BMC Nephrology

RESEARCH

Open Access

Long-term efficacy of Rituximab in steroid dependent and frequent relapsing adult nephrotic syndrome

Omri Feder[1*†], Dana Amsterdam[1†], Mohamad Ershed[2], Ayelet Grupper[3,4], Doron Schwartz[3,4] and Orit Kliuk-Ben Bassat[3,4]

Abstract

Background Corticosteroids are highly efficient for treatment of minimal change disease (MCD), however a substantial number of patients become steroid dependent (SD) or frequent relapsing (FR). Response rate is lower in primary Focal Segmental Glomerulosclerosis (FSGS). Since prolonged exposure to corticosteroids should be avoided, an effective alternative is required. Rituximab is a promising agent. We aimed to evaluate the efficacy of Rituximab in adults with SD/FR nephrotic syndrome (NS).

Methods A retrospective cohort study, evaluating patients with SD/FR NS treated with Rituximab in a tertiary hospital. Rituximab was given at induction, with additional doses subjected to the treating nephrologist decision. Primary outcome was number of relapses and time to first relapse. Safety was assessed.

Results Twenty-one adults were included. Among them, 14 (66.7%) were diagnosed with MCD, 5 (23.8%) with FSGS, in 2 cases kidney biopsies were not performed. Median age was 54.6 years. Median follow up was 39.6 months. Number of relapses decreased significantly after Rituximab compared to before treatment (median relapses 0 compared to 3, respectively, W = 3.70, $p < .001$). Time to first relapse was significantly shorter before Rituximab compared to after (median 11 vs. 536 days, respectively, W = 3.05, $p = .002$). Hazzard Ratio for relapse was higher in patients who received one Rituximab course compared to those who received an additional maintenance (HR = 4.31, 95% CI: 1.13–16.39, $p = .032$). Treatment was well-tolerated, serious adverse events included cholecystitis and severe COVID-19.

Conclusions Rituximab emerges as an efficient safe steroid sparing in patients with SD/FR NS, with longer remission achieved when an additional maintenance dose is given after the first course.

Keywords Rituximab, Nephrotic syndrome, Steroid dependent, Frequent relapsing

†Omri Feder and Dana Amsterdam have contributed equally to this work.

*Correspondence:
Omri Feder
Omri.feder@gmail.com

[1]Department of Internal Medicine H, Tel Aviv Sourasky Medical Center, Tel-Aviv, Israel
[2]Division of Oncology, Tel Aviv Sourasky Medical Center, Tel-Aviv, Israel
[3]Department of Nephrology and Hypertension, Tel Aviv Sourasky Medical Center, Tel-Aviv, Israel
[4]Faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel

Background

Minimal change disease (MCD) carries a favorable prognosis under glucocorticoids treatment, which is recommended as a first-line therapy of adult MCD according to the Kidney Disease: Improving Global Outcome (KDIGO) guidelines [1]. However, while complete response is achieved in 75–90% of patients, up to 25% of steroid responders develop frequent relapses (FR), and 30–40% of them become steroid-dependent (SD) [2]. Response rate is lower in primary Focal Segmental Glomerulosclerosis (FSGS), estimated below 50%, with a relapse rate of 36% and 52% in patients who previously achieved complete remission and partial remission, respectively, resulting in prolonged steroid exposure [3, 4]. Long-term steroid treatment is associated with serious side effects such as hyperglycemia, hypertension, dyslipidemia, and osteoporosis [1]. Therefore, non-steroid immunosuppressive treatments are essential for safe and effective treatment of adult steroid responsive nephrotic syndrome (NS).

Alternate immunosuppressants such as calcineurin inhibitors (CNI), cyclophosphamide, and mycophenolate mofetil are reserved as a second line for FR, SD and steroid-resistant (SR) patients. However, these agents have shown limited results in maintaining remission and reducing relapses and are associated with significant side effects [5].

The pathogenesis of podocytopathy in MCD and FSGS was poorly understood for many years. It was thought to be caused by lymphocyte dysregulation in which the permeability circulating factor, released by T cells, led to podocyte injury [6, 7]. In addition, B cells also play an essential role in podocytopathy through interaction with T cells, secretion of antibodies, or production of cytokines [8–10]. Recently, significant progress has been made in understanding the pathogenesis of the MCD, as circulating antinephrin autoantibodies appeared to be a marker of disease activity in patients with MCD and idiopathic steroid responsive NS [11].

Rituximab is a chimeric monoclonal antibody that targets CD20 antigen, a B cell differentiation marker [12]. The direct binding of Rituximab to surface protein CD20 results in B lymphocyte depletion through inducing cell apoptosis, complement-dependent cytotoxicity, and antibody-dependent cell-mediated cytotoxicity [12–14].

Rituximab has been used since 2006 to treat pediatric patients with FR NS [15]. Several randomized clinical trials (RCTs) have been conducted in the pediatric population to evaluate its efficacy and safety [16–20]. Emerging evidence indicates that Rituximab may also aid in managing SR NS in pediatric patients. A study conducted across 28 pediatric nephrology centers highlights that Rituximab enhances remission rates in a subset of children with SR NS, with effects observed during a follow-up period of 24 months post-treatment [21]. Observational studies have been previously conducted to assess its efficacy and safety in adult MCD and FSGS [3, 22–28]. These studies have confirmed that Rituximab therapy led to complete remission, low relapse rate, and enabled gradual tapering or discontinuation of steroids in SD NS patients [22, 23, 25, 27, 28]. Currently, there are no published RCTs assessing Rituximab use in adult population with SD/FR NS, although there are several trials ongoing [29]. Due to the limited studies and available information to determine the effectiveness and safety of Rituximab use in adult SD/FR NS, additional studies are needed for treatment guidance.

In this study, we carried out a retrospective analysis of adult patients with SD/FR MCD/FSGS who have been treated with Rituximab at our Nephrology department of a tertiary hospital. Our aim is to evaluate the long-term efficacy and safety of Rituximab therapy in adult patients with SD/FR NS.

Method

This single-center retrospective cohort study was performed at the Nephrology department of tertiary hospital between January 2014 to December 2023 to evaluate the efficacy and safety of Rituximab treatment among patients with MCD and FSGS. This study complies with the Declaration of Helsinki and was performed according to ethics committee approval under protocol TLV-23-0087.

Inclusion criteria include (1) a minimum age of 18 years (2) a diagnosis of MCD or FSGS according to KDIGO criteria [1] (3) Steroid-dependent, frequent relapses NS or significant side effects to current immunosuppression (4) Patients who were treated with Rituximab.

Primary outcome includes the frequency of relapses and time to first relapse after Rituximab therapy. We also evaluated adverse events related to Rituximab during the first 24 months.

Steroid-dependence was defined as two or more relapses that occurred within two weeks after completing a course of steroid treatment and frequent relapses were defined as more than two relapses in a period of six months or four relapses within a year.

Complete remission was defined according to KDIGO guidelines as reduction of proteinuria to below 300 mg/day and serum albumin above 3.5 g/l. Partial remission was defined as reduction of proteinuria to 300-3,500 mg/day and a decrease above 50% from baseline [1].

Relapse was defined as proteinuria above 3,500 mg/day after achieving complete remission, or an increase in proteinuria demonstrated on at least 2 consecutive urine analysis that was considered sufficient by the managing clinician to re-introduce immunosuppressive therapy.

The demographic and clinical data were collected through electronic medical records. The data include age, gender, past medical history, habits, family history, chronic diseases, previous immunosuppressive therapy and concurrent medication. Laboratory data include creatinine, Blood Urea Nitrogen, lipid profile, and serum albumin. Estimated glomerular filtration rate (eGFR) was calculated according to CKD-EPI formula [30]. Proteinuria was quantified using a urine protein/creatinine ratio (uPCR) or 24-hours urine collection.

Prior to first Rituximab course, patients were immunized with pneumococcal vaccine if possible. Hepatitis B status was assessed in all patients before Rituximab treatment to rule out active infection / chronic carrier condition. Positive cases were designated for antiviral treatment before initiating Rituximab. Before each dose, patients were clinically assessed to rule out active infection, and a complete blood count was performed to exclude neutropenia. In cases treated with a combination of Prednisone above 20 mg daily or other immunosuppressant, prophylaxis for Pneumocystis pneumonia was given.

Pretreatment with acetaminophen, anti-histamines and intravenous steroids were given before each infusion, even on repeated doses. Rituximab initial dose was administered in conjunction with steroids, preferably while the patient is in complete remission. In most cases, Rituximab was given in two doses of 1,000 mg each, two weeks apart, for induction. A single maintenance dose of 1 gram was administered 6 month following induction to some of the patients based on the treating nephrologist decision. Additional doses were given only if a relapse occurred. Relapses were treated with a short glucocorticoids course in addition to Rituximab.

Serious adverse events (SAEs) and adverse events (AEs) were documented in patients' medical records during treatment and follow-up.

Table 1 Patients' baseline characteristics ($N=21$)

Characteristic	*N* (%)	Median (IQR)
Age		54.61 (34.2–62.5)
Gender (female)	11 (52.4%)	
Family history		
Steroid sensitive NS	1 (4.8%)	
Other kidney disease	5 (23.8%)	
Current / past Smoker	3 (14.3%)	
Hypertension	9 (42.9%)	
Obesity	4 (20.0%)	
Diabetes mellitus	3 (14.3%)	
Thyroid disease	3 (14.3%)	
eGFR (ml/min/1.73m^2)		106.0 (89.5-120.5)
Medications		
Diuretics	11 (52.4%)	
ACEi/ARB	14 (66.6%)	
MRAs	4 (19%)	
Anticoagulants	3 (14.3%)	
Statins	16 (76.2%)	
Oral hypoglycemics	2(9.5%)	

Statistical analysis

Continuous variables are presented as median with interquartile range (IQR) to account for potential non-normality in the data distribution. Categorical variables are presented as number of patients and the corresponding percentage. Differences in the number of relapses and time to first relapse before and after Rituximab therapy were assessed using the non-parametric Wilcoxon signed-rank test. Time to first relapse after Rituximab therapy was further evaluated using Cox Regression survival analysis for differences between disease type (MCD vs. FSGS) and administration of additional maintenance doses (maintenance vs. no-maintenance).

P-value < 0.05 was considered statistically significant. All statistical tests were two tailed. IBM SPSS Statistics for Windows, version 28 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

Results

Twenty-one patients were included in the cohort. Patients' baseline characteristics are presented in Table 1 and 2. Median age was 54.61 years (IQR 34.2–62.5), 52.4% were females. Patients did not have significant cardiovascular history and kidney function was normal in 20 patients. There were no positive cases of Hepatitis B infection or carriage.

Fourteen patients (66.6%) were diagnosed with MCD, 5 (23.8%) with FSGS. In 2 cases kidney biopsies were not performed: one patient had childhood onset SD NS, and another adult with steroid responsive NS, who had recurrent episodes of life-threatening arterial thrombosis that precluded withdrawal of anticoagulation. Five patients experienced more than 5 relapses before Rituximab treatment. In 5 patients with SD NS, relapses occurred at a relatively high Prednisone dose - above 20 mg.

Eleven patients received Rituximab first dose while in complete remission, 4 were in partial remission and 6 patients failed to achieve remission before Rituximab treatment; Five of them with FSGS and one with SD MCD relapsing at a high prednisone dose of 40 mg daily. Most patients (18/21) received concomitant steroid therapy alongside their first Rituximab dose. Most patients received an induction therapy with 2,000 mg Rituximab, divided to 2 doses, however 2 females received only one dose for induction– one due to financial reasons and the other due to SAE occurring after the first dose. Despite that, both cases sustained prolonged remission with no relapses during long term follow up. Fourteen patients

Table 2 Kidney disease characteristics of patients prior to rituximab treatment

Patient	Sex	Diagnosis	Response to initial immunosuppressive treatment	Age at diagnosis/ Rituximab treatment†	Previous IS therapy	Number of relapses
1	F	MCD-SD	CR	45/46	GC	2
2	M	FSGS	CR	57/65	GC, CYA	>5
3	M	MCD-SD	CR	51/59	GC, CYA, CP	>5
4	M	MCD-FR	CR	33/37	GC, CYA	4
5*	M	SSNS-SD	CR	8/28	GC, CYA, MMF, CP	>5
6	M	FSGS	PR	43/47	GC, CYA, MMF, CP, TAC	NA
7*	F	SSNS-FR	CR	70/73	GC, CYA	3
8	F	MCD	CR	47/57	GC, CP	1
9	M	MCD-SD	CR	47/55	GC, CYA, CP	3
10	M	MCD-FR	CR	30/33	GC, CYA, MMF	3
11	F	MCD-SD	CR	38/38	GC, CYA	1
12	F	MCD-SD	CR	42/43	GC, CYA, TAC	1
13	F	FSGS	CR	11/19	GC, CYA, TAC	2
14	F	FSGS	CR	32/36	GC, TAC	2
15	M	MCD-FR	CR	62/64	GC	2
16	F	FSGS	PR	20/28	GC, CYA, MMF	>5
17	F	MCD-SD	CR	29/29	GC	2
18	M	MCD-SD	CR	26/26	GC	4
19	F	MCD-SD	CR	52/63	GC, CYA	>5
20	M	MCD-FR	CR	52/54	GC, CYA	4
21	F	MCD-SD	CR	62/63	GC, CYA	1

MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; IS, immunosuppressive; NA, not available; GC, glucocorticoids; CYA, cyclosporine A; CP, cyclophosphamide; MMF, mycophenolate mofetil; TAC, tacrolimus; CR, complete remission; PR, partial remission

*Patient without biopsy performance

†At first course of Rituximab

received repeated Rituximab doses, in 5 cases the second course was due to relapse, the others received prophylactic maintenance dose due to pre-Rituximab disease severity, according to the managing physician decision. Median total dose of Rituximab was 3000 mg (IQR: 2000–4750 mg), administered over a median of 3 courses (IQR: 1.0–4.0 courses). Median follow up time was 39.6 months (IQR: 17.0–62.0).

Following first course of Rituximab therapy, 14 patients maintained prolonged remission and did not require steroid treatment until the end of follow up. Number of relapses decreased significantly after Rituximab compared to before treatment, with 66.7% of patients maintaining prolonged remission without relapses, 9.5% with 1 relapse, 9.5% with 2 relapses, and 14.3% with 3 relapses (median relapses 0 after Rituximab compared to 3 before treatment, $W = 3.70$, $p < .001$, with a large effect size, $r = .82$ (Fig. 1)). Patients experienced an average of 0.21 relapses per year following Rituximab treatment. This effect remained robust even after excluding patients with less than three years of follow-up post-Rituximab ($W = 2.57$, $p = .010$).

Time to first relapse was significantly shorter before receiving Rituximab compared to after (median 11 vs. 536 days, respectively, $W = 3.05$, $p = .002$, with a large effect size, $r = .76$) (Fig. 2).

Cox regression survival analysis was conducted to assess the Hazard Ratio (HR) for relapse over time with Rituximab treatment. There was no significant difference observed between the MCD and FSGS groups (HR = 1.16, 95% CI: 0.28–4.50, $p = .877$, Fig. 3). Individuals who received only one course of induction therapy (no-maintenance group) experienced a notably higher HR for relapse compared to those in the maintenance group (HR = 4.31, 95% CI: 1.13–16.39, $p = .032$), as depicted in Fig. 4.

Safety profile of the treatment was favorable. Two events were considered treatment related SAE: hospitalization due to severe acute cholecystitis a week after first Rituximab dose; and severe COVID-19 necessitating mechanical ventilation and renal replacement therapy initiation in a vaccinated patient with FSGS and chronic kidney disease stage IV. Other AEs included significant hypogammaglobulinemia in one patient; dyspnea in one patient during Rituximab infusion, that resolved after decreasing infusion rate; one patient developed joint pain that lasted several weeks after treatment and 2 patients

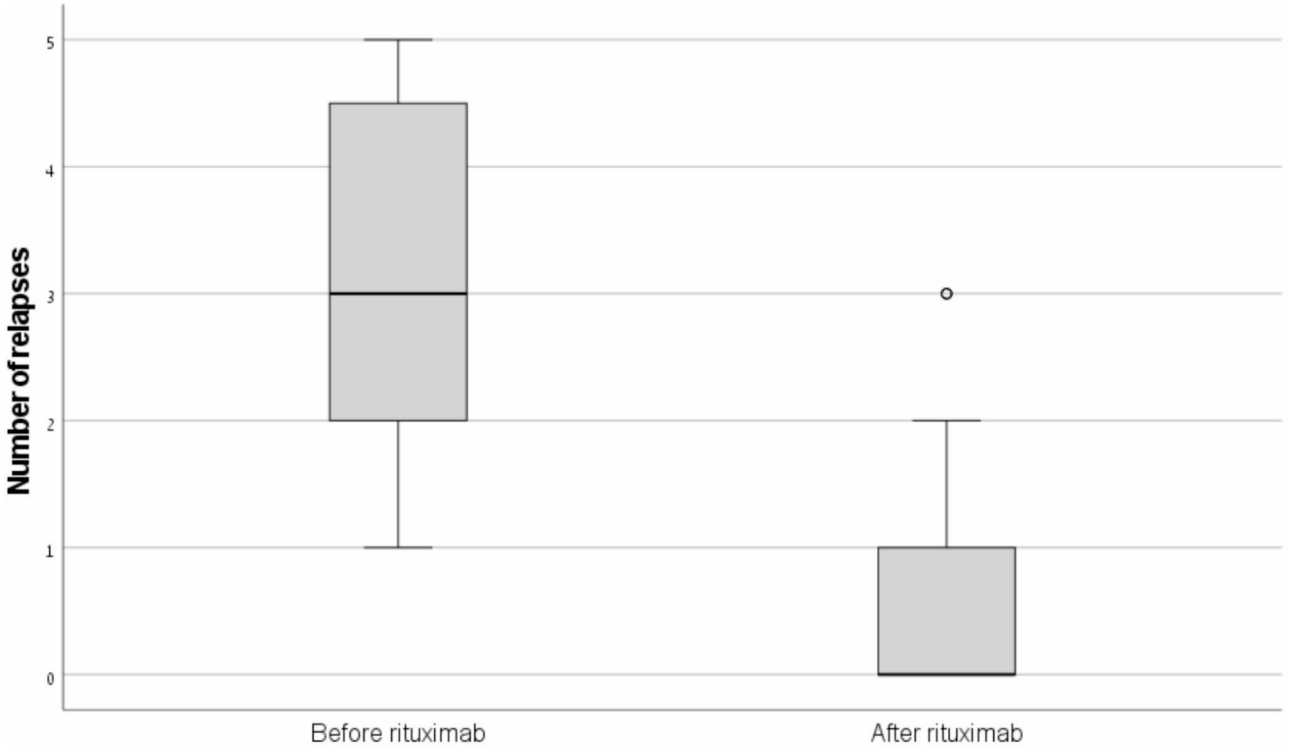

Fig. 1 Number of relapses before and after Rituximab

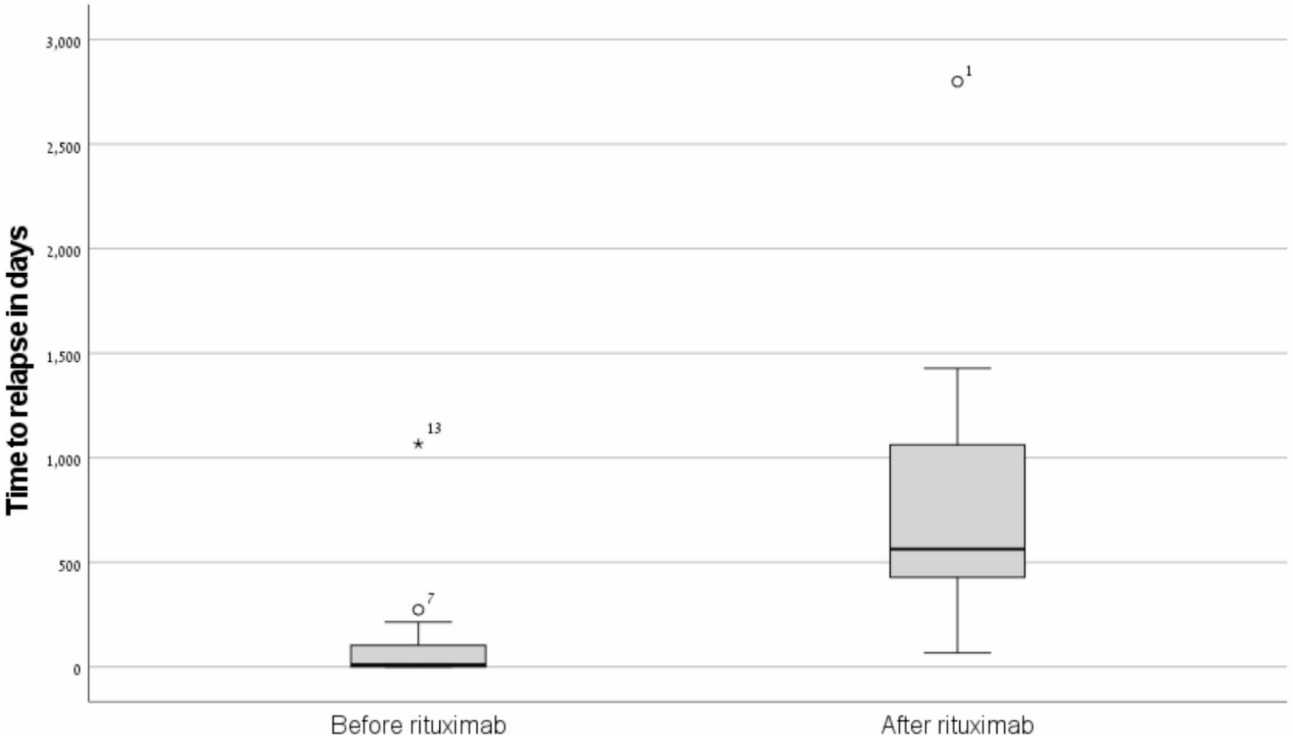

Fig. 2 Time to first relapse before and after Rituximab

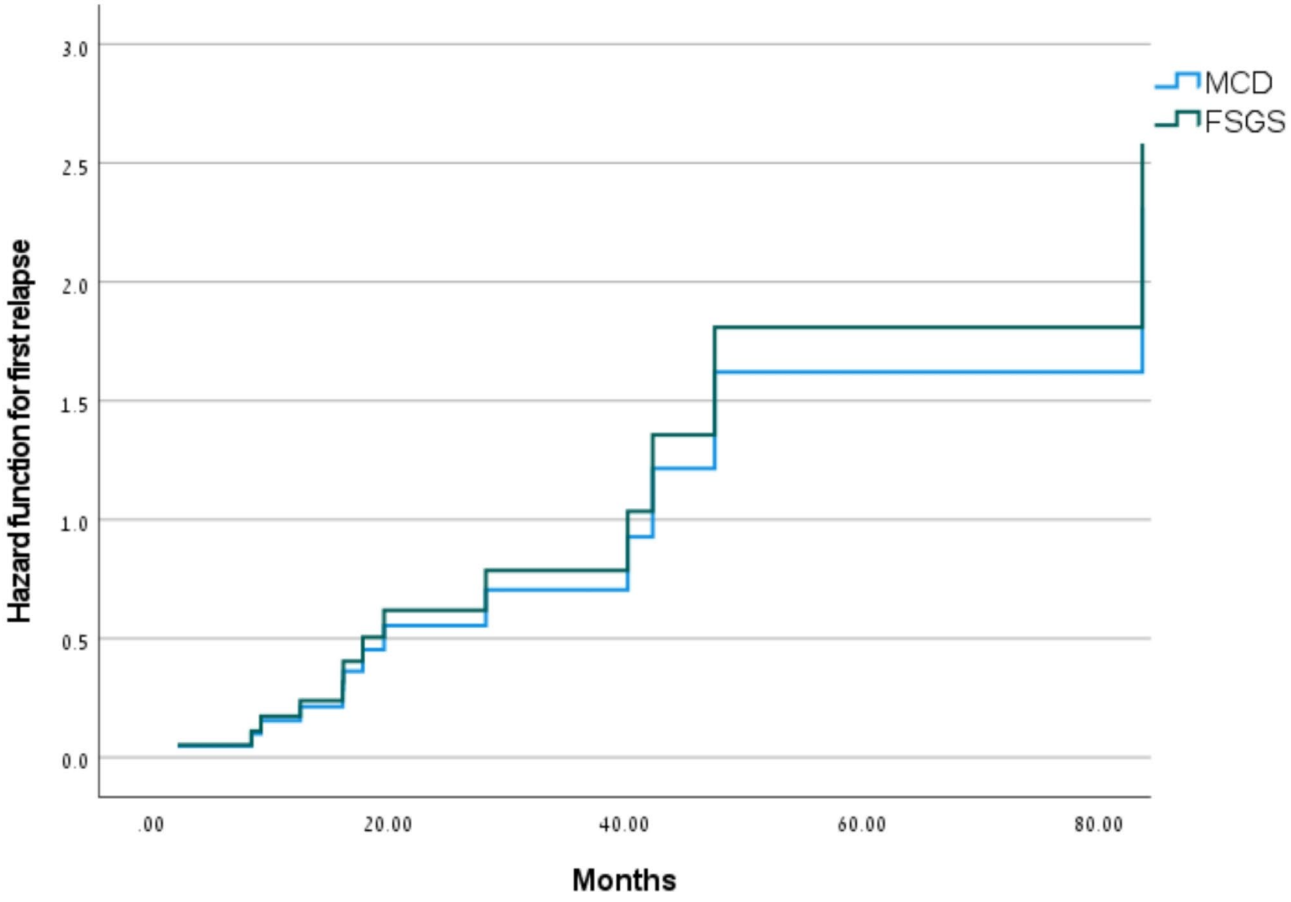

Fig. 3 Cox regression curves for first relapse hazard after first course of Rituximab therapy (MCD vs. FSGS)

had gastrointestinal symptoms that resolved within several days.

Discussion

In this retrospective cohort, we found that Rituximab significantly decreased number of relapses and increased time to relapse in a cohort of steroid responsive MCD / FSGS during long term follow-up.

While MCD was regarded as a T-cell mediated disease for decades, the essential role of B-lymphocytes was previously identified, partially in an attempt to search for an explanation for the effectiveness of Rituximab in the treatment of the disease [6, 10]. Detection of disease-specific circulating antinephrin autoantibodies in a large proportion of patients with active MCD and FSGS further emphasizes the importance of B-lymphocytes in the pathogenesis of the disease [11, 31]. Since Rituximab induces prolonged B-cells depletion, it may induce prolonged remission. We demonstrated a significant reduction in relapse rate after Rituximab use, and longer time to first relapse, that maintained during long term follow-up. Our results are compatible with previous findings of observational and retrospective studies in the adult population [22, 23, 27, 32].

Although the 2021 KDIGO guidelines reports that Rituximab was effective in inducing remission and reduction of relapses in observational studies performed in patients with SD/FR MCD, since the experience with the drug is limited, the guidelines did not recommend Rituximab over other commonly used immunosuppressants. Moreover, it proposes Cyclophosphamide first in patients with SD/FR MCD, unless previously exposed to the drug or according to patient's preference [1]. However, due to its significant toxicity and side effects, and since Rituximab was associated with reasonable side effects in our cohort, in recent years we practically abandoned Cyclophosphamide use in our center, which we reserve only for extreme cases resistant to treatment. This routine is in line with the current ERA Immunonephrology working group recommendation for Rituximab to be preferred over cyclophosphamide as second line for SD/FR MCD [33].

There is an unmet need for an effective tool to improve decision making about the duration and dosage of Rituximab therapy. In our cohort, Rituximab was given in

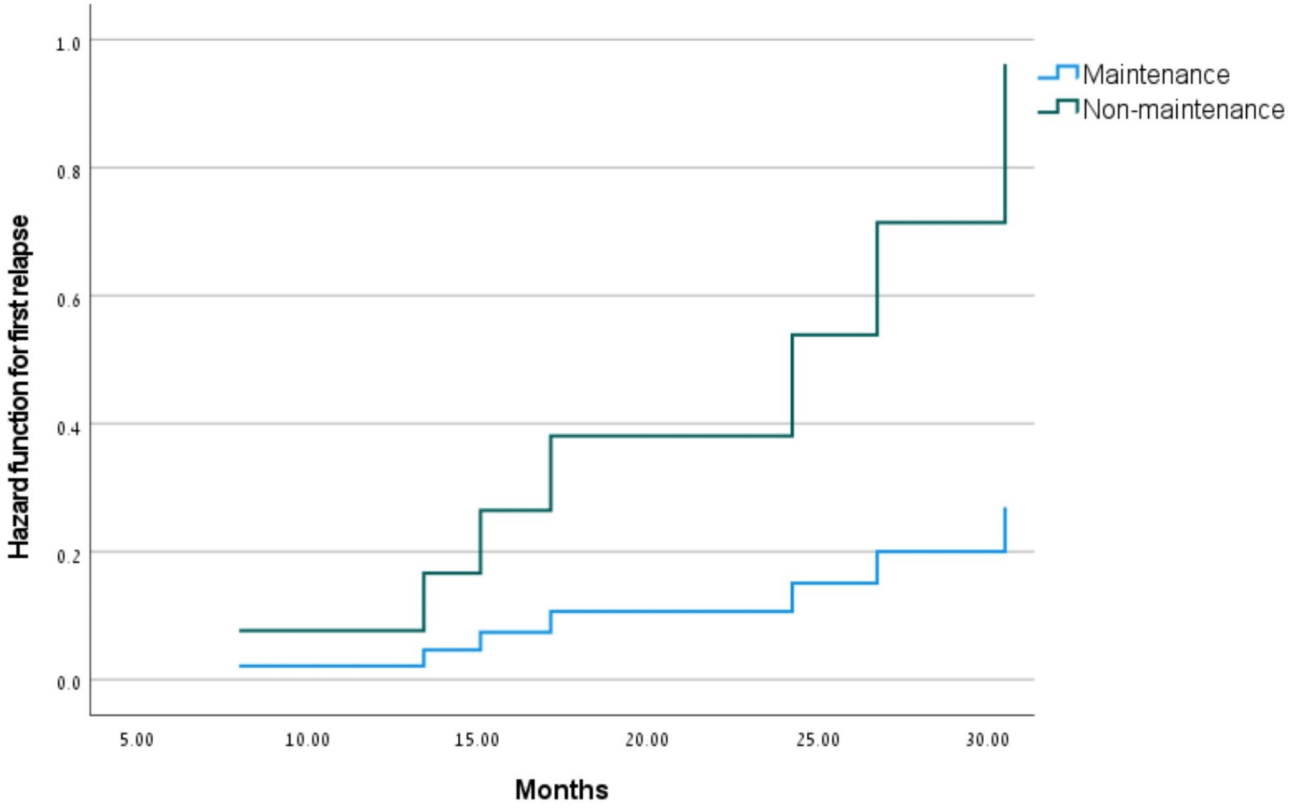

Fig. 4 Cox regression curves for first relapse hazard after first course of Rituximab therapy (Maintenance vs. No-Maintenance)

different maintenance protocols according to the treating nephrologist decision, based partially on disease severity, previous relapse rates and steroids side effects, as well as previous experience to the drug, without an objective tool to guide treatment decisions. Accordingly, 5 patients in our cohort experienced relapse 8–31 months after Rituximab induction, all cases in patients treated before 2019, that driven the treating nephrologists to frequently use maintenance doses since 2020. Adding a maintenance dose in our cohort has proven to be extremely efficient in achieving long term remissions, with a HR of 4.31 for relapse in cases treated with a single induction course compared to those treated with a maintenance dose. Reports on Rituximab recurrent maintenance doses are emerging, however there is no standardized protocol [34, 35]. Recently, Gauckler et al. conducted a comprehensive investigation on the long-term outcomes of Rituximab-treated adult patients with SD, FR and SR nephrotic syndrome, emphasizing the importance of maintenance dosing in sustaining remission [28]. This aligns with our findings, which highlight Rituximab's potential to reduce relapse rates without the continuous use of steroids.

Circulating CD19 + B-cells levels were considered a promising tool to evaluate treatment response and reconstitution of B-lymphocytes [36]. However, although some reported the efficacy of a "CD-19 targeted approach", which takes into consideration CD19 + B-cell level to guide decision making, others failed to demonstrate a correlation between CD19 + B-cells count and clinical response [37, 38]. Therefore, as efficiency was not proved, we do not routinely measure CD19 + B-cells levels to guide clinical decisions. Recent evidence of antinephrin antibodies level correlation with disease activity is encouraging, as it may support clinical decisions in the future [11].

A question arises whether Rituximab can be used as an alternative to corticosteroids, even in the first occurrence of NS, in patients at high risk for steroid toxicity. In our cohort, all patients received corticosteroids to induce remission promptly, and relapses were treated with a combination of corticosteroids and Rituximab, that allowed rapid tapering down. Fenoglio et al. previously reported a case series of 6 patients with MCD treated with Rituximab alone as first line. At 3 months, 3 achieved complete remission, and 2 patients achieved complete remission at 6 and 9 months [15]. This treatment strategy raises two major concerns: leaving these patients nephrotic for several months carries the risk of subjecting them to complications of nephrotic syndrome. Furthermore, since Rituximab is an antibody, its renal clearance increases significantly in patients with NS, compared to a negligible clearance in other populations,

leading to a rapid drop in serum concentration [39]. This is potentially supported by a recent study which demonstrated that a non-selective proteinuria, characterized by urinary excretion of IgG, and consequently of therapeutic monoclonal antibodies, was associated with partial response or no response to rituximab in adults with MCD and FSGS [40]. Therefore, Rituximab administered to patients during active NS may have economic implications as higher doses should probably be used. Consequently, we recommend reserving the strategy of Rituximab as first line therapy only for patients with absolute contraindication to corticosteroids, until further evidence will be available.

While Rituximab was generally safe within our study cohort, it raises concerns regarding response to COVID-19 vaccination. Recent studies have demonstrated that patients receiving Rituximab exhibit a diminished antibody response to both two-dose and three-dose mRNA COVID-19 vaccine regimens, potentially leading to an increased risk of severe breakthrough infections [41, 42]. In our study cohort, the patient infected with COVID-19 had received four doses of messenger ribonucleic acid (mRNA) vaccines prior to infection. Despite this extensive vaccination, the risk associated with Rituximab necessitates careful consideration in clinical practice, emphasizing the need for vigilant monitoring and possibly supplemental protective measures for such individuals.

The study has several limitations. It is a retrospective study performed on a small cohort of patients. However, each case was meticulously examined to obtain as much information as possible. Patients' disease characteristics were different, as both MCD and FSGS were included in the analysis. We looked for differences among them however the cohort was too small to detect such variations. Another limitation is the diverse treatment protocols. Its main strength is the long follow-up time.

Conclusions

Rituximab appears to offer an efficient safe alternative to prolonged steroid treatment in patients with SD/FR NS, with longer remission achieved when an additional maintenance dose is given after the first course. RCTs are needed to confirm its efficacy and safety, define treatment indications and optimal regimen.

Abbreviations

AE	Adverse events
CNI	Calcineurin inhibitors
eGFR	Estimated glomerular filtration rate
FR	Frequent relapsing
FSGS	Focal Segmental Glomerulosclerosis
IQR	Interquartile range
MCD	Minimal change disease
mRNA	Messenger ribonucleic acid
NS	Nephrotic syndrome
RCTs	Randomized clinical trials
SAEs	Serious adverse events
SD	Steroid dependent
SR	Steroid-resistant
uPCR	Urine protein/creatinine ratio

Acknowledgements

We thank Shir Lerner for statistical advise.

Author contributions

O.F., D.A. and O.K. developed the study concept and design. O.F., D.A. and M.E. conducted the data acquisition. O.F. and M.E. drafted the manuscript. O.K., A.G. and D.S. supervised the study. All authors read and approved the final manuscript.

Funding

There was no funding for this study.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study complies with the Declaration of Helsinki and was approved by the ethics committee of Tel Aviv Sourasky Medical Center under protocol TLV-23-0087.

Consent for publication

Need for consent for publication was waived because the claims database was anonymized.

Competing interests

The authors declare no competing interests.

Received: 4 December 2024 / Accepted: 20 February 2025
Published online: 06 March 2025

References

1. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Published online. October 2021. https://kdigo.org/wp-content/uploads/2024/05/KDIGO-2021-Glomerular-Diseases-Guideline_English_2024-Chapter-Updates.pdf
2. Waldman M, Crew RJ, Valeri A, et al. Adult minimal-change disease: clinical characteristics, treatment, and outcomes. Clin J Am Soc Nephrol. 2007;2(3):445–53. https://doi.org/10.2215/CJN.03531006.
3. Tedesco M, Mescia F, Pisani I, et al. The role of rituximab in primary focal segmental glomerular sclerosis of the adult. Kidney Int Rep. 2022;7(8):1878–86. https://doi.org/10.1016/j.ekir.2022.05.024.
4. Troyanov S, Wall CA, Miller JA, Scholey JW, Cattran DC. Focal and segmental glomerulosclerosis: definition and relevance of a partial remission. J Am Soc Nephrol. 2005;16(4):1061–8. https://doi.org/10.1681/ASN.2004070593.
5. Kyrieleis HAC, Löwik MM, Pronk I, et al. Long-term outcome of biopsy-proven, frequently relapsing minimal-change nephrotic syndrome in children. Clin J Am Soc Nephrol. 2009;4(10):1593–600. https://doi.org/10.2215/CJN.05691108.
6. Bakker WW, van Luijk WH. Do Circulating factors play a role in the pathogenesis of minimal change nephrotic syndrome? Pediatr Nephrol. 1989;3(3):341–9. https://doi.org/10.1007/BF00858545.
7. Candelier JJ, Lorenzo HK. Idiopathic nephrotic syndrome and serum permeability factors: a molecular Jigsaw puzzle. Cell Tissue Res. 2020;379(2):231–43. https://doi.org/10.1007/s00441-019-03147-y.
8. van den Berg JG, Weening JJ. Role of the immune system in the pathogenesis of idiopathic nephrotic syndrome. Clin Sci (Lond). 2004;107(2):125–36. https://doi.org/10.1042/CS20040095.
9. Hackl A, Zed SEDA, Diefenhardt P, Binz-Lotter J, Ehren R, Weber LT. The role of the immune system in idiopathic nephrotic syndrome. Mol Cell Pediatr. 2021;8(1):18. https://doi.org/10.1186/s40348-021-00128-6.

10. Liu J, Guan F. B cell phenotype, activity, and function in idiopathic nephrotic syndrome. Pediatr Res. 2023;93(7):1828–36. https://doi.org/10.1038/s41390-022-02336-w.
11. Hengel FE, Dehde S, Lassé M, et al. Autoantibodies targeting nephrin in podocytopathies. N Engl J Med Published Online May. 2024;25:NEJMoa2314471. https://doi.org/10.1056/NEJMoa2314471.
12. Rougé L, Chiang N, Steffek M, et al. Structure of CD20 in complex with the therapeutic monoclonal antibody rituximab. Science. 2020;367(6483):1224–30. https://doi.org/10.1126/science.aaz9356.
13. Selewski DT, Shah GV, Mody RJ, Rajdev PA, Mukherji SK. Rituximab (Rituxan). AJNR Am J Neuroradiol. 2010;31(7):1178–80. https://doi.org/10.3174/ajnr.A2142.
14. Avivi I, Stroopinsky D, Katz T. Anti-CD20 monoclonal antibodies: beyond B-cells. Blood Rev. 2013;27(5):217–23. https://doi.org/10.1016/j.blre.2013.07.002.
15. Fenoglio R, Sciascia S, Beltrame G, et al. Rituximab as a front-line therapy for adult-onset minimal change disease with nephrotic syndrome. Oncotarget. 2018;9(48):28799–804. https://doi.org/10.18632/oncotarget.25612.
16. Ahn YH, Kim SH, Han KH, et al. Efficacy and safety of rituximab in childhood-onset, difficult-to-treat nephrotic syndrome: A multicenter open-label trial in Korea. Medicine. 2018;97(46):e13157. https://doi.org/10.1097/MD.0000000000001315717.
17. Iijima K, Sako M, Nozu K, et al. Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet. 2014;384(9950):1273–81. https://doi.org/10.1016/S0140-6736(14)60541-9.
18. Ravani P, Rossi R, Bonanni A, et al. Rituximab in children with Steroid-Dependent nephrotic syndrome: A multicenter, Open-Label, noninferiority, randomized controlled trial. J Am Soc Nephrol. 2015;26(9):2259–66. https://doi.org/10.1681/ASN.2014080799.
19. Basu B, Sander A, Roy B, et al. Efficacy of rituximab vs tacrolimus in pediatric Corticosteroid-Dependent nephrotic syndrome: A randomized clinical trial. JAMA Pediatr. 2018;172(8):757. https://doi.org/10.1001/jamapediatrics.2018.1323.
20. Boumediene A, Vachin P, Sendeyo K, et al. NEPHRUTIX: A randomized, double-blind, placebo vs Rituximab-controlled trial assessing T-cell subset changes in minimal change nephrotic syndrome. J Autoimmun. 2018;88:91–102. https://doi.org/10.1016/j.jaut.2017.10.006.
21. Chan EY, Sinha A, Yu ELM, et al. An international, multi-center study evaluated rituximab therapy in childhood steroid-resistant nephrotic syndrome. Kidney Int. 2024;106(6):1146–57. https://doi.org/10.1016/j.kint.2024.09.011.
22. Munyentwali H, Bouachi K, Audard V, et al. Rituximab is an efficient and safe treatment in adults with steroid-dependent minimal change disease. Kidney Int. 2013;83(3):511–6. https://doi.org/10.1038/ki.2012.444.
23. 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 Dialysis Transplantation. 2014;29(4):851–6. https://doi.org/10.1093/ndt/gft312.
24. Guitard J, Hebral AL, Fakhouri F, et al. Rituximab for minimal-change nephrotic syndrome in adulthood: predictive factors for response, long-term outcomes and tolerance. Nephrol Dialysis Transplantation. 2014;29(11):2084–91. https://doi.org/10.1093/ndt/gfu209.
25. 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. https://doi.org/10.1097/MD.0000000000000300.
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. https://doi.org/10.1007/s10157-015-1139-6.
27. DaSilva I, Huerta A, Quintana L, 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. https://doi.org/10.1007/s40259-017-0221-x.
28. Gauckler P, Matyjek A, Kapsia S, et al. Long-Term outcomes of Rituximab-Treated adult patients with podocytopathies. J Am Soc Nephrol Published Online Oct. 2024;16. https://doi.org/10.1681/ASN.0000000520.
29. Assistance Publique - Hôpitaux de Paris. RItuximab from the first episode of idiopathic nephrotic syndrome (RIFIREINS). Published Online July 13, 2021. https://clinicaltrials.gov/study/NCT03970577
30. Inker LA, Eneanya ND, Coresh J, et al. New Creatinine- and Cystatin C–Based equations to estimate GFR without race. N Engl J Med. 2021;385(19):1737–49. https://doi.org/10.1056/NEJMoa2102953.
31. Raglianti V, Angelotti ML, Cirillo L, et al. Anti-slit diaphragm antibodies on kidney biopsy identify pediatric patients with steroid-resistant nephrotic syndrome responsive to second-line immunosuppressants. Kidney Int. 2024;106(6):1124–34. https://doi.org/10.1016/j.kint.2024.09.006.
32. Xue C, Yang B, Xu J, 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. https://doi.org/10.1093/ckj/sfaa191.
33. Mirioglu S, Daniel-Fischer L, Berke I, et al. Management of adult patients with podocytopathies: an update from the ERA immunonephrology working group. Nephrol Dialysis Transplantation. 2024;39(4):569–80. https://doi.org/10.1093/ndt/gfae025.
34. Saito E, Oura A, Kyo T, et al. Relapse during and after regular single-dose rituximab treatment in adult patients with steroid-dependent nephrotic syndrome. Clin Exp Nephrol. 2024;28(11):1082–9. https://doi.org/10.1007/s10157-024-02508-4.
35. Taguchi S, Ohtake T, Mochida Y, et al. Efficacy of repeat-dose rituximab maintenance therapy for minimal change disease in adults. Clin Exp Nephrol. 2020;24(12):1132–9. https://doi.org/10.1007/s10157-020-01943-3.
36. Del Vecchio L, Allinovi M, Rocco P, Brando B. Rituximab therapy for adults with nephrotic syndromes: standard schedules or B Cell-Targeted therapy? JCM. 2021;10(24):5847. https://doi.org/10.3390/jcm10245847.
37. Ramachandran R, Bharati J, Nada R, Minz R, Kohli HS. Rituximab in maintaining remission in adults with podocytopathy. Nephrology. 2020;25(8):616–24. https://doi.org/10.1111/nep.13717.
38. Fernandez-Fresnedo G, Segarra A, González E, et al. Rituximab treatment of adult patients with Steroid-Resistant focal segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2009;4(8):1317–23. https://doi.org/10.2215/CJN.00570109.
39. Counsilman CE, Jol–van Der Zijde CM, Stevens J, Cransberg K, Bredius RGM, Sukhai RN. Pharmacokinetics of rituximab in a pediatric patient with therapy-resistant nephrotic syndrome. Pediatr Nephrol. 2015;30(8):1367–70. https://doi.org/10.1007/s00467-015-3120-8.
40. Allinovi M, Trivioli G, Lugli G, et al. Proteinuria selectivity index predicts response to rituximab in adults with minimal change disease and focal segmental glomerulosclerosis. Nephrol Dial Transpl. 2022;37(4):789–91. https://doi.org/10.1093/ndt/gfab323.
41. Ma AL, Leung D, Chan EY, et al. Antibody responses to 2 doses of mRNA COVID-19 vaccine in pediatric patients with kidney diseases. Kidney Int. 2022;101(5):1069–72. https://doi.org/10.1016/j.kint.2022.01.035.
42. Leung D, Chan EY, Mu X, et al. Humoral and cellular immunogenicity of 3 doses of BNT162b2 in children with kidney diseases. Kidney Int Rep. 2023;8(11):2356–67. https://doi.org/10.1016/j.ekir.2023.08.014.

Publisher's note