# Review of the Role of Rituximab in the Management of Adult Minimal Change Disease and Immune-Mediated Focal and Segmental Glomerulosclerosis

Ahsan Aslam[a]    Abbal Koirala[b]

[a]Division of Nephrology and Hypertension, Assistant Professor of Clinical Medicine, Indiana University School of Medicine, Indianapolis, IN, USA; [b]Division of Nephrology, Clinical Assistant Professor of Medicine, University of Washington, Seattle, WA, USA

**Abstract**

***Background:*** Minimal change disease and primary FSGS are podocytopathies but are also immune-mediated diseases. Rituximab acts via multiple mechanisms by tilting the balance between autoreactive B and T cells in favor of regulatory B and T cells. The consequences are decreased production of cytokines, chemokines, and permeability factors by these cells. In the past decade, we have seen the discovery of autoantibodies mediating nephrotic syndrome (anti-annexin A2 antibody, anti-UCHL1 antibody, and anti-nephrin antibody), and rituximab decreases their production. Rituximab also binds to podocyte SMPDL3b and has direct podocyte actions. ***Summary:*** Rituximab's role in managing these primary podocytopathies has been discussed in this brief review. Rituximab has been used extensively in children and adults with frequently relapsing and steroid-dependent nephrotic syndrome. However, rituximab is not very promising in adult steroid-resistant nephrotic syndrome. Although ofatumumab would cause prolonged B-cell depletion and is fully humanized, it is unclear if it is superior to rituximab in preventing relapse of nephrotic syndrome. ***Key Messages:*** Rituximab therapy can induce prolonged remission in adults with frequently relapsing and steroid-dependent nephrotic syndrome. However, no good data exist on using rituximab in steroid-resistant nephrotic syndrome.

© 2023 The Author(s).
Published by S. Karger AG, Basel

## Introduction

Rituximab (RTX) is a chimeric, anti-CD20, monoclonal antibody with a molecular weight of 145 kD. The Fab portion of RTX has a murine variable region in light and heavy chains, whereas the Fc region is fully humanized [1]. RTX binds to CD20 on B cells and depletes them via complement-dependent cytotoxicity, FcγR or complement-dependent phagocytosis (ADCC), and direct cell lysis by NK cells [2].

Minimal change disease (MCD) and focal and segmental glomerulosclerosis (FSGS) are disorders of the podocytes (podocytopathies). These diseases are pathological

Correspondence to:
Abbal Koirala, abbalk@uw.edu

Karger
OPEN ACCESS

diagnoses based on tissue morphology, and many distinct mechanisms result in similar pathological phenotypes. Some of the FSGS lesions are immunologically mediated. MCD and immune-mediated FSGS may be on the spectrum and vary in the intensity of podocyte injury and depletion [3, 4]. Severe podocyte injury and depletion, followed by secretion of ECM by migrating parietal epithelial cells, lead to FSGS [5].

The underlying pathophysiology of MCD/FSGS remains unclear. However, a large body of observational and experimental data links the immune system with MCD/FSGS (read excellent review article by Campbell and Thurman [6]). In the absence of clearly deposited immunoglobulin or complement in kidney biopsies, prior studies have focused on the role of T-cell dysfunction [6–8]. Dampening of T-regulatory cell responses has been described, which leads to unchecked activation of T-effector cells [9]. In addition, the upregulation of CD80, a transmembrane protein present in antigen-presenting cells that acts as a costimulatory signal for T-cell activation, has been noted [10].

Recently, the role of B cells in the pathogenesis of MCD/FSGS has been noted. In addition to depleting CD20 B cells, RTX binds directly to podocyte SMPDL3b and stabilizes the podocyte cytoskeleton, leading to direct antiproteinuric effects [11]. Furthermore, the depletion of antigen-presenting B cells by RTX may restore the balance between autoreactive T cells and regulatory T cells [12] and suppress interleukin-13 secretion by Th2 cells [13].

Sinha and Bagga [14], and Ravani et al. [15] have published a comprehensive review of the role of RTX in podocytopathies. The objective of this review article was to provide a comprehensive and up-to-date analysis of the current knowledge and evidence regarding the use of RTX as a potential treatment for FSGS/MCD. By addressing these objectives, the review article aims to provide healthcare professionals and researchers with a comprehensive and evidence-based understanding of the role of RTX in FSGS and MCD management, helping inform clinical decision-making and future research in this field.

### Role of Autoantibodies in MCD

Research on autoantibodies in MCD/FSGS has been an active area of investigation. Increasing evidence suggests that autoantibodies may have a direct role in the pathogenesis of idiopathic nephrotic syndrome. Two of them were discovered in the pediatric population and one in adult MCD. Jamin et al. [16]

discovered the presence of autoantibodies against podocyte UCHL1 in French children with NS relapses. The antibody titers improved upon remission. Injection of purified antibodies in mice resulted in the emergence of nephrotic syndrome. This suggests that anti-UCHL1 IgG may be a potential novel biomarker of the disease in some INS patients.

Ye et al. [17] discovered the presence of anti-annexin A2 antibodies in 17.8% of children with primary nephrotic syndrome in China. These antibodies disappeared with the treatment of the nephrotic syndrome.

Watts et al. [18] discovered the presence of anti-nephrin antibodies in 29% of the patients with MCD from the NEPTUNE cohort. Furthermore, anti-nephrin antibody titers improved with remission of nephrotic syndrome. This evidence points to the potential role of B cell-targeted therapy in patients with positive antibodies. RTX might deplete these autoreactive antibodies and lead to remission of nephrotic syndrome.

### Role of RTX in Treatment-Naive MCD and FSGS

Fenoglio et al. [19] published a study on six adults with naive MCD. The baseline characteristics were age 62.7, UPCR 11.75 g/d, and albumin 2.05 g/dL. They had contraindications to steroid induction; hence, four doses of RTX ($375/mg/m^2$/week for 4 weeks) were administered. Five patients attained CR (3 within 3 months, 1 within 6 months, and one at 9 months). One patient had >75% proteinuria reduction within 9 months. They all maintained CR during a median follow-up of 9–30 months. This study seems promising, but it must be replicated in a larger setting before RTX could be used for treatment-naive MCD.

Roccatello et al. [20] conducted a prospective cohort study on 8 patients with naive FSGS. All patients were on RAAS blockers at baseline; their baseline characteristics were age 63.9, Cr 2.6 mg/dL, UPCR 5.3 g/d, and albumin 2.75 g/dL. RTX ($375/mg/m^2$/week) was given for 8 weeks. Only 1 patient attained PR after 18 months, whereas the rest did not attain any remission with a follow-up of 24–42 months (proteinuria 5.3 g–3.9 g at follow-up, Cr 2.6–3.5 mg/dL at follow-up). One patient had a deterioration of renal function over time. There were no differences in clinical or laboratory characteristics or the CD20 B lymphocyte count after RTX between the responder and the seven nonresponder patients. This should trigger the investigation of more effective drugs in FSGS patients.

Aslam/Koirala

### Role of RTX in Frequently Relapsing and Steroid-Dependent Nephrotic Syndrome

RTX has been shown to have promising results in patients with frequently relapsing and steroid-dependent NS. Metaanalysis [21] was conducted on 21 studies with steroid-dependent MCD and FSGS ($n$ = 382). The mean age of included patients ranged from 19 to 63.9 years old at RTX treatment. Nearly, all the studies reported previous immunosuppressive treatments in MCD/FSGS patients, which included azathioprine, cyclosporine, cyclophosphamide, tacrolimus, prednisone, levamisole, MMF, mizoribine, chlorambucil, rapamycin, and sirolimus. RTX's dose varied in different studies, ranging from $1 \times 375$ mg/m$^2$ to 11 g. RTX treatment induced a pooled CR rate of 84.2%. MCD patients had a higher CR rate than FSGS patients (91.6% vs. 43%). The relapse rate was 27.4%. The pooled PR and NR rates were 5.8% and 5.2%. Most patients tolerated RTX well with trivial adverse events; the median follow-up duration was 12–43 months.

Characteristics of multiple studies with RTX in MCD and FSGS have been highlighted in Tables 1–4. Tedesco et al. [22] conducted a cohort study of 31 primary FSGS patients treated with RTX within the Italian Society of Nephrology Immunopathology Working Group. The baseline characteristics were age 37, creatinine 1.17 mg/d, mean proteinuria 5.2 g/d, and albumin 2.78 g/dL. 58% were on prednisone, 23% of the patients were on calcineurin inhibitor (CNI) at baseline, and 90% were on RAAS blockers. Patients were treated with various doses of RTX (375 mg/m$^2$/week for four doses, 1 g 2 weeks apart, 1 g once). The follow-up was 12 months. Response rates at 3, 6, and 12 months were 39%, 52%, and 42%; the rest were nonresponders. 6/31 were retreated with RTX within 12 months. Nonresponders to the first RTX infusion did not respond to retreatment. Responders at 6 months were likely to have baseline proteinuria <5 g/d and have steroid-dependent nephrotic syndrome. There were nine relapses in 8 patients with the response at any point. The median time to first relapse was 11 months. RTX treatment reduced the relapse rate from 47 to 17 per 100 patient-years.

So far, we do not have RCT data with RTX on adult patients with MCD and FSGS. RIFIREINS [41] is a phase 2b multicenter RCT from France in patients with relapsing MCD with plans to recruit up to 148 patients. MCD patients, once in remission with steroid treatment, will be randomized at 8 weeks in a 1:1 fashion to continue steroid taper over 24 weeks versus RTX (375 mg/m$^2$/week 1 week apart for a total of two doses) with steroid taper by 9 weeks. The primary outcome is the occurrence of relapse between the two groups at 12 months after randomization.

TURING [42] is a phase 3 RCT trial recruiting treatment-naive or relapsing nephrotic syndrome patients from the UK with the goal of 112 patients with kidney biopsy-proven MCD/FSGS. The relapsing patients will be treated with prednisolone and randomized at 4 weeks to either RTX (1 g 2 weeks apart) or placebo. Both groups will receive one dose of RTX or placebo at 26 weeks. Prednisolone will be tapered based on current guidelines. The primary outcome is the time from partial remission to relapse between the two arms.

The NEMO study [39] evaluated the effects of RTX therapy followed by immunosuppression withdrawal on disease recurrence in 10 children and 20 adults with MCD/MesGN ($n$ = 22) or FSGS who had suffered ≥2 recurrences over the previous year and were in steroid-induced remission for ≥1 month. Adult baseline characteristics were age 22.7, creatinine 0.75 mg/dL, UPCR 0.12 g/d, and albumin 4 g/dL. Participants received one dose ($n$ = 28) or two doses of RTX (375 mg/m$^2$ intravenously). All patients were in remission at 1 year: 18 were treatment-free, and 15 never relapsed. Total relapses decreased from 88 the year before RTX to 22 during 1 year of follow-up. The reduction was significant across subgroups (children, adults, MCD/MesGN, and FSGS; $p < 0.01$). After RTX, the per-patient steroid maintenance median dose decreased from 0.27 mg/kg to 0 mg/kg ($p < 0.001$). Most patients were able to reduce the dose of other immunosuppressants.

### Standard Dosing of RTX in MCD and FSGS

There is no standard dosing for RTX. Most studies have used 375 mg/m$^2$/week for 1–4 weeks (adopted from lymphoma dosing). Some studies have used 1 g 2 weeks apart. We often use 1 g 2 weeks apart in patients with frequently relapsing and steroid-dependent nephrotic syndrome due to ease of administration in the outpatient setting. RIFIREINS(42) and TURING(43) trial results will be informative.

### Role of RTX in the Maintenance of Remission of MCD and FSGS

At least two studies have shown favorable outcomes regarding maintenance of remission in MCD/FSGS with RTX use. Ramachandran et al. [43] conducted a prospective observational study in India of 24 adults with steroid-dependent (62.5%) or steroid-resistant (37.5%) nephrotic syndrome who were in remission with a calcineurin inhibitor. The baseline characteristics were age 24, proteinuria 0.63 g/d, albumin 4.01 g/dL, creatinine 0.82 mg/dL, 46% MCD, and 54% FSGS. All patients were

**Table 1.** Rituximab in the treatment of adult frequently relapsing and steroid-dependent MCD (remission rates)

| Author | Setting | Sample size | Previous failed treatments | RTX dose | CR, $n$ (%) | Follow-up, months |
|---|---|---|---|---|---|---|
| Cortazar et al. [23] (2019), USA | Retrospective, single-center study | 8 MCD | Pred, CsA, FK, MMF, Abat, Cyc, Aza | 9 g (7.5–11 g), 1 g IV dose, 4-month interval | 7/8 (87.5) | 35 (19–57) |
| King et al. [24] (2017), UK | Retrospective, single-center study | 13 MCD | Pred, CsA, FK, MMF, Cyc, Lev, rapamycin, sirolimus | 2 × 1 g, 2 weeks apart | 12/13 (92.3) | 20 (6–85) |
| Brown et al. [25] (2017), USA | Retrospective, single-center study | 5 MCD | Pred, CsA, FK, MMF, Cyc | 2 × 1 g 2–3 weeks interval | 5/5 (100) | 39.5 (20–80) |
| Miaybe et al. [26] (2016), Japan | Retrospective, single-center study | 10 MCD | Pred, CsA, FK, MMF, Cyc, MZ | 4 × 375 mg/m² (10), 6-month interval | 10/10 (100) | 24 |
| Bruchfield et al. [27] (2014), Sweden | Retrospective, single-center study | 16 MCD | Pred, CsA, FK, MMF, Cyc, MZ | 2 × 500 mg (8), 2 × 1 g (3), 3 × 375 mg/m² (1), 4 × 375 mg/m² (4) | 13/16 (81.3) | 44 (12–70) |
| Guitard et al. [28] (2014), France | Prospective, multicenter study | 41 MCD | Pred, CsA, FK, MMF, Cyc, Aza | 1 × 1 g (1), 2 × 1 g (21), 2 × 1 g (5), 3 × 375 mg/m² (2), 4 × 375 mg/m² (12) | 25/41 (61) | 39 (6–71) |
| Iwabuchi et al. [29] (2014), Japan | Prospective, single-center study | 25 MCD | Pred, CsA, FK, MMF, Cyc, MZ | 4 × 375 mg/m², 6-month interval | 25/25 (100) | 24 |
| Takei et al. [30] (2013), Japan | Prospective, single-center study | 25 MCD | Pred, MMF, CsA, MZ | 2 × 375 mg/m² (25), 6-month interval | 25/25 (100) | 12 |
| Munyentwali et al. [31] (2013), France | Retrospective, single-center study | 17 MCD | Pred, CsA, FK, MMF, Cyc, Aza, Lev, chlorambucil | 1 × 375 mg/m² (1), 2 × 375 mg/m² (7), 3 × 375 mg/m² (4), 4 × 375 mg/m² (3) | 15/17 (88.2) | 29.5 (5.1–82.2) |
| Kong et al. [32] (2013), Australia | Retrospective, single-center study | 7 MCD | Pred, CsA, FK, MMF, Cyc, Aza, chlorambucil | 1 × 500 mg, 1 × 600 mg, 4 × 600 mg, 1 × 700 mg, 2 × 700 mg | 6/7 (85.7) | 31.5 (15–44) |
| Hoxha et al. [33] (2011), Germany | Prospective, single-center study | 6 MCD | Pred, CsA, FK, MMF, Cyc, Aza, Lev | 1 × 375 mg/m² | 5/6 (83.3) | 17.2±4.8 |

**Table 2.** Rituximab in adult frequently relapsing and steroid-dependent FSGS (remission rates)

| Author | Setting | Sample size | Previous failed treatments | RTX dose | CR, $n$ (%) |
|---|---|---|---|---|---|
| Cortazar et al. [23] (2019), USA | Retrospective, single-center study | 5 FSGS | Pred, CsA, FK, MMF, Abat, Cyc, Aza | 9 g (7.5–11 g), 1 g IV dose, 4-month interval | 4/5 (80) |
| Kong et al. [32] (2013), Australia | Retrospective, single-center study | 4 FSGS | Pred, CsA, FK, MMF, Cyc, Aza, chlorambucil | 1 × 500 mg, 1 × 600 mg, 4 × 600 mg, 1 × 700 mg, 2 × 700 mg | 3/4 (75) |

Aslam/Koirala

**Table 3.** Relapse rates of MCD studies with rituximab treatment

| Author | Setting | Sample size | Previous failed treatments | RTX dose | Relapse rate, $n$ (%) | Follow-up, months |
|---|---|---|---|---|---|---|
| Cortazar et al. [23] (2019), USA | Retrospective, single-center study | 8 MCD | Pred, CsA, FK, MMF, Abat, Cyc, Aza | 9 g (7.5–11 g), 1 g IV dose, 4-month interval | 0/8 (0) | 35 (19–57) |
| Iwabuchi et al. [34] (2018), Japan | Retrospective, single-center study | 19 MCD | Pred, CsA, FK, MMF, Cyc, MZ | $4 \times 375$ mg/m$^2$, 6-month interval | 4/19 (21.1) | 24 |
| Katsuno et al. [35] (2019), Japan | Retrospective, single-center study | 8 MCD | Pred, CsA, FK, MMF, Cyc, MZ | $1 \times 500$ mg (3), $2 \times 500$ mg (3), $3 \times 500$ mg (1), 3,100 mg (1, seven times) | 3/8 (37.5) | 13.9 (11.6–20) |
| -Da Silva et al. [36] (2017), Spain | Retrospective, multicenter study | 22 MCD | Pred, CsA, FK, MMF, Cyc | $1 \times 1$ g (10), $2 \times 1$ g (9), $3 \times 1$ g (5), $4 \times 1$ g (4), 1,788±704 mg | 4/22 (18.2) | 31±26 |
| King et al. [24] (2017), UK | Retrospective, single-center study | 13 MCD | Pred, CsA, FK, MMF, Cyc, Lev, rapamycin, sirolimus | $2 \times 1$ g, 2 weeks apart | 7/13 (53.8) | 20 (6–85) |
| Brown et al. [25] (2017), USA | Retrospective, single-center study | 5 MCD | Pred, CsA, FK, MMF, Cyc | $2 \times 1$ g 2–3 weeks interval | 2/5 (40) | 39.5 (20–80) |
| Papakrivopoulou et al. [37] (2016), UK | Prospective, single-center study | 15 MCD | Pred, CsA, FK, MMF, Cyc, Aza, Lev | $2 \times 1$ g, 6 months apart, 1–3 g | 5/15 (33.3) | 43 |
| Dekkers et al. [38] (2015), The Netherlands | Retrospective, single-center study | 10 MCD | Pred, CsA, FK, MMF, Cyc | $2 \times 375$ mg/m$^2$ | 3/10 (30) | 43±23.5 |
| Miyabe et al. [26] (2016), Japan | Retrospective, single-center study | 54 MCD | Pred, CsA, FK, MMF, Cyc, MZ | $4 \times 375$ mg/m$^2$ (25), 6-month interval | 12/54 (22.2) | 24 |
| Bruchfield et al. [27] (2014), Sweden | Retrospective, single-center study | 16 MCD | Pred, CsA, FK, MMF, Cyc, MZ | $2 \times 500$ mg (8), $2 \times 1$ g (3), $3 \times 375$ mg/m$^2$ (1), $4 \times 375$ mg/m$^2$ (4) | 7/16 (43.8) | 44 (12–70) |
| Guitard et al. [28] (2014), France | Prospective, multicenter study | 41 MCD | Pred, CsA, FK, MMF, Cyc, Aza | $1 \times 1$ g (1), $2 \times 1$ g (21), $2 \times 1$ g (5), $3 \times 375$ mg/m$^2$ (2), $4 \times 375$ mg/m$^2$ (12) | 18/41 (43.9) | 39 (6–71) |
| Iwabuchi et al. [29] (2014), Japan | Prospective single-center study | 25 MCD | Pred, CsA, FK, MMF, Cyc, MZ | $4 \times 375$ mg/m$^2$, 6-month interval | 7/25 (28) | 24 |
| Takei et al. [30] (2013), Japan | Prospective single-center study | 25 MCD | Pred, MMF, CsA, MZ | $2 \times 375$ mg/m$^2$ (25), 6-month interval | 4/25 (16) | 12 |
| Munyentwali et al. [31] (2013), France | Retrospective, single-center study | 17 MCD | Pred, CsA, FK, MMF, Cyc, Aza, Lev, chlorambucil | $1 \times 375$ mg/m$^2$ (1), $2 \times 375$ mg/m$^2$ (7), $3 \times 375$ mg/m$^2$ (4), $4 \times 375$ mg/m$^2$ (3) | 6/17 (35.3) | 29.5 (5.1–82.2) |
| Kong et al. [32] (2013), Australia | Retrospective, single-center study | 7 MCD | Pred, CsA, FK, MMF, Cyc, Aza, chlorambucil | $1 \times 500$ mg, $1 \times 600$ mg, $4 \times 600$ mg, $1 \times 700$ mg, $2 \times 700$ mg | 2/7 (28.6) | 31.5 (15–44) |
| Hoxha et al. [33] (2011), Germany | Prospective single-center study | 6 MCD | Pred, CsA, FK, MMF, Cyc, Aza, Lev | $1 \times 375$ mg/m$^2$ | 3/6 (50) | 17.2±4.8 |

**Table 4.** Relapse rate of FSGS studies with rituximab treatment

| Author | Setting | Sample size | Previous failed treatments | RTX dose | Relapse rate, $n$ (%) | Follow-up, months |
|---|---|---|---|---|---|---|
| Ruggenenti et al. [39] (2014), Italy | Prospective multicenter study | 8 FSGS | Pred, CsA, Cyc, Aza, MMF | $1 \times 375$ mg/m$^2$ or $2 \times 375$ mg/m$^2$ | 3/8 (37.5) | 12 |
| Kronbichler et al. [40] (2013), Austria | Retrospective single-center study | 3 FSGS | Pred, CsA, MMF | $4 \times 375$ mg/m$^2$ | 1/3 (33.3) | 22.6±7.1 |
| Cortazar et al. [23] (2019), USA | Retrospective single-center study | 5 FSGS | Pred, CsA, FK, MMF, Abat, Cyc, Aza | 9 g (7.5–11 g), 1 g IV dose, 4-month interval | 0/5 (0) | 35 (19–57) |
| Kong et al. [32] (2013), Australia | Retrospective, single center | 4 FSGS | Pred, CsA, FK, MMF, Cyc, Aza, chlorambucil | $1 \times 500$ mg, $1 \times 600$ mg, $4 \times 600$ mg, $1 \times 700$ mg, $2 \times 700$ mg | 1/4 (25) | 31.5 (15–44) |
| DaSilva et al. [36] (2017), Spain | Retrospective, multicenter | 4 FSGS | Pred, CsA, FK, MMF, Cyc | $1 \times 1$ g (10), $2 \times 1$ g (9), $3 \times 1$ g (5), $4 \times 1$ g (4), 1,788±704 mg | 3/4 (75) | 31±26 |

on a calcineurin inhibitor at enrollment, and RTX was given at 375 mg/m$^2$ at entry with an additional 100 mg if the CD-19 level increased to >5/μL or >1%. At the end of 1st month, all patients were weaned off steroids or CNI. The follow-up duration was 12 months. At the end of 6 and 12 months, 87.5% and 79.1% of the patients achieved remission, respectively. The relapse rate was 33%, and the time to relapse was 7 months. The mean dose of RTX in the first year was 791 mg, with an average cost of $487.17.

Cortazar et al. [23] performed a retrospective chart review on continuous B-cell depletion in 20 patients with frequently relapsing (1/20), steroid-dependent (12/20), and steroid-resistant nephrotic syndrome (7/20). There were 13 patients with MCD and 7 with FSGS at baseline. All patients had failed multiple prior immunosuppressive regimens, and 100% were on corticosteroids at baseline. The baseline characteristics were age 50, albumin 2.5 g/dL, UPCR 10.3 g/d, and creatinine 1.29 mg/dL. Patients received RTX 1,000 mg 2–4 weeks apart and then 1,000 mg every 4 months for a median of 9 infusions. B-cell depletion was monitored before each dose with the goal of CD-19 cells <5/μL. Prednisone and other immunosuppressive agents were initially administered with RTX in most patients. Tapering off prednisone/immunosuppressive agents and the duration of RTX therapy were at the treating physician's discretion. Patients were treated for 28 months. 100% of the patients attained PR, but complete remission was more common in FR/SD patients compared to SR patients (85% vs. 14%). RTX permitted successful prednisone weaning from 60 to 4.5 mg by 12 months. At the last follow-up, 16 patients were in remission, and 4 relapses were in steroid-resistant patients. RTX caused 3 serious infections over 70 patient-years.

It is still unclear about the patients most likely to benefit from maintenance RTX infusions. Whether the dosing should be 500 mg every 6 months, similar to MAINRITSAN trials in ANCA vasculitis [44, 45], or should be based on the reemergence of CD-19 B cells after B-cell depletion (MAINRITSAN 2 trial [46]) is unclear.

### Role of RTX in Steroid-Resistant Disease

Fernandez-Fresnedo et al. [47] published a study on 8 patients with FSGS. The baseline characteristics were age 31, UPCR 14 g/d, albumin 1.75 g/dL, and creatinine 1.4 mg/dL. The mean disease duration was 47.1 months; all had failed multiple prior immunosuppressive medications. RTX was given at 375 mg/m$^2$/week for 4 weeks. 5/8 patients did not respond. Only 3 patients responded (1 transient response, 1 PR, and 1 with some improvement in proteinuria but not PR). The follow-up was 16.4 months. All 3 patients that had some response received extra doses of RTX. It is unclear if extra doses of RTX can overcome some steroid resistance. RTX is also lost in the urine in nephrotic syndrome patients, and the half-life is reduced to 11.5 days in membranous nephropathy patients with an average UPCR of 11.9 g/d compared to RA patients with a half-life of 18 days [48], so extra doses of RTX may be required in heavy nephrotic patients.

Hladunewich et al. [49] conducted a pilot study at Mayo Clinic on 9 patients with steroid-resistant FSGS with elevated suPAR levels (>3,500 pg/mL) and evidence of podocyte β3 integrin activation at baseline. Baseline characteristics were age 37, eGFR 67 mL/min, and

albumin 3 g/dL. All patients were exposed to prior immunosuppression. Patients received 1 g of RTX 2 weeks apart. At 6 months, 1 patient attained PR, and one had CR. GFR declined to 60 mL/min, and 1 patient progressed to ESRD. There was no change in UPCR at 12 months (UPCR 7.7 g/d at baseline vs. 7.27 g/d at 12 months). Even though weaning of other immunosuppressive drugs was desired at the end of the trial, patients remained on prednisone, CNI, or both as removal was deemed too precarious owing to lack of response to RTX. Additionally, RTX did not alter the level of suPAR and had no impact on the activation of $\beta3$ integrin.

There is little positive evidence favoring RTX for steroid-resistant nephrotic syndrome in adults. Most studies with FSGS patients have been criticized for including all patients with histological FSGS diagnoses. Including only immune-mediated FSGS patients and excluding secondary and genetic FSGS patients would likely help improve patient selection for clinical trials.

### Other Anti-CD20 Antibodies in MCD and FSGS

RTX has murine variable regions in light and heavy chains, but the Fc portion is humanized [50]. Both ofatumumab and obinutuzumab are fully humanized mAbs, which reduces unintended immune responses against the therapies. Ofatumumab also has a glyco-engineered Fc region, resulting in better binding with immune effector cells [50]. They all differ in their ability to eliminate CD20 B cells via different mechanisms (direct killing, antibody-dependant phagocytosis, complement-dependent cytotoxicity, and antibody-dependent cell-mediated cytotoxicity [50]). RTX is known to bind to the long loop of the CD20 receptor, whereas ofatumumab binds to both short and long loops of CD20, causing prolonged B-cell depletion [51]. Ofatumumab has been used to treat refractory membranous nephropathy [52–54]. Ravani et al. [55] conducted a superiority randomized controlled trial in children and adults (age 2–24) with steroid-dependent nephrotic syndrome. The median age was 11; all were maintained in remission with corticosteroids and calcineurin inhibitors. The baseline characteristics were creatinine 0.5 mg/dL, albumin 4 g/dL, UPCR 80 mg/d, and GFR 146 mL/min/1.73 m$^2$. One hundred forty patients were randomized to a single dose of ofatumumab (1,500 mg/1.73 m$^2$) or RTX (375 mg/m$^2$). Steroids and CNI were withdrawn within 60 days of RTX and ofatumumab infusions. The relapse rates at 12 months (51.4% vs. 52.8%) and 24 months (65.7% vs. 75.7%) were not different between RTX and ofatumumab. There was a trend toward earlier relapse with ofatumumab in patients less than 9 years of age. B-cell depletion was more prolonged with ofatumumab, and anti-RTX antibodies developed over time in the RTX group, but they had no bearing on the risk of relapse. It was postulated that ofatumumab, though fully humanized, is still generated in the Golgi of animal cell lines; hence, it is still immunogenic and leads to the production of sialic acid, *N*-glycolylneuraminic acid (Neu5Gc.) antibodies in the hosts. In the subsequent study [56] in the same population, titers of Neu5Gc antibodies were calculated at baseline and at various time points during follow-up. The presence and/or titers of Neu5Gc antibodies did not affect subsequent response to RTX or ofatumumab. More studies are required to clarify the role of ofatumumab, so presently, ofatumumab is only used in cases of RTX allergy in nephrotic syndrome due to MCD and FSGS.

### Conclusions

RTX has been used extensively in children and adults with frequently relapsing and steroid-dependent nephrotic syndrome. Most of the evidence in adults is observational, and randomized controlled trials are lacking. RTX works through multiple pathways in immune cells and shifts the balance of autoreactive B and T cells in favor of regulatory B and T cells. RTX also has direct podocyte stabilization properties. Presently, favorable data regarding the role of RTX in steroid-resistant nephrotic syndrome is sparse. Although ofatumumab would cause prolonged B-cell depletion and is fully humanized, it is unclear if it is superior to RTX in preventing relapse of nephrotic syndrome.

# References

1 Sinha R, Agrawal N, Xue Y, Chanchlani R, Pradhan S, Raina R, et al. Use of rituximab in paediatric nephrology. Arch Dis Child. 2021; 106(11):1058–65.

2 Taylor RP, Lindorfer MA. Drug insight: the mechanism of action of rituximab in autoimmune disease: the immune complex decoy hypothesis. Nat Clin Pract Rheumatol. 2007; 3(2):86–95.

3 Maas RJ, Deegens JK, Smeets B, Moeller MJ, Wetzels JF. Minimal change disease and idiopathic FSGS: manifestations of the same disease. Nat Rev Nephrol. 2016;12:768–76.

4 De Vriese AS, Wetzels JF, Glassock RJ, Sethi S, Fervenza FC, Fervenza FC. Therapeutic trials in adult FSGS: lessons learned and the road forward. Nat Rev Nephrol. 2021;17(9): 619–30.

5 Kopp JB, Anders H-J, Susztak K, Podestà MA, Remuzzi G, Hildebrandt F, et al. Podocytopathies. Nat Rev Dis Primers. 2020; 6(1):68.

6 Campbell RE, Thurman JM. The immune system and idiopathic nephrotic syndrome. Clin J Am Soc Nephrol. 2022;17(12):1823–34.

7 Shalhoub RJ. Pathogenesis of lipoid nephrosis: a disorder of T-cell function. Lancet. 1974;2(7880):556–60.

8 Saleem MA, Kobayashi Y. Cell biology and genetics of minimal change disease. F1000Res. 2016;5:F1000 Faculty Rev-412.

9 Araya C, Diaz L, Wasserfall C, Atkinson M, Mu W, Johnson R, et al. T regulatory cell function in idiopathic minimal lesion nephrotic syndrome. Pediatr Nephrol. 2009; 24(9):1691–8.

10 Garin EH, Diaz LN, Mu W, Wasserfall C, Araya C, Segal M, et al. Urinary CD80 excretion increases in idiopathic minimal-change disease. J Am Soc Nephrol. 2009; 20(2):260–6.

11 Fornoni A, Sageshima J, Wei C, Merscher-Gomez S, Aguillon-Prada R, Jauregui AN, et al. Rituximab targets podocytes in recurrent focal segmental glomerulosclerosis. Sci Transl Med. 2011;3(85):85ra46.

12 Datta SK. Anti-CD20 antibody is an efficient therapeutic tool for the selective removal of autoreactive T cells. Nat Clin Pract Rheumatol. 2009;5(2):80–2.

13 Kim JE, Park SJ, Ha T-S, Shin JI. Effect of rituximab in MCNS: a role for IL-13 suppression? Nat Rev Nephrol. 2013;9(9):551.

14 Sinha A, Bagga A. Rituximab therapy in nephrotic syndrome: implications for patients' management. Nat Rev Nephrol. 2013; 9(3):154–69.

15 Ravani P, Bonanni A, Rossi R, Caridi G, Ghiggeri GM. Anti-CD20 antibodies for idiopathic nephrotic syndrome in children. Clin J Am Soc Nephrol. 2016;11(4):710–20.

16 Jamin A, Berthelot L, Couderc A, Chemouny JM, Boedec E, Dehoux L, et al. Autoantibodies against podocytic UCHL1 are associated with idiopathic nephrotic syndrome relapses and induce proteinuria in mice. J Autoimmun. 2018;89:149–61.

17 Ye Q, Zhang Y, Zhuang J, Bi Y, Xu H, Shen Q, et al. The important roles and molecular mechanisms of annexin A2 autoantibody in children with nephrotic syndrome. Ann Transl Med. 2021;9(18):1452.

18 Watts AJB, Keller KH, Lerner G, Rosales I, Collins AB, Sekulic M, et al. Discovery of autoantibodies targeting nephrin in minimal change disease supports a novel autoimmune etiology. J Am Soc Nephrol. 2022;33(1): 238–52.

19 Fenoglio R, Sciascia S, Beltrame G, Mesiano P, Ferro M, Quattrocchio G, et al. Rituximab as a front-line therapy for adult-onset minimal change disease with nephrotic syndrome. Oncotarget. 2018;9(48):28799–804.

20 Roccatello D, Sciascia S, Rossi D, Alpa M, Naretto C, Radin M, et al. High-dose rituximab ineffective for focal segmental glomerulosclerosis: a long-term observation study. Am J Nephrol. 2017;46(2):108–13.

21 Xue C, Yang B, Xu J, Zhou C, Zhang L, Gao X, et al. Efficacy and safety of rituximab in adult frequent-relapsing or steroid-dependent minimal change disease or focal segmental glomerulosclerosis: a systematic review and meta-analysis. Clin Kidney J. 2021;14(4): 1042–54.

22 Tedesco M, Mescia F, Pisani I, Allinovi M, Casazza G, Del Vecchio L, et al. The role of rituximab in primary focal segmental glomerular sclerosis of the adult. Kidney Int Rep. 2022;7(8):1878–86.

23 Cortazar FB, Rosenthal J, Laliberte K, Niles JL. Continuous B-cell depletion in frequently relapsing, steroid-dependent and steroid-resistant nephrotic syndrome. Clin Kidney J. 2019;12(2):224–31.

24 King C, Logan S, Smith SW, Hewins P. The efficacy of rituximab in adult frequently relapsing minimal change disease. Clin Kidney J. 2017;10(1):16–9.

25 Brown LC, Jobson MA, Payan Schober F, Chang EH, Falk RJ, Nachman PH, et al. The evolving role of rituximab in adult minimal change glomerulopathy. Am J Nephrol. 2017; 45(4):365–72.

26 Miyabe Y, Takei T, Iwabuchi Y, Moriyama T, Nitta K. Amelioration of the adverse effects of prednisolone by rituximab treatment in adults with steroid-dependent minimal-change nephrotic syndrome. Clin Exp Nephrol. 2016;20(1):103–10.

27 Bruchfeld A, Benedek S, Hilderman M, Medin C, Snaedal-Jonsdottir S, Korkeila M. Rituximab for minimal change disease in adults: long-term follow-up. Nephrol Dial Transplant. 2014;29(4):851–6.

28 Guitard J, Hebral A-L, Fakhouri F, Joly D, Daugas E, Rivalan J, et al. Rituximab for minimal-change nephrotic syndrome in adulthood: predictive factors for response, long-term outcomes and tolerance. Nephrol Dial Transplant. 2014;29(11):2084–91.

29 Iwabuchi Y, Takei T, Moriyama T, Itabashi M, Nitta K. Long-term prognosis of adult patients with steroid-dependent minimal change nephrotic syndrome following rituximab treatment. Medicine. 2014;93(29): e300.

30 Takei T, Itabashi M, Moriyama T, Kojima C, Shiohira S, Shimizu A, et al. Effect of single-dose rituximab on steroid-dependent minimal-change nephrotic syndrome in adults. Nephrol Dial Transplant. 2013;28(5): 1225–32.

31 Munyentwali H, Bouachi K, Audard V, Remy P, Lang P, Mojaat R, et al. Rituximab is an efficient and safe treatment in adults with steroid-dependent minimal change disease. Kidney Int. 2013;83(3):511–6.

32 Kong WY, Swaminathan R, Irish A. Our experience with rituximab therapy for adult-onset primary glomerulonephritis and review of literature. Int Urol Nephrol. 2013;45(3): 795–802.

33 Hoxha E, Stahl RAK, Harendza S. Rituximab in adult patients with immunosuppressive-dependent minimal change disease. Clin Nephrol. 2011;76(2):151–8.

34 Iwabuchi Y, Miyabe Y, Makabe S, Nakano M, Manabe S, Karasawa K, et al. Comparison of the response of frequently relapsing steroid-dependent minimal change nephrotic syndrome to rituximab therapy between childhood-onset and adult-onset disease. Medicine. 2018;97(42):e12704.

35 Katsuno T, Masuda T, Saito S, Kato N, Ishimoto T, Kato S, et al. Therapeutic efficacy of rituximab for the management of adult-onset steroid-dependent nephrotic syndrome: a retrospective study. Clin Exp Nephrol. 2019; 23(2):207–14.

36 DaSilva I, Huerta A, Quintana L, Redondo B, Iglesias E, Draibe J, et al. Rituximab for steroid-dependent or frequently relapsing idiopathic nephrotic syndrome in adults: a retrospective, multicenter study in Spain. BioDrugs. 2017;31(3):239–49.

37 Papakrivopoulou E, Shendi AM, Salama AD, Khosravi M, Connolly JO, Trompeter R. Effective treatment with rituximab for the maintenance of remission in frequently relapsing minimal change disease. Nephrology. 2016;21(10):893–900.

38 Dekkers MJ, Groothoff JW, Zietse R, Betjes MGH. A series of patients with minimal change nephropathy treated with rituximab during adolescence and adulthood. BMC Res Notes. 2015;8:266.

39 Ruggenenti P, Ruggiero B, Cravedi P, Vivarelli M, Massella L, Marasà M, et al. Rituximab in steroid-dependent or frequently relapsing idiopathic nephrotic syndrome. J Am Soc Nephrol. 2014;25(4):850–63.

40 Kronbichler A, König P, Busch M, Wolf G, Mayer G, Rudnicki M. Rituximab in adult patients with multi-relapsing/steroid-dependent minimal change disease and focal segmental glomerulosclerosis: a report of 5 cases. Wien Klin Wochenschr. 2013;125(11–12):328–33.

41 RItuximab From the FIRst Episode of Idiopathic Nephrotic Syndrome: full text view–ClinicalTrials.Gov. [cited 15 Nov 2022]. Available from: https://clinicaltrials.gov/ct2/show/NCT03970577.

42 TURING. [cited 15 Nov 2022]. Available from: https://cctu.org.uk/portfolio/core/trials-open-to-recruitment/turing.

43 Ramachandran R, Bharati J, Rao I, Kashif AW, Nada R, Minz R, et al. Persistent CD-19 depletion by rituximab is cost-effective in maintaining remission in calcineurin-inhibitor dependent podocytopathy. Nephrology. 2019; 24(12):1241–7.

44 Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaître O, Cohen P, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med. 2014;371(19):1771–80.

45 Charles P, Perrodeau É, Samson M, Bonnotte B, Néel A, Agard C, et al. Long-term rituximab use to maintain remission of antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med. 2020;173(3):179–87.

46 Charles P, Terrier B, Perrodeau É, Cohen P, Faguer S, Huart A, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). Ann Rheum Dis. 2018;77(8):1143–9.

47 Fernandez-Fresnedo G, Segarra A, González E, Alexandru S, Delgado R, Ramos N, et al. Rituximab treatment of adult patients with steroid-resistant focal segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2009;4(8): 1317–23.

48 Fervenza FC, Abraham RS, Erickson SB, Irazabal MV, Eirin A, Specks U, et al. Rituximab therapy in idiopathic membranous nephropathy: a 2-year study. Clin J Am Soc Nephrol. 2010;5(12):2188–98.

49 Hladunewich MA, Cattran D, Sethi SM, Hayek SS, Li J, Wei C, et al. Efficacy of rituximab in treatment-resistant focal segmental glomerulosclerosis with elevated soluble urokinase-type plasminogen activator receptor and activation of podocyte β3 integrin. Kidney Int Rep. 2022;7(1):68–77.

50 Pierpont TM, Limper CB, Richards KL. Past, present, and future of rituximab: the world's first oncology monoclonal antibody therapy. Front Oncol. 2018;8:163.

51 Hill BT, Kalaycio M. Profile of obinutuzumab for the treatment of patients with previously untreated chronic lymphocytic leukemia. Onco Targets Ther. 2015;8:2391–7.

52 Ruggenenti P, Fervenza FC, Remuzzi G. Treatment of membranous nephropathy: time for a paradigm shift. Nat Rev Nephrol. 2017;13(9):563–79.

53 Podestà MA, Ruggiero B, Remuzzi G, Ruggenenti P. Ofatumumab for multirelapsing membranous nephropathy complicated by rituximab-induced serum-sickness. BMJ Case Rep. 2020;13.

54 Ahmadian E, Khatibi SMH, Vahed SZ, Ardalan M. Novel treatment options in rituximab-resistant membranous nephropathy patients. Int Immunopharmacol. 2022; 107:108635.

55 Ravani P, Colucci M, Bruschi M, Vivarelli M, Cioni M, DiDonato A, et al. Human or chimeric monoclonal anti-CD20 antibodies for children with nephrotic syndrome: a superiority randomized trial. J Am Soc Nephrol. 2021;32(10):2652–63.

56 Angeletti A, Bruschi M, Kajana X, Lugani F, Candiano G, Ghiggeri GM. Anti-Neu5Gc antibodies do not affect response to human or chimeric monoclonal anti-CD20 antibodies in children with nephrotic syndrome. J Am Soc Nephrol. 2022;33(11):1985–7.