

Efficacy of tacrolimus in the treatment of children with focal segmental glomerulosclerosis

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Background: Focal segmental glomerulosclerosis (FSGS) is the most common glomerular condition leading to end-stage renal disease (ESRD) and the third most common cause of ESRD in pediatric patients.

Methods: This is a retrospective study consisting of 22 pediatric patients with FSGS and heavy proteinuria. After demonstrating steroids resistance, the patients were treated with tacrolimus, targeting a trough level 5-8 ng/mL. The primary outcome is the induction of remission with tacrolimus.

Results: Thirteen patients (59%) achieved remission (complete in 31.8% and partial in 27.2%) and 12 patients showed stable or improved renal function over an average follow-up of 2.9 years (range: 0.5-7 years). There was no significant difference in response rate between African American and Caucasian patients. None of the patients had significant side-effect to tacrolimus and none of the repeat biopsies showed an increase in interstitial fibrosis compared to baseline. The best renal outcome was for patients who achieved complete remission. Partially responsive patients had improved renal function compared with resistant patients.

Conclusion: Tacrolimus is a viable option in the treatment of children with idiopathic steroid resistant FSGS.

World J Pediatr 2014;10(2):151-154

Key words: chronic kidney disease;
focal segmental glomerulosclerosis
(FSGS);
proteinuria;
tacrolimus

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doi: 10.1007/s12519-014-0484-y

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Introduction

Focal segmental glomerulosclerosis (FSGS) accounts for 10%-20% of pediatric cases of nephrotic syndrome.^[1,2] It is the most common glomerular disease resulting in end-stage renal disease (ESRD) in children^[2] and the third most common cause for ESRD in children.^[3,4] FSGS carries a poor prognosis, and 50% of the patients will develop advanced chronic kidney disease within 5-10 years of diagnosis.^[1,5] Risk factors for progression include nephrotic range proteinuria, renal insufficiency and African American race.^[2] Although several therapies have been tried, no satisfactory treatment currently exists for FSGS.

There is growing support for the use of calcineurin inhibitors (CNIs) in managing FSGS patients. The mechanism of action of CNIs in patients with FSGS is still poorly understood. Both tacrolimus and cyclosporine inhibit intracellular calcineurin, thus decreasing calcium-dependent T-cell activation. Recent studies^[6-9] support the theory that calcineurin inhibitors have direct effects on podocytes by stabilizing their actin cytoskeleton. There are few studies on the use of tacrolimus in pediatric cases of FSGS, and most of them are retrospective and uncontrolled.^[7-9] In this study we report our experience with the use of tacrolimus in pediatric FSGS patients.

Methods

We reviewed the medical records of patients with FSGS in our center for the last 10 years (2000-2010). During this period, we treated 93 patients with FSGS and heavy proteinuria. Patients with primary FSGS and nephrotic range proteinuria who were resistant to steroids (a minimum of 4 weeks of steroids at 2 mg/kg per day, a maximum of 60 mg/day) and subsequently were treated with tacrolimus were included. The following exclusion criteria were considered for this retrospective review: secondary types of FSGS, patients treated with immunosuppressive drugs other than tacrolimus and FSGS associated with human immunodeficiency virus infection. We identified a total of 22 patients who met our criteria. The primary outcome was the

number of patients with complete or partial remission. Secondary outcomes were the preservation of renal function during the follow up period (average of 2.9 years), racial differences in response rate and prognosis, and signs of tacrolimus toxicity on repeated kidney biopsies. Proteinuria was quantified by a random urine protein/creatinine ratio (P/Cr=mg/mg). Proteinuria and remission were defined as follows: 1) nephrotic-range proteinuria: urine P/Cr ratio ≥ 2 ; 2) complete remission: urine P/Cr ratio ≤ 0.5 with stable or improving kidney function; 3) partial remission: urine P/Cr ratio >0.5 , with $\geq 50\%$ reduction of baseline; 4) non-responsive: urine P/Cr ratio >0.5 with $<50\%$ of proteinuria reduction.

Renal function was measured by the estimated glomerular filtration rate (eGFR) using the Schwartz formula [$eGFR=0.413 \times \text{height (cm)}/\text{serum Cr}$] in children older less than 16 years, or by using the Modification of Diet in Renal Disease formula in children older than 16 years. A renal biopsy was performed to confirm the diagnosis of FSGS after steroid resistance was demonstrated, and tacrolimus was then initiated. Trough levels were measured within 2 weeks after initiating the medication and then with every visit (every 3-6 months), targeting a trough level of 5-8 ng/mL. Repeat renal biopsies were performed by the treating clinician to monitor for evidence of renal toxicity. Trichrome and hematoxylin/eosin stained sections were evaluated for the presence of tubular atrophy and interstitial fibrosis. All renal biopsies were interpreted by the same pathologist.

For statistical analysis, the paired Student's *t* test was used to compare the initial and follow-up laboratory data. Wilcoxon's signed-rank test was used to compare responsive and non-responsive patients. Analysis was performed with GraphPad Prisma 5, and $P < 0.05$ was considered statistically significant.

Results

Of the 22 patients included in this study, 10 were males (45%) and 12 females (55%) (Table 1). The mean age of the patients at presentation was 8.8 years (1-17 years), and most of the patients were present at the period of adolescence (12/22). Sixty percent of our patients were African American and 31% were Caucasian. At the initial visit, 12 patients (54%) had normal kidney function ($eGFR > 90 \text{ mL/min/1.73 m}^2$), while 7 had chronic kidney disease (CKD) stage 2 ($eGFR$, 60-90 mL/min/1.73 m^2) and 3 had CKD stage 3 ($eGFR$, 30-60 mL/min/1.73 m^2). While Caucasian patients tended to present at earlier age compared with African American patients (6.11 years vs. 11.69 years, respectively), there

Table 1. Demographic characteristics and clinical presentation of 22 patients at time of diagnosis

Demographic characteristics	Values
Patients, <i>n</i>	22
Age, <i>y</i>	8.8 (1-17)
Sex, <i>n</i>	Male, 10; Female, 12
Race	Caucasian, 7; African American, 13; Hispanic, 2
Serum albumin, gm/dL	2.35 (0.7-4.5)
Urine protein/creatinine ratio	12.0 (2.2-48.64)
Renal function (eGFR)	92.30 (31.3-142)

eGFR: estimated glomerular filtration rate (mL/min/1.73 m^2); protein/creatinine ratio (mg/mg). Data are presented as mean with the range.

Table 2. Clinical summary of African American vs. Caucasian patients at presentation

Variables	African American	Caucasian	<i>P</i> value
Age, <i>y</i>	11.69 (5-17)	6.11 (1-14)	0.0016*
Serum albumin (gm/dL)	2.29 (0.7-4.0)	2.32 (0.7-4.5)	0.941
Protein/creatinine ratio	14.06 (2.26-31.40)	11.37 (2.20-48.60)	0.593
eGFR	105.9 (79.5-138)	81.65 (31.3-142)	0.066

eGFR: estimated glomerular filtration rate (mL/min/1.73 m^2). Data are presented as mean with the range in parenthesis. *: $P < 0.05$, with clinical significance.

Table 3. Clinical summary of estimated glomerular filtration rate (mL/min/1.73 m^2) at presentation and at last follow-up for all patients

Outcome	Presentation	Last follow-up	<i>P</i> value
Complete remission	94.25 (55-137)	109.50 (77-161)	0.29
Partial remission	97.00 (64.8-138)	76.20 (9.3-117)	0.22
Non-responsive	87.36 (31.3-142)	39.16 (15.3-86.8)	0.0022

Data are presented as mean with the range in parenthesis.

was no significant difference in degree of proteinuria and renal function between the two groups (Table 2). Histologic variants of FSGS were non-otherwise specified-NOS ($n=9$), cellular ($n=6$), collapsing ($n=5$), and perihilar ($n=2$).

In 13 patients with remission (59%), 7 (32%) had complete remission, and 6 (27%) had partial remission. Most patients achieved remission within 4-8 weeks after starting tacrolimus, and the dose of prednisone was gradually tapered down in 2 patients or stopped in 20 patients. The decision of stopping the steroids vs. continuing on a low dose was made by the treating physician. Four of the 9 non-responsive patients had low tacrolimus levels suggesting poor compliance with the treatment.

At the last follow-up visit and while patients were on tacrolimus, responsive patients had stable or improved eGFR from their baseline ($P=0.29$, Fig. 1), and none of them progressed to CKD stage 4-5 over a follow-up period of 2.9 years (average: 0.5-7 years). In the tacrolimus resistant group, 55% of the patients

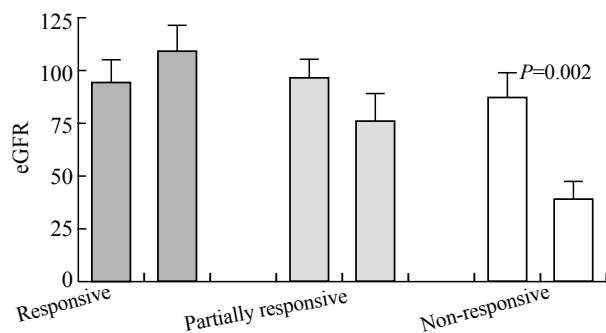


Fig. 1. Renal function based on response to tacrolimus. Renal function (estimated glomerular filtration rate, eGFR) in our patients between initial presentation and the last follow-up visit (measured by mL/min/1.73 m²).

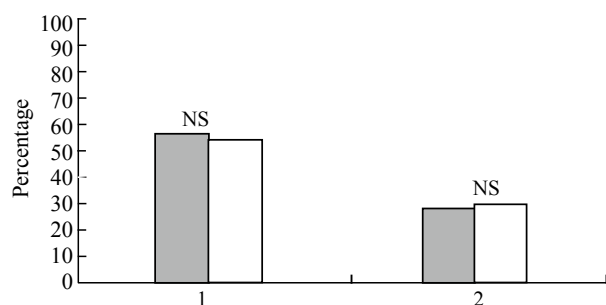


Fig. 2. Comparison of tacrolimus response rate (1) and progression to advanced kidney disease (2) by the end of the study between Caucasian (gray) and African American (white) patients. NS: no statistical difference, $P>0.05$.

had significant deterioration of renal function and 5 of these 9 patients progressed to CKD stage 4-5. In the 7 patients who achieved partial response, only one progressed to stage 4-5 ($P=0.22$, Table 3, Fig. 1).

Repeat biopsies were performed in 15 of the 22 patients on an average of 14 months (range: 7-36 months) after tacrolimus treatment. Three patients had evidence of tacrolimus toxicity manifested by mild isometric tubular vacuolization. None of the biopsies showed an increase in interstitial fibrosis when compared to the baseline.

With regard to racial effect, there was no significant difference in response rate between Caucasian (4/7) and African American (7/13) patients. Similarly, there was no difference in progression rate to advanced CKD between the two groups (Fig. 2).

Discussion

Children with FSGS have a high risk of developing chronic kidney disease, and multiple therapies have been tried to induce remission and preserve renal function. In this retrospective study of 22 patients with steroids resistant FSGS, we found that tacrolimus was

effective for inducing remission in 59% of our patients. In the 9 non-responsive patients, 4 had low tacrolimus levels suggesting poor compliance with the treatment. The rate of remission in FSGS patients after tacrolimus treatment was variable between studies, and ranged between 50%-80% of patients.^[7,8,9,10] In a study,^[11] 84% of the children with steroid resistant nephrotic syndrome had a complete remission. However, 41% of the patients had biopsy-proven minimal change disease, and the mean follow-up time was less than 12 months. In another placebo controlled study,^[12] 49 adult patients with steroid resistant FSGS were treated with cyclosporine plus low-dose prednisone, compared with placebo plus prednisone. It was found that 70% of the treatment group versus 4% of the placebo group had a partial or complete remission by 26 weeks. Most of those patients (60%) had a recurrence of proteinuria when cyclosporine was discontinued.

During an average follow-up period of 2.9 years, patients responsive to tacrolimus had a favorable renal outcome. The best renal outcome was for patients with complete remission who had stable eGFR and none of them progressed to advanced kidney disease. We also observed that partial response improved the renal outcome, and only one (14%) of the patients progressed to advanced kidney disease. Non-responsive patients, on the other hand, had the worse renal outcome and 55% of them progressed to advanced kidney disease. Our findings are similar to those reported by Gipson et al^[10] who reported that those patients with partial remission have a better renal survival than non-responsive patients. Previous studies^[2,13] have reported that African American patients have a worse renal outcome than Caucasian patients with FSGS. We found that the response rate to tacrolimus in African American patients was comparable to Caucasian patients. In the African American patients, 54% of them responded to tacrolimus and 30% of them progressed to advanced CKD. On the other hand, the response rate in Caucasian patients was 57% and 28.5% of them progressed to advanced CKD ($P>0.05$). This finding is limited by the small number of pediatric FSGS patients included in our study, and a large cohort study with a long follow-up period is needed to further confirm our finding.

Few studies showed that patients treated with tacrolimus developed significant side effects, including diarrhea, acute kidney injury, glucose intolerance and infections.^[11,14] Several others, including our study, have shown minimal side-effects related to the long-term use of tacrolimus in pediatric population.^[9] We noted minimal clinical side-effects and mild histological evidence of tacrolimus toxicity on repeat biopsies. This is similar to the results reported by Bhimma et al,^[8] who treated 20 patients with steroid resistant FSGS with

tacrolimus. In this cohort study, 85% of the patients achieved a partial or complete remission by 12 months, and none of the repeat biopsies showed evidence of calcineurin toxicity. Fujinaga et al^[15] reported an increased risk of cyclosporine toxicity in pediatric patients less than 5 years. While our study included only 5 patients younger than 5 years of age, none of them showed evidence of calcineurin toxicity.

In summary, we conclude that tacrolimus is effective in inducing remission and preserving renal function in pediatric FSGS patients. We also conclude that African American patients have comparable response to tacrolimus to Caucasian patients. We noted minimal adverse effects in our patients. Our findings suggest that FSGS with nephrotic range proteinuria should be treated aggressively since even partial remission improves renal survival. There is still a need for prospective studies evaluating treatment options for children with FSGS.

Funding: None.

Ethical approval: This study was approved by LSUHSC and Children's Hospital IRB.

Competing interest: None declared.

Contributors: Kallash M wrote the main body of the article under the supervision of Aviles D. Aviles D is the guarantor.

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Accepted after revision May 17, 2013