ISSN-E: 18735347-02779536

# Rituximab Treatment Outcomes in Children with Steroid Resistant Nephrotic Syndrome

**Nouf Alyaseen**

**pediatric nephrology**

**KSMC,neefan@hotmail.com**

**Khalid Alsaran**

**pediatric nephrology**

**KSMC,Kl-saran@moh.gov.sa**

**Abdulaziz Alshathri**

**pediatric nephrology**

**ksmc,aalshathri@moh.gov.sa**

**Khalid mirza**

**pediatric nephrology**

**ksmc,drmkhalid61@hotmail.com**

**Wala felemban**

**pediatric nephrology**

**walaa.felemban@gmail.com**

ISSN-E: 18735347-02779536

## Abstract

Background

Idiopathic steroid resistant nephrotic syndrome (SRNS) in children is often difficult to treat. Calcineurin inhibitors comprise the first-line induction therapy but have significant side effects. Rituximab has been used successfully in treatment for refractory SRNS.

**Objectives**

To determine the efficacy and safety of rituximab for treating children with SRNS over a relatively long follow-up period.

Patients and methods

A retrospective cohort study was conducted as all children with idiopathic SRNS who failed to achieve remission after 4 weeks of prednisolone 60 mg/m2/day were enrolled. All patients underwent renal biopsies and genetic studies before rituximab treatment. Intravenous rituximab was administered weekly at 375 mg/m2 for four doses.

Response to treatment was defined as maintaining remission with no relapse for 1 year.

**Results**

A total of 21 patients (male: female=15:6) were followed-up for 1 year. Twelve (57.1%) patients showed no relapse in the first year and six (28.6%) had no remission, but three (50%) of these six patients developed ESRD. The histopathological findings for the patients who respond to rituximab therapy (no relapse in the first 1 year) were: Focal segmental glomerulosclerosis“FSGS” (25%) and minimal change (66.7%). The histopathological findings for the patients who did not respond to rituximab therapy (no remission in the first year) were as follows: FSGS (83.3%) and diffuse change (16.7%). There were no side effects from rituximab therapy noted during the follow-up period.

**Conclusion**

Rituximab was found to be effective and relatively safe for idiopathic SRNS, but large controlled clinical trials with long-term follow-up are required for confirmation.



Keywords:

Rituximab, Steroid Resistant Nephrotic Syndrome, Pediatric Nephrology, Immunosuppressive Therapy, Nephrotic Syndrome Outcomes, Childhood Kidney Disease, B-cell Depletion Therapy.

## Introduction

Childhood idiopathic nephrotic syndrome is responsive to steroid therapy in the majority of cases. However, children with steroid resistantnephrotic syndrome (SRNS) account for approximately 10%–15% of childhood idiopathic nephrotic syndrome cases[1]. SRNS is defined as a failure to achieve remission after 4weeks of prednisolone at 60 mg/m$^2$/day (full dose) [2]. Treatment of SRNS remains a challenge for pediatric nephrologists. Among available treatment options, calcaneus in inhibitors (CNI) are most successful in inducing remiss SRNS but have a significant burden of nephrotoxicity and prolonged duration of treatment[3,4]. High-dose intravenous steroids, mycophenolate mofetil, and alkylating agents have also been used with less success. Children who failed to respond to treatment progress to end-stage renal disease (ESRD)5. The treatment protocol for refractory SRNS is not well established6.In the last decade, rituximab has been increasingly used for the management of idiopathic SRNS7, with widely variable response rates in children. There is a real need for a relatively safe drug that does not require frequent administration. In recent years, rituximab has been shown to be an efficient treatment for idiopathic nephrotic syndrome, but few studies have reported its efficacy and safety. This study assessed the efficacy and safety of rituximab for treating children with SRNS over a relatively long follow-up assessment period, expressed as the number of relapses in the first year after administration of the last doses well as to discuss the role of the histopathological pattern in the outcome of these patients.

## Materials and methods

A retrospective cohort study was conducted at Pediatric Hospital of King Saud Medical City (KSMC), Riyadh, Kingdom of Saudi Arabia (KSA). KSMC belongs to the Ministry of Health, is one of the tertiary care centers in Riyadh, and is considered to be the largest medical cities in the KSA. Pediatric Hospital is one of the main hospitals in KSMC.

This study included all patients diagnosed with idiopathic SRNS (initial or late) from January 2013 to September 2022 provided that they were >1 year and ≤14 years old as well as having negative genetic renal panel results. Patients who did not complete the follow-up for 1 years and those who did not complete the full rituximab dose were excluded from the study.

**A data-collection form was constructed to collect the following medical records data.**

a) Patient’s characteristics: age, sex, nationality, urine for protein/creatinine ratio, urine

analyses, serum albumin, and serum creatinine.

b) Disease characteristics: histopathological findings, immune-suppressive drug received

before four doses of rituximab.

c) Outcome: number of relapses after rituximab, side effects of rituximab

(Infusion-related reaction, cytopenia, infections, major respiratory, and cardiovascular

events).

The study proposal was approved by the Institutional Review Board (IRB) of the local Research and Ethics Committee at KSMC, Riyadh, KSA.
SPSS software version 28(IBM SPSS Statistics for Windows, Armonk, NY) was used for data management. Descriptive statistics are presented as frequency and percentage.

## Results

A total of 21 patients (male: female=15:6) were enrolled in the study and finished at least 1 year of follow-up. Twelve (57.1%) patients showed no relapse in the first year, three (14.3%) patients developed only one relapse in the first year, and six (28.6%) patients had no remissions [three of the six (50%) developed ESRD and one of the six (16.7%) developed chronic kidney disease (CKD)]. The histopathological findings for the patients who responded to rituximab therapy (no relapse in the first 1 year) were as follows: Focal segmental glomerulosclerosis "(FSGS)" (25%), minimalchange (66.7%) and renal biopsy was not performed in one patient because of logistic reasons. The histopathological findings for the patients who did not respond to rituximab therapy (no remission in the first year) were as follows: FSGS (83.3%) and diffuse change (16.7%). The four patients who developed ESRD/CKD were in the FSGS category. No side effects from rituximab therapy were noted during the follow-up period.

## Discussion

SRNS is a rare disease, and the choice of treatment modalities differs greatly among pediatric nephrologists according to each patient's needs and their nephrologist's preferences.[10] In recent years, rituximab has been increasingly utilized for the treatment of idiopathic SRNS, with variable results in pediatric patients.[11]
In this study, 57.1% of pediatric patients diagnosed with idiopathic SRNS showed no relapse in the first year of treatment with rituximab, 14.3% developed only one relapse in the first year, and 28.6% had no remission; among the patients who progressed,50% developed ESRD, and one (16.7%) patient developed CKD. These findings agree with those reported in numerous studies that have shown the efficacy of rituximab therapy in pediatric patients with SRNS.[12-15]
In the current study, rituximab was administered weekly in four doses of 375 mg/m$^2$each. Previously, rituximab's success rate reportedly depended on the dosing strategy and duration of followup.[20]In patients who received one dose of 375 mg/m$^2$, 25%–40% were in sustained remission at 12–17 months,[21] whereas among patients who received 2–4 doses of rituximab, >70% were in sustained remission at 6–38 months.[22]However, the association between the number of rituximab doses and responses has not been confirmed.[20]

In our study, 25% of the patients were classified as FSGS and 66.7% as minimal change, whereas the histopathological findings for the patients who did not respond to rituximab the rapy but show edno remission in the first year were classified as either FSGS (83.3%) or diffuse change (16.7%). In a recent Turkish study, the overall remission rate in patients with SRNS was 27%. FSGS was diagnosed in six patients and the remission rate was 33% in this group of patients.[23] However, the effect of histological subtype on the response to rituximab treatment remains unclear[23]; some studies reported that rituximab was effective in about half of their patients with FSGS,[24] whereas others observed that FSGS was associated with a higher probability of nonresponse.[25, 26]

In accordance with the findings of most studies,[11, 23]our study found that rituximab was generally well-tolerated, with no side effects noted during the follow-up period. However, some studies have reported mild infusion-related reactions, which typically resolved with antipyretics and antihistamines.[27–29]Guigonis et al. (2008) reported severe anaphylactic reactions or hypotension in a very few cases.[30]The long-term safety of rituximab remains questionable because it might be associated with more serious side effects.[11]
Two important limitations of this study were the small sample size and single-center site, which might limit the applicability of the findings to broader populations.
In conclusion, rituximab was found to be an effective and safe therapy for idiopathic SRNS. However, large controlled clinical trials with long-term follow-up are required to confirm the efficacy and safety of rituximab for treating children with SRNS.

**References**

Tarshish P, Tobin JN, Bernstein J, Edelmann Jr CM (1997). Prognostic significance of the early course of minimal change nephrotic syndrome: report of the international study of kidney disease in children. J. Am. Soc. Nephrol. 8:769-776. doi: 10.1681/ASN.V85769.

Niaudet P (1994). Treatment of chldhood steroid-resistant idiopathic nephrosis with a combination of cyclosporine and prednisone. French society of pediatric nephrology. J. Pediatr. 125:981-986. doi: 10.1016/s0022-3476(05)82020-7.

Liu ID, Willis NS, Craig JC, Hodson EM (2019). Interventions for idiopathic steroid-resistant nephrotic syndrome in children. Cochrane Database Syst. Rev. 2019:CD003594. doi: 10.1002/14651858.CD003594.pub6.

El-Husseini A, El-Basuony F, Mahmoud I, Sheashaa H, Sabry A, Hassan R, et al (2005). Long-term effects of cyclosporine in children with idiopathic nephrotic syndrome: a single-centre experience. Nephrol. Dial. Transplant. 20:2433-2438. doi: 10.1093/ndt/gfi059.

Kang HG (2011). Treatment of steroid-resistant pediatric nephrotic syndrome. Korean J. Pediatr.54:317-321. doi:10.3345/kjp.2011.54.8.317.

Trautmann A, Schnaidt S, Lipska-Ziętkiewicz BS, Bodria M, Ozaltin F, Emma F, et al (2017). Long-term outcome of steroid-resistant nephrotic syndrome in children. J. Am. Soc. Nephrol. 28:3055-3065. doi: 10.1681/ASN.2016101121.

Suri M, Tran K, Sharma AP, Filler G, Grimmer J (2008). Remission of steroid-resistant nephrotic syndrome due to focal and segmental glomerulosclerosis using rituximab. Int. Urol. Nephrol. 40:807-810. doi: 10.1007/s11255-008-9393-0.

Bagga A, Sinha A, Moudgil A (2007). Rituximab in patients with the steroid-resistant nephrotic syndrome. N. Engl. J. Med. 356:2751-2752. doi: 10.1056/NEJMc063706.

Nakayama M, Kamei K, Nozu K, Matsuoka K, Nakagawa A, Sako M, Iijima K (2008). Rituximab for refractory focal segmental glomerulosclerosis. Pediatr. Nephrol. 23:481-485. doi: 10.1007/s00467-007-0640-x.

Lee JM, Kronbichler A, Shin JI, Oh J (2021). Current understandings in treating children

with steroid-resistant nephrotic syndrome. Pediatr. Nephrol. 36:747-761. doi:

10.1007/s00467-020-04476-9.

Kallash M, Smoyer WE, Mahan JD (2019). Rituximab use in the management of childhood nephrotic syndrome. Front. Pediatr. 7:178. doi: 10.3389/fped.2019.00178.

Fujinaga S, Hirano D, Nishizaki N, Kamei K, Ito S, Ohtomo Y, et al (2010). Single infusion of rituximab for persistent steroid-dependent minimal-change nephrotic syndrome after long-term cyclosporine.Pediatr. Nephrol. 25:539-544.

Sellier-Leclerc AL, Baudouin V, Kwon T, Macher MA, Guérin V, Lapillonne H, et a

(2012)l. Rituximab in steroid-dependent idiopathic nephrotic syndrome in childhood–follow-up after CD19 recovery.Nephrol. Dial. Transplant. 27:1083-1089.

Hoxha E, Stahl RA, Harendza S (2011). Rituximab in adult patients with immunosuppressive-dependent minimal change disease.Clin. Nephrol. 76:151-158.

Kemper MJ, Gellermann J, Habbig S, Krmar RT, Dittrich K, Jungraithmayr T,et al.

(2012) Long-term follow-up after rituximab for steroid-dependent idiopathic nephrotic syndrome.Nephrol. Dial. Transplant. 27:1910-1915.

Guigonis v, Dallocchio A, Baudouin V, Dehennault M, Hachon-Le Camus C, Afanetti, et al (2008). Rituximab treatment for severe steroid- or cyclosporine-dependent nephrotic

syndrome: a multicentric series of 22 cases.Pediatr. Nephrol. 23:1269-1279.

Gulati A, Sinha A, Jordan SC, Hari P, Dinda AK, Sharma S, et al (2010). Efficacy and safety of treatment with rituximab for difficult steroid-resistant and -dependent nephrotic syndrome: multicentric report. Clin. J. Am. Soc. Nephrol. 5:2207-2212.

Sinha A, Bhatia D, Gulati A, Hari P, Bagga A (2012). The 45th Annual Meeting on

September 6th–8th 2012, Krakow, Poland. Pediatr. Nephrol. 27:1605-1829.

Ito S, Kamei K, Ogura M, Udagawa T, Fujinaga S, Saito M, et al (2013). Survey of rituximab treatment for childhood-onset refractory nephrotic syndrome. Pediatr. Nephrol.

28:257-264.

Sinha A, Bagga A (2013). Rituximab therapy in nephrotic syndrome: implicationsforpatients'management. Nat. Rev. Nephrol. 9:154-169.

Kamei K, Ito S, Nozu K, Fujinaga S, Nakayama M, Sako M et al (2009). Single dose of rituximab for refractory steroid-dependent nephrotic syndrome in children. Pediatr. Nephrol. 24:1321-1328.

Kisner T, Burst V, Teschner S, Benzing T, Kurschat CE. Rituximab treatment for adults with refractory nephrotic syndrome: a single-center experience and review of the literature.Nephron Clin. Pract. 2012; 120:c79-c85.

Girişgen İ, Yüksel S, Pekal Y (2020). Rituximab experience in children with nephrotic syndrome: what have we observed differently. Turk Pediatri Ars. 55:60-66.

Chan CY, Liu ID, Resontoc LP, Ng KH, Chan YH, Lau PY-W, et al (2016). T Lymphocyte activation markers as predictors of responsiveness to rituximab among patients with FSGS.Clin. J. Am. Soc. Nephrol. 11:1360-1368.

Sinha A, Bhatia D, Gulati A,Rawat M, Dinda AK, Hari P, et al (2015). Efficacy and safety of rituximab in children with difficult-to-treat nephrotic syndrome.Nephrol. Dial. Transplant. 30:96-106.

Iijima K, Sako M, Kamei K, Nozu K *2018). Rituximab in steroid-sensitive nephrotic syndrome: lessons from clinical trials. Pediatr. Nephrol. 33:1449-1455.

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

Bonanni A, Calatroni M, D'Alessandro M, Signa S, Bertelli E, Cioni M, et al (2018). Adverse events linked with the use of chimeric and humanized anti-CD20 antibodies in children with idiopathic nephrotic syndrome. Br. J. Clin. Pharmacol. 84:1238-1249.

Kamei K, Ogura M, Sato M, Ito S, Ishikura K (2018). Infusion reactions associated with rituximab treatment for childhood-onset complicated nephrotic syndrome. Pediatr. Nephrol. 33:1013-1018.

Guigonis V, Dallocchio A, Baudouin V, Dehennault M, Hachon-Le Camus C, Afanetti M, et al (2008). Rituximab treatment for severe steroid- or cyclosporine-dependent nephrotic syndrome: a multicentric series of 22 cases. Pediatr. Nephrol. 23:1269-1279.

## Appendix

### Table1. Renal biopsy findings in the patients who received rituximab

| Pathology | Number of patients | Response | Onerelapse | No response |
|---|---|---|---|---|
| FSGS | 10 | 3 (25%) | 2 (66.7%) | 5 (83.3%) |
| MCD | 8 | 8 (66.7%) | 0 | 0 |
| Membranous nephropathy | 1 | 0 | 0 | 1 (16.7%) |
| Not done | 2 | 1 (8.3%) | 1 (33.3%) | 0 |
| total | 21 | 12 | 3 | 6 |

Values are presented as number and percentage (%).FSGS: focal segmental glomerulosclerosis;MCD: minimal change disease

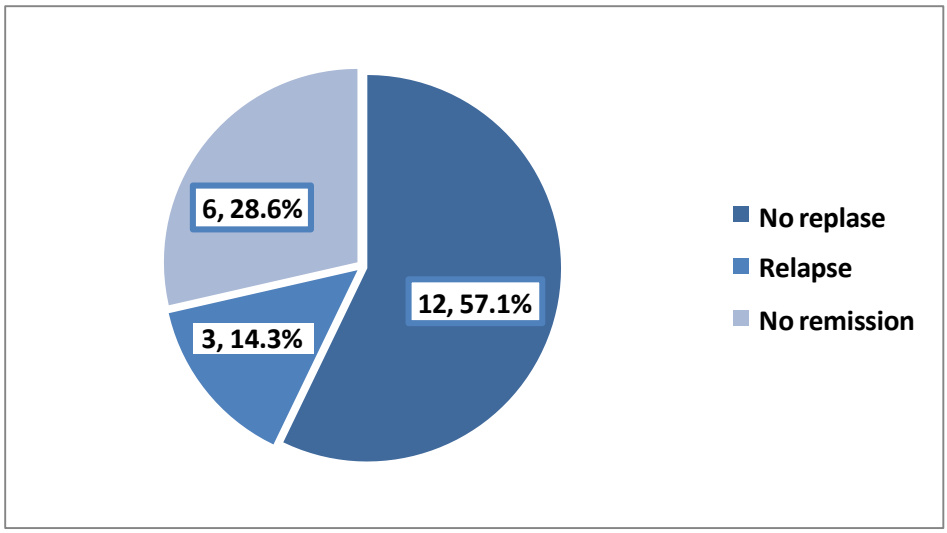


**Figure 1: Outcomes of rituximabfortreating steroid resistant nephrotic syndromein children (n=21)**

**Table1. Renal biopsy findings in the patients who received rituximab**

| Pathology | Number of patients | Response | Onerelapse | No response |
|---|---|---|---|---|
| FSGS | 10 | 3 (25%) | 2 (66.7%) | 5 (83.3%) |
| MCD | 8 | 8 (66.7%) | 0 | 0 |
| Membranous nephropathy | 1 | 0 | 0 | 1 (16.7%) |
| Not done | 2 | 1 (8.3%) | 1 (33.3%) | 0 |
| total | 21 | 12 | 3 | 6 |

Values are presented as number and percentage (%).FSGS: focal segmental glomerulosclerosis;MCD: minimal change disease

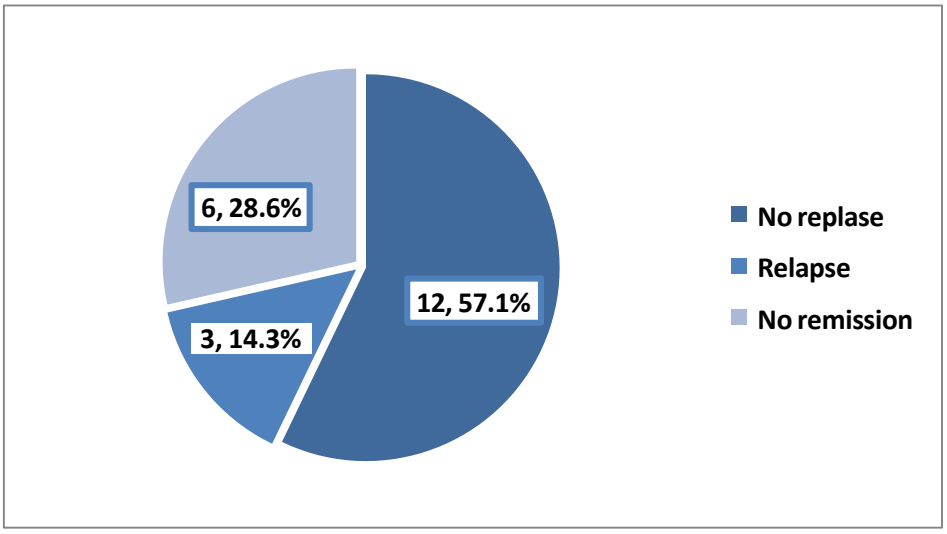


**Figure 1: Outcomes of rituximabfortreating steroid resistant nephrotic syndromein children (n=21)**