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Editorial Comment

EDITORIAL COMMENT

Rituximab in the treatment of primary FSGS: time for its use in routine clinical practice?

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ABSTRACT

Focal segmental glomerulosclerosis (FSGS) is a common cause of nephrotic syndrome and whilst advances have been made in the pathophysiology, diagnostics and management of other podocytopathies, primary FSGS remains the most elusive. It has been assumed for a long time that a circulatory permeability factor exists that mediates podocyte injury, and the potential for autoantibody-mediated disease therefore raises the question as to whether patients may benefit from targeted B-cell therapy with rituximab. The prospective case series of seven patients by Roccatello *et al*. adds to the limited but growing evidence suggesting that B-cell depletion therapy can be safe and effective in the treatment of primary FSGS. In this editorial we explore the available evidence that suggests how and in whom rituximab may play a role in the management of primary FSGS, as well as the limitations and other potential future treatments. Further research and randomized controlled trials are needed to include larger numbers of patients, feature genetic screening and incorporate data on B-cell kinetics as a potential guide for dosing and frequency of rituximab.

Keywords: FSGS, immunosuppressive treatment, rituximab

INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) characterizes a histopathological pattern of disease that is representative of a podocytopathy with a diverse range of aetiologies and varied treatment options. Amongst these, primary FSGS remains the most elusive, when considering both the current putative pathogenesis and therapeutic strategies. Primary FSGS is typified by abrupt-onset nephrotic syndrome caused by diffuse foot process effacement and podocyte injury leading to sclerosis [1]. In the absence of a functional biomarker for primary FSGS, the diagnosis often requires a lengthy process of excluding of other causes before considering treatment [2]. These include genetic causes, virus-associated disease and drug-induced forms of FSGS. Adequately powered clinical trials on the treatment of primary FSGS remain few and far between, and there is only a limited body of evidence to help guide management in those with severe nephrotic syndrome and rapid progression, and those who fail to achieve remission with standard therapy [3]. A recent paper by Roccatello *et al*. looked at a prospective case series of seven patients with FSGS who were managed with rituximab [4]. Over recent years several small studies have looked at the use of B-cell depleting agents in the management of FSGS and report varying outcomes.

PATHOGENESIS

In the case of primary FSGS, the widely accepted underlying pathogenesis centres around the presence of an unidentified circulating factor that mediates podocyte injury. The presence of disease recurrence post-transplantation and treatment response lends the most support to this concept [5, 6]. Proteinuria occurring within minutes of transplantation, treatment response to plasma exchange and B-cell depleting therapy strongly suggests a pathogenic role for circulating factor [7, 8].

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A recent large study placed the risk of disease recurrence post-transplantation at approximately 32% (95% confidence interval 25%–39%) [6]. In this setting, plasma exchange with or without the use of B-cell depleting therapy constituted the most commonly adopted treatment strategy, with partial or complete remission achieved in just over half of all patients [6].

Studies into circulating factors have explored numerous potential candidates. Mouse models have highlighted the potential role of anti-Crb2 autoantibodies in podocyte injury [9] and the increased expression of the urokinase protein receptor (uPAR) has been identified on podocytes with resultant foot process effacement and proteinuria [10]. Soluble uPAR (suPAR) has therefore been proposed as a key mediator of disease. Its generation of an FSGS-like glomerulopathy has been demonstrated in animal models, with subsequent studies identifying elevated levels in patients with primary FSGS compared with controls [11–13]. Despite this, larger studies have found no association with suPAR and disease or treatment response [14, 15]. Similarly, angiopoietin-like-4 (Angplt4) has been identified as a key molecular mediator in nephrotic syndrome [16] and whilst experiential studies have shown its use in identifying specific disease states to be limited, its potential as a circulatory factor in proteinuric glomerular diseases such as FSGS remains an area of novel research [1, 17]. More recently work by Watts *et al.* has shown anti-nephrin autoantibodies to be significant in podocytopathies, particularly minimal change disease (MCD) [18]. The research suggests an autoimmune aetiology as the potential cause for nephrotic states and given the similarity in MCD and primary FSGS, these findings present a target for immune modulating therapy such as rituximab.

ROLE OF RITUXIMAB

The use of rituximab in FSGS has been limited, in part due to the unknown mechanism by which it acts in this disease group. Many lines of enquiry have evaluated autoimmunity. In 2009, Berre *et al.* demonstrated that deoxyspergualin derivative LF15-0195 successfully ameliorated disease in rats through the increased activity of regulatory T cells [19]. Both B and T cells were subsequently identified in paediatric cases of primary FSGS, with resulting B-cell depletion in tissue on repeat renal biopsy and clinical remission in those treated with rituximab [20]. It was noted as early as 2004 that rituximab could alter the course of FSGS in paediatric patients [21]. Strengthening the hypothesis of immune-mediated disease was the presence of high levels of anti-CD40 antibodies in patients with relapsing FSGS post-transplantation and in a separate study, the deleterious effect of CLCF-1 through B-cell stimulation [22, 23]. This also complemented initial findings regarding the potential role of suPAR, with the potential ability of anti-CD40 antibodies to enhance suPAR mediated proteinuria in wild-type mice [22]. The presence of potential antibody-mediated disease has therefore prompted the evaluation of B-cell depleting therapy with the anti-CD20 monoclonal antibody, rituximab.

In a recent issue of *Clinical Kidney Journal*, Roccatello *et al.* provided a prospective case series of seven patients with FSGS managed with combination therapy, inclusive of rituximab [4]. All cases were biopsy proven, with active nephrotic syndrome and a background of either relapsing or steroid-dependent disease. Extensive genetic screening was undertaken and three patients were identified as having a genetic mutation, one of whom had a mutation for *IFN2* gene which is known to cause FSGS. The remainder were considered to have primary FSGS on the basis of extensive diffuse podocyte effacement and nephrotic syndrome, in keeping with the proposed classification presented in the recent KDIGO guidelines [24]. Details on histopathology classification and immunofluorescence were not presented in this case series, but all patients had >70% podocyte effacement and half had evidence of interstitial fibrosis and arteriolosclerosis [4, 25]. Treatment consisted of six doses of rituximab 375 mg/m^2. The initial four doses were given weekly over the first 4 weeks, followed by monthly dosing on Months 2 and 3. Alongside this two doses of cyclophosphamide 10 mg/kg were given intravenously on Days 4 and 17, as well as three intravenous doses of methylprednisolone 15 mg/kg followed by a tapering course of prednisolone 50 mg/day to a dose of zero at 3 months. Supportive therapy consisted of antiproteinuric measures with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, although dosing and blood pressure control were not reported. In line with KGDIO guidance complete remission was defined as <0.3 g/day proteinuria and normalization of serum albumin. Partial remission was defined as a 50% drop in proteinuria and a uPCR 30–350 mg/mmol with an albumin of 3.5 g/dL. At 12 months the number of patients with primary FSGS in complete and partial remission were zero and five, respectively. Mean follow-up was 30 months and amongst those with a partial response, outcomes remained unchanged in four patients at last follow-up and one achieved complete remission. The response was measured by CD20$^+$/CD19$^+$ B cells every 3 months and these were depleted in the peripheral blood for a median of 12 months.

The multi-targeted strategy in the Roccatello *et al.* case series makes it difficult to attribute response to B-cell depletion therapy alone. This is particularly true with a subpopulation of patients with steroid-dependent disease who may have had a favourable response to high-dose oral and intravenous glucocorticoid therapy. The only study comparing the use of glucocorticoids vs no glucocorticoids alongside supportive therapy in primary FSGS is a randomized control trial of 102 patients in a Chinese population. This demonstrated a significantly higher remission rate with therapy (73% vs 50%, $P = .01$) with a median response time of 3 months [26]. With emerging data of *apolipoprotein L1* (*APOL1*) mutation playing instrumental genetic predisposition in Black ethnicity, these results are difficult to extrapolate across other races. Considering the role of cyclophosphamide, previous studies [27] have demonstrated improved outcomes in steroid-dependent and steroid-resistant disease, albeit with a higher cumulative dose compared with that used by Roccatello *et al.* Overall, although the sample size limits any inference from the data reported by Roccatello *et al.*, it supports the hypothesis that B-cell depleting and multitargeted therapy can be effective in the treatment of primary FSGS.

Further to this, work by Fornoni *et al.* looked at 41 renal transplant patients who were considered high risk for FSGS recurrence [28]. Of these, 27 patients were treated with rituximab at the time of transplantation. They found that instead of having a purely immune modulating effect, rituximab may also act by modulating podocyte function and prevent disruption of the cytoskeleton to reduce apoptosis of podocytes [28]. Additionally, B cell–T cell crosstalk has implications for immune dysregulation through activation of T cells and downregulation of regulatory T cells. In a paediatric retrospective study observational study of 22 patients, those responding to rituximab therapy tended to exhibit lower levels of T-cell activation [29]. Both bodies of work suggests that the use and success of rituximab may not be a solely B-cell-dependent process and other mechanisms may exist by which to treat primary FSGS.

Table 1: Summary of the studies that demonstrate the use of rituximab in the treatment of FSGS.

Study title	Author	Date	Summary	Limitations
Focal segmental glomerular sclerosis can be effectively treated using an intensive B cell depletion therapy [4]	Roccatello *et al.*	2023	Seven patients with FSGS managed with combination therapy including 6 doses of RTX. Five patients had partial response at 12 months and one remained in complete remission at 36 months	Small case series. Three patients were identified as having a genetic mutation, one of whom had a mutation for *IFN2* gene
The role of rituximab in primary focal segmental glomerular sclerosis of the adult [34]	Tedesco *et al.*	2022	Thirty-one patients were treated with RTX. Response rates at 3, 6 and 12 months was 39%, 52% and 42%, respectively. 80% of responders at 12 months maintained a sustained response with ongoing treatment	Patients included had a long disease course prior to RTX treatment. No genetic analysis was undertaken and there was variation in the RTX and standard glucocorticoid dosing
Rituximab therapy for focal segmental glomerular sclerosis and minimal change disease disease in adults: a systematic review and meta-analysis [44]	Hansrivijit *et al.*	2020	Sixteen studies included with a total of 221 patients (23.1% with FSGS). Over half (53.6%) of FSGS patients achieved remission with RTX but there was a significant relapse rate	The majority of patients had MCD rather than FSGS. Only observational studies were included without any control cohorts
High-dose rituximab ineffective for focal segmental glomerulosclerosis: a long-term observation study [31]	Roccatello *et al.*	2017	Eight patients were treated with high-dose RTX (8 weekly doses of 375 mg/m^2). Seven out of eight patients failed to improve and remained nephrotic	Small case series. Patients included all had major risk factor precluding standardized glucocorticoid treatment
T lymphocyte activation markers as predictors of responsiveness to rituximab among patients with FSGS [29]	Chan *et al.*	2016	Twenty-two paediatric patients treated with RTX following a lack of sustained remission treatment with either calcineurin inhibitors, mycophenolate or cyclophosphamide. Twelve responded to therapy with reduced T-cell activation compared with non-responder on immunological profiling	Small retrospective observational study. No genetic analysis was undertaken, with limited response rate and biomarker findings remain unvalidated
Rituximab in adult patients with multi-relapsing/steroid-dependent minimal change disease and focal segmental glomerulosclerosis: a report of 5 cases [32]	Kronbichler *et al.*	2013	Five patients were treated with RTX and achieved complete remission even when other immunosuppressive treatment was withdrawn. One patient relapsed after 23 months but was treated successfully with further RTX	Small case series with only three FSGS patients included
Rituximab treatment for adult patients with focal segmental glomerulosclerosis [33]	Ochi *et al.*	2012	Four patients: two were steroid resistant and two were steroid dependent. The two patients with steroid-dependent FSGS achieved complete remission in contrast to those who had steroid-resistant disease	Small study size and only a single dose of RTX was given. Those with steroid resistant disease had a longer duration of disease and worse renal function by comparison
Rituximab targets podocytes in recurrent focal segmental glomerulosclerosis [28]	Fornoni *et al.*	2011	Forty-one transplant patients at high risk of recurrent FSGS. Twenty-seven received RTX and demonstrated lower incidence of post-transplant proteinuria and renal impairment	Although there has a trend to higher graft survival in the RTX treated patients at 6 and 12 months, this was not statistically significant

Table 1: Continued

Study title	Author	Date	Summary	Limitations
Rituximab treatment of adult patients with steroid-resistant focal segmental glomerulosclerosis [37]	Fernandez-Fresnedo *et al.*	2009	Eight patients, three had a positive response with RTX and the remaining five had on going nephrotic syndrome and in two cases worsening renal function	The three patients who improved received additional doses of RTX compared with those that did not improve
Rituximab for refractory focal segmental glomerulosclerosis [45]	Nakayama *et al.*	2008	A case series of two children with steroid resistant FSGS. Both achieved partial remission at 1 month, with one patient achieving complete remission for 8 months and the other relapsing	Small case series with short follow-up time. Only a single dose of rituximab was given
Change of the course of steroid-dependent nephrotic syndrome after rituximab therapy [21]	Benz *et al.*	2004	A single case report of a 16-year-old with steroid dependent FSGS. RTX was given and the patient achieved remission	Single case series with no longitudinal data

RTX, rituximab.

Considering other published work, reports of on the effectiveness of rituximab in primary FSGS have been variable, as shown in Table 1. A non-blinded open label study of rituximab in in nine patients with treatment-resistant FSGS and raised suPAR levels demonstrated no benefit [30]. This study contained more patients than that presented by Roccatello *et al.* and aimed to assess whether rituximab in the context of a high suPAR was efficacious, given the previous evidence suggesting its role in pathogeneis. Despite rituximab being shown to be ineffective, it is unclear whether patients would have benefited from repeated rituximab dosing.

A previous case series of eight patients by Roccatello *et al.* in 2017, all of whom had major risk factors precluding standardized glucocorticoid treatment, reported a poor response to rituximab in all but one case, whereas other limited case series have suggested more favourable results [31–33]. Recently Tedesco *et al.* reported the outcomes of 31 patients with primary FSGS who were treated with rituximab in a prospective observational study [34]. Dosing ranged from 375 mg/m^2/week for 4 weeks, two doses of 1 g given 2 weeks apart or a single dose of 1 g. All patients had either relapsing disease, persistent disease or an indication for avoidance of other therapeutic options. Of those with data available at 6 and 12 months, the complete and partial remission rate was 26% and 21%, respectively. The partial remission rate matched this. After inclusion of patients who were retreated with rituximab, the partial remission rate at 12 months increased from 21% to 27%, whereas the number in complete remission remained unchanged. The overall response in those with steroid-resistant disease was poor, whereas treatment response was better in those with a history of steroid-dependent disease, an eGFR >60 mL/min/1.73 m^2 and <5 g/day proteinuria. The latter raises the question about rituximab dosing in nephrotic patients and increased urinary losses as a compounding factor for suboptimal treatment response in those with more severe proteinuria. Only 50% (n = 15) of the reported cohort had available data on B-cell kinetics, restricting any meaningful analysis with treatment response and further subgroup analysis according to induction dosing. However, it is feasible that the observed relapse rate amongst patients with an initial treatment response may reflect earlier B-cell repopulation with lower effective induction dosing. Whilst Roccatello *et al.* demonstrated depleted B-cell subsets for up to 12 months, previous pharmacokinetic studies of rituximab in patients with nephrotic syndrome have confirmed high urinary losses with reduced serum concentration and a shorter half-life [35, 36]. Further to this, the GLOSEN (Spanish Group for the Study of Glomerular Diseases) group identified eight patients treated with rituximab and of these only three improved [37]. The only difference between those who improved and those who did not was a difference in rituximab administration, with those who improved receiving additional doses. Subsequently, patients with primary FSGS and poor treatment response may require higher or more frequent dosing of rituximab.

GENETICS

The presence of an underlying genetic aetiology for disease is another significant consideration for the variable and potentially limited outcomes with rituximab or any immunosuppression therapy. Amongst the reported studies, the lack of genetic screening may cast the diagnosis of primary FSGS into doubt and failure to adequately exclude patients with a genetic cause would compound any findings [31–34]. Genetic causes for FSGS have been associated with a heterogenous pattern of disease and inheritance. Multiple genes have been identified and these have been shown to corelate with different disease manifestations including renal limited FSGS as well as extra-renal involvement [38]. One of the more commonly understood genetic links with FSGS is the *APOL1* genotype, which is a recognized risk factor for end-stage renal disease amongst affected patients and is associated with a range of renal pathology inclusive of FSGS [39]. Many genetic cases of FSGS have shown to be resistant to glucocorticoids and have limited response to calcineurin inhibitors (CNIs) [38, 40]. Challenges in treating primary FSGS with immunosuppressive treatment may in part be explained by unknown genetic causes. Patients labelled as 'steroid resistant' who have responded poorly to glucocorticoid treatment and rituximab may reflect a proportion of patients with unknown genetic mutations rather than a poor response to immunosuppressive therapies. This raises the question about the role of wider

genetic testing in FSGS, not just in patients with an obvious family history or syndromic presentation, but also in patients where the cause is not immediately obvious. Consequently this may allow for more patient-centred management in those who are most likely to benefit from immunotherapy, and avoid high glucocorticoid exposure or immunosuppression in patients with genetic mutations as the underlying cause of FSGS.

FUTURE MANAGEMENT

When evaluating other immunosuppressive medications, the evidence base is limited owing to the relatively few number of studies, small sample size and often the comparison of varied combination strategies, each of which remain untested on their own merit in an appropriate trial design [41, 42]. In addition, FSGS histology predicts clinical outcomes and a trial with a non-homogenous group has limitations and much higher level of genetic predisposition. Nevertheless, there is a potential signal of benefit and the current body of evidence favours therapy with glucocorticoids and CNIs, with benefit of CNIs in steroid-resistant disease [2, 41, 42].

Given the potential promise of B-cell depleting therapy, the use of rituximab is being assessed in the TURING (Efficacy of Rituximab in Comparison to Continued Corticosteroid Treatment in Idiopathic Nephrotic Syndrome) trial against high-dose prednisolone (NCT03298698). This trial will not only compare clinical outcomes, but will also address patient-reported outcomes and quality of life, which have been shown to be reduced in those with FSGS [43]. A small case series by Ochi *et al.* demonstrated that those with steroid-sensitive disease responded better to rituximab treatment than those with steroid-resistant FSGS [33]. The reasons for this remain unclear and likely reflect the variations in pathophysiology associated with FSGS. However, it proposes rituximab treatment as a potential alternative to those that would have otherwise been exposed to high levels of glucocorticoids and associated toxicity. On the whole, the studies that have used rituximab treatment have demonstrated it to be safe and without significant adverse events [21, 31, 34].

CONCLUSION

FSGS is a histological entity with multiple aetiologies, making it one of the more difficult glomerulopathies to manage. Primary FSGS remains a complex condition which poses challenges to diagnosis, classification and treatment. Current treatment options in primary FSGS are often unsatisfactory. Although the underlying pathophysiology remains debated, there is a suggestion of potential autoantibody-mediated disease which may benefit from targeted B-cell therapy with rituximab. The study by Roccatello *et al.* [4] is small but adds further evidence to the suggestion that B-cell depletion therapy can be safe and effective. The lack of efficacy to date, at least in some patients, may reflect failure to exclude participants with a potential underlying genetic disease and suboptimal dosing in nephrotic patients with increased urinary losses. The evidence to suggest that rituximab may become routine treatment for many patients with FSGS is thin but tangible. Following exclusion of an underlying genetic mutation and other secondary causes, we propose that rituximab can be considered in those with high risk of glucocorticoid toxicity, CNI nephrotoxicity or failed initial treatment following exclusion of other causes, and that repeated dosing may be required to achieve therapeutic effect. However, a need remains for better trial design in those with FSGS to identify which patients are most likely to benefit from rituximab. Further studies

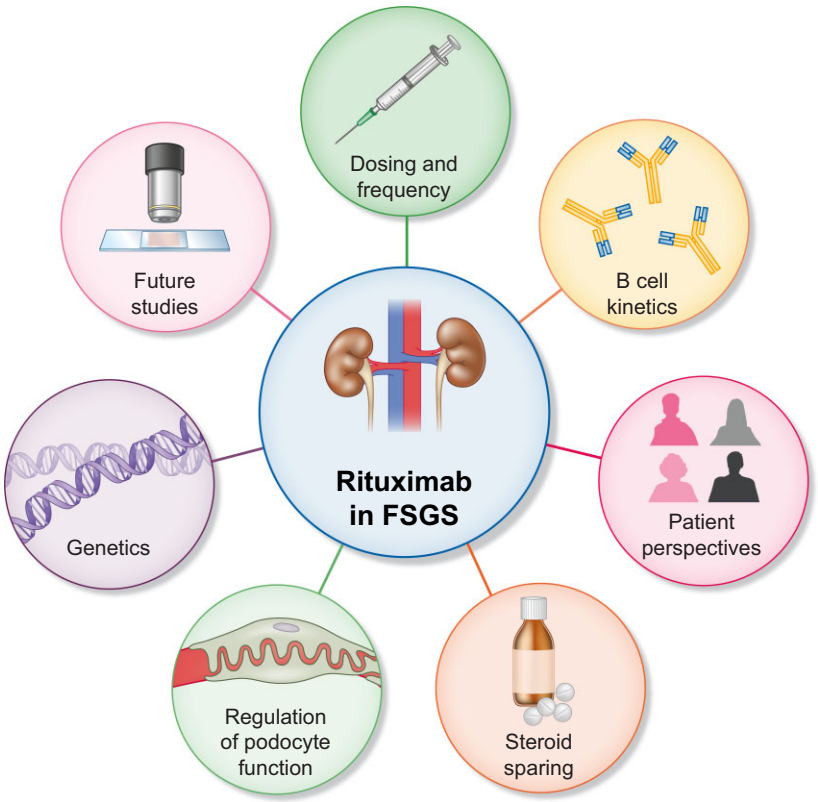

Figure 1: The scientific questions and unknowns that exist in clinical practice when using rituximab as treatment for primary FSGS.

should include larger number of patients and incorporate histology, genetic testing and data on data on B-cell kinetics into the study inclusion criteria (Fig. 1).

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this paper have not been published previously in whole or part. A.W. holds the position of Editorial Board Member for *Clinical Kidney Journal* and is anonymized from reviewing or making decisions for the manuscript.

(See related article by Roccatello et al. Focal segmental glomerular sclerosis can be effectively treated using an intensive B-cell depletion therapy. *Clin Kidney J* (2023) 16: 1258–1264.)

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