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ORIGINAL ARTICLE

Tacrolimus therapy in adult-onset steroid-resistant nephrotic syndrome due to a focal segmental glomerulosclerosis single-center experience

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ABSTRACT

Introduction. Management of adults with steroid-resistant (SR) nephrotic syndrome due to focal segmental glomerulosclerosis (FSGS) is a challenging task. Is tacrolimus (TAC) effective in this situation without serious adverse effects? This prospective study was done to answer this question.

Materials and methods. In patients with SR nephrotic syndrome due to FSGS, oral TAC (0.1 mg/kg/day) was started targeting a trough level of 5–10 ng/mL along with oral prednisolone (0.15 mg/kg/day) for 48 weeks. In patients with complete

remission (CR), TAC dose was reduced to a target of 3–6 ng/mL whereas in partial responders, TAC trough levels were kept at 5–10 ng/mL. TAC was discontinued in those with no remission at 24 weeks and was deemed TAC resistant. Outcome, namely CR and partial remission (PR), was assessed at the end of 24 and 48 weeks. All patients were prospectively followed for 60 weeks. Relapses after CR or PR were recorded; adverse effects, namely nephrotoxicity (>25% rise in creatinine), cosmetic effects, infections and hyperglycemia, were recorded every month.

Results. A total of 44 SR-FSGS [not otherwise specified 33 (75%), tip lesion 03 (6.8%) and cellular variant 8 (18.1%)] were analyzed. Mean age was 25.16 ± 8.26 (18–51) years. Of 44 patients, CR and PR were achieved in 17 (38.6%) and 06 (13.6%) patients, respectively. TAC resistance was seen in 21 (47.7%) patients. Time taken to achieve remission was 15.2 ± 6 weeks. Five (21.7%) patients with CR had relapse on tapering the dose and seven (30.4%) after stopping TAC. Reversible nephrotoxicity was seen in seven (15.9%) and irreversible in four patients (9%). TAC-related diarrhea was the problem in 10 (22.7%), and infections were seen in 19 patients (43.1%). Impaired fasting glucose and diabetes mellitus were seen in 10 patients (22.7%).

Conclusion. TAC is an effective agent in the management of SR-FSGS. However, strict renal function and blood sugar monitoring is required due to its potential nephrotoxicity and diabetogenic potential.

Keywords: FSGS, eGFR, TAC

INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is the leading cause of adult nephrotic syndrome, accounting for 20–25% of cases [1]. A wide range of therapeutic agents have been tried in the management of FSGS; glucocorticoids are the most accepted initial therapy for FSGS. Incidence of complete remission (CR) and partial remission (PR) with glucocorticoids ranges from 18 to 47% and 33 to 58%, respectively [2–4]. Therapeutic options for steroid-resistant FSGS (SR-FSGS) include cyclosporine (CSA), tacrolimus (TAC), cyclophosphamide and mycophenolate mofetil (MMF) [5–7]. Most of the studies have reported a remission rate of ∼50% with the above agents in SR-FSGS.

K-DIGO guidelines suggest calcineurin inhibitors as the first-line agent in the management of SR-FSGS [8]. Two randomized control trials (RCTs) of CSA in FSGS reported a remission rate (CR + PR) of 57–69% [9, 10]. Tacrolimus is a macrolide immunosuppressant and calcineurin inhibitor that has immunosuppressant properties similar to CSA and has a relatively selective inhibitory action on CD4 T-helper lymphocyte activation and proliferation. Although the first case report on the use of tacrolimus in childhood steroid-resistant nephrotic syndrome was published in 1990, data from clinical trials on use of TAC in adult SR-FSGS are very limited. The study on use of tacrolimus in adult Chinese SR nephrotic syndrome patients reported a remission rate of 82.4% [6]. This prospective study was done to evaluate the efficacy and safety of TAC in adult nephrotic patients with SR-FSGS.

MATERIALS AND METHODS

A prospective observational study was carried out at Department of Nephrology, PGIMER, Chandigarh, India, from January 2011 to June 2013. Adult (18–60 years) patients with steroid-resistant nephrotic syndrome with an underlying histopathological lesion of FSGS were included. Patients who had a renal biopsy of >1 year before the commencement of TAC were re-biopsied before the study to exclude chronicity. Only patients with an estimated glomerular filtration rate (eGFR) of >60 mL/min/1.73 m^2 by MDRD formulae, receiving the maximum tolerable dose of angiotensin II receptor blockers (ARBs) (telmisartan/losartan), were the subjects of the study. Patients with active infection, diabetes mellitus, hepatitis B/C or human immunodeficiency virus infection, liver function abnormalities, neoplasia, diarrhea, pregnancy, secondary FSGS, collapsing variant of FSGS, tubular atrophy and interstitial fibrosis >25% of the biopsy area and previous therapy with MMF, azathioprine, cyclophosphamide and CSA were excluded from the study. The study was conducted after approval from the department review committee, and all patients enrolled in the study provided informed consent.

Treatment

In patients with SR-FSGS, TAC was started at 0.1 mg/kg/day to achieve a target trough level of 5–10 ng/mL (Figure 1). TAC trough levels [microparticle enzyme-linked immunoassay (MEIA), Abbott IMx Tacrolimus II assay, Abbott Laboratories, Abbott Park, Ill, USA] were performed every 10 days till target trough levels were achieved. Subsequently, levels were done every 12 weeks for the first 24 weeks and were repeated once in the next 24 weeks. Further measurements were made if there was a relapse of nephrotic syndrome after the initial response, rise in blood sugar or if there was an increase in serum creatinine by >25% from baseline. In patients who achieved CR at 24 weeks, the dose of TAC was reduced to achieve a tacrolimus C0 of 3–6 ng/mL, and if patients relapsed, the dose of TAC was increased to achieve a trough level of 5–10 ng/mL and continued for 48 weeks. After 24 weeks, TAC was stopped in patients who had not obtained either CR or PR. After the study period, TAC was stopped by reducing the dose by 50% every 2 weeks. All patients were prospectively followed for a period of 60 weeks (48 weeks of TAC therapy and 12 weeks of follow-up). All patients were advised against taking erythromycin, cotrimoxazole, aminoglycosides, oral contraceptives, non-steroidal anti-inflammatory drugs and/or anti-epileptic drugs, which could affect either TAC metabolism or urinary protein excretion during the study period. TAC dose was reduced by 50% if there was a new-onset renal dysfunction, serum potassium > 5.5 meq/L, uncontrolled blood sugars, infection, diarrhea and refractory hypertension.

Oral prednisolone was tapered from 1 mg/kg/day to 0.15 mg/kg/day in 4–6 weeks and continued for a total of 48 weeks, then tapered off over 4 weeks. All patients received the maximum tolerable dose of ARBs and atorvastatin.

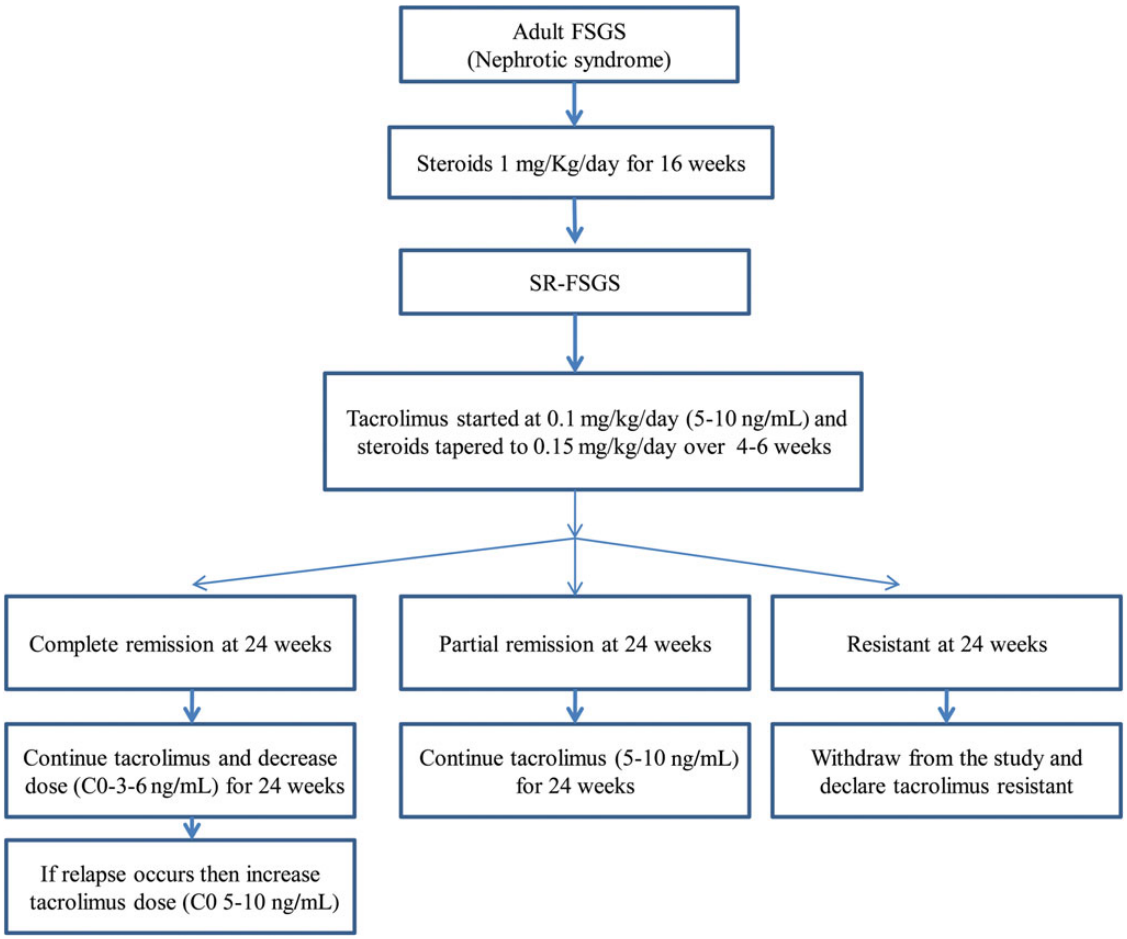

FIGURE 1: Tacrolimus in adult-onset steroid- resistant focal segmental glomerulosclerosis: study plan.

Follow-up was done every two weeks for the first 4 weeks and then every 4 weeks till the completion of the study. Urine analysis (including 24-h urine protein), serum creatinine and albumin were performed at every visit. Lipid profile, potassium, liver function tests and blood glucose were performed at baseline and every 12 weeks till the completion of the study.

Outcomes

The primary outcome was the cumulative number of patients who experienced remission. The secondary outcome was the estimated glomerular filtration rate (eGFR) at the completion of therapy, doubling of baseline serum creatinine levels (increase by 100%), time required for complete or partial remission and adverse effects (tremors, nephrotoxicity, gum hypertrophy, impaired glucose tolerance (IGT)/diabetes mellitus, diarrhea and impaired fasting lipid profile).

Definitions

Nephrotic syndrome was defined by proteinuria ≥ 3.5 g/d or ≥1.5 g/d along with a serum albumin < 2.5 g/dL, edema and hyperlipidemia. Relapse was defined as nephrotic-range proteinuria after achieving remission. SR was persistence of nephrotic syndrome due to FSGS despite oral prednisolone (1 mg/kg/d) for 16 weeks. Complete remission was the reduction of proteinuria to <0.5 g/d and with creatinine clearance of >60 mL/min/1.73 m^2 and serum albumin of >3.5 g/dL. Partial remission was the reduction of proteinuria to 0.5–3.5 g/day and stable serum creatinine (change in serum creatinine <25%) or a decrease in proteinuria >50% from baseline and stable serum creatinine (change in serum creatinine <25%) with serum albumin >3.5 g/dL. Renal dysfunction was defined as an >25% increase in serum creatinine from baseline after starting tacrolimus. New-onset hypertension was defined as patients with a systolic blood pressure of >140 mmHg or diastolic blood pressure of >90 mmHg after starting therapy with TAC. Worsening of preexisting hypertension was a rise in systolic or diastolic blood pressure of ≥20/10 mmHg, respectively, in preexisting hypertensive patients after starting TAC. Impaired fasting glucose (IFG) and diabetes mellitus (DM) were defined as fasting blood glucose of 100–125 and >125 mg/dL, respectively [11]. Impaired lipid profile was defined as total cholesterol of >250 mg/dL or low density lipoprotein of >125 mg/dL.

Statistical analysis

Data are expressed as mean ± SD and range for continuous variables and percentage for categorical variables. *T*-test was used to compare means obtained at various time points. Fisher's exact test was used for the analysis of contingency variables. $P < 0.05$ was considered significant. All analyses were performed using Graph Pad Prism 6.

RESULTS

During the study period, a total of 83 patients had steroid-resistant FSGS; of these, 44 patients who consented and met the inclusion criteria were enrolled into the study. The study included 33 (75%) male and 11 (25%) female patients. Thirty-three (75%) patients had FSGS-not otherwise specified (NOS) variant, 8 (18.1%) cellular and 3 (6.8%) had tip variants. The mean duration of nephrotic syndrome and time from first biopsy were 66.8 ± 56 (20–260) weeks and 56 ± 56.4 (16–248) weeks, respectively. Sixteen (36.3%) patients in this study had their first biopsy of >1 year previously and were re-biopsied prior to the study. There were no cases of familial nephrotic syndrome. There was no dropout during the study period, and all patients completed the study. The mean duration of follow-up was 76.64 ± 16.86 weeks (range 60–96 weeks); baseline characteristics are shown in Table 1.

Response to therapy

After 24 weeks of therapy, 23 (52.2%) patients experienced remission. Seventeen patients (38.6%) experienced CR and 06 (13.6%) had partial remission (Table 2). All twenty-three patients maintained remission till the end of 48 weeks of therapy. Twenty-one (47.7%) patients did not achieve remission at 24 weeks of therapy. Patients who did not achieve any remission at 24 weeks of TAC therapy were stopped. The mean time to achieve remission was 15.28 ± 6.08 weeks (4–24 weeks). Of the FSGS-NOS, 13 (39.3%) had CR and 5 (15.1%) achieved PR. Of the cellular variant, three (37.5%) achieved CR. Among the tip variant, one (33.3%) patient had CR and one (33.3%) had PR. There was no difference in the response rate between various variants of FSGS (P > 0.05).

There were no significant differences in the baseline parameters of TAC-sensitive and TAC-resistant cases. TAC-sensitive patients had a significant reduction in proteinuria at 6 months from baseline as compared with TAC-resistant cases. TAC-sensitive patients had a significant increase in serum albumin at 6 months from baseline compared with TAC-resistant cases. TAC-sensitive patients also had a significantly higher serum albumin compared with TAC-resistant patients at 6 months of therapy. TAC-resistant patients had a significantly higher serum creatinine and decrease in eGFR at 24 weeks compared with baseline. However, no such significant increase in serum creatinine or decrease in eGFR compared with baseline was seen in TAC-sensitive patients at the end of 24 and 48 weeks of therapy. The TAC-resistant patients also had a significant higher serum creatinine and decrease in GFR at 6 months compared with TAC-sensitive patients (Table 3).

Five (21.7%) patients with CR at 24 weeks had relapse of proteinuria during reduction of the TAC dose, which responded to an increase in the dose. Relapse of nephrotic range proteinuria occurred in seven (30.4%) patients after cessation of TAC therapy.

Table 1. Baseline parameters

Number of patients	44
Age (years)	25.1 ± 8.2 (18–51)
Male:female	33:11
Duration of FSGS (weeks)	56 ± 56.4 (16–248)
24-h urine protein (g/day)	4.5 ± 3.6 (1.1–19)
Serum albumin (g/dL)	2.25 ± 0.83 (0.64–4.5)
Serum creatinine (mg/dL)	0.89 ± 0.15 (0.7–1.5)
eGFR (mL/min/1.73 m^2)	101.6 ± 24.4 (60.5–146.9)
FSGS variants	*N* (%)
FSGS-NOS	33 (75%)
Cellular variant	8 (18.1%)
Tip variant	3 (06.8%)

FSGS, focal segmental glomerular sclerosis; NOS, not otherwise specified; eGFR, estimated glomerular filtration rate.

Table 2. Outcomes with TAC in SR-FSGS

Parameter	Value	
Total remission	23 (52.2%)	
CR	17 (38.6%)	
Partial remission	6 (13.6%)	
Time to remit (weeks)	15.28 ± 6 (04–24)	
FSGS variants	TAC responsive	TAC resistant
FSGS-NOS (*n* = 33)	18 (54.5%)	15 (45.4%)
Cellular variant (*n* = 08)	3 (37.5%)	5 (62.5%)
Tip variant (*n* = 03)	2 (66.7%)	1 (33%)
Relapse during tapering	5 (21.7%)	
Relapse after completion of therapy	7 (30.4%)	
Complications	29 (65.9%)	

SR-FSGS, steroid-resistant focal segmental glomerular sclerosis; NOS, not otherwise specified; TAC, tacrolimus.

Adverse events

Twenty-nine patients (65.9%) experienced one or the other adverse effects during therapy (Table 4). TAC-related diarrhea was seen in 10 (22.7%) patients, who responded to a reduction in the dose of TAC. Infections were seen in 19 (43.1%) patients. Nine (20.4%) patients had diarrhea and 10 (22.7%) had non-diarrheal infections. Non-diarrheal infections included six (13.6%) patients with bacterial pneumonia, who responded to antibiotics, one (2.2%) with nocardiosis that was managed with cotrimoxazole, one (2.2%) developed candidiasis and was treated with fluconazole, one (2.2%) developed bone tuberculosis and was treated with 12 months of anti-tuberculosis therapy (non-rifampicin based), orbital cellulitis was seen in one (2.2%) patient and improved with antibiotics. All patients with infections responded to therapy. Eight patients (18.1%) developed new-onset DM during therapy and two (4.5%) developed IFG. All eight patients with DM had a family history of DM, six (16.7%) patients continued to require oral glucose-lowering agents even after completion of the study. Two patients with IFG (4.5%) and DM (4.5%) each improved by lowering the dose of TAC. Tremors and deranged liver function tests were seen in four (9%) and two (4.5%) patients, respectively. Impaired fasting lipid profile was seen in four (9%) patients. Nausea/vomiting and gum hypertrophy was seen in one (2.2%) patient each; all of the above-mentioned complications responded to a reduction in TAC dose. Eleven patients developed nephrotoxicity (25% rise in serum creatinine anytime during study) during the study period. Doubling of serum creatinine was seen in six (13.6%) patients, which normalized in two (4.5%) after decreasing the dose and persisted to remain elevated in four (9%) cases even after stopping therapy at 24 weeks. At the completion of 60 weeks, seven patients (15.9%) had reversible nephrotoxicity and four (9%) patients developed irreversible nephrotoxicity. Of the four with irreversible

Table 3. Response to therapy

	Baseline ($n = 44$)	24 weeks ($n = 44$)	48 weeks ($n = 23$)
24-h urine proteins (g)			
Total	4.57 ± 3.60[a] (1.1–19)	2.67 ± 3.11[b] (0.2–15.2)	0.52 ± 0.50[c] (0.04–2.4)
TAC responsive	4.57 ± 4.16[d] (1.1–19)	1.05 ± 1[e] (0.2–3.4)	0.52 ± 0.50[f] (0.04–2.4)
TAC resistant	4.57 ± 2.98[g] (1.2–13.2)	4.43 ± 3.66[h] (1.2–15.2)	
Serum creatinine (mg/dL)			
Total	0.89 ± 0.15[j] (0.7–1.5)	1.18 ± 0.60[k] (0.7–3.3)	0.95 ± 0.17[l] (0.6–1.5)
TAC responsive	0.90 ± 0.17[m] (0.8–1.5)	0.94 ± 0.19[n] (0.7–1.4)	0.95 ± 0.17[o] (0.8–1.5)
TAC resistant	0.87 ± 0.13[p] (0.70–1.18)	1.43 ± 0.78[q] (0.8–3.3)	
Serum albumin (g/dL)			
Total	2.25 ± 0.83[s] (0.64–4.5)	3.01 ± 1.04[t] (1.13–5.03)	4.04 ± 0.34[w] (3.6–4.75)
TAC responsive	2.28 ± 0.81[x] (1–4.2)	3.88 ± 0.43[y] (3.5–5.03)	4.04 ± 0.34[z] (3.6–4.75)
TAC resistant	2.21 ± 0.86[X] (0.64–4.5)	2.04 ± 0.53[Y] (1.1–3.3)	
eGFR (mL/min/1.73 m^2)			
Total	101.6 ± 24.40[#] (60.5–146.9)	84.22 ± 29.43[$] (22–124.5)	91.87 ± 21.63[@] (47.2–124.5)
TAC responsive	98.42 ± 22.37[A] (61–125.9)	94.33 ± 22.27[B] (45.5–125.9)	91.87 ± 21.63[@] (47.2–124.5)
TAC resistant	105.1 ± 21.56[D] (60.5–146.9)	73.15 ± 32.71[E] (22–124.5)	

a*b = 0.009, a*c < 0.0001, d*e = 0.0009, d*f = 0.0001, g*h > 0.05, s*t = 0.0003, s*w < 0.0001, y*Y < 0.0001, m*n = 0.23, m*o = 0.04, n*q = 0.0061, p*q = 0.0034, e*h = 0.0001, j*k = 0.002, j*l = 0.04, n*q = 0.005, #*$ = 0.0005, #*@ = 0.06, B*E = 0.02, C*E = 0.06, A*D = 0.37, A*B = 0.36, A*C = 0.06, D*E = 0.0003, B*E = 0.01.
TAC, tacrolimus; eGFR, estimated glomerular filtration rate.
The results are represented as mean ± SD. Parametric data were compared using a paired two-tailed Student's t-test. P < 0.05 was considered significant.

Table 4. Complications of tacrolimus therapy

Complication	Total ($N = 44$)	TAC sensitive ($N = 23$)	TAC resistant ($N = 21$)
TAC-related diarrhea	10 (22.7%)	6 (26%)	4 (19%)
Infections	19 (43.1%)	9 (39.1%)	10 (47.6%)
Nephrotoxicity	11 (25%)	2 (8.69%)[a]	9 (42.8%)[b]
Reversible nephrotoxicity	9 (20.4%)	2 (8.69%)	5 (23.8%)
Irreversible nephrotoxicity	2 (04.5%)	None	4 (19.0%)
Diabetes mellitus	8 (18.0%)	4 (17.3%)	4 (19%)
Impaired fasting glucose	2 (04.5%)	2 (8.7%)	None
Tremors	5 (11.3%)	3 (13%)	2 (9.5%)
Gum hypertrophy	1 (02.25%)	1 (4.3%)	None
New onset/worsening of preexisting hypertension	9 (20.4%)	5 (21.7%)	4 (19%)
Deranged liver functions	2 (04.5%)	1 (4.3%)	1 (4.76%)
Impaired lipid profile	4 (09%)	2 (8.69%)	2 (9.5%)

a*b, P < 0.05.

Table 5. Comparison of steroid-resistant FSGS with and without nephrotoxicity

Parameter	Nephrotoxicity ($n = 11$)	No nephrotoxicity ($n = 33$)
Age (years)	30 ± 2.8[a] (18–43)	23.5 ± 1.2[b] (18–51)
Duration of disease (weeks)	44 ± 39.6 (16–152)	60.4 ± 60.8 (16–248)
Baseline 24-h urine protein (g)	4.8 ± 3.7 (1.2–13.2)	4.4 ± 3.6 (1.1–19)
Baseline serum creatinine (mg/dL)	0.9 ± 0.1 (0.7–1.2)	0.8 ± 0.1 (0.6–1.5)
Baseline serum albumin (g/dL)	2.1 ± 0.8 (1.2–4.5)	2.2 ± 0.8 (0.6–4.2)
Mean TAC C0 (ng/mL)	7.2 ± 1.4 (5.6–9.8)	7.1 ± 1.2 (4.5–10)

a*b < 0.05.
TAC, tacrolimus; C0, tacrolimus trough levels.

nephrotoxicity, two underwent biopsy and the histopathology revealed progressive glomerulosclerosis with suspected chronic CNI toxicity (nodular hyalinosis, tabular atrophy and stripped interstitial fibrosis) with FSGS-NOS in one patient and collapsing glomerulonephritis in another patient, whose first biopsy was suggestive of FSGS-NOS. Acute nephrotoxicity was significantly associated with increased age (30.28 ± 2.8 years versus 23.5 ± 1.2 years; P = 0.01). There was no association of baseline serum creatinine, baseline eGFR and TAC trough levels with nephrotoxicity (Table 5). New-onset hypertension and worsening of preexisting hypertension were seen in eight (22.2%) and one (2.7%) patient, respectively.

DISCUSSION

FSGS is the most common primary glomerular disease, and its incidence is rising. Therapy for SR-FSGS is a CNI, either CSA or TAC. The KDIGO recommends use of steroids (oral prednisolone 1 mg/kg/day) in FSGS for a period of 16 weeks before declaring steroid resistance [8]. In most of the studies using CNIs in FSGS, steroids were given for variable duration (as shown in Table 6) before labeling them as steroid resistant, raising doubts about the steroid resistance of the illness. Only in the study by Cattran *et al.* and Meyrier *et al.*, was steroid duration before labeling resistance 14 and 16 weeks, respectively [10, 12]. The present study included patients who had received steroids for at least 16 weeks.

There are many trials that have evaluated the role of CSA in SR-FSGS in adults with remission rates of 57–69% (Table 6) [9, 10, 12–16]. However, there is paucity of data on the role of TAC in SR-FSGS. There are at least four RCTs that have evaluated the role of CSA in FSGS. The study by Cattran *et al.* included 26 SR-FSGS patients treated with CSA; CR and PR were seen in 12 and 57% of cases, respectively [10]. The prospective study by Meyrier *et al.* included 14 patients of SR and steroid-dependent FSGS treated with CSA; the authors reported CR and PR in 35% each, respectively [12]. Ponticelli

Table 6. Various studies on use of CNIs in SR-FSGS

	CNI	*N*	Study	Steroid duration (weeks)	CNI duration	Response (%)	CR (%)	PR (%)	Relapse	Nephrotoxicity (%)
Ponticelli *et al.* [9]	CSA	22	RCT	6	6–12	57	25	32	43	4.5
Cattran *et al.* [10]	CSA	26	RCT	14	06	69	12	57	50	15.4
Meyrier *et al.*[a] [12]	CSA	14	POS	16	>06	70	35	35	NA	NA
Ittel *et al.* [5]	CSA	22	POS	Nil		57.2	14.3	42.9		09
Heering P *et al.* [13]	CSA	34	RCT	Nil	24	61	23	38		11.7
Gipson *et al.* [14]	CSA	72	RCT	04	48	65	19	46	33	6.9
Segarra *et al.* [17]	TAC	25	POS	24	24	68	40	28	76	40
Li *et al.* [6]	TAC	07	POS	12	48	57.2	42.9	14.3	25	2.7
Duncan *et al.* [18]	TAC	06	POS	Nil		100	00	100		16.7
Present study	TAC	44	POS	16	48	52.4	38.8	13.6	30.4	25

CNI, calcineurin inhibitor; CR, complete remission; PR, partial remission; RCT, randomized control study; POS, prospective observational study; CSA, cyclosporine A; TAC, tacrolimus.
[a]Steroid-resistant and -dependent FSGS.

et al. studied 22 patients of SR-FSGS who received CSA for a period of 6–12 months. The authors reported CR and PR in 25 and 32% of patients, respectively [9]. The two other RCTs that had evaluated the role of CSA in FSGS were by Gibson *et al.* and Heering *et al.* [13, 14]. In the RCT by Gibson *et al.*, patients with SR-FSGS (definition: 4 weeks of steroids) received CSA for a period of 12 months. CR and PR were reported in 19 and 46% of the patients, respectively [14]. The patients who responded in the above-mentioned study were followed prospectively by Hogg *et al.* for 6 more months and reported sustained improvement in urine protein/creatinine ratio and eGFR at the end of follow-up [15]. In an RCT comparing up front use of CSA and steroids versus chlorambucil and steroids for a period of 6 months by Heering *et al.*, CR and PR were seen in 23 and 48% of patients, respectively [13]. Ittel *et al.* had prospectively followed 22 nephrotic MCD/FSGS patients treated with CSA and observed CR and PR in 14.3 and 42.9% of patients with FSGS [5]. In the systematic review of immunosuppressive drugs in FSGS, Braun *et al.* concluded that CSA in combination with oral prednisolone (0.15 mg/kg/d) are more likely to achieve a partial remission of the nephrotic syndrome compared with symptomatic treatment or prednisolone alone [16]. In the three trials that have evaluated the role of TAC in adult FSGS, only two looked at SR-FSGS [6, 17]. Li *et al.* had carried out a prospective observational study of the role of TAC in adult SR and cyclophosphamide-resistant nephrotic syndrome in seven patients whereas Segarra *et al.* included 25 SR, which were either CSA dependent or CSA resistant [6, 17]. The remission rates were 57.2 and 68% in the studies by Li *et al.* and Segarra *et al.*, respectively [6, 17]. In the present study, only steroid-resistant but calcineurin inhibitor (CNI)-naive patients were included. The remission rate in the present study was 52.2% (CR 38.6%, PR 13.6%), which is slightly less than that reported by Segarra *et al.* A better response rate in the study by Segarra *et al.* could probably be explained by the prior use of CSA in all of the study subjects [17]. Duncan *et al.* evaluated the role of TAC in six patients with FSGS and reported partial remission in all of the patients. However, none of the patients received steroids prior to TAC [18]. There are no RCTs comparing CSA and TAC in adult SR-FSGS patients [19]. The study, however, is not a comparison of two CNIs *viz.* CSA and TAC, the remission rate in the present study with TAC was numerically comparable to the results reported previously from various RCTs and prospective studies using CSA. It may be prudent to use CSA first for SR-FSGS and reserving TAC for CSA-resistant cases as done by Segarra *et al.* [17]. Patients in this study with FSGS-NOS and glomerular tip variant had a better response rate to TAC compared with the cellular variant ($P > 0.05$). The data on clinical behavior and therapeutic response of the cellular variant of FSGS are scanty. However, poor response of the cellular variant to standard therapy and CNIs is well described [20].

Relapse with CNIs may occur during tapering of the drug after achieving CR or after stopping the drug. Relapse after completion of therapy has been the major problem with CNIs. The incidence of relapse in adults with SR-FSGS after stopping CSA ranges from 43 to 50% [9, 10]. Segarra *et al.* had reported a relapse rate of 76% after 6 months of TAC therapy [17]. Li *et al.* reported a relapse rate of 35.7% (25% with FSGS) and 10.5% during tapering and after cessation of therapy, respectively [6]. The relapse rate in our study was 21.7% during tapering after CR (after 24 weeks) and 30.4% after cessation of therapy. The relapse rate in our study was slightly less than those experienced with CSA. The above-mentioned observation may probably be due to the better immunosuppressive potential of TAC compared with CSA and shorter duration of follow-up. Segarra *et al.* had a higher relapse rate with TAC compared with our study; the higher relapse rate may be due to shorter duration of TAC therapy (6 months) compared with our study (48 weeks) [17].

Nephrotoxicity is very common in patients receiving CNIs. Nephrotoxicity is reversible in most of the patients after stopping CNIs. However, a small minority has irreversible nephrotoxicity and progresses to chronic kidney disease. The incidence of histological confirmed CNI nephrotoxicity (clinical + subclinical) in patients undergoing protocol biopsy is 76.4% after 12 months of therapy [21]. TAC is less nephrotoxic than CSA. The incidence of nephrotoxicity in patients with FSGS on CSA and TAC varies from 43 to 50% and 5.2 to 40%, respectively [6, 9, 10, 17]. TAC nephrotoxicity was seen in ~25% of the patients in the present study and is comparable to the incidence reported from various other studies [6, 17]. In two patients with irreversible nephrotoxicity, the histology revealed chronic CNI toxicity in one and collapsing glomerulonephritis in other patient. Segarra *et al.* had reported

nephrotoxicity in 40% of the patients on TAC; higher baseline serum creatinine, trough levels and older age were associated ($P < 0.05$) with acute nephrotoxicity [17]. However, in our study, a statistically significant association was found only with higher age and there was no association of acute nephrotoxicity with higher serum creatinine and trough levels. Patients with TAC-resistant FSGS had a higher incidence of nephrotoxicity than TAC-sensitive patients; the above-mentioned observation of nephrotoxicity might be more influenced by the nature of the kidney disease than that attributable to TAC. It is important to know the timing at which a patient can be labeled as resistant to TAC as this would avoid unnecessary TAC exposure thus preventing nephrotoxicity. In the present study, a substantial number (30%) responded at the end of 24 weeks of therapy; hence, this cut-off has to be used to define TAC resistance. The remission rate of 52.4% in SR-FSGS with TAC was achieved at the cost of infections and DM. Infections were seen in 43.1% in this study and were probably due to the combined effect of TAC and glucocorticoids and prevailing epidemiological conditions. The incidence of infections in the present study was higher when compared with Li *et al.* [6]. The pattern of infections was also different as one patient each in this study had skeletal tuberculosis, nocardiosis and orbital cellulitis in addition to bacterial pneumonia and candidiasis. Infections as such are more common in this part of the world posing a challenge to the use of immunosuppressive drugs.

Incidence of hyperglycemia was 22.7% (18.1% had DM and 4.5% had IFG) in this study. The incidence of IFG/DM was higher when compared with Li *et al.* (5.2%); our observation could be explained by genetic predisposition of our population to increased risk of DM [6, 22]. All eight patients with DM had a family history of DM; six (13.6%) patients continued to require oral glucose-lowering agents even after completion of the study. Family history is an important risk factor for development of DM after TAC initiation and was very apparent in our study [22]. Two patients each with IFG (4.5%) and DM (4.5%) improved by lowering the dose of TAC. In retrospect, patients with a family history of DM should probably undergo an oral glucose tolerance test (OGTT) before TAC therapy. CSA may possibly be preferred over TAC in these patients. Prior steroid use could have significantly contributed to DM and infections rather than TAC per se; whether steroid-free TAC therapy alone will minimize these side effects needs to be validated.

What is the answer to the question addressed in the present study 'Is tacrolimus effective in SR-FSGS?' The answer is possibly that it is just as effective as any other CNI, but this effectiveness comes at the cost of increased infections and IFG/DM. TAC is one of the weapons in the armamentarium to treat difficult SR-FSGS, but not the final answer.

CONFLICT OF INTEREST STATEMENT

The present manuscript was partly presented as a poster presentation (TH-PO1018) at Kidney Week 2013, Atlanta.

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