²⁴ and in the adult series the prednisone duration usually was 8 to 10 weeks with only 1 series reporting 14 weeks on average before CSA treatment.²⁰⁻²⁵ The latter is the only level 1 study in adults with steroid-resistant FSGS.²⁰ It compared 6

months of CSA (n = 26) with 6 months of placebo (n = 23) with all patients receiving low-dose prednisone at 0.15 mg/kg. Entry criteria required a minimum of 8 weeks of steroids but the actual prednisone exposure was between 100 and 120 mg/kg, with a mean duration of treatment of 14 weeks in the placebo patients and 13 weeks in the CSA patients. In addition, approximately 25% of the patients in both arms had failed a prolonged course of cytotoxic therapy. All patients were observed for a 6-month period off all immunosuppressive agents and had to remain within nephrotic range proteinuria, a creatinine clearance level of 42 mL/min or greater, and blood pressure averages of 135/90 mm Hg or less before entering the medication period. At the end of 6 months of therapy, 69% of the CSA group were in remission (12% complete, 57% partial) compared with only 4% partial remission in the placebo group. Time to complete remission was 7 weeks, ranging from 1 to 15 weeks. The relapse rate was substantial with 2 of the 3 in complete remission and 6 of the 15 in partial remission relapsing by 52 weeks. A further 3 relapses and 1 new partial remission occurred by week 78. The percentage of patients in remission remained almost constant at week 78 and 104 (ie, 50% of the initial responders remained in partial or complete remission 18 months after coming off treatment). This response rate is not dramatically different from the other adult series but they are at lower levels of evidence.

Ponticelli et al.²¹ have performed the only other prospective trial in which patients were randomized to CSA or supportive therapy only.²¹ Their definition of resistant was, however, only 6 weeks of prednisone therapy. Their age group was mixed, with both children and adults included in the study.

Table 2. Grading System for Recommendations

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- A. The recommendation was based on 1 or more studies at level 1.
 - B. The best level of evidence available was at level 2.
 - C. The best level of evidence available was at level 3.
 - D. The best level of evidence was lower than level 3 and included expert opinion.
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Table 3. CSA Treatment Studies in Children

Study	Level of Evidence	Previous Corticosteroid Duration (wk)	Number CSA Treated	Dose/mg/kg/d Duration mo	Remission % Total/complete	Relapse %/Time
Lieberman ²⁰	1	4	12	6/6	67/25	N/A
Chishti ²¹	5	6	22	5/3-20	76/52	66/1.5 y
Waldo ²²	5	6	10	6-3*/3-36	80/60	23/2 y
Singh ²³	5	8	42	6-10/2-6	60/60	72/2 y
Niaudet ²⁴	5	4	20	/6†	40/30	50/4 y

* Plus pulse methylprednisone and oral prednisone.

† CSA at 150 mg/m²/d.

They received CSA for 6 months at full dose and in those that had either a partial or complete remission the drug was continued but the dose was tapered to zero over 6 months. Fifty-seven percent of their treated patients had either a partial or complete remission and approximately 40% of these were still in remission at 2 years of follow-up evaluation although the details separating their FSGS from their minimal change patients was incomplete in the published article. The highest rate of remission was in a recent study by Lee et al.²² However, the level of evidence was only 4, given that it was a descriptive study and there were only 5 patients with the biopsy specimen-proven diagnosis of FSGS. Even in this group with 80% initial remission, relapse was high at 50% after 1 year off drugs.

The studies by Meyrier et al^{24,31} deserve special comment. In Meyrier et al's^{24,31} report, 2 open trials are combined for a total of 112 adult patients treated with CSA. This was a very highly mixed group with both steroid-dependent and steroid-resistant cases. It would appear that in their steroid-

resistant, biopsy specimen-proven FSGS cases (n = 27) only one-third responded.³⁰ However, it is difficult to know which specific cases had biopsy specimen-proven FSGS and were followed-up for at least 12 months. Clear data specifically relating to their FSGS cases is missing from this report, so it is classified as a level 5 study. The study by Ittel et al²⁵ is interesting from a couple of points of view. The first is, although there were 22 patients treated long term with CSA, only 7 had the histologic diagnosis of FSGS. Of particular relevance is that all of the patients had to be resistant to 16 weeks of prednisone therapy, although the specific dose in mg/kg is not given. In these 7 patients, 1 had a complete remission, 3 had a partial remission, and 2 others had a significant reduction in proteinuria (the last 2 are not included in the percent remission in Table 3). However, all of their patients, despite treatment for as long as 36 months, had a relapse of their proteinuria when the drug was discontinued, usually within 2 to 3 months of stopping the medication. Three of their patients also went on to have a repeat renal biopsy

Table 4. CSA Treatment Studies in Adults

Study	Level of Evidence	Previous Corticosteroid Duration (wk)	Number CSA Treated	Dose/mg/kg/d Duration mo	Remission % Total/complete	Relapse %/Time
Catran ²⁵	1	14	26*	3-4*/6	69/12	50/2 y
Ponticelli ²⁶	3	6	14†	5-6/6-12	57/25	43/2 y
Lee ²⁷	4	8	5*	5*/4	80/20	50/1 y
Walker ²⁸	4	6-9	9†	5-10/6	66/0	N/A
Meyrier ²⁹	5	N/A	27*	5*/6>	30/N/A	N/A
Ittel ³⁰	6	16	7	3-5/7-91	57/25	100/N/A

Abbreviation: N/A, not available.

* Plus low-dose prednisone.

† Mixed age.

after 1 to 82 months of CSA therapy and specific renal lesions related to CSA toxicity were relatively minor and changes in function were attributed to the underlying renal disease progression rather than drug toxicity.

In children there is a similar dearth of level 1 studies; in fact there is only a single trial at this level by Lieberman and Tejani.²⁶ In that study, pretreatment was a standard 4 weeks of prednisone at 60 mg/m² given in divided doses. The patient had to have continued to experience heavy proteinuria and a glomerular filtration rate (GFR) of at least 30 mL/min before trial entry. At the end of the 6 months of therapy, 66% of patients had a complete remission with 25% in complete remission compared with no significant change in the protein/creatinine ratio in the placebo group. There also was no significant change in the GFR in the CSA group compared with the placebo group at the end of the trial. Unfortunately, there is no follow-up evaluation in terms of relapse rate or effect on renal function in this study. All of the other studies in children were level 5. However, in the total of 98 patients treated with a CSA dose between 5 and 8 mg/kg for between 3 and 36 months, the response rate was in the range of 60% to 80%. Approximately half of the responders had a complete remission and half had a partial remission. Waldo et al's²⁸ study had the highest response rate as well as the highest sustained remission rate of 77% at 2 years. However, in addition to CSA, all their patients also were treated with both pulse methylprednisolone and oral prednisone therapy. The other studies had substantial relapse rates between 50% and 72% within 2 to 4 years of discontinuing the medication.

The question of nephrotoxicity risk versus drug benefit remains a real issue. Some of the early studies by Meyrier et al²⁴ had indicated that on repeat biopsy examinations the underlying disease could progress despite significant reduction in proteinuria and that this histologic progression may be induced or aggravated by the drug treatment. Certainly nephrotoxicity clearly has been shown in solid-organ transplantation, most notably in an early heart transplant series in which doses of between 10 and 20 mg/kg were maintained for prolonged periods.³² In other nonrenal diseases such as psoriasis and uveitis, several investigators have shown both an acute and a chronic effect of CSA on GFR.³³⁻³⁵ In most cases, however, these

appear reversible and dose dependent. These studies, in general, indicate CSA given at 5mg/kg/d or less is unlikely to produce nephrotoxicity, even if used for prolonged periods. Other side effects with this drug are well known and include gingivitis, hypertrichosis, hepatic dysfunction, hyperuricemia, and either new-onset or worsening of underlying hypertension. In the studies reported in Tables 3 and 4, however, these were relatively minor in nature and rarely caused the therapy to be discontinued. This most likely is owing to the much more gradual introduction of the agent and the lower concentration targeted in the primary glomerular diseases. The duration often is limited to 6 month \pm tapering, further reducing the risk for nephrotoxicity. Also, the majority of these patients have preserved renal function and, in general, are less symptomatic in terms of their overall disease state and are not diabetic in contrast to many trials in solid-organ transplantation, thus reducing the variability in drug absorption and underlying vascular disease. Furthermore, the majority of these studies also had an automatic drug reduction point, usually when the creatinine level rose more than 30% above baseline. All of these factors are important and probably contribute to the lower risk for CSA nephrotoxicity in these patients compared with solid-organ transplant series.

A major remaining question is whether renal function is preserved in the CSA responders. This is one of the important points addressed in the recent, randomized, controlled trial by Cattran et al,²⁰ which showed that CSA preserves renal function. At the end of 4 years of follow-up evaluation, over 50% of the placebo group versus only 25% of the CSA-treated patients had halved their initial renal function as measured by creatinine clearance ($P \leq .05$). This point is supported by the work of Ingulli et al³⁶ in children, but this was a review of 21 patients treated with CSA with no controls (level 5). Earlier similar data had been reported by Niaudet,³⁰ but there was no control group in regard to long-term outcome.

After 15 years of experimenting with CSA in FSGS, what can we conclude about its place in the armamentarium of therapy? Should we consider it only as a second-line agent? To truly define patients as steroid resistant it has been suggested that a minimum of 16 weeks of daily therapy is required in adult patients. Although this was the maximum time of therapy beyond which no pa-

tients responded in one of the earlier studies retrospectively examining the role of steroids, the medium time to respond was more in the range of 3 months.¹⁶ This seems a more reasonable limit for high-dose daily prednisone even in an otherwise healthy individual because undoubtedly the effects of therapy are cumulative and rapidly increase as the total dose in mg/kg increases. A similar definition of steroid resistance in children beyond the one used in minimal change disease also needs to be agreed on. If one examines the CSA data in FSGS with the newer steroid-resistant definition, its efficacy becomes more difficult to assess because of the variability of steroid use before labeling the patient resistant (Tables 3 and 4). There are, however, some consistent themes that emerge when examining these trials. There is a defined response rate in terms of proteinuria reduction that varies from the most pessimistic study at 30% to the most optimistic at 100%, with the mean remission rate in the 2 level 1 studies being very similar at 67% and 69% of the total patients treated. The percent that achieved complete remission is smaller and varies between 0% and 60% in the studies, but is in the lower range of between 12% and 25% in the level 1 trials. Similarly, the relapse rate is substantial in all of the studies reported regardless of their level of evidence. In some cases this cannot be discerned because of the lack of information in the reports and in other cases in which the drug is continued indefinitely. However, in the remaining studies the relapse rate is wide but substantial, varying between 23% and 100% of cases, with the majority of the relapses occurring within the first 3 to 6 months of discontinuing the medication. This is confirmed by the only level 1 study with a substantial follow-up period in which at 2 years 50% of those patients who had responded either partially or completely had relapsed.²⁰

The effective but safe dose seems fairly consistent. In the great majority of case it averages 5 mg/kg/d or less over the duration of therapy. The duration of therapy, however, remains a major question. Although the studies to date have a wide range from 4 to 91 months, the mean time is between 6 and 12 months. However, the time to remission (either partial or complete) is long and hence the minimum duration before labeling the drug a failure is substantial. For instance, in the level 1 study in adults the time to remission varied

between 1 and 25 weeks of the 26 weeks of therapy, and in the children's level 1 study remission occurred between 2 and 10 weeks.^{20,26} This would suggest the minimum duration of exposure should be 6 months. The side-effect profile seems acceptable and with the caveats of the need for strict management of the patients' hypertension and alertness for possible nephrotoxicity, the drug is surprisingly well tolerated and safe.

In summary, although level 1 evidence is limited, both studies in this category as well as supporting studies in lower levels strongly indicate that CSA is effective and safe in the treatment of primary FSGS. This makes the evidence grade A in terms of its recommendation as appropriate therapy in this disease. The selection of patients for treatment in terms of their risk/benefit ratio currently is not clear. The duration of prednisone therapy given before determining the patient as resistant and CSA started is an important variable. At a practical level each individual's risk profile must be taken into account rather than an absolute requirement that must be met before defining a patient as truly resistant and initiating CSA therapy. Knowing that CSA is effective and relatively safe should mean that it is introduced earlier than currently is performed rather than later. In some cases, perhaps, it should even be considered first-line therapy when the risk for high-dose prednisone exceeds its potential benefit such as in the obese, the elderly, or the borderline diabetic patient. Whether low-dose prednisone is required in addition to CSA is unclear. Traditionally, it seems to prolong remission time but if the risk of additional steroids is high it is probably not necessary to add to CSA. The total duration of therapy also remains unknown. Undoubtedly there is a substantial relapse rate when this drug is withdrawn. However, even today in the difficult case in which the proteinuria is severe and unremitting, it must be remembered that the complications of the nephrotic syndrome can lead to early death from infection and venous thrombosis as well as substantially reducing the quality of life of the individual.³⁷ Recent data also would suggest proteinuria per se is nephrotoxic and is an important factor leading to progressive renal failure. This suggests prolonged, even partial remission, will be of long-term benefit to the patient. Rather than defining a precise duration of therapy the studies would indicate it is reasonable to treat initially for 6 to 12

month before determining the patient is CSA resistant and starting a reduction in dosage. Equally important is to recognize if the patient has a response followed by relapse to nephrotic level proteinuria, then reintroduction of CSA should be considered immediately rather than labeling the patient a failure of CSA therapy because in the majority of the studies reported, reintroduction of the drug reestablished control of the proteinuria. Prolonged therapy even for years should be considered if on reintroduction, remission can be maintained on a low CSA dose (1-2 mg/kg).

CSA has been shown to be both efficacious and safe in FSGS patients and its specific role in this disease is becoming more clear as time progresses. It certainly is the best studied of the agents currently available and is the only drug that has been tested and proven to be effective in level 1 studies in children and adults with FSGS. Although all the answers are not in and many questions remain in regard to its duration and mechanism of action, CSA has emerged at the end of the 20th century to be a major player in the treatment of this serious type of glomerulonephritis.

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