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Original Article

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Cyclosporine therapy in primary steroid-dependent and steroid-resistant focal segmental glomerulosclerosis in adults

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ABSTRACT

Objective: There is scant data on treatment responses to cyclosporine and outcomes of idiopathic focal segmental glomerulosclerosis. The aim of this study was to share our experience on the use of cyclosporine in adults with primary focal segmental glomerulosclerosis at a single center in Pakistan.

Methods: This retrospective study was carried out in the Nephrology Department, Sindh Institute of Urology and Transplantation (SIUT), Karachi between January 1995 and June 2018. Clinical records of adult patients (≥16 years) with biopsy-proven idiopathic focal segmental glomerulosclerosis were reviewed to determine the relevant data items. Data were analyzed using Statistical Package for the Social Sciences version 22.

Results: Over a period of 22.5 years, 102/426 (23.9%) patients with a mean age of 26.3 ± 9.7 years with focal segmental glomerulosclerosis failed to achieve remission with steroids or relapsed during tapering and were treated with cyclosporine, including 33 (32.3%) steroid-dependent and 69 (67.6%) steroid-resistant patients. Among these, 44 (43.1%) patients achieved remission: 25 (24.5%) complete remission and 19 (18.6%) partial remission, while 58 (56.8%) showed no response. Among steroid-dependent focal segmental glomerulosclerosis, remission was excellent; 25 (75.7%) patients achieved remission. At the last follow-up, 32 (31.3%) patients had abnormal kidney function, 29 (42.0%) in steroid-resistant group versus only 3 (9.1%) in steroid-dependent group (P = .001). In the steroid-resistant group, 14 (22.6%) patients developed kidney failure and 7 (11.3%) required kidney failure with replacement therapy, while 4 (6%) died. None in steroid-dependent focal segmental glomerulosclerosis required kidney failure with replacement therapy or expired till the last follow-up.

Conclusion: In conclusion, this study shows that cyclosporine is effective as second-line therapy in a sizable number of adults with idiopathic focal segmental glomerulosclerosis, particularly in steroid-dependent cases.

Keywords: Adults, cyclosporine, focal segmental glomerulosclerosis, steroids

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INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is a heterogeneous disorder defined by the presence of focal and segmental sclerosis of the glomeruli on kidney biopsy.[1-4] Idiopathic FSGS poses significant challenges in its management because of its markedly varied clinical course and heterogeneous nature.[5] The specific therapeutic approach is still largely experiential, and very little evidence-based guidelines exist because of a paucity of large prospective randomized controlled trials.[6-10] Spontaneous remissions are not a common occurrence and probably occur in less than 5% of cases. Corticosteroids, in one form or the other, are the treatment of choice for the initial management of idiopathic FSGS.[11-15]

The introduction of cyclosporine (CyA) as the second line of treatment in glomerular diseases commenced soon after its introduction in solid organ transplantation in the mid- to late 1970s. Randomized controlled trials (RCTs) and uncontrolled studies revealed that CyA at a

therapeutic dose of 4-10 mg/kg/day may be of benefit in patients with idiopathic FSGS not responding to corticosteroids.[7,9,14-16] The calcineurin inhibitors (CNIs) including CyA may cause nephrotoxicity and currently it is recommended not to use them in patients with abnormal kidney function.[14-16] Cyclosporine-induced remission is associated with better survival in patients with nephrotic syndrome (NS) due to FSGS. It is important to study which type of patients are more likely to respond to CyA treatment so that those patients who are unlikely to show any response may be saved from adverse effects of CyA.[17-20]

The data are scant on CyA treatment and long-term kidney and patient outcomes of idiopathic FSGS in adult patients.[14-20] The number of RCTs on the efficacy and safety profile of this drug is even rarer. No data is available on the effectiveness and safety profile of CyA in adult patients with idiopathic FSGS from Sindh Institute of Urology and Transplantation (SIUT), Pakistan. The aim of this study was to analyze our experience of using CyA in adults with biopsy-proven idiopathic FSGS dependent on or resistant to corticosteroid therapy at our institution, which is a tertiary care hospital for nephrologic and urologic diseases.

METHODS

This is a single-center retrospective study of patients with idiopathic FSGS presenting to the nephrology outpatient department of Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan between January 1995 and June 2018 with a minimum of 1 year of follow-up. Cases of secondary FSGS including adaptive and genetic types were excluded by a careful review of clinical charts. Age at entry was ≥16 years. The study was approved by the institutional ethical review committee (approval number: XXXX-ERC-2019-PA-190, approval date: November 7, 2019), and it was conducted according to the ethical principles as envisaged in the Declaration of Helsinki. Clinical charts of patients were used to determine their age, sex, blood pressure, level of proteinuria, serum creatinine, and serum albumin. All patients had underwent real-time ultrasound-guided percutaneous native kidney biopsies. The biopsy specimens were evaluated by 2 experienced nephropathologists.

MAIN POINTS

- Focal segmental glomerulosclerosis (FSGS) is one of the dominant causes of adult nephrotic syndrome and leads to kidney failure in a significant number of cases.
- Treatment of FSGS is challenging and still largely empirical.
- Steroids are the treatment of choice for idiopathic FSGS; however, not all patients respond to steroids or develop steroid dependency.
- Cyclosporine is used as second-line therapy, but evidence is still scarce on its efficacy and safety.
- Cyclosporine was effective in a sizable number of cases of FSGS when used as second-line therapy in the present study.
- The response rate was markedly higher in steroid-dependent as compared to steroid-resistant cases.

Kidney biopsies were studied by light microscopy, immunofluorescence, and electron microscopy as described in detail in our previous study.[4] Raised serum creatinine was defined as serum creatinine >1.4 mg/dL in males and >1.2 mg/dL in females. We used the therapeutic regimens and dosages as envisaged in our institutional protocol.[10] In brief, the patients were started with prednisone at 1 mg/kg/day for 6 weeks, followed by a reduction to 0.75 mg/kg/day for additional 6 weeks, which was then steadily tapered over 3 months. Complete remission (CR) was defined as a decrease in the rate of proteinuria to ≤0.2 g/day, with serum creatinine persistently <1.5 mg/dL. Partial remission (PR) was defined as a decrease in the rate of proteinuria to between 0.21 and 2 g/day, with serum creatinine <1.5 mg/dL.

Time to remission was defined as the duration from the starting date of the first treatment to the date of the first remission. Relapse was defined in terms of the return of nephrotic-range proteinuria and edema associated with tapering the steroid dosage or stopping steroid treatment. Relapses were treated with a second course of steroid treatment alone or combined with CyA. Doubling of values of serum creatinine over baseline was considered as a surrogate marker for chronic kidney disease (CKD) progression. Chronic kidney disease was defined as per standard definition.[10]

We used CyA at a starting dose of 4 mg/kg/day. If CR or PR occurred, CyA was continued for at least 1 year. In case of no response by the end of 2 months, CyA was discontinued. In either case, CyA was started in conjunction with low doses of steroids in an overlapping fashion. Steroids were discontinued when patients either achieved remission with CyA or no response at 2 months, as alluded to earlier. Steroid-dependent FSGS was defined as cases who achieved CR after an initial 4- to 6-week course of daily steroids but relapsed during tapering of steroid dosage. Steroid-resistant FSGS was defined as cases who failed to respond to an initial course of 8 weeks of daily steroids. The final outcome of each patient was determined at the last available follow-up in terms of development of KF, kidney failure with replacement therapy (KFRT), or death of the patient. The parameters that were noted at this time included, among others contemporary medications, hypertension, serum creatinine and albumin values, urinalysis, and 24-hour urinary protein excretion.

Statistical Analysis

Data were entered and analyzed in Statistical Package for the Social Sciences (SPSS) software version 20.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used for summarizing the continuous and categorical variables. Continuous variables were presented as mean ± standard deviation or median ± interquartile range. Categorical variables were reported as frequency and percentages. Mean differences for continuous variables were compared between groups using the student's *t*-test and the proportion differences for categorical variables by chi-square or Fisher's exact tests as appropriate. *P*-value < .05 was taken as significant.

RESULTS

Over a study period of 22.5 years, 426 cases of biopsy-proven FSGS were identified. Among these, 102 (23.9 %) patients failed to achieve remission with steroids (SRNS) or relapsed during tapering of steroids (SDNS) and were treated with CyA as second-line therapy. The latter constitute the subjects of the present study.

Although steroids were started at a dose of 1 mg/kg body weight/day, they were generally well tolerated in both groups. However, mild forms of adverse events were noted in 55 (53.9%) of all patients. These included acne in 17 (16.6%), weight gain in 14 (14.2%), gastric discomfort in 9 (8.8%), hypertension in 6 (5.8%), diabetes in 4 (3.9%), proximal myopathy in 3 (2.9%), and cataract and psychosis in 1 patient (0.9%) each.

Table 1. The Main Demographic, Clinical, and Laboratory Findings at Presentation and Overall Treatment Responses to Cyclosporine for All Patients with Primary FSGS (n = 102)

Parameters	Values
Age (years) mean ± SD (range)	26.3 ± 9.7 (16-54)
Male-to-female ratio	2:1
Systolic BP (mmHg) mean ± SD	127.2 ± 17.7
Diastolic BP (mmHg) mean ± SD	83.2 ± 12.3
Initial proteinuria (G/24 h) mean ± SD	4.155 ± 2.19
Serum albumin (g/dL) mean ± SD	1.9 ± 1.5
Serum creatinine (mg/dL) mean ± SD	1.0 ± 0.8
Follow-up duration (weeks) mean ± SD	191.4 ± 113.6
Duration of CyA treatment (weeks) mean ± SD	30.2 ± 33.8
Total CyA dose (mg) mean ± SD	24311.9 ± 23544.4
Complete remission	25 (24.5%)
Partial remission	19 (18.6%)
No response	58 (56.8%)
Time to remission (weeks) mean ± SD	37.2 ± 16.9

BP, blood pressure; CyA, cyclosporine; FSGS, focal segmental glomerulosclerosis; SD, standard deviation

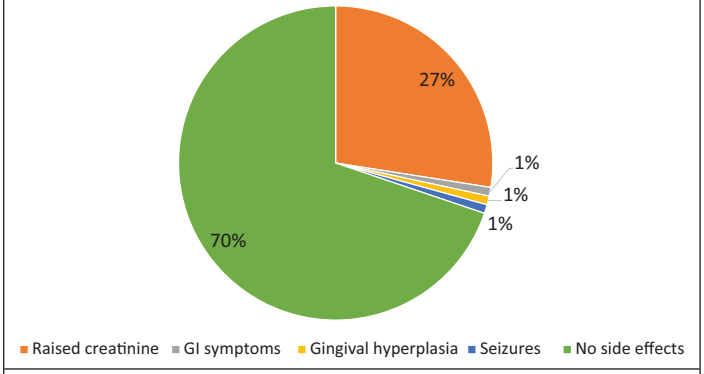

Figure 1. Safety profile of cyclosporine in all patients (n = 102).

The main demographic, clinical, and laboratory characteristics of 102 patients at the time of presentation and response to treatment are shown in Table 1. The mean age was 26.3 ± 9.7 years with a range of 16-54 years. Males were dominant with a male-to-female ratio of 2:1. In all, 102 patients were treated with CyA and steroids as envisaged in our treatment protocol. Treatment with CyA was started at a mean of 9.6 ± 11.3 months after diagnosis of FSGS. Among all, 44 (43.1%) patients achieved remission and 58 (56.8%) showed no response to CyA treatment. Among responders, 25 (24.5%) showed CR, while 19 (18.6%) showed PR. The response rates to CyA varied

Table 2. Comparison of Demographic, Clinical, Laboratory, and Treatment Response to Cyclosporine Parameters Among Steroid-Dependent and Steroid-Resistant Primary FSGS Groups

Parameters	Steroid-Dependent Group (n = 33)	Steroid-Resistant Group (n = 69)	*P*
Age (years) (mean ± SD)	25.9 ± 9.6	26.5 ± 11.5	.776
Gender (M:F)	1.8 : 1	2.1 : 1	.653
Systolic BP (mmHg)	122.7 ± 16.4	129.5 ± 18.0	.077
Diastolic BP (mmHg)	80.9 ± 11.9	84.0 ± 12.1	.225
Initial protein (g/24 h)	3.65 ± 1.62	4.36 ± 2.36	.204
Initial serum creatinine (mg/dL)	1.0 ± 0.6	1.0 ± 0.9	.995
Initial serum albumin (g/dL)	2.5 ± 2.3	1.7 ± 0.8	.074
Total steroid dose (mg) (median [IQR])	3768.2 ± 2504.5	3846.9 ± 2403.3	.882
Steroid duration (weeks)	24.1 ± 21.9	25.7 ± 20.7	.913
CyA total dosage (mg)	28390.5 ± 28799.4	2286.7 ± 21461.7	.347
CyA duration (weeks)	43.0 ± 40.7	21.4 ± 28.1	**.028**
Duration of follow-up (weeks)	197.0 ± 105.9	151.9 ± 114.9	.068
Abnormal kidney function on presentation	2 (5.7%)	9 (13.0%)	.327
Abnormal kidney function on the last follow-up	3 (9.1%)	29 (42.0%)	**.001**
CKD progression	0(0.0%)	13 (19.4%)	**.008**
Hypertension	7(21.2%)	19 (27.5.4%)	.493
Complete remission	14 (42.4%)	11 (15.9%)	**.004**
Partial remission	11 (33.3%)	8 (11.5%)	**.008**
No response	8 (24.2%)	50 (72.4%)	**<.001**

BP, blood pressure; CKD, chronic kidney disease; CyA, cyclosporine; FSGS, focal segmental glomerulosclerosis; IQR, interquartile range
Bold entries represent significant *p* values.

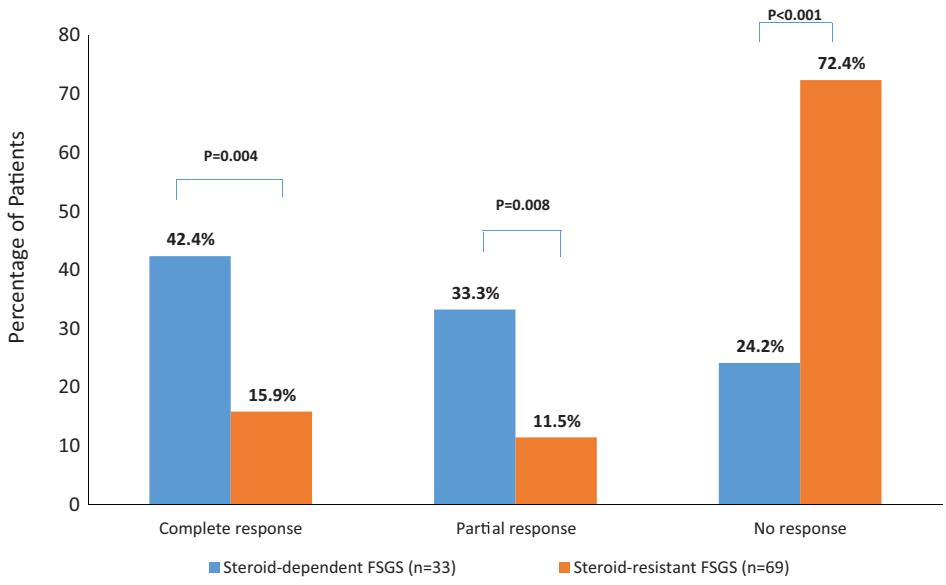

Figure 2. Comparison of responses to cyclosporine according to steroid-dependent and steroid-resistant nature of focal segmental glomerulosclerosis (n = 102).

depending on the primary response to steroids. The mean duration to remission was 37.2 ± 46.9 weeks. The drug was safe in the majority of cases and side effects were uncommon as shown in Figure 1. The most common side effect observed was a rise in serum creatinine, which was noted in 28 (27.4%) patients.

A comparison of demographic, clinical, and laboratory parameters at the time of presentation and treatment responses to CyA between patients with steroid-dependent FSGS and those with steroid-resistant FSGS is shown in Table 2. This table shows that baseline demographic, clinical, and laboratory characteristics were generally similar in the 2 groups. Corticosteroids were the first line of therapy in all 102 patients. Cyclosporine was initiated in 33 (32.3%) steroid-dependent patients and 69 (67.6%) steroid-resistant FSGS patients. The duration of CyA treatment was significantly higher in steroid-dependent (43.0 ± 40.7 weeks) group versus steroid-resistant (21.4 ± 28.1 weeks) group (P = .028). At the last follow-up, 32 (31.3%) patients were found to have elevated serum creatinine, with 29 (42.0%) in steroid-resistant FSGS group versus only 3 (9.1%) in steroid-dependent group (P = .001). Abnormal kidney function in terms of doubling of values of serum creatinine at the last recorded follow-up was observed in 13 (19.4%) patients of steroid-resistant FSGS group while none of the steroid-dependent FSGS patients developed doubling of serum creatinine (P = .008). Among steroid-dependent FSGS group, the remission rate was excellent; 25 (75.7%) patients achieved remission. Among these, 14 (42.4%) achieved CR, while 11 (33.3%) showed PR. No remission was achieved in 8 (24.2%) patients. Among steroid-resistant FSGS group, remission was achieved in 19 (27.5%) patients; among these, 11 (15.9%) achieved CR and 8 (11.5%) PR. No remission was achieved in 50 (72.4%) patients (P = .004, .008, and <.001, respectively), as shown in Figure 2. The hazard ratio of overall treatment response (both CR and PR) to CyA was 0.501 with 95% CI of 0.052-4.860 (P = .55).

A comparison of relevant demographic data and clinical and laboratory parameters both at the time of presentation and at the last follow-up among patients with CyA-responsive and CyA-non-responsive FSGS groups is depicted in Table 3. It is evident from the table that only initial proteinuria, serum creatinine at the last follow-up, and duration of CyA treatment differed significantly between the 2 groups. In addition, the incidences of tip and collapsing variants were significantly different among the 2 groups. Interestingly, the overall incidence of collapsing FSGS was also high (23.5%) in this study population. This may partly be due to sampling bias as the majority of collapsing FSGS cases do not respond well to steroids. The mean serum creatinine in collapsing FSGS cohort was 1.04 ± 0.94 mg/dL (range: 0.33-6.4 mg/dL) and the mean glomerular filtration rate (GFR) was 105.8 ± 39.14 min/1.73 m^2/mL/ (range: 7.6-173.4 mL/min/1.73 m^2). Thus, the kidney functions were relatively preserved in collapsing variant of FSGS in this study. The mean serum creatinine values were 0.91 ± 0.43 mg/dL (range: 0.47-2.1 mg/dL) and 0.86 ± 0.34 mg/dL (range: 0.4-1.77 mg/dL) in FSGS, not otherwise specified (NOS) and tip variants, respectively. Similarly, the mean GFR values were 113.04 ± 36.03 (range: 34.9-165.7 min/1.73 m^2) and 112.94 ± 35.35 (range: 42.6-172.4 min/1.73 m^2) mL/min/1.73 m^2 in the 2 variants.

The final clinical outcomes in both steroid-dependent and steroid-resistant groups are shown in Table 4. In the steroid-resistant group, 14 (20.2%) patients developed KF and 7 (10.1%) required KFRT, while 4 (5.7%) died. None of the patients in steroid-dependent FSGS required KFRT or expired till the last follow-up. The mean serum creatinine was also significantly higher

Table 3. Comparison of Demographic, Clinical, Laboratory and Histology Parameters Among Cyclosporine-Responsive and Cyclosporine-Non-Responsive Groups (n = 102)

Parameters	Cyclosporine-Responsive Group (n = 44)	Cyclosporine-Non-Responsive Group (n = 58)	*P*
Age (years) mean ± SD	25.9 ± 10.4	26.6 ± 11.3	.785
Male-to-female ratio	2.1 : 1	1.9 : 1	.777
Systolic BP (mmHg) mean ± SD	127.9 ± 16.2	126.6 ± 18.9	.712
Diastolic BP (mmHg) mean ± SD	82.7 ± 10.8	83.3 ± 12.9	.800
Initial proteinuria (mg/24 h) mean ± SD	3501.6 ± 1656.9	4641.3 ± 2423.0	**.025**
Serum albumin at presentation (g/dL) mean ± SD	1.8 ± 0.9	1.9 ± 1.7	.618
Abnormal kidney function, *n* (%)	4 (9.1%)	7 (12.1%)	.753
Serum creatinine at presentation (mg/dL) mean ± SD	1.1 ± 0.9	0.9 ± 0.7	.440
Serum creatinine at last follow-up (mg/dL) mean ± SD	1.0 ± 0.7	2.3 ± 3.3	**.008**
Follow-up duration (weeks) mean ± SD	163.6 ± 116.1	168.4 ± 112.6	.840
Total dose of CyA (mg) mean ± SD	28378.9 ± 26045.2	22167.5 ± 220665.1	.253
Duration of CyA therapy (weeks) mean ± SD	40.8 ± 42.1	19.2 ± 23.7	**.011**
Histological Variants of FSGS			
FSGS, NOS variant, *n* (%)	23 (52.3%)	27 (46.6%)	.567
FSGS, tip variant, *n* (%)	15 (34.1%)	10 (17.2%)	**.050**
FSGS, collapsing variant, *n* (%)	5 (11.4%)	19 (32.8%)	**.012**

BP, blood pressure; CyA, cyclosporine; FSGS, focal segmental glomerulosclerosis; SD, standard deviation.
Bold entries represent significant *p* values.

in steroid-resistant cohort as compared to steroid-dependent cohort, as shown in Figure 3.

DISCUSSION

Idiopathic FSGS is one of the leading causes of NS in adults and is continuously increasing in incidence over the last 4 decades, especially in African Americans.[1] Lesions of FSGS have been documented in up to 35% of adult patients undergoing a kidney biopsy for NS.[2-4] Focal segmental glomerulosclerosis is also among the commonest causes of NS in adults in Pakistan, and it is reported as the most common histopathological diagnosis in some studies.[4]

Calcineurin inhibitors, particularly CyA, have been tried in steroid-resistant idiopathic FSGS, but the evidence supporting their use as the first-line therapy for FSGS is weak and is chiefly based on small observational studies or anecdotal series.[5-9] The effectiveness of CNIs has been studied in these patients, and these are more effective than mycophenolate mofetil and alkylating agents. A systematic review and meta-analysis by Laurin et al[9] concluded that there is no evidence supporting the role of CNIs as first-line therapy in FSGS. They also found that CyA in combination with low-dose steroids is effective in achieving remission but is associated with high relapse rates upon its discontinuation.

A recent study from our institute found that 48% of patients with FSGS achieved remission with steroids and 52% of patients failed to respond or relapsed after the initial response to steroids.[10] This is in contrast to the study of Chun et al[11] who reported that 63% of patients with FSGS had sustained response to steroids and the remaining 37% either not responded or relapsed after discontinuation of steroids. However, there is a paucity of literature and no published data from Pakistan about the use and efficacy of CyA in adult patients with FSGS.

Results from this study show that out of 102 patients treated with CyA in this study, 43.1% of patients achieved remission; 24.5% achieved CR, while 18.6% showed PR. Interestingly, the response rate was higher in steroid-dependent FSGS (75.7%) as compared to steroid-resistant FSGS (27.5%). These results are somewhat similar to those reported by Ponticelli and Graziani[12] which showed that among adult FSGS patients who did not respond to prednisone, only 17% of those treated with CyA had CR, and another 20% had a PR. In contrast, Goumenos et al[8] found that a combination of low-dose prednisolone with CyA resulted in remission in 85.7% of patients as compared to 62.5% of patients treated with prednisolone alone and 80% of patients treated with a combination of prednisolone and azathioprine. The initial outcome seemed good, but it was a small

Table 4. Clinical Outcomes in Steroid-Dependent and Steroid-Resistant FSGS Groups Treated with Cyclosporine

Outcome	Steroid-Dependent Group (n = 33)	Steroid-Resistant Group (n = 69)	*P*
Chronic kidney disease	0	14 (20.2%)	**.002**
Hemodialysis	0	7 (10.1%)	.091
Death	0	4 (5.7%)	.533

FSGS, focal segmental glomerulosclerosis.
Bold entries represent significant *p* values.

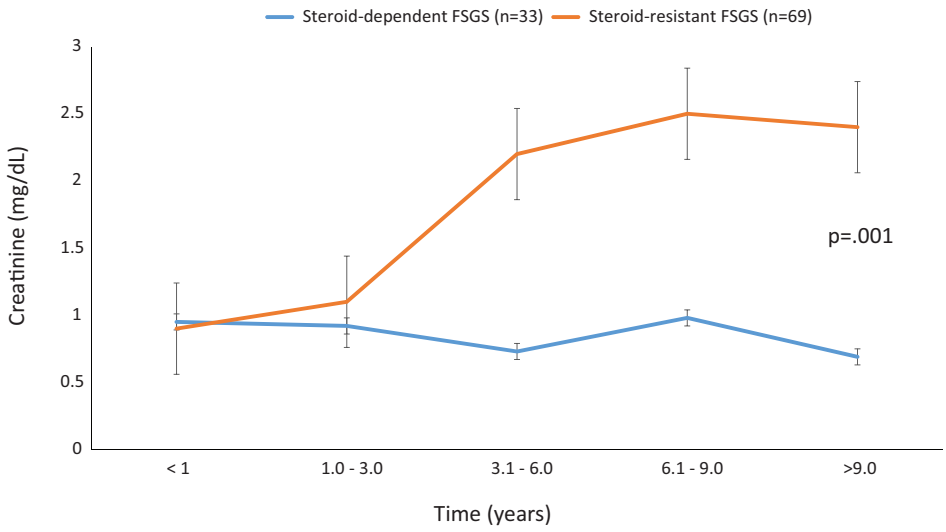

Figure 3. Comparison of mean serum creatinine between steroid-dependent and steroid-resistant focal segmental glomerulosclerosis.

retrospective study and limited to remission of NS and most of the patients (68%) who reached end-points had persistent NS during the follow-up.

The mean time to remission in CyA-treated patients in the present study was around 9.3 months. Gorsane et al[13] from Tunisia had a follow-up of 16.5 months with CyA and there was CR of NS in 35% of patients after a mean duration of 12 months. There was no significant difference between steroid-dependent versus steroid-resistant groups, while the present study shows significant differences in CR and PR and no response rates among the 2 groups. Collaborative Study Group of Sandimmun in NS found that the maximum cumulative rate of CR was achieved at 6 months after starting CyA and pursuing CyA for a longer period is not beneficial in terms of additional remissions but exposes to the risk of nephrotoxicity (nearly 4% patients required discontinuation of cyclosporine).[14] In contrast to this, the present study noted a rise in serum creatinine in 27.4% of patients receiving CyA, which required cessation of CyA therapy.

Gorsane et al[13] from Tunisia conducted a retrospective observational analysis of their FSGS patients and reported CR in around one-third of cases after a mean duration of 12 months, PR in around one-fifth of cases after a mean interval of 3 months, a dose-dependent remission to CyA (2.87 mg/kg/day) in 4 (17%) cases, and no remission in around one-fourth of cases. Their proportion of steroid-dependent and steroid-resistant cases was almost similar to that found in the present study. The response to CyA was better in their study as compared to the present study. The reasons for this are not clear.

A controlled, prospective study by Heering et al[15] found that CyA led to CR/PR in approximately 60% of patients with steroid-resistant FSGS. Patients received either CyA or chlorambucil along with steroids. Complete remission was achieved in 23% of the patients who received CyA versus 17% of patients in the chlorambucil group. Partial remission was achieved in 38% of patients on CyA versus 48% on chlorambucil (n = 11).

The duration of CyA treatment in this study was significantly higher in steroid-dependent FSGS group as compared to steroid-resistant FSGS group. This is in contrast to the study from Tunisia where CyA treatment duration was 41.57 versus 21.69 months in the 2 groups, but it was not statistically significant.[13] This may be because of the small sample size in the later study.

As in all forms of NS, the achievement of either CR or PR of NS is a reliable predictor of better outcomes in FSGS.[16-20] Many new agents are being developed and tested for achieving remission of proteinuria in FSGS but are still at the experimental stage.[20-25]

An interesting finding that has emerged from this study is the relatively high incidence of collapsing variants of FSGS in this cohort of patients. This may partly be due to selection bias, as we mostly excluded secondary cases of FSGS such as perihilar variant. In most cases of collapsing FSGS, we did not find a plausible cause; hence, they were categorized into the primary type. Because the response to steroids is uniformly poor in this variant of FSGS, this variant was over-represented in this study cohort. We also used liberal histopathological criteria for the diagnosis of collapsing FSGS, as also envisaged in Columbia classification of FSGS. The presence of even a single glomerulus with segmental collapse was considered sufficient to diagnose a particular case as collapsing FSGS. The etiology, pathogenesis, presenting features, treatment, and prognosis of collapsing FSGS have shown tremendous advances, and its spectrum is continually expanding beyond the original etiology of HIV. However, the exact cause of the higher incidence of collapsing variant in our setup needs further research.[26]

Additionally, serum creatinine and GFR values were lower at presentation in collapsing variant in this study. This is in contrast to western studies where collapsing variant typically presents with heavy proteinuria and marked KF. In a cohort of 55 patients with collapsing FSGS, the mean serum creatinine is 1.4 ± 0.9 mg/dL (data not shown). The reasons for this discrepancy are not entirely clear, but we noted short pre-biopsy durations in this cohort. So, early pick up of cases might be related to better preservation of renal functions in this subset of patients. This needs further research in our setting.[27]

The frequency of development of KF, requirement of replacement therapy (KFRT), and death were significantly different among the 2 groups in this study. None of the patients in steroid-dependent FSGS group treated with CyA developed KF or required replacement therapy or died. In contrast, 14 patients in steroid-resistant FSGS group treated similarly developed KF, 7 developed KFRT, and 4 died. From these results, it can be inferred that response to steroids is the most important prognostic factor in adults with primary FSGS.

Our study has certain limitations too, such as its single-center origin, retrospective nature, and lack of measurement of trough levels for monitoring response to therapy in the case of CyA. The follow-up duration was also not very long. We also did not perform genetic analysis on any of these patients.

CONCLUSION

In conclusion, this study shows that CyA is an effective treatment in a significant number of adult patients with FSGS who fail to respond or relapse after initial treatment with steroids. Remission rates are significantly higher in steroid-dependent FSGS as compared to the steroid-resistant group. The optimal regimen and treatment duration are still not known, and RCTs and meta-analysis of available data are needed to find the best treatment option for FSGS.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of SIUT, Karachi, Pakistan (Approval Date: November 7, 2019; Approval Number: SIUT-ERC-2019/PA-190).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – N.H.J., M.M.; Design – N.H.J., M.M.; Supervision – N.H.J., M.M., E.A.; Resources – N.H.J., M.M., E.A.; Data Collection and/or Processing – N.H.J., M.M., S.Q.; Analysis and/or Interpretation – N.H.J., M.M., S.Q.; Literature Review – N.H.J., M.M., S.Q.; Writing – N.H.J., M.M.; Critical Revision – M.M., E.A.

Declaration of Interests: The authors declare that they have no conflict of interest.

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