Rituximab in Steroid-Dependent and Resistant Primary Focal Segmental Glomerular Sclerosis in Adults; A Retrospective Single-Center Study

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Abstract

Introduction: In recent decades, the prevalence of focal segmental glomerulosclerosis (FSGS) has increased globally, becoming a significant cause of nephrotic syndrome. While rituximab (RTX) has been proven effective in treating pediatric FSGS, its administration in adults requires further evidence. **Objectives:** We studied the administration of RTX in adult-onset FSGS both steroid-dependent (SD) and steroid-resistant (SR). **Patients and Methods:**We conducted a single-centre retrospective, observational study from January 2018 to December 2023. Patients aged over 18 years with primary FSGS both steroid-dependent and steroid-resistant treated with rituximab were included in this study. The RTX dose used was either 500 mg or 1000 mg. **Results:** This study included 12 adult patients with biopsy-confirmed primary FSGS, with an equal gender distribution and a mean age of 36.8 ± 9.21 years. Of these, 6 (50%) were steroid-dependent, and 6 (50%) were steroid-resistant. The overall remission rate (partial remission+complete remission) at 3, 6, and 12 months was 75%, 66.7%, and 58.4%, respectively. Renal function remained stable in patients who responded to therapy. The first relapse occurred at 16 months and 6 months in steroid-dependent and steroid-resistant patients, respectively, following RTX administration. During follow-up, all three steroid-resistant patients who did not respond to RTX developed end-stage renal disease, with one death. **Conclusion:** Rituximab was effective in treating adult steroid-dependent FSGS and may also be beneficial in steroid-resistant FSGS. However, further prospective research is needed to determine the role of RTX dosing and retreatment strategies in both steroid-dependent and steroid-resistant FSGS.

Keywords: Rituximab, Steroid-dependent,Focal segmental glomerular sclerosis, Nephrotic syndrome, Steroid-resistant

Introduction

Focal segmental glomerulosclerosis (FSGS) is a pathological lesion that frequently occurs in adults and children with primary nephrotic syndrome, for whichimmunosuppressive agents are usually required. The long-term prognosis for FSGS remains poor, with approximately 50% of patients progressing to end-stage kidney disease (ESKD) within 6 to 8 years. (Wang et al., 2023). FSGS can be considered a primary or hereditary form, as well as occurringin response to an array of secondary factors (Tedesco et al., 2022). The exact cause of primary FSGS is unknown. Multiple theories suggest that aberrant interactions between B cells and autoreactive T cells, potentially involving an unidentified circulating permeabilizing factor, may play a role (Wang et al., 2023). Furthermore, some molecular factors include anti-Crb2 autoantibodies, which have been postulated to cause the urokinase plasminogen activator receptor (uPAR), and angiopoietin-like-4 (Angptl4), have been implicated in nephrotic syndrome, though robust evidence supporting these theories is lacking (Morris et al., 2023).The conventional approach to FSGS for many years has been immunosuppressive treatment because of the believed immunologic etiologic mechanism. However, despite this approach, only about 50% of patients achieve partial or complete remission. Remission rates vary significantly across clinical trials, reflecting differences in study inclusion criteria and treatment strategies.

The Kidney DiseaseImproving Global Outcomes (KDIGO) guideline recommends high-dose oral glucocorticoids as the first-line immunosuppressive treatment for primary FSGS. Adults with primary FSGS who respond positively to glucocorticoid therapy should continue treatment for at least six months or longer(Disease et al., 2021).However, the long-term use of steroids is associated with adverse effects, including dyslipidemia, impaired fasting glucose, reduced bone mineral density, hypertension, and an increased risk of cardiovascular diseases (Hansrivijit et al., 2020). For patients who are intolerant of or have contraindications to glucocorticoid therapy, calcineurin inhibitors are considered the first-line alternative for immunosuppression in primary FSGS. Tacrolimus or cyclosporine administration; however, has been linked to frequent relapses after drug cessation. For steroid-resistant (SR) primary FSGS, cyclosporine or tacrolimus should be administered for longer than six months instead of glucocorticoids alone. In cases of patients unable to respond to/cannot tolerate or do not respond to cyclosporine or tacrolimus, second-line options such as mycophenolate mofetil and cyclophosphamide may be considered (Disease et al., 2021).Since it is proposed that primary FSGS has autoimmune nephrotic factors immune-modulating therapies have been tried more recently, including in

steroid-dependent and steroid-resistant nephrotic syndrome with mixed responses.

Rituximab (RTX) is a chimeric monoclonal antibody (mAb) comprising human and murine components. It specifically targets the CD20 transmembrane protein expressed in B cells(Pescovitz, 2006). There are two possible ways in which RTX induces remission in patients with FSGS. The first mechanism involves the suppression of CD20-positive B cells which is likely the primary way RTX functions. This suppression reduces circulating permeability factors that compromise podocyte integrity(Gauckler et al., 2020).In patients with multidrug-resistant FSGS, it has been suggested that the antiproteinuric effect of RTX might also be occurring through a B-cell-independent mechanism. Some of the RTX effects discovered indicate that it can regulate T-cell subsets and even impact the podocyte directly. Specifically, RTX appears to preserve podocyte cytoskeletal stability and prevent podocyte apoptosis by targeting proteins such as sphingomyelin phosphodiesterase acid-like 3b(Morris et al., 2023). Currently, KDIGO guidelines recommend the use of RTX for treating steroid-dependent minimal change disease (Disease et al., 2021). However, its role in managing steroid-dependent (SD) and steroid-resistant (SR) focal segmental glomerulosclerosis (FSGS) is limited to cases where patients cannot tolerate or have contraindications to calcineurin inhibitors.We conducted a retrospective analysis to assess the remission levels in both steroid-resistantandsteroid-dependent patients.

Methodology

Study participants

This study enrolled all patients diagnosed with steroid-dependent and steroid-resistant primary focal segmental glomerulosclerosis (FSGS) who received rituximab (RTX) treatment. Inclusion criteria included patients aged 18 years or older with biopsy-confirmed primary FSGS. Exclusion criteria included a glomerular filtration rate (GFR)<15 ml/min, the presence of other glomerular diseases, kidney transplant recipients, secondary glomerular diseases, membranous nephropathy, and membranoproliferative glomerulonephritis.

Data collection

Patient demographics and clinical variables were recorded. Follow-up evaluations were made at baseline, 3 months, 6 months, and 12 months after treatment to assess patient response.

Rituximab dosing

Rituximab was given in doses of 500 mg or 1000 mg, according to the decision of the treating nephrologist.

Outcome measures

- Complete remission (CR): 24-hour proteinuria ≤0.3 g, normal kidney function, stable serum creatinine levels, and serum albumin ≥3.5 g/dL.
- Partial remission (PR):>50% reduction in proteinuria from baseline, with 24-hour proteinuria <3.5 g and normal kidney function.
- Relapse**:** A >50% increase in proteinuria during partial remission or proteinuria >3.5 g/day (or PCR >3500 mg/g) following complete remission(Disease et al., 2021).

Statistical analysis

Categorical data were reported as frequencies and percentages, while continuous data were expressed as meanstandard deviation or median and range, depending on data distribution. Statistical analyses were performed using Jamovi2.3 software, with a p-value <0.05 considered statistically significant.

Results

Twelve adult patients with biopsy-proven primary FSGS were enrolled in the study. The majority (83.3%) had thefocal segmental glomerulosclerosis - not otherwise specified (FSGS-NOS) subtype, while one patient (8.3%) had the FSGS-cellular variant, another (8.3%) had the FSGS-Tip variant. There were no cases of collapsing variant FSGS in our study. The gender distribution was evenly split with 6 (50%) males and 6 (50%) females. The mean age of the patients was 36.8±9.21 years. The median duration of the disease was 66 months ranging from 48 to 216 months. The most common co-morbidity among the patients was hypertension which affected 11(97%) individuals. This was followed by steroid-induced diabetes mellitus 4 (33.3%), 5 (41.7%) dyslipidemia, and 4 (33.3%) hypothyroidism.

Before commencing RTX therapy, all patients treated with immunosuppression were subjected to100% prednisolone. Moreover, ten patients (83.3%) had been treated with tacrolimus, three patients (25%) had received cyclophosphamide and two patients (16.7%) had been on cyclosporine. At baseline, all patients presented with nephrotic-range proteinuria with values ranging from 3.6 to 10.3 gm. The Baseline serum albumin was 3.30g/dL (1.60-4.70) and the serum creatinine was 0.890 mg/dL (0.490-3.06). In our study, six patients (50%) were steroid-dependent, and the other 6 patients (50%) were steroid-resistant.

Meanwhile, ten patients received two doses of 500 mg RTX each separated by four weeks, while two patients received a single dose of 500 mg RTX.

Table 1. Clinical characteristics of FSGS patients (n=12)

Variables	No of patients(n=12) %
FSGS Variants	
NOS	10(83.3%)
Cellular variant	1(8.3%)
Tip-variant	1(8.3%)
Collapsing	-
Gender	
Male	6(50%)
Female	6(50%)
Age (mean±SD) years	36.8±9.21
Duration of disease median months	66 (48-216)
Co-morbidities	
Hypertension	11(97%)
Steroid-induced diabetes mellitus	4(33.3%)
Hypothyroidism	4(33.3%)
Previous treatments	
Prednisolone	12(100%)
Tacrolimus	10(83.3%)
Cyclosporine	2(16.7%)
Cyclophosphamide	3(25%)
Baseline serum albumin median [range]	3.30 [1.60-4.70]
Baseline Serum creatinine median [range]	0.890 [0.490-3.06]
Steroid-dependent	6(50%)
Steroid-resistant	6(50%)
RTX Dosing	
1*500 mg	2(16.7%)
2*500 mg	10(83.3%)

Abbreviations: NOS, Not otherwise specified; RTX, Rituximab;

Response to RTX therapy

All steroid-dependent patients achieved remission with RTX therapy (100%), whilethree (50%) steroid-resistant patients responded to treatment. Overall response rates (partial remission+ complete remission) to RTX therapy were 9(75%) at three months, 8(66.7%) at sixmonths, and 7(58.4%) at 12 months.In steroid-dependent group, no relapses were observed following the RTX treatment. However, in the steroid-resistant group, one patient experienced a relapse at six months while two patients relapsed at 12 months. Among those who responded to the therapy, renal function remained stable throughout the follow-up period indicating a positive renal outcome. Steroid therapy was continued at a dose of 5–10 mg along with RTX treatment. A detailed summary of the responses to RTX therapy at three, six, and 12 months is presented in Table 2.

Table 2. Response to rituximab therapy three, six and12 months

Response	SD (n=6)			SR(n=6)			Remission CR+PR (n=12)		
	3M	6M	12M	3M	6M	12M	3M	6M	12M
PR	3	2	1	1	1	1	9(75%)	8(66.7%)	7(58.4%)
CR	3	4	5	2	1	-			
NR	-	-	-	3	3	3			
RELAPSE	-	-	-	-	1	2			

Abbreviations: PR, Partial remission; CR, Complete remission; NR,No response ;SD, Steroid dependent ;SR, Steroid Resistant;

Follow up

In total, six patientswere retreated with RTX. Five of these patients received two doses of 500 mg each, while one received a single 500 mg dose. Of the six steroid-dependent patients, two received RTXagain due to a relapse of the disease that occurred after 16 months of RTX treatment. Notably, all two patients who received retreatment achieved complete remission. During follow-up, all the steroid-dependent patients were in full remission.

Of three steroid-resistant patients that responded to RTX, one of them relapsedwhich occurred at six months, and received two doses of 500 mg RTX all three are in remission on follow-up. Three patients who did not respond to the initial RTX treatment were retreated with two additional 500 mg doses, but they still did not respond even at the maximum dosage. At follow-up, all three

patients who did not respond to RTX had developed end-stage renal disease, and one of the patients died.

Serious adverse events

No patients reported any serious adverse events or require any hospitalization following rituximab administration. All were on sulfamethoxazole and trimethoprim prophylaxis.

Discussion:

Managing steroid-dependent and steroid-resistant FSGS in adults remains a significant clinical challenge. The primary goal of treatment is to achieve at least partial remission to prevent progression to end-stage renal disease end-stage renal disease (Tedesco et al., 2022).Current treatment strategies include various immunosuppressive agents such as steroids, calcineurin inhibitors, cyclophosphamide, and mycophenolate mofetil (Disease et al., 2021). However, these options maintain low remission rates and relatively high relapse rates, especially with calcineurin inhibitors that are independently associated with considerable long-term morbidities. This highlights the importance of approaches that do not adversely impact long-term outcomes while providing treatment options for those who are likely to experience relapse. Rituximab emerges as a potential alternative with a favorable safety profile. Although the efficacy of RTX in maintaining remission in adults with minimal change disease is well-established, its role in adult primary FSGS remains less clear. Specifically, more evidence is needed to confirm its effectiveness in maintaining remission and preventing relapse in these patients.

Our study focuses on adult patients with primary focal segmental glomerulosclerosis, encompassing both steroid-dependent and steroid-resistant types. The findings support the use of rituximab as an effective treatment. We observed overall remission rates (partial remission+ complete remission) of 75%, 66.7%, and 58.4% at three, six, and 12 months, respectively. During the first 12 months of treatment, patients who responded demonstrated stable renal function, improved proteinuria, and increased serum albumin levels. Our results align with findings from other studies, confirming the consistency of RTX's effectiveness in treating adult FSGS patients, although response rates have varied across studies (Hansrivijit et al., 2020; Tedesco et al., 2022). For instance, our findings are comparable to those of Tedesco et al, a study conducted in Italy, which reported response rates of 39%, 52%, and 42% at 3, 6, and 12 months, respectively (Tedesco et al., 2022).Similarly, a study conducted in China by Wang et al involving nine steroid-dependent nephrotic syndrome patients reported that seven achieved completeremission(Wang et al., 2023).In a case series by Ochi et

alinvolving four FSGS patients, the two steroid-dependent nephrotic syndrome cases attained complete remission(Ochi et al., 2012). In our cohort, all steroid-dependent patients responded positively to RTX treatment. Based on the results of our study and previous studies, we confirm that RTX is effective in improving outcomes for patients with steroid-dependent FSGS.

In our study, only three steroid-resistant patients responded to RTX treatment, while the others had a prolonged disease duration and ultimately did not respond to retreatment, eventually progressing to end-stage renal disease. In a case series by Ochi et al two steroid-resistant nephrotic syndrome cases had no response, resulting in a longer duration of disease and worse renal function (Ochi et al., 2012). In our study, even after administering additional doses, the steroid-resistant patients who initially didnot respond showed no further improvement. It is also unclear if steroid-resistant patients with poor responses would benefit in any way from greater RTX dosages.A case series by Fernandez-Fresnedo et al of three steroid-resistant patients who went into remission following the administration of the greatest cumulative dose of RTX(Fernandez-Fresnedo et al., 2009).However, other studies observed late-onset neutropenia and advancing hypogammaglobulinemia which are associated with an increased risk of serious infections(Barmettler et al., 2018). Therefore, it was recommended to monitor serum immunoglobulin routinely and neutrophil counts both before and after giving RTX treatment. In the therapy of FSGS, striking the correct balance between managing disease activity and reducing drug-induced toxicity can be challenging (Tedesco et al., 2022). Those who responded to RTX required only 500-1000 mg to achieve remission. Similar to the studies by Ramachandran etal(India) andOchi et al(Japan)administered a single dose of RTX(Ochi et al., 2012; Ramachandran et al., 2019). Meanwhile, other Western countries require higher doses of RTX to achieve remission.A summary of the studies indicates that rituximab can be effectively used to treat FSGS, as presented in Table 3

Table 3. Summary of the studies that used rituximab in FSGS

Author & year	Sample size /type of Patients/ Study design (SD/SR)	Conclusion	RTX dosage

(Tedesco et al., 2022)	31 (17 SD, 9 SR) Retrospective study	At 3 months: 65% of SD patients responded, and SR patients showed no response. At 6 months: 69% of SD-patients responded, and 22% of SR patients showed a response. At 12 months: 57% of SD patients responded, and 11% of SR patients responded.	A single dose of 1000 mg and two doses of 1000 mg each, given two weeks apart, total 375 mg/m²/wk for four weeks
(Ramachandran et al., 2019)	53(39 SD, 14 SR)	At 6 months: 30.76% patients attained CR, 46.16% attained PR. At 12 months: 38.46% achieved CR, and 15.38 achieved PR.	Mean RTX dose: 791.66 ± 131.60 mg, range 600-1000 mg
(Roccatello et al., 2023)	8 Case series	Seven out of eight patients did not show any progress during the treatment course and continued to be nephrotic.	Eight weekly doses of 375 mg/m².
(Kronbichler et al., 2013)	3 (3 SD) Case series	All three patients received complete remission using RTX treatment. Even though other immunosuppressive therapies are withdrawn.	Four weekly infusions of 375 mg/m² RTX.
(Ochi et al., 2012)	4 (2 SD, 2 SR) Case series	Two SD patients showed complete remission, in contrast with SR patients.	single dose of RTX 375 mg/m²
(Fernandez-Fresnedo et al., 2009)	8 (All SR) Case series	Three were positive response, five were nephrotic syndrome cases and two developed renal function.	Four weekly consecutive infusions of 375 mg/m².

Conclusion

Our study supports RTX as a promising therapeutic option for patients with steroid-dependent FSGS.RTX has demonstrated efficacy in reducing proteinuria and maintaining remission in patients who have become dependent on corticosteroids. RTX may also be considered for treating steroid-resistant FSGS patients. Future studies involving larger patient cohorts and prospective randomized trials are needed to define RTX's precise role in the management of adult-onset FSGS, including potential long-term outcomes and the identification of predictive markers for treatment response.

Strengths and limitations of the study

Only a few studies from India have examined the use of RTX in FSGS, and our study uniquely includes both steroid-dependent and steroid-resistant patients in the cohort. However, the study has several limitations, including a small sample size, retrospective design, absence of genetic testing, lack of monitoring for hypogammaglobulinemia, and no pre-emptive RTX treatment. Despite these limitations, the inclusion of both steroid-dependent and steroid-resistant patients in our cohort represents a significant strength, contributing valuable insights to the limited data available from India.

Authors'contribution

Conceptualization: Mohan VaradanayakanahalliBhojaraja, Shankar Prasad Nagaraju. **Data curation:** Swathi Nayak Ammunje

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Conflicts of interest

The authors declare that they have no conflict of interest. No funding was received for conducting this study.

Ethical issues

This study adhered to the principles of the Declaration of Helsinki. Prior to any intervention, all participants provided written informed consent. This

retrospective study was also conducted after approval from the Institutional Ethics Committee (#IEC1; 401/2023). The study screened a total of 12 cases of primary FSGS from January 2018 to December 2023 using electronic medical records.

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