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Rituximab in Steroid-Dependent Podocytopathies

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Keywords
Minimal change disease · Focal and segmental glomerulosclerosis · Podocitopathies · Nephrotic syndrome · Rituximab

Abstract

Introduction: Rituximab (RTX) has been reported as an effective treatment alternative in primary forms of minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) associated with steroid dependence and frequent relapses. However, the optimal RTX regimen and the outcomes of further doses of RTX remain unclear. This study aimed to evaluate the use of induction and maintenance RTX therapy for adults with primary podocytopathies. ***Methods:*** We performed a retrospective case series on adult patients with steroid-dependent podocytopathies who received an induction RTX therapy. Maintenance therapy was performed at physician's discretion. Remission and relapse rates, concomitant corticosteroids and immunosuppressants use, B-cell depletion and adverse events were analyzed. ***Results:*** Fourteen patients (mean age at start of RTX 29.1 ± 21.9 years) with MCD ($n = 7$) or FSGS ($n = 7$) were treated with 2 doses of 1,000 mg 2 weeks apart ($n = 13$) or four doses of 375 mg/m^2 ($n = 1$) of RTX. At last follow-up (mean 47.3 ± 101.7 months), 10 patients were in complete remission and two remained in partial remission. A reduction in the number of relapses, number of patients under corticosteroids and immunosuppressants, and dose of prednisolone was observed when compared to baseline (14 [100%] vs. 5 [35.7%]; 8/14 [57.1%] vs. 4/12 [33.3%]; 13/14 [92.9%] vs. 7/12 [58.3%]; 20 mg/day vs. 5.25 mg/day, respectively). Maintenance RTX therapy was used in 6 patients, with sustained complete remission. Infusion reactions were observed in 4 patients (one required treatment withdrawal). ***Conclusions:*** Our findings support the use of RTX for a steroid-free remission in podocytopathies and suggest that maintenance RTX is well-tolerated and associated with prolonged remission. Further studies are needed to confirm its efficacy and safety and establish the optimal induction and maintenance RTX regimen in steroid-dependent podocytopathies.

Plain Language Summary

Rituximab (RTX) seems to be an effective treatment alternative in primary forms of MCD and FSGS, particularly in cases of steroid dependence and frequent relapses. Our findings support the use of RTX for a steroid-free remission in podocytopathies and suggest that maintenance RTX is well-tolerated and associated with prolonged remission. Further studies are

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needed to confirm its efficacy and safety and establish the optimal induction and maintenance RTX regimen in steroid-dependent podocytopathies.

Introduction

Primary minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are rare diseases that affect the podocytes (podocytopathies). The underlying pathophysiology of these podocytopathies remains unclear, although it is believed to be immune mediated [1, 2].

Glucocorticoids are the recommended first-line immunosuppressive treatment by 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, in both entities, as the response rate is reported to be high [3, 4]. Nevertheless, particularly in adults with MCD and FSGS, relapses, steroid-dependence, or steroid-resistance are frequent and demand reintroduction of steroids and/or other immunosuppressants, such as calcineurin inhibitors, cyclophosphamide, and mycophenolate mofetil [5]. These cases present with poor prognosis, mainly due to ongoing complications of nephrotic syndrome or treatment toxicity and are associated with a high risk of progression to end-stage renal disease [5–7]. Thus, effective steroid-sparing and less toxic immunosuppressive agents are urgently needed, in particular when disease course is complex [5].

Rituximab (RTX), a chimeric murine/human monoclonal antibody targeted against the pan-B-cell marker CD20, is recommended as treatment for several glomerular diseases by the recent KDIGO 2021 guidelines [4, 8]. Specifically, in podocytopathies, RTX seems to emerge as an effective and safer alternative after failure of the conventional agents [9]. However, scarce studies have answered questions concerning long-term efficacy, drug-safety, and the optimal regimen for RTX-treatment [5]. Herein, we present a case series of steroid dependent patients with podocytopathies treated with RTX and provide a literature review of RTX treatment in podocytopathies.

Methods

This is a single-center retrospective study of patients with steroid-dependent podocytopathies treated with RTX at Centro Hospitalar Universitário Lisboa Norte, EPE (CHULN) between February 2013 and May 2023. The study was approved by the Comissão de Ética do Centro Hospitalar Universitário Lisboa Norte and Centro Académico de Lisboa, in agreement with institutional guidelines. Informed consent was not required by the Ethical Committee, given the retrospective and non-interventional nature of the study.

Patients and Definitions

We selected as eligible all adult patients who fulfilled the following criteria: (1) biopsy-proven FSGS or MCD and (2) steroid-dependent nephrotic syndrome. We excluded patients with genetic or other secondary causes of podocytopathies, and previous history of RTX treatment. Patients were defined as steroid-dependent if they experienced at least one relapse occurring during or within 2 weeks of completing glucocorticoid therapy [4].

Relapse was defined for MCD as proteinuria >3.5 g/24 h or urine protein/creatinine ratio (uPCR) >3,500 mg/g measured in the first urine sample of the morning, after complete remission (CR) has been achieved, and for FSGS as proteinuria >3.5 g/24 h or uPCR >3,500 mg/g after CR has been achieved or an increase in proteinuria >50% during partial remission (PR) [4].

CR was defined as a reduction of proteinuria to <0.3 g/day or uPCR to <300 mg/g, stable serum creatinine (SCr) and serum albumin (Alb) >3.5 g/dL. PR was defined as reduction of proteinuria to <0.3–3.5 g/day or uPCR to 300–3,500 mg/g and a decrease of >50% from baseline (4). B-cell depletion was defined as <1% of CD19+ lymphocytes [10].

Treatment Regimen

RTX was administered as an intravenous infusion (in isotonic saline at a concentration of 10 mg/mL) for 5–6 h. Patients received two fixed doses of 1,000 mg on day 1 and after 14–20 days. One patient (no. 14) received four weekly doses of 375 mg/m^2. The use of a maintenance therapy and its regimen were defined according to the attending physician's discretion.

Premedication included 1 g of oral paracetamol, 100 mg of methylprednisolone intravenous, and 25 mg of oral hydroxyzine, to prevent possible hypersensitivity reactions. Patients were closely monitored for infusion-related reactions, such as headache, chills, fever, rash, or hypotension. Co-trimoxazole (a tablet of 960 mg 3 times weekly) prophylaxis was given to all patients for at least 6 months after RTX therapy. Previous immunosuppressants could be continued or withdrawn by the treating physician after the administration of RTX, according to treatment response.

Variables and Outcomes

Data were collected from individual electronic clinical records. Data collection was performed in October 2023. The analyzed variables included patient demographic characteristics (age at diagnosis, sex, race), laboratory values (SCr, Alb, uPCR) at the time of diagnosis, at 3 months, 6 months, and 12 months after RTX, and at last follow-up, biopsy proven diagnosis, comorbidities, previous, and/or ongoing immunosuppression (corticosteroids, calcineurin inhibitors, mycophenolate mofetil, cyclophosphamide), clinical response to corticosteroids, dosing and prescription of RTX, relapses, CD19 level after 3 months and at the time of relapse, withdrawal of immunosuppressant, adverse effects associated.

The primary outcome was complete or PR at 6 and 12 months after RTX therapy. Secondary outcomes were complete or PR at the last follow-up, withdrawal of corticosteroids or other immunosuppressants, and number of relapses after RTX.

Statistical Methods

Categorical variables were presented as the total number and percentage of cases for each category. Continuous variables were presented as the mean ± standard deviation, median with interquartile range (IQR) and percentage, as appropriate.

Table 1. Demographics and baseline characteristics of patients

Patient, *n*	Sex	Age at diagnosis, years	Diagnosis on renal biopsy	Age at first RTX therapy, years	At presentation			Previous IS	Follow-up since RTX, months
					SCr, mg/dL	uPCR, mg/g	Alb, g/dL		
1	Female	24	MCD	40	0.4	7,000	N/A	CS, MMF, CNI	44
2	Male	13	MCD	34	0.77	N/A	3.2	CS, MMF, CNI	23
3	Male	12	MCD	23	0.69	5,950	2.0	CS, CNI	22
4	Female	27	MCD	29	0.4	N/A	2.1	CS, MMF, CNI, CYC	149
5	Female	19	MCD	21	1.1	13,000	1.3	CS, CNI	30
6	Male	26	MCD	31	0.9	4,916.8	1.9	CS, CNI	9
7	Male	20	MCD	22	0.65	6,100	4.9	CS, CNI	6
8	Male	37	FSGS	38	0.8	10,708	1.5	CS, CNI	37
9	Female	18	FSGS	29	0.5	11,000	1.9	CS, MMF	62
10	Male	8	FSGS	16	0.42	3,900	3.9	CS, MMF, CNI, CYC	77
11	Female	38	FSGS	51	0.56	N/A	2.0	CS, CNI	20
12	Male	43	FSGS	44	6.7	24,000	1.0	CS, CNI	20
13	Female	6	FSGS	21	0.11	300	3.1	CS, MMF, CNI, CYC	35
14	Male	3	FSGS	9	0.19	N/A	3.2	CS, MMF	128

FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; IS, immunosuppression; RTX, rituximab; SCr, serum creatinine; Alb, serum albumin; uPCR, urine protein/creatinine ratio; SD, steroid-dependent; CS, corticosteroids; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; CYC, cyclophosphamide.

Results

Fourteen patients were treated with RTX. The majority were male (57.1%, $n = 8$), and the mean age at diagnosis was 21.0 ± 10.5 years. Five patients (35.7%) had childhood-onset disease. Baseline characteristics and follow-up are shown in Table 1.

Seven patients (50%) were diagnosed with FSGS and seven (50%) with MCD. Twenty-one percent of patients had previous pulmonary embolism/deep venous thrombosis ($n = 3$), sixty-four percent had dyslipidemia ($n = 9$), and 14.3% hypertension ($n = 2$).

At clinical presentation, median SCr was 0.61 mg/dL (IQR 0.4–0.8 mg/dL), uPCR was 6,550 mg/g (IQR 4,916.8–11,000 mg/g), and Alb was 2.0 g/dL (IQR 1.7–3.2 g/dL). All patients had been previously treated with corticosteroids (GC) (100%, $n = 14$) and were steroid-dependent. Previous immunosuppression also included calcineurin inhibitors (85.7%, $n = 12$), either cyclosporine A or tacrolimus, mycophenolate mofetil (50%, $n = 7$), and cyclophosphamide (21.4%, $n = 3$).

At the time of treatment with RTX, mean age was 29.1 ± 21.9 years, median SCr was 0.73 mg/dL (IQR 0.46–0.87 mg/dL), uPCR was 1,540.1 mg/g (IQR 375.2–2,667.6 mg/g), and Alb was 3.5 g/dL (IQR 3.3–3.8 g/dL). Most patients (85.7%) were in partial ($n = 10$) or CR ($n = 2$), and RTX was given in order to stop or reduce the dose of PDN and other immunosuppressants. Thirteen patients (92.9%) were on other immunosuppressants: eight (57.1%) on prednisone (median dose of 20 mg/day [IQR 10–40 mg/day]), ten (71.4%) with calcineurin inhibitor, either tacrolimus ($n = 6$) (median 5 mg/day [IQR 3–6 mg/day]) or cyclosporine A ($n = 4$) (median 200 mg/day [IQR 200–225 mg/day]), and 3 patients (21.4%) with mycophenolate mofetil (median 1,000 mg/day [IQR 500–1,500 mg/day]).

Table 2. RTX induction and maintenance therapies

Patient, *n*	Dose of RTX induction therapy	Maintenance RTX therapy	Time interval until maintenance RTX (months)
1	2 × 1 g		
2	2 × 1 g	2 × 1 g every 6 months	15
3	2 × 1 g	2 × 1 g every 6 months	6
4	2 × 1 g		
5	2 × 1 g		
6	2 × 1 g		
7	2 × 1 g		
8	2 × 1 g		
9	2 × 1 g		
10	2 × 1 g	2 × 1 g every 6 months	58
11	2 × 1 g	2 × 1 g every 6 months	6
12	2 × 1 g		
13	2 × 1 g	2 × 1 g every 6 months	29
14	375 mg/m^2	2 × 1 g every 6 months	127

RTX, rituximab.

Treatment with RTX and Clinical Response

Mean follow-up time after RTX was 47.3 ± 43.4 months. Induction treatment included 2 doses of RTX 1,000 mg 2 weeks apart in 13 patients, and one was treated with 4 doses of RTX 375 mg/m^2 body surface area (600 mg) (Table 2). Complete CD19 cell depletion (<1%) 3 months after initial dose of RTX was confirmed in 6 patients (42.8%).

At 12 months of follow-up, 11 patients (91.7%) achieved remission: seven (63.6%) CR and four (36.4%) PR. Median SCr was 0.73 mg/dL (IQR 0.49–0.91 mg/dL), uPCR decreased to 94.2 mg/g (IQR 68.4–757.5 mg/g), and Alb was 4.3 g/dL (IQR 4.0–4.9 g/dL) (Table 3). Four patients (30.8%) had ceased corticosteroids and prednisolone dose tapering was possible in two (15.4%). A reduction of 73.8% on the prednisolone dose was observed to a median of 5.25 mg/day (IQR 2.75–8.75 mg/day). Five patients were still treated with tacrolimus, at a lower median dose of 2 mg/day (IQR 1.0–3.5 mg/day), and two (14.3%) with mycophenolate mofetil (dose of 1,500 mg/day), all of the patients gradually reducing immunosuppressants doses (Table 4).

Relapses were observed in 5 patients (35.7%), who were successfully treated with corticosteroids as induction treatment along with RTX in four of these, having achieved remission. At the time of relapse, restitution of CD19+ cells was confirmed in 2 patients who had relapse. Mean time to relapse was 17.2 ± 9.2 months. Three patients with relapse received maintenance therapy with RTX, having attained CR. One patient presented with sCr 6.7 mg/dL, uPCR 24 000 mg/g. and Alb 1.0 g/dL did not respond to RTX treatment and started hemodialysis within 6 months, due to progressive worsening of renal function.

Maintenance RTX was administered in 6 patients (42.9%), with cycles of 1,000 mg given 2 weeks apart, with a 6-month interval, during a 2-year period, and at different time intervals after RTX induction therapy (Table 2). All patients who received maintenance RTX (n = 6) showed CR and no relapses were observed.

At the last follow-up (47 ± 43 months), 12 patients (92.3%) were in remission (10 complete and 2 partial). Median SCr was 0.84 mg/dL (IQR 0.60–0.90 mg/dL), uPCR was 77 mg/g (IQR 47.6–539.7 mg/g) and Alb 4.4 g/dL (IQR 4.2–4.8 g/dL). CD19+ cell counts were 0% in 6 patients and 6.2% in one. Complete withdrawal (n = 5) or reduction (n = 5) of immunosuppressive regimen was possible in 10 patients (76.7%). Laboratory values and remission rates with RTX are summarized in Table 3.

Adverse Events

Most patients (n = 10, 71.4%) tolerated RTX without any report of adverse effects. Infusion reactions were observed in 4 patients (28.6%). Two patients developed light skin rash, myalgias, and arthralgias, and 1 patient developed fever, all of which were successfully treated with follow-up doses of RTX after using a desensitization protocol. One patient (no. 11) experienced fever, skin rash, and hepatitis, which required RTX treatment withdrawal. Other adverse events, such as infectious diseases or bone marrow suppression, were not observed.

Table 3. Laboratory values and remission rates with RTX therapy

	Before RTX	3 months after RTX	6 months after RTX	12 months after RTX	Last follow-up
SCr, mg/dL	0.73 (0.46–0.87)	0.84 (0.68–1.06)	0.84 (0.64–0.91)	0.73 (0.49–0.91)	0.84 (0.60–0.90)
uPCR, mg/g	1,576.1 (550.3–2,657.6)	67.8 (56.0–2,436.5)	116.5 (48.7–1,263.1)	94.2 (68.4–757.5)	77 (47.6–539.7)
Alb, g/dL	3.5 (3.3–3.8)	4.4 (3.7–4.5)	4.5 (3.7–4.7)	4.3 (4.0–4.9)	4.4 (4.2–4.8)
Remission rates, *n* (%)	12/14 (85.7)	13/14 (92.9)	12/14 (85.7)	11/12 (91.7)	12/13 (92.3)
CR, *n* (%)	2/14 (14.3)	10/14 (71.4)	10/14 (71.4)	7/12 (58.3)	10/13 (76.9)
PR, *n* (%)	10/14 (71.4)	3/14 (21.4)	2/14 (14.3)	4/12 (33.3)	2/13 (15.4)

Values are shown as either medians with interquartile ranges or numbers denoted as percentage. RTX, rituximab; SCr, serum creatinine; Alb, serum albumin; uPCR, urine protein/creatinine ratio; CR, complete remission; PR, partial remission.

Table 4. Immunosuppressants use and relapse rate, before and after RTX

	Before RTX	At last follow-up
Immunosuppressive therapy, *n* (%)	13/14 (92.9)	7/12 (58.3)
CS, *n* (%)	8/14 (57.1)	4/12 (33.3)
Dose of PDN, mg/day	20 (10–40)	5.25 (2.75–8.75)
CNI, *n* (%)	10/14 (71.4)	5/12 (41.7)
Dose of tacrolimus, mg/day	5 (3–6)	5.25 (2.75–8.75)
Dose of CSA, mg/day	200 (200–225)	–
MMF, *n* (%)	3/14 (21.4)	2/12 (16.7)
Dose of MMF, mg/day	1,000 (500–1,500)	1,500
Relapse, *n* (%)	14/14 (100)	5/14 (35.7)

Values are shown as either medians with interquartile ranges or numbers denoted as percentage. RTX, rituximab; CS, corticosteroids; PDN, prednisolone; CNI, calcineurin inhibitor; CSA, cyclosporine A; MMF, mycophenolate mofetil.

Discussion

This retrospective case-series of 14 patients with steroid-dependent primary podocytopathies supports the available evidence that RTX treatment allows for steroid-free disease remission in the majority, with a lower rate of relapses and few side effects. Six months and 1 year after the first RTX administration, almost 86% and 92% of our cohort achieved disease remission, respectively. A recent retrospective study included 13 patients with MCD and FSGS and after 6 months of treatment with RTX CR was attained in 72% and PR in 26% of cases, results similar to our cohort. This supports the efficacy of RTX as an induction treatment in podocytopathies attaining fast remission in the majority of cases.

At time of the diagnosis, all patients of this cohort were treated according to the published KDIGO guidelines at that time [11, 12], with either corticosteroids, CNI, and MMF as in other studies [13]. In steroid sensitive patients, RTX has been demonstrated as effective in reducing the dose of other immunosuppressants and low relapse rates. In the NEMO study [14], the reduction of prednisone was statistically significant. In our cohort, we observed a reduction of 74% on PDN dose (from a median of 20 mg–5 mg/day) and discontinuation occurred in 50% of the patients, possibly explained by a slower taper and short follow-up. Two recent reviews of studies available so far, on the management of MCD and FSGS using RTX confirming its efficacy in reducing proteinuria, increasing albumin and reducing the dose of immunosuppressants [7, 15–22].

There is no standard dosing described for RTX in primary podocytopathies. Different dosing protocols (375 mg/m^2 of 1–4 weekly doses, 1 g as single dose, or 1 g 2 weeks apart) were used in subgroups of a few retrospective studies and prospective trials [5]. Neither a correlation was found between the different treatment protocols, nor conclusions could be made due to the small size of the subgroups [5, 14]. The RItuximab From the FIRst Episode of Idiopathic Nephrotic Syndrome

(RIFIREINS) [23] and The Use of Rituximab In the treatment of Nephrotic Glomerulonephritis (TURING) [24] are ongoing trials which will add important information on this matter [14]. In our center, the most frequent induction scheme was RTX 1 g 2 weeks apart as it was a more suitable strategy in the outpatient setting.

The efficacy of RTX in treating podocytopathies supports the hypothesis that these are driven by pathogenic B-cell circulating permeability factors that disrupt podocyte integrity [5, 9]. In fact, several autoantibodies related with nephrotic syndrome have been identified in the past decade, such as anti-annexin A2, anti-UCHL1, and anti-nephrin [2, 14]. In a recent multicenter study, Hengel et al. [25] demonstrated that circulating anti-nephrin autoantibodies were common in patients with MCD and their levels correlated with disease activity. The authors also performed an experimental immunization of anti-nephrin antibodies in mice that manifested clinically as nephrotic syndrome and histologically as IgG located in the podocyte slit diaphragm, supporting the pathogenic role of these antibodies and an even more relevant role of B cell-targeted therapies for the treatment of podocytopathies, specifically in this subset of patients with positive auto-antibodies. Additionally, direct effects of RTX have been reported, as a direct modulator of podocyte function, by stabilization of sphingomyelinase-like phosphodiesterase 3b, which prevents podocyte cytoskeleton disruption and apoptosis [5, 26]. There is also a possible role in inducing T regulatory cells suggested by the delayed effect of RTX in inducing remission in recurrent FSGS after transplantation [9, 26].

The systematic review and meta-analysis from Xue et al. showed a pooled rate of relapse of 27.4% after RTX (20 studies, 95% CI: 20.7–34.5%), adjusted by sample size, with a significant and consistent reduction of relapses by 2.15 times/year (eight studies, 95% CI: 1.72–2.58 times/year, $p < 0.001$). Most relapses usually occurred between months 7 and 18 [13]. This was similar to our cohort, in which the relapse rate was 35.7%, with a significant decrease in relapses after RTX.

Maintenance with RTX is not routine clinical practice and guidelines on this matter are unspecific on dosing and frequency. On the other hand, several studies have shown favorable outcomes regarding the decision to initiate maintenance RTX after remission [16]. In our cohort, 6 patients were started on maintenance RTX at variable times after the first RTX administration, according to the attending physician's discretion. This raises the question whether we should be giving fixed doses of RTX. At the last follow-up, 12 patients (92.3%) were in remission.

Cortazar et al. [27] published a retrospective study on continuous B-cell depletion in 20 patients (65% MCD and 35% FSGS). Patients received RTX 1 g 2–4 weeks apart and then 1 g every 4 months, for a median of 9 infusions. B-cell depletion was monitored before each dose to a goal of CD-19 cells <5/μL. Patients were treated for 28 months and all attained at least PR, though CR was more common in frequently relapsing/steroid-dependent patients.

The largest prospective observational study included 53 adult patients with steroid-dependent, frequently relapsing or steroid resistant nephrotic syndrome (58% MCD and 41% FSGS). Induction RTX was given at 375 mg/m^2 with an additional maintenance dose of 100 mg when absolute CD-19 level increased to >5/μL or >1% of the total lymphocyte count, which occurred at a median time of 5 (IQR: 3–7) months. At the end of 6 and 12 months, 87.5% and 79.1% of the patients had achieved remission, respectively [9]. Reappearance of CD19+ cells was confirmed only in 2 of the patients in our cohort, which demonstrates that cell recovery after RTX might be an unreliable marker to predict relapses in patients with NS [5].

Contrasting with regimens of continuous B-cell depletion, Osterholt et al. [28] presented a retrospective study that included 13 adult patients with biopsy-proven MCD or FSGS with complicated disease courses, treated with RTX (4 × 375 mg/m^2 body surface area 1 week apart), who received a new administration only if a disease relapse occurred. Median relapse-free survival was 17 months for the first administration, 51 for the second course and 21 months for subsequent courses, which was comparable to uncomplicated MCD/FSGS courses and allowed for a lower RTX exposure. After 6 months, 72% were in CR, 26% in PR, and there was an extension of relapse-free survival from 4.5 to 21 months (CI: 16–32 months) compared to the previous immunosuppression [28].

In our study, 6 patients received maintenance treatment with RTX (2 × 1 g every 6 months) which was started at different time intervals after the first administration (median of 22 months), at physician's discretion. All patients (100%) are in CR after a median of 10.5 months (IQR 1–19) after starting maintenance RTX, with 3 patients having been weaned off immunosuppressive agents and 3 patients on a reduced dose. It is predictable that, with longer follow-up, these patients will be able to completely wean off other immunosuppressants, with the likely need to maintain RTX therapy, whether it is at fixed doses every 6 months, whether it is according to B-cell depletion or clinical relapse, remains uncertain, as well as the duration of RTX maintenance therapy.

Therefore, maintenance RTX appears to be a viable therapeutic option for patients with podocytopathies, particularly those who have multiple relapses, have not responded well to other classes of immunosuppressants or who have experienced drug-related toxicity. RTX

usually persists in the circulation for 3–6 months, followed by recovery of B cells to pretreatment levels by 12 months, but a shorter half-life of RTX among patients with nephrotic syndrome may require respective dose adjustments [5]. In MCD and FSGS, the optimal timing and dosing of RTX to maintain remission or after relapse are unknown. Remission may persist despite complete B-cell restitution and relapses can occur in the presence of sustained depletion of B cells [5].

RTX has shown a favorable safety profile [5, 15]. A systematic review and meta-analysis with 382 adult patients with MCD/FSGS treated with RTX reported adverse events in 18 studies, but RTX was mostly well tolerated. The most common complications described were infusion reactions [13, 28]. In the NEMO study, after 1 year of follow-up, five serious infections were observed in the adult subgroup. At the time of infection, all patients were still receiving concomitant immunosuppressive treatment, and all fully recovered [5]. This is similar to the results from our cohort in which 71% of the patients tolerated RTX without any report of adverse effects.

Long-term follow-up data are not available. A retrospective study analyzing the malignancy risk of 323 patients with AAV over a mean follow-up of 5.6 years showed that RTX was not associated with increased malignancy risk in patients with AAV compared with the general population [5]. To address this appropriately, studies with a follow-up period of 60 months or longer are needed.

Noteworthy limitations include the retrospective and single-center nature, with a small number of patients which limits the generalization of our results. Nevertheless, as rare diseases, most studies on podocytopathies have low number of patients. Second, although were adults when treated with RTX, we also included patients with disease presentation in childhood, which could influence the disease trajectory. Third, RTX scheme and total dose was variable which could influence the results, although no comparison has shown higher efficacy of either scheme. Also, the decision for maintenance was at physicians' discretion without a defined protocol, and as such no comparison was made. Finally, the follow-up time was approximately 2 years which limits assessment of long-term outcomes and adverse events.

Still, this is an important study which adds to existing data on treatment of primary podocytopathies, namely by presenting data on maintenance therapy with RTX and demonstrating its efficacy. Additionally, we reviewed the published maintenance RTX schemes used in podocytopathies, and we appended data on the low rate of adverse events of RTX in these cases.

Conclusion

Our findings support the use of RTX for a steroid-free remission in podocytopathies and suggest that maintenance RTX is well-tolerated and associated with prolonged remission. Further studies are needed to confirm its efficacy and safety and establish the optimal induction and maintenance RTX regimen in podocytopathies.

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Statement of Ethics

This study protocol was reviewed and approved by Comissão de Ética do Centro Hospitalar Universitário Lisboa Norte and Centro Académico de Lisboa, Approval No. 103/20, date of decision July 31, 2020. This consent protocol was reviewed and the need for written and informed consent was waived by Comissão de Ética do Centro Hospitalar Universitário Lisboa Norte and Centro Académico de Lisboa, Approval No. 103/20, date of decision July 31, 2020. The authors give their consent for publication.

Conflict of Interest Statement

There is no conflict of interest. The results presented in this paper have not been published previously in whole or part.

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Author Contributions

Cláudia Costa, Amélia Antunes, and Joana Gameiro: conception, design, acquisition, analysis, interpretation of data, and final approval of the version to be published; João Oliveira: acquisition; Marta Pereira and Iolanda Godinho: analysis, interpretation of data, and final approval of the version published; Paulo Fernandes, Sofia Jorge, and José António Lopes: revision and final approval of the version to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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