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A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis

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Background. A clinical trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis (FSGS) was conducted. Despite the fact that it is the most common primary glomerulonephritis to progress to renal failure, treatment trials have been very limited.

Methods. We conducted a randomized controlled trial in 49 cases of steroid-resistant FSGS comparing 26 weeks of cyclosporine treatment plus low-dose prednisone to placebo plus prednisone. All patients were followed for an average of 200 weeks, and the short- and long-term effects on renal function were assessed.

Results. Seventy percent of the treatment group versus 4% of the placebo group ($P < 0.001$) had a partial or complete remission of their proteinuria by 26 weeks. Relapse occurred in 40% of the remitters by 52 weeks and 60% by week 78, but the remainder stayed in remission to the end of the observation period. Renal function was better preserved in the cyclosporine group. There was a decrease of 50% in baseline creatinine clearance in 25% of the treated group compared with 52% of controls ($P < 0.05$). This was a reduction in risk of 70% (95% CI, 9 to 93) independent of other baseline demographic and laboratory variables.

Conclusions. These results suggest that cyclosporine is an effective therapeutic agent in the treatment of steroid-resistant cases of FSGS. Although a high relapse rate does occur, a long-term decrease in proteinuria and preservation of filtration function were observed in a significant proportion of treated patients.

Focal segmental glomerulosclerosis (FSGS) is now the most common primary glomerulonephritis in the United States that leads to end-stage renal disease in both adults and children. Its incidence rate in Caucasians is three times more common, and in African Americans, it is six times more common than the second leading cause [1, 2]. Although its pathology, natural history, and response to corticosteroids treatment in both children and adults have been more clearly defined since its initial description over 40 years ago [3–16], the number of randomized controlled drug trials in this disorder has been very limited [17–19], and such a study in adults with pathology restricted to FSGS has never been reported.

Cyclosporine is a well known and effective immunosuppressive agent that has become a cornerstone of immunotherapy in solid organ transplantation since the first trial was published over a decade ago [20]. This drug has been used in the treatment for FSGS for over 10 years, but the studies have been open label and nonrandomized or have been a mixture of pathology and/or age groups [17–19, 21–31]. Although a benefit in both children and adults has been reported, enthusiasm for its use has been tempered by both a high relapse rate and a concern about the known nephrotoxicity of the agent [30, 32, 33]. We report the first long-term prospective controlled trial using cyclosporine in adults with biopsy-proven FSGS resistant to corticosteroid therapy.

METHODS

This prospective single-blind, randomized trial was performed in 12 clinical centers in North America. The study protocol was reviewed and approved by each center's institutional review board, and a signed informed consent was obtained from all patients prior to entry.

Entry criteria

Age at entry was between 18 and 70 years. All patients must have failed to achieve a remission of the proteinuria

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after a minimum of eight weeks of prednisone at ≥1 mg/kg/day. The following qualifiers had to be fulfilled for the full six months prior to randomization: (*a*) proteinuria ≥3.5 g/day or ≥50 mg/kg, (*b*) creatinine clearance (C_{Cr}) ≥42 ml/min/1.73 m^2, (*c*) blood pressure ≤135/90 mm Hg, and (*d*) dietary protein intake ≤0.8 g/kg. All patients were required to have a renal biopsy performed within three years of trial entry, and the local pathology review had to confirm the presence of at least one classic FSGS lesion [3]. Patients with features of collapsing glomerulopathy were excluded. The renal tissue was subsequently reviewed by a nephropathologist masked to patient assignment who scored each biopsy 0 to 3+ (none, mild, moderate, or severe) with regards to three areas: the percentage of glomeruli with either segmental or global sclerosis, interstitial fibrosis, and vascular damage. Immunofluorescence and electron microscopy were also reviewed to rule out other types of renal disease known to be associated with segmental sclerotic lesions.

Exclusion criteria included women unwilling to take effective birth control measures, comorbid conditions with expected survival of less than two years, any serious systemic infection and associated disorders requiring daily nonsteroidal anti-inflammatory medications. Patients with diabetes mellitus and conditions known to be associated with FSGS lesions such as obesity and unilateral renal agenesis were also excluded. No immunosuppressive agents, plasma exchange therapy, or antilymphocyte products were allowed in the six months prior to the start of the test medication period.

Randomization and treatment

Randomization was performed by the clinical coordinating center from a table of random numbers and was stratified by center in blocks of two to ensure a balance between groups. The patients were masked in regards to active versus placebo assignment, but the physicians were not for safety reasons and because the end points were objective and measured centrally by a lab masked to patient designation. Cyclosporine in a drink solution (100 mg/ml) and an identical placebo made from the same carrier were provided by Novartis Canada Ltd. (Whitby, Ontario, Canada). Treatment was started at a dose of 3.5 mg/kg/day in the active group and 0.035 ml/kg in the placebo group. The daily quantity was divided and given in two equal doses at 12-hour intervals. Adjustments in dose were made in the cyclosporine group to achieve a whole blood 12-hour trough level measured by monoclonal assay, between 125 and 225 μg/liter. A comparable number of adjustments were made in the placebo volume to ensure that masking was maintained. The test medications were continued for 26 weeks and then tapered to zero over four weeks. All study patients also received prednisone at 0.15 mg/kg/day (maximum daily dose of 15 mg). This was reduced after 26 weeks by thirds at four-week intervals to zero by eight weeks. A seated blood pressure of ≤130 mm Hg systolic and ≤85 mm Hg diastolic was targeted as the upper limit of accepted values during the study. Any patient who was on either an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor antagonist from the start of the pretrial six-month run-in period could remain on it during the study, but the introduction of these classes of drug was forbidden during the test medication period. All other antihypertensive agents were allowed. Patients were placed on a diet consisting of ≤0.8 g/kg of protein plus, in most cases, a no added salt, low cholesterol intake at the start of the observation period.

Each patient had a minimum of three protocol visits prior to randomization with two mandated within the six-week period prior to the start of the test medication. At randomization, a full history and physical evaluation, as well as laboratory tests, including serum creatinine, 24-hour urinary excretion estimates of protein, creatinine and urea, a lipid profile including cholesterol and triglyceride estimations, and screening tests to rule out potential secondary causes of FSGS, were performed. An inclusion/exclusion checklist was maintained centrally and reviewed prior to group assignment. The renal function tests were repeated on the day of randomization, and follow-up visits were scheduled for one, two, four, six, and eight weeks and then at four-week intervals until the end of the test medication period, and then at eight-week intervals until a study end point was reached or data closure (January 1, 1998). If specific immunosuppressive drugs or corticosteroids were started at any time after the test medication period, the patients were censored at that point. At each visit, the patient's clinical status and vital signs were recorded, and electrolytes, hematology, renal, and liver functions were monitored. As well, cyclosporine trough values were obtained at these intervals during the first 26 weeks. Compliance was determined by the consistency of the cyclosporine level and by a monthly check of the total volume consumed of the test medication. Serum creatinine and 24-hour urinary excretion of creatinine, protein, and urea at each visit were measured by a central laboratory using standard methods.

Outcome measures

The primary outcome was the number of complete or partial remissions in proteinuria by week 26. This was also assessed at 52, 78, and 104 weeks, and at the last follow-up. Complete remission was defined as ≤0.3 g/day proteinuria plus stable renal function. A partial remission was defined as a 50% reduction of initial proteinuria and ≤3.5 g/day with stable renal function. Stable function was defined as a C_{Cr} estimate that was within 15% of the initial value. Secondary analyses included time to a 50% reduction in baseline C_{Cr} and time to doubling of

Table 1. Baseline demographic and laboratory data of the 49 randomized patients

Characteristics	Placebo $N = 23$	Cyclosporine $N = 26$
Age (range)	40 ± 14 (20–73)	38 ± 10 (19–59)
Gender % *males*	74	65
Blood pressure *mm Hg*		
Systolic	134 ± 16	136 ± 13
Diastolic	85 ± 8	87 ± 7
Racial group *N* (%)		
Caucasians	20 (87)	23 (88)
African Americans	3 (13)	1 (4)
Other	—	2 (8)
Serum albumin *g/dl*	3.0 ± 0.9	3.1 ± 0.9
Creatinine *mg/dl*[a]	1.4 ± 0.6	1.3 ± 0.4
Creatinine clearance *ml/min/1.73 m²*	86 ± 31	86 ± 27
Proteinuria *g/day*	8.7 ± 4.7	6.9 ± 3.3
Urine urea *g/day*	9.8 ± 3.9	9.7 ± 3.4

Data that are ± values are standard deviations.
[a] To convert to μmol/l, multiply by 88.4

Table 2. Central review of renal pathology

Characteristics	Placebo	Cyclosporine
Glomeruli		
% Segmental sclerosis	20 (15–50)[a]	27 (4–60)
% Global sclerosis	16 (0–20)	13 (5–30)
Interstitial disease		
% ≤1+	78	65
% ≥2+	22	35
Vascular damage		
% ≤1+	78	81
% ≥2+	22	19

[a] Numbers in parentheses signify range

baseline creatinine. Study end points included end-stage renal disease defined as a C_{Cr} <12 ml/min, start of dialysis, or transplantation or study closure. Early stop points of the test medication included a confirmed ≥30% rise in baseline serum creatinine. Confirmed meant that the creatinine was not improved by two 25% reductions in the dose of the test medication, spaced out over a four-week period. Other premature stop points included doubling of baseline liver enzymes and intolerable side effects. As well, the test medication was discontinued early if complete remission of proteinuria was achieved and persisted for a minimum of one month.

Data analysis

A prospective construction of sample size based on an analysis of two independent proportions using an α of 0.05 and a β of 0.2 and a difference in remission rates in proteinuria at 26 weeks of 30% plus a drop out rate of 10%, indicated that 25 patients per arm were needed. The subsequent results were analyzed by chi square for proportions and, if appropriate, the nonparametric Mann–Whitney rank sum test. The length of time to event analysis utilized Kaplan–Meier product-limit life-table survival estimates compared by the log-rank test. All tests were two sided and analyzed on the basis of all patients maintained in their original assigned group. Proportional hazards regression was used to determine possible interactions between treatment groups and baseline covariates, including age, gender, proteinuria, albumin, systolic and diastolic blood pressure, and grade of interstitial fibrosis on biopsy, as well as to estimate the reduction in the number of events within groups. Differences in renal functions over time were compared by *t*-test of the slopes of C_{Cr} and reciprocal of creatinine over the 26 weeks of the test medications and over the total observation period. Values in the tables are means ± SD unless otherwise stated. The analyses were performed with the Statistical Analysis System Software [34]. The relative benefit of treatment was also assessed by calculating the number of patients who would need to be treated to prevent one outcome event defined by a 50% reduction in baseline C_{Cr} [35].

RESULTS

Sixty patients were screened and deemed eligible by the local principal investigator, and signed a consent form. Review subsequently excluded 11 patients prior to randomization because of a failure to confirm the histological diagnosis ($N = 4$), central measurement of proteinuria < 3.5 g/day ($N = 2$), C_{Cr} < 42 ml/min ($N = 4$), and a positive antinuclear factor ($N = 1$).

The total prednisone dose given prior to the six-month run-in period was not different in the two groups. In the placebo patients, the mean was 100 mg/kg (range 80 to 140), and in the cyclosporine patients, it was 120 mg/kg (range 70 to 150). The mean duration of treatment was also similar at 14 weeks in the placebo patients (range 10 to 48) and 13 weeks in the cyclosporine patients (range 10 to 60). In addition, 11 patients (5 placebo and 6 cyclosporine) had received a course of a cytotoxic agent (9 cyclophosphamide and 2 azathioprine) in a dose range of 1 to 3 mg/kg for a mean of two months (range 1 to 16).

There were no significant differences in any of the demographic or laboratory features at baseline (Table 1). The racial group was predominantly Caucasian, and the male to female ratio was approximately 2:1. The urine urea, a reflection of dietary protein intake, was equal in both groups at entry. The central pathology review of the renal biopsy tissue is detailed in Table 2. All patients were documented to have at least one focal segmental sclerotic lesion. The percentage of glomeruli with segmental lesions was variable from patient to patient, but the mean was not different between groups. The overall interstitial fibrosis score and degree of vascular damage and their ranges were also very similar in both populations.

The effects of the test medication on the proteinuria

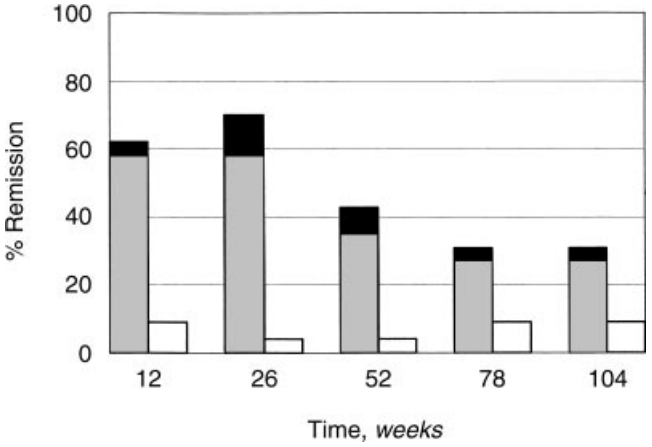
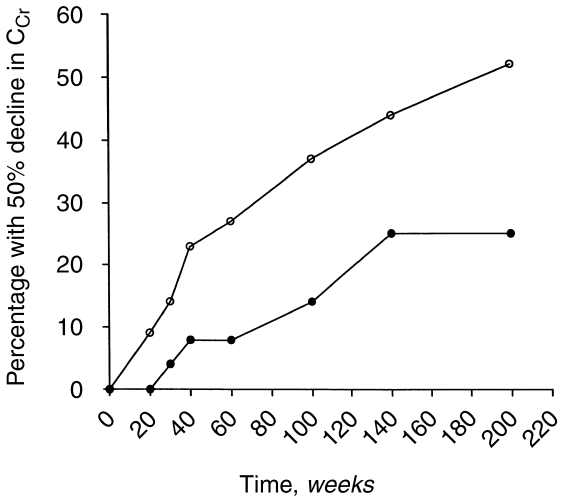


Fig. 1. Remission in proteinuria in the cyclosporine treated (■, partial; ■, complete) compared with the placebo treated (□, partial) at different time points of the study. At week 26, $P < 0.001$, and at 104 weeks $P < 0.05$.



Placebo (N)	23	22	19	18	12
Cyclosporine (N)	26	25	18	15	7

Fig. 2. Percentage of cyclosporine patients (●) compared with placebo (○) who had a 50% loss in renal function as measured by C_{Cr} over the observation period. The number of patients being followed at different time points is listed in the table under the figure ($P < 0.05$).

in the two groups over time is illustrated in Figure 1. Remission of proteinuria occurred in 69% of the cyclosporine group (12% complete and 57% partial) compared with a 4% partial remission rate in the placebo group by the end of the 26 weeks of active treatment ($P < 0.001$). The time to complete remission ranged from 1 to 25 weeks and to partial remission from 1 to 15 weeks with a mean of seven weeks. Two of three (66%) in complete remission and 6 of 15 (40%) in partial remission in the cyclosporine group relapsed by week 52. A further three relapses and one new partial remission occurred by week 78 in this group. One further partial remission occurred in the placebo group at week 65. The percentage in remission then remained essentially unchanged at week 78 and 104. There was no statistical relationship in those who relapsed versus those who remained long-term remitters between either the nadir or percentage reduction achieved from their baseline proteinuria.

Renal failure by log-rank test using a 50% reduction in baseline C_{Cr} as an end point was seen in 25% of the cyclosporine-treated patients compared with 52% of placebo patients by four years ($P < 0.05$; Fig. 2). Partial or complete remission of proteinuria whether they subsequently relapsed was also significantly correlated with long-term preservation of renal function ($P < 0.03$). This was not absolute because four partial remission patients (treatment = 3, placebo = 1) went on to reach a C_{Cr} end point. The number of patients needed to treat to prevent one occurrence of this end point was five. The associated reduction in risk of progression was 70% (95% CI, 9 to 93) unaltered by any of the initial covariates examined, including age, gender, systolic and diastolic blood pressure, severity of baseline proteinuria, and degree of tubular interstitial disease on biopsy. The slope of C_{Cr} in ml/min/year in the two groups at the end of six months of active treatment was the same, but over the study period, the mean was -5.5 ml/min $\pm$ 18 in the cyclosporine group compared with -23 ml/min $\pm$ 39 in the placebo group ($P < 0.05$). Fourteen patients reached end-stage renal disease by study closure (10 placebo and 4 cyclosporine). The renal survival rate was 72% in the cyclosporine group compared with 49% in the placebo group at four years ($P = 0.1$). Seven patients were followed less than 78 weeks because of the onset of end-stage renal disease in six and because of relocation outside of North America in one. The latter patient was in the cyclosporine group, and her proteinuria and creatinine had remained unchanged during both the treatment period and in follow-up to week 36.

The mean dose of cyclosporine over the treatment period was 4.2 $\pm$ 2.1 mg/kg. All patients completed six months of the test medication, except one on cyclosporine, who had a complete remission by week 8 and stopped the drug at week 12 and one who stopped cyclosporine after 12 weeks because of persistent nausea and vomiting. An increase in baseline creatinine of 30% incurred in six patients, two on placebo and four on cyclosporine. After a dose adjustment, none in the placebo group but all four in the cyclosporine group had an improvement in their creatinine value and remained on the test medication to week 26. Compliance, as judged by a monthly measurement of the volume of the test medications used, was $\geq$90% in all patients.

At randomization, 26% ($N = 13$) of patients were

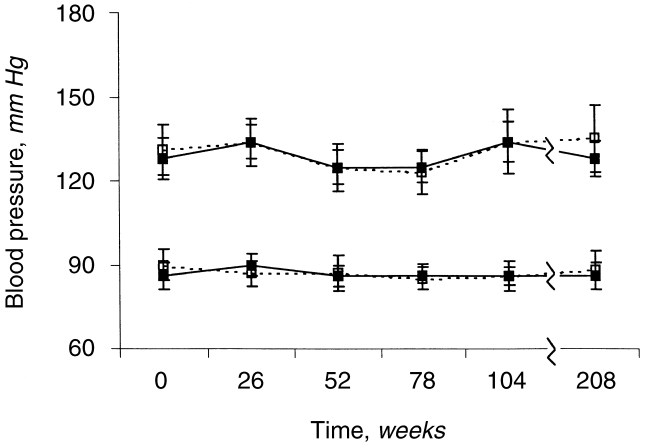


Fig. 3. Mean sitting systolic and diastolic pressures at the end of each time period by groups. Symbols are: (■) cyclosporine; (□) placebo. The bars represent standard deviations.

normotensive (5 placebo and 8 cyclosporine), and 74% ($N = 36$) were hypertensive. In the latter group, 21 were on ACEi (10 placebo and 11 cyclosporine), and 15 were on other antihypertensive drugs (8 placebo and 7 cyclosporine). No significant differences in supine, sitting, or mean arterial blood pressure were noted during either the active medication period or during the postdrug period (Fig. 3). During the post-test medication period, hypertension worsened in both groups, and additional antihypertensive drugs were required. By the time the patient reached either a stop point or the last observation point, 88% (23 patients) in the cyclosporine group and 87% (20 patients) in the placebo group were on at least one antihypertensive agent. At that point, an ACEi was employed either alone or in combination with other antihypertensive agents in 65% of the cyclosporine group and 85% of the placebo group (P = NS).

Adverse effects

Although the mean blood pressure in the cyclosporine patients was maintained at the same level as the placebo group during the treatment period, a new agent or an increase in their antihypertensive drug dosage was required in eight of the cyclosporine patients and only two of the placebo group. The other significant adverse effect was in one patient who had gastrointestinal symptoms on cyclosporine and had to stop the medication after 12 weeks of treatment. All 49 patients were maintained on their prescribed prednisone dose for 26 weeks without any adverse effect.

Dietary compliance over the study period was good with only 16% of the patients (4 placebo and 3 cyclosporine) consistently more than 20% above the recommended dietary protein intake, as assessed by monthly 24-hour urinary urea estimates.

DISCUSSION

Focal segmental glomerulosclerosis was initially described 40 years ago. It is currently the most common primary glomerular disease to progress, and its incidence rate is increasing [1, 2, 12]. Although never formally tested, corticosteroid treatment is associated with a complete remission rate of between 20 and 40% [5–8]. This type of response has also been noted to be the best single guide to an excellent long-term prognosis. In contrast, patients who do not respond have a higher likelihood of progressing to renal failure. This was our rationale for the entry criteria of failure to respond to a minimum of eight weeks of daily prednisone. The actual mean prednisone dose and duration were significantly greater than this minimum, and in addition, 22% had failed a course of cytotoxic therapy. The total dose and duration of prednisone were equal to or above the amount given to induce remission in our earlier studies [5, 36]. In spite of this selection bias, our results demonstrated a significant effect of treatment with a reduction in proteinuria in 69% of the cyclosporine group, either partial (57%) or complete remission (12%), compared with a very low partial remission (4%) in the placebo group. Although the relapse rate was substantial with approximately 60% relapsing within the first-year post-test medication, the remainder stayed in remission until the last follow-up. As well, the remission group, even if they subsequently relapsed, generally had a better long-term preservation of filtration function, although as discussed, there were exceptions. Overall, however, a loss of 50% of renal function as measured by the halving of baseline C_{Cr} was seen in only one quarter of our cyclosporine patients, but over half of our placebo group. In our multivariate analysis, the risk reduction of progression in the cyclosporine group was 70% (95% CI, 9 to 93) compared with placebo.

A report from the only randomized controlled trial in children with FSGS demonstrated a mean reduction in proteinuria of 70 ± 20% compared with 11 ± 29% in the placebo group after six months of treatment [18]. The quantitative reduction was from 152 mg/kg to 37 mg/kg body wt in the treated versus no change in the placebo group. In the only other controlled trial that included both adults and children but a mixture of minimal change and FSGS pathology, the authors found a remission rate of 60% with cyclosporine compared with 15% with conservative treatment after 12 months [17]. They also found that long-term remission was preserved in approximately half of their responders assessed at 12 months post-treatment.

There was no follow-up with regards to renal function in the study in children [18]. In the adult trial, although the postmedication period was limited in both numbers of patients and the observation time, the decline in C_{Cr}, albeit not statistically significant, was slower, both during the treatment and in the 12 months of follow-up in the cyclosporine group [17].

Cyclosporine has been previously tried as therapy in adults with FSGS but in nonrandomized open label studies and in case controlled trials. These studies have generally shown a short-term benefit with reductions in proteinuria of between 50 and 80%, but the long-term nephrotoxic potential has been a constant concern [21–30]. These studies have also reported that up to 40% of cases can be maintained in a state of remission when cyclosporine was combined with alternate day steroid. In the largest reported series, cyclosporine was given for between 7 and 84 months, and 40% of their steroid-resistant FSGS patients obtained either a partial or complete remission.

These articles expressed concern about the acute and chronic nephrotoxic potential of cyclosporine. To avoid both, a daily dose limit of <5 mg/kg has been suggested by us and others [21, 37] and was the rationale for the targeted levels and automatic dose reductions in our protocol. The latter happened more frequently in the active medication group but resolved with the dose reduction, suggesting that it was a reversible hemodynamic effect [38, 39]. In contrast, no improvement was seen in the two placebo patients, most likely indicating that their progressive decline in renal function was the natural history of the underlying nephropathy. We observed similar findings with dose adjustments in our trial of cyclosporine in patients with progressive membranous nephropathy [40].

A reduction in proteinuria in a variety of glomerular-based diseases has been reported with the use of ACEi and with dietary protein restriction [41–45]. We controlled for the former by prohibiting their introduction during the active treatment phase. Although their use may have modified the changes in proteinuria in the follow-up period, they were used in a higher percentage of the placebo group; hence, if they did introduce bias, it would have favored that group. The urine urea excretion was similar over the observation period, suggesting that dietary protein intake was not the explanation for the differences in outcome.

Cyclosporine treatment does not work in every case of FSGS, and the relapse rate was significant; however, a short-term remission to subnephrotic range proteinuria in 69% of cases was observed. A longer treatment period and/or retreatment of relapses were not part of this trial. Both options should perhaps be considered in future trials and outside of clinical studies, in the management of any individual patient. This therapy was also associated with improved long-term preservation of renal function. This was a secondary end point and should be viewed with some caution and substantiated in other trials, but a reduction in risk of progression of 70% was observed. Both of these findings suggest an important role for this drug in the treatment of patients with steroid-resistant FSGS.

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