

The Role of Rituximab in Focal Segmental Glomerulosclerosis—Update From Italy



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[See Research Letter on Page 1893](#)

Rituximab use has revolutionized the management of many glomerular diseases. In this issue of *KI Reports*, a multicentric Italian retrospective study by Tedesco *et al.*¹ addresses the question about whether rituximab could be an efficient treatment option for patients with focal segmental glomerulosclerosis (FSGS) and nephrotic-range proteinuria.

When discussing therapeutic efficacy and approaches in FSGS, one must acknowledge the complexity of this disease, which is summarized in [Figure 1](#). The term FSGS describes a histopathologic glomerular lesion that can either be detected as a rather unspecific result of a variety of underlying pathogenic processes (secondary FSGS), in the setting of distinct genetic disorders affecting podocyte integrity or as a primary form for which an immune-mediated pathogenesis is assumed. The podocyte injury

(podocytopathy) reflects a unifying correlate of all underlying causes but specific treatment varies substantially, because only primary forms may benefit from immunosuppressive measures.² In contrast, optimal supportive or anti-proteinuric treatment is crucial in all other forms to decelerate progressive loss of kidney function. Consequently, making this differentiation is equally complex and relevant for further patient management, not only in routine clinical practice. Establishing the diagnosis of primary FSGS always reflects a thorough diagnostic workup, occasionally over the course of several years, including repeat kidney biopsies and genetic analyses. These factors may explain in part why data on efficacy of therapeutic measures in patients with FSGS is substantially heterogenous. Furthermore, current trial evidence is impacted by small numbers of included patients, with the ongoing DUPLEX trial being a noteworthy exception (NCT03493685).

Patients treated according to current guideline recommendations are exposed to a high-dose glucocorticoid regimen, occasionally

over several months.³ Frequent relapses and steroid dependent disease courses are common and further aggravate the significant treatment-associated comorbidities. Therefore, research on steroid-sparing agents is urgently needed. B cell targeting agents such as rituximab proved to be efficient and comparably safe in a variety of immune-mediated kidney diseases. Although the pathogenesis of primary FSGS is still unknown, a causative immune-circulating factor is plausible, considering the risk of early and fulminant disease recurrence after kidney transplantation and response to plasma exchange.⁴ Some of these cases may be explained by presence of antinephrin antibodies, providing a further rationale for B cell targeting therapies.⁵ Whereas increasing evidence shows beneficial effects of rituximab for minimal change disease, available efficacy data for FSGS remains conflictive.⁶ Still, no controlled prospective trial is available studying rituximab in primary podocytopathies, and especially in FSGS. Interpretation of retrospective studies is difficult as these are likely impacted by a selection bias, and often might have included patients with secondary forms such as undiagnosed genetic cases.

In this context, the present study represents the largest published cohort of rituximab-treated patients with “assumed” primary FSGS. Tedesco *et al.*¹ included data of 31 patients treated with rituximab at different expert centers of the Italian Society of Nephrology Immunopathology Working Group between 2009 and 2017. A thorough workup, including comprehensive clinical, laboratory and imaging diagnostics was performed at each center to exclude secondary causes. Rituximab was chosen for these patients because

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of steroid dependence (18 of 31), steroid resistance (11 of 31), or because of a relative contraindication to steroids (2 of 31). Clinical response, defined as 24-hour proteinuria <3.5 g and <50% compared with baseline, and a stable estimated glomerular filtration rate was achieved at 6 months and 12 months in 52% and 42%, respectively. Notably, response occurred in all responders within the first 6 months and steroid dependent patients showed a substantially higher response rate (69%). Of 6 patients receiving retreatment with rituximab within 12 months, only 2 patients diagnosed with steroid dependent FSGS, who already responded to the first rituximab application, showed response to retreatment. The other 4 patients (2 steroid dependent and 2 steroid resistant) received retreatment because of refractory disease without success. A total of 9 severe adverse events (4 fluid overload, 3 infections, 1 end stage kidney disease, and 1 need for i.v. therapy) occurred in 4 patients who never responded to rituximab or prior therapies.

Results of this study highlight that rituximab can be an effective treatment option in FSGS, especially as a steroid-sparing agent for steroid dependent patients. Unfortunately, our understanding of the FSGS-complex is still poor and even patients who were diagnosed as primary FSGS at an expert center comprise a highly heterogeneous group. In this context, the diagnosis of primary FSGS is at least doubtful and the lack of genetic testing, especially for steroid resistant patients in this cohort is clearly a limiting factor, although reflecting daily clinical practice in the real-life setting.

Our take home messages therefore should not only be “who to treat,” but to *primum non nocere*, “who not to treat.” We must not forget that half of the patients were

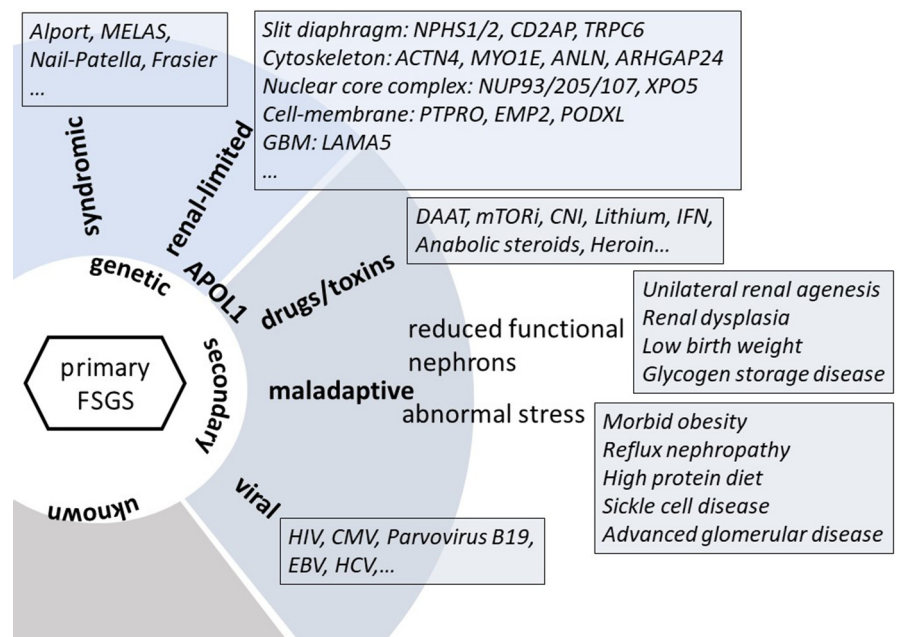


Figure 1. Overview of selected FSGS causes. APOL1, apolipoprotein L1; CMV, cytomegalovirus; CNI, calcineurin inhibitors; DAAT, direct-acting antiviral therapy; EBV, Epstein-Barr virus; FSGS, focal segmental glomerulosclerosis; HCV, hepatitis C virus; IFN, interferon; MELAS, mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes; mTORi, inhibitors of the mammalian target of rapamycin.

exposed to potentially harmful immunosuppressive treatments. As long as no causative “circulating factor” has been identified, identification of primary, immune-mediated FSGS will remain a considerable clinical challenge. A systematic approach to identify underlying genetic causes is needed and should be implemented both in clinical practice and in future studies.⁷ Until then, practical approaches are needed to find the right individual treatment.

A lesson learned from the present work may be that patients not responding to prior steroids and/or other immunosuppressants appear to have little chance to benefit from rituximab or from rituximab-retreatment after an ineffective initial application. We need to question ourselves about what the target of therapy is, in cases where remission seems not to be achievable. One pivotal approach is to optimize supportive, nonimmunosuppressive, antiproteinuric treatments including lifestyle interventions, a maximal

tolerated dose of renin-angiotensin system blockade, and eventually initiation of *SGLT2* inhibitors or sparsentan. Nevertheless, it seems to be even more important to have discussions about the potential disease course and prognosis with a high risk of end stage kidney disease in nonresponsive patients.

DISCLOSURE

PG has received consulting fees or honoraria from Vifor Pharma, Delta 4 and UriSalt. AK has received consulting fees or honoraria from Alexion, Vifor Pharma, Otsuka, Catalyst Biosciences, Delta 4, and UriSalt.

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