Vol 45 (2) June , 2021

Print: ISSN 0304 4904
Online: ISSN 2305-820X

# PAKISTAN PEDIATRIC JOURNAL

A JOURNAL OF PAKISTAN PEDIATRIC ASSOCIATION

Indexed in EMBASE/Excerpta Medica, Index Medicus WHO
IMEMR & Global Health/CAB Abstracts and UDL-EDGE Products and Services

www.pakpedsjournal.org.pk

http://www.pakmedinet.com/PPJ

**ORIGINAL ARTICLE**

# A Single Center Experience of Rituximab in Treating Refractory Steroid Dependent and Steroid Resistant Childhood Nephrotic Syndrome

**MUHAMMAD IMRAN, HASHIM RAZA, KHURAM RASHID, Shahid Ishaq, Mudassar Adnan**

Pak Pediatr J 2021; **45(2):** 154-60

**Correspondence to:**

**Muhammad Imran,**
Department of Pediatric Nephrology at the Children's Hospital & the Institute of Child Health, Multan, Pakistan

**E-mail:** imranpedneph@gmail.com

Received 14th April 2021;
Accepted for publication
26th May 2021

**ABSTRACT**

**Objective:** To determine the efficacy of Rituximab (RTX) in refractory steroid dependent and steroid resistant childhood nephrotic syndrome.

**Study Design:** Prospective single-arm interventional study

**Place and Duration:** Department of Pediatric Nephrology at the Children's Hospital & the Institute of Child Health, Multan, Pakistan from June 2019 to November 2020.

**Materials and Methods:** Total 26 patients age 3.25-11.25 years of either gender were included; 17 children with refractory steroid dependent nephrotic syndrome (SDNS) and 09 children with refractory steroid resistant nephrotic syndrome (SRNS). After induction of remission, refractory SDNS patients were given two pulses of intravenous RTX two weeks apart. The children with SRNS were given 4 weekly pulses of RTX with concomitant prednisolone; 12 weeks at they were categorized as either complete responder, partial responder, or non-responder. All the patients were followed up to 18 months to look for long-term response and any complications.

**Results:** Mean age of the patients was 6.91 $\pm$ 2.40 years, and males constituted 61.54% of the study participants. All 17 SDNS patients remained relapse free for 10 months to more than 12 months following RTX treatment. On the other hand, only one patient (11.11%), out of total 09 patients with refractory SRNS, achieved complete remission**,** and 03 (33.33%) patients went into partial remission, while 05 (55.55%) were resistant to RTX also. Safety profile of RTX was excellent.

**Conclusion:** Rituximab is a safe and effective option for difficult-to-treat SDNS children.

**Key Words**: *Steroid resistant nephrotic syndrome, Steroid dependent nephrotic syndrome children, Rituximab, Focal segmental glomerulosclerosis*.

## INTRODUCTION

Idiopathic nephrotic syndrome is the most common glomerular disease in children and is characterized by heavy proteinuria, hypoalbuminemia and progressive generalized edema.[1] About 80-90% of cases respond to steroid therapy and are labeled steroid sensitive

nephrotic syndrome (SSNS) while 10-20% are steroid resistant nephrotic syndrome (SRNS).[2] About 60-80% of the SSNS patients have a relapsing disease; of these about 60% have a frequently relapsing course or are steroid dependent nephrotic syndrome (SDNS). Both SDNS and SRNS patients pose treatment challenges. Patients with SDNS may go into prolonged remission with various immunosuppressive agents like cyclophosphamide (CP); an alkylating agent, levamisole (LEV); an anti-helminthic with immunomodulating effects, cyclosporine A (CysA) or tacrolimus (TAC); calcineurin inhibitors (CNIs), or mycophenolate mofetil (MMF); a de novo purine synthesis inhibitor etc.[3,4] Different studies show that about 50-60% patients with SRNS may also respond to CNIs, MMF or methylprednisolone pulse therapy with complete or partial remission.[5,6] Some SDNS patients, over a period of time, start relapsing on high doses of alternate day prednisolone plus the above mentioned immunosuppressives. Similarly, some SRNS patients, who did initially respond to combined immunosuppressive treatment, ultimately become unresponsive to all such treatment modalities. These difficult to treat patients are labeled refractory SDNS and refractory SRNS and predict poor renal outcomes if remission is not achieved by some means.[7] A cohort study of 1354 SRNS patients enrolled in the Podo Net Registry in Europe showed that 10-year end-stage renal disease (ESRD)-free survival rate was 94%, 72%, and 43% in children with complete remission, partial remission, and no remission, respectively.[8]

Rituximab (RTX) is a chimeric anti-CD20 monoclonal antibody which depletes B-cells and may delay or prevent relapses in SDNS.[9,10] However, efficacy of RTX as an initial inducing agent in SRNS or as a rescue therapy in refractory SRNS remains uncertain.[11,12] Some initial studies[13,14] showed promising response of rituximab in refractory SRNS children, but other studies could not show encouraging results.[15,16]

There looks to be a lack of local published studies about the efficacy of rituximab in our children with difficult-to-treat NS. Therefore, this study was conducted to elucidate the role of RTX in refractory SDNS and refractory SRNS children coming to our hospital.

## MATERIAL AND METHODS

This prospective interventional single-arm study was conducted at the Department of Pediatric Nephrology, the Children's Hospital & the Institute of Child Health, Multan, Pakistan from June 2019 to November 2020 after approval from the institutional ethical review committee. We enrolled a total 26 patients aged 3-12 years of either gender; 17 refractory SDNS and 09 refractory SRNS patients (06 initial SRNS and 03 late non-responders). All these patients were, previously, treated with steroids and various alternative immunosuppressive medications like cyclophosphamide, cyclosporine A tacrolimus and mycophenolate mofetil. But, they were either still relapsing while on these medications, or were not responding to these drugs.

All SRNS children had undergone renal biopsies. Seven patients showed focal segmental glomerulosclerosis (FSGS), and 02 patients showed mesangioproliferative glomerulonephritis (MesPGN) with IgM nephropathy (IgMN) as the underlying histopathologic lesion. Two SDNS patients were also biopsied due to their parent's concern and both showed FSGS.

All SDNS patients were first re-induced with prednisolone 2 mg/kg/day. After achieving remission, they were given 02 intravenous RTX pulses (375-400mg/$m^2$) two weeks apart. Prednisolone was then switched to 1.5 mg/kg every other day for 4 weeks and then tapered and stopped over the next 8 weeks.

All SRNS patients were given 04 RTX pulses 1 week apart with concomitant prednisolone 1 mg/kg/day for the first 4 weeks and then in the same dose every other day for the next 8 weeks. Response to the treatment was assessed with daily monitoring of proteinuria by dipsticks at home and regular follow up every 2-4 weeks. According to the response to treatment, patients were categorized as complete responder, partial responder, and non-responder (see operational definitions section)

All the patients were given RTX infusion as per desensitization protocol and were intensively monitored during the infusion with cardiac monitor and pulse oximeter to look for any infusion related untoward reactions (with documentation of

cytokine release syndrome). They were followed up for at least 12 months and up to 18 months to look for the continued response to treatment as well as any long-term complications and side effects related to RTX. All patients were also given alternate day cotrimoxazole to prevent Pneumocystis carinii pneumonia. Monitoring included fortnightly CBC and reporting by parents of any danger signs of infections like fever, lethargy, drowsiness, severe cough, respiratory distress, diarrhea, vomiting everything, and seizures etc. We could not monitor immunoglobulin levels or various lymphocytes subsets like CD3, CD4, CD8, CD19, or CD20 due to their high cost.

All the data were recorded on a pre-designed proforma. Data were analyzed using the statistical software IBM SPSS-22. Quantitative variables are presented as mean $\pm$ SD, median, range and qualitative variables as frequency and percentages. Data was stratified with respect to age groups, category of SRNS and histopathological lesions to determine the effect on response to Rituximab therapy.

**Operational definitions**

**Remission:** Nil or trace proteinuria on dipstick for 3 consecutive days

**Partial remission:** Resolution of edema but persistent 2+ proteinuria after a standardized treatment protocol

**No remission:** Persistent edema and 3+ or more proteinuria after a standardized treatment protocol

**Relapse:** Recurrence of proteinuria 2+ or more for 3 consecutive days after the patient had gone into remission

**SDNS:** Two consecutive relapses while still on a dose of steroid, usually during tapering, or within two weeks of stopping steroids.

**Refractory SDNS:** A patient who continues to relapse while on high alternate day dose of steroid (1.0-1.5 mg/kg) plus another immunosuppressive medicine like CP, CNIs, or MMF.

**SRNS:** A patient who does not achieve complete remission after 4 weeks of oral prednisolone 2 mg/kg/ day.

**Late non-responder/Late SRNS:** A patient who initially ran a steroid sensitive course but relapsed and then could not achieve remission with full dose of prednisolone (2 mg/kg/day) for 4 weeks.

**Refractory SRNS:** A patient who, initially, did achieve remission with steroids plus other immunosuppressives like CNIs, or MMF, but then relapsed and could not achieve remission with the same or other treatment combinations (multidrug resistant).

## RESULTS

Mean age was 6.91 $\pm$ 2.40 years (age range 3.25-11.25 years) and male to female ratio 2.6. All of the SDNS patients (n=17) showed excellent response to intravenous RTX infusions achieving prolonged periods of remission. Early withdrawal of prednisolone after 2-3 months of RTX infusions was also possible in all these patients. Six patients (35.29%) developed relapse at about 10 months after rituximab pulses and 04 patients (23.53%) relapsed at about 12 months of treatment. Seven patients (41.17%) did not still relapse after more than 12 months time. The relapsing patients were given repeat 1-2 doses of RTX and were in remission till the completion of study period of 18 months (table 1).

**TABLE 1: Response of SDNS (n=17) patients to Rituximab**

| Age range (years) | No. of patients | Relapse at 10 months (%) | Relapse at 12 months (%) | No relapse > 12 months (%) |
|---|---|---|---|---|
| 3.25-5 | 05 | 02 (40.00) | 01 (20.00) | 02 (40.00) |
| 6-10 | 10 | 03 (30.00) | 02 (20.00) | 05 (50.00) |
| 11-11.25 | 02 | 01 (50.00) | 01 (50.00) | Nil |
| **Total** | **17** | **06 (35.29)** | **04 (23.53)** | **07 (41.17)** |

However, the response of the refractory SRNS patients (n= 09) to 4 doses of RTX was not very encouraging with only 01 (11.11%) patient achieving complete remission in age group 6 – 10 years and 03 (33.33%) patients going into partial remission (one 3.5-5 years age and two in 6-10

year age groups). Remaining 05 (55.55%) multidrug resistant SRNS patients did not respond to RTX (two in 3.5-5 and 6-10 years each group and one in > 10 years age group) over the period of observation of the study (table 2).

**TABLE 2: Response of SRNS (n=09) patients to Rituximab**

| Age range (Years) | No. of patients | Complete remission (%) | Partial remission (%) | No remission (%) |
|---|---|---|---|---|
| 3.25-5 | 03 | Nil | 01 (33.30) | 02 (66.70) |
| 6-10 | 05 | 01 (20.00) | 02 (40.00) | 02 (40.00) |
| 11-11.25 | 01 | Nil | Nil | 01 (100.00) |
| **Total** | **09** | **01 (11.11)** | **03 (33.33)** | **05 (55.55)** |

Taking into consideration the category of SRNS, out of the 03 late SRNS patients, one patient achieved complete remission and 02 patients achieved partial remission. While, out of 06 initial SRNS patients, only 01 patient went into partial remission and remaining 05 patients were still refractory to all treatments (table 3).

**TABLE 3 : Response of SRNS (n=09) to rituximab according to category of SRNS**

| Category | Complete Remission (%) | Partial Remission (%) | No Remission (%) |
|---|---|---|---|
| Initial SRNS (n=6) | 00 | 01 (16.7) | 05 (83.3) |
| Late SRNS (n=3) | 01 (33.3) | 02 (66.7) | 00 |

Regarding the response to RTX according to histopathological lesions, both SDNS patients having FSGS went into prolonged remission, while, out of 07 SRNS patients with FSGS, only 02 patients achieved partial remission, and 05 patients were refractory to RTX. Out of 02 SRNS patients with MesPGN and IgM nephropathy, one patient achieved complete remission and the other had partial remission (table 4).

**TABLE 4 : Response to Rituximab according to histopathology (n=11)**

| Category | Complete Remission (%) | Partial Remission (%) | No Remission (%) |
|---|---|---|---|
| FSGS (n=9) | 02 (22.2) | 02 (22.2) | 05 (55.6) |
| MesPGN / IgMN (n=2) | 01 (50.0) | 01 (50.0) | 00 |

As regards safety profile of RTX, we observed no significant infusion related reactions in any patient except one patient who developed mild itching with urticarial rash, which was easily treated with intravenous antihistamine and hydrocortisone. There were no episodes of sepsis or any other significant complications related to RTX. Minor routine infections did occur and were easily treated on outdoor basis.

## DISCUSSION

Rituximab (RTX) is a chimeric murine-human-anti-CD20 monoclonal antibody, which inhibits CD20-mediated B cell proliferation and differentiation. It has been used in B-cell non-Hodgkin's lymphoma and connective tissue disorders[18,19]. It has also been shown to induce remission and decrease steroid load in FRNS and SDNS[20]. The aim of RTX administration is to prevent relapse in refractory SDNS patients, while it is to induce remission in refractory multi-drug resistant SRNS patients.

Our study showed excellent outcome in refractory SDNS patients who were repeatedly relapsing on high steroid doses (1-1.5 mg/kg every other day) plus other immunosuppressives like cyclophosphamide, tacrolimus, cyclosporine A, and mycophenolate mofetil. All these children remained relapse-free for prolonged periods ranging from 10 months to more than 12 months despite early (about 3 months) tapering and stoppage of steroids; thus decreasing the steroid load. Studies from around the world show similar results. In a randomized placebo-controlled trial of

RTX in children with NS, 04 weekly pulses of 375 mg/m2 resulted in a median relapse-free period of 267 days in the RTX group compared to 101 days with placebo (hazard ratio 0.27, p = < 0.0001)[9]. Other reports also show RTX to be efficacious in FRNS/SDNS.[10,12] Weaning/cessation of other immunosuppression (both steroids and other agents) is often performed following RTX administration. However, firm conclusions cannot be drawn due to the small number of data.[7]

Our study showed poor overall response to RTX in patients with refractory SRNS. Review of recent case reports and case series of RTX therapy in childhood SRNS shows positive as well as negative outcomes. Bagga A et al.[13] administered weekly 375 mg/m$^2$ pulses for 4 weeks and showed excellent outcomes in 5 SRNS children (04 complete remissions and one partial remission). In another study, Suri M et al also reported positive response in refractory FSGS using RTX.[14] However, many other studies have reported negative outcomes. Gulati et al[15] treated 33 patients with refractory SRNS with 4 doses of RTX; 09 (27.2%) patients achieved complete remission, 07 (21.2%) patients achieved partial remission, and 17 (51.5%) showed no response. Magnasco et al[11] in 2012 published an RCT examining RTX therapy in 31 children with refractory SRNS. Patients in the RTX group received two doses of rituximab. After 3 months of treatment, three patients in both the groups achieved complete remission. They concluded that addition of RTX to the treatment protocol did not improve clinical outcomes.

Taking into consideration the category of SRNS, our study showed better outcome in late SRNS patients than the initial SRNS. Sinha et al[12], Gulati et al[15], and Magnasco et al[11] showed 43.9% overall remission rates in initial SRNS while it was 57.7% in patients who developed late steroid resistance.

Response of RTX according to underlying histopathologic lesion also shows significant difference as regards SRNS patients in our study, as only one patient, out of seven SRNS patients with FSGS, had partial response to RTX, the rest 06 FSGS patients were completely non-responsive to RTX. On the other hand, out of 02 patients with MesPGN with IgMN, one patient achieved complete remission and the other was a partial responder. Studies from around the world also show lower remission rates with RTX treatment in patients with FSGS than those with minor glomerular abnormalities.[12,17] In our study two SDNS children were also biopsied due to very frequent relapses on high steroid doses and parental concern. Both biopsied patients showed FSGS, but they still achieved complete and prolonged remission. Therefore, this study shows that initial response to steroids has more prognostic significance than the type of histopathologic lesion and this is also true in case of response to RTX.

There looks to be limited efficacy of RTX for refractory SRNS, but in other studies using concomitant treatments such as high dose methyl-prednisolone pulses, and other immunosuppressives like MMF and CNIs resulted in better overall outcome.[7,17] We did not employ other immunosuppressives along with RTX. Therefore, it may imply that concomitant use of other immunosuppressive drugs along with RTX might yield better results in childhood refractory SRNS.

Looking at the adverse effects of RTX, as reported in the literature[21-23], our patients receiving RTX showed no significant adverse effects either during RTX infusions or on long-term follow-up. Only one patient developed urticarial rash with pruritus during the RTX infusion which was easily controlled with intravenous antihistamine and hydrocortisone. There were no episodes of sepsis or any other significant complication like agranulocytosis, immune mediated ulcerative colitis, fulminant myocarditis, interstitial lung disease, progressive multifocal leukoencephalopathy, or erythema nodosum in any patient over the period of observation of the study. Minor respiratory infections and gastroenteritis episodes did occur in few patients but no Pneumocystis pneumonia was reported. So, we have observed a very good safety profile of RTX in our patients so far.

There is no local published study on the role of RTX in childhood nephrotic syndrome in Pakistan. So, multicenter studies with larger sample size may further elaborate its efficacy and safety in difficult cases of SDNS, SRNS and other glomerulopathies in children and adolescents.

## CONCLUSION

Rituximab was found to be an excellent option for difficult-to-treat SDNS patients, achieving prolonged remissions and sparing the patients of severe side effects of steroids with early tapering and stopping of steroids. But, its efficacy, as monotherapy, along with prednisolone, in refractory childhood SRNS looks limited. However, further clinical trials combining RTX with other immunosuppressives like MMF and CNIs might yield better outcomes in refractory childhood SRNS. Rituximab was good in our patients with nephrotic syndrome.

**Conflict of interest:** Nil

---

**Authors' affiliation**

**Muhammad Imran, Hashim Raza, Khuram Rashid, Shahid Ishaq, Mudassar Adnan**
Department of Pediatric Nephrology at the Children's Hospital & the Institute of Child Health, Multan, Pakistan

## REFERRENCES

1. Kikunaga K, Ishikura K, Terano C, Sato M, Komaki F, Hamasaki Y, et al. High incidence of idiopathic nephrotic syndrome in East Asian Children: a nationwide survey in Japan (JP-SHINE Study). Clin Exp Nephrol 2017; 21:651-7. 9.
2. Lombel RM, Gipson DS, Hodson EM; Kidney Disease: Improving Global Outcomes. Treatment of steroid-sensitive nephrotic syndrome: new guidelines from KDIGO. Pediatr Nephrol. 2013;28(3):415-26.
3. Kemper MJ, Valentin L, van Husen M. Difficult-to-treat idiopathic nephrotic syndrome: established drugs, open questions and future options. Pediatr Nephrol. 2018;33(10):1641-9.
4. Sinha MD, Macleod R, Rigby E, Clark AG (2006) Treatment of severe steroid-dependent nephrotic syndrome (SDNS) in children with tacrolimus. Nephrol Dial Transplant 21(7):1848-54.
5. Hodson EM, Habashy D, Craig GC. Intervention for idiopathic steroid resistant nephrotic syndrome in children. Chochrane Database Syst Rev 2006;(2):CD003594
6. Imran M, Ali Z, Khan WI, Raza H. Treatment outcome in Childhood Steroid Resistant Nephrotic Syndrome with Different Therapeutic Regimens. Med Forum 2014;10(25):40-457.
7. Koichi K, Kenji I, Mayumi S, Shuichi I, Kandi N, Kazumoto I. Rituximab therapy for steroid-resistant nephrotic syndrome in children. Pediatr Nephrol. 2020;35:17-24.
8. Trautmann A, Schnaidt S, Lipska-Ziętkiewicz BS, Bodria M, Ozaltin F, Emma F, et al. Long-Term Outcome of Steroid-Resistant Nephrotic Syndrome in Children. J Am Soc Nephrol. 2017;28(10):3055-3065.
9. Iijima K, Sako M, Nozu K, Mori R, Tuchida N, Kamei K, et al. Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicenter, double-blind, randomized, placebo-controlled trial. Lancet. 2014;384(9950):127381.
10. Ravani P, Rossi R, Bonanni A, Quinn RR, Sica F, Bodria M, et al. Rituximab in Children with Steroid-Dependent Nephrotic Syndrome: A Multicenter, Open-Label, Non-inferiority, Randomized Controlled Trial. J Am Soc Nephrol. 2015;26(9):2259-66. 23.
11. Magnasco A, Ravani P, Edefonti A, Murer L, Ghio L, Belingheri M, et al. Rituximab in children with resistant idiopathic nephrotic syndrome. J Am Soc Nephrol. 2012;23(6):1117-24.
12. Sinha A, Bhatia D, Gulati A, Rawat M, Dinda AK, Hari P, et al. Efficacy and safety of rituximab in children with difficult-to-treat nephrotic syndrome. Nephrol Dial Transplant 2015;30(1):96-106. 18.
13. Bagga A, Sinha A, Moudgil A. Rituximab in patients with the steroid-resistant nephrotic syndrome. N Engl J Med. 2007;356(26):2751-2.
14. Suri M, Tran K, Sharma AP, Filler G, Grimmer J. Remission of steroid-resistant nephrotic syndrome due to focal and segmental glomerulosclerosis using rituximab. Int Urol Nephrol. 2008;40(3):807-10.
15. Gulati A, Sinha A, Jordan SC, Hari P, Dinda AK, Sharma S, et al. Efficacy and safety of treatment with rituximab for difficult steroid-resistant and -dependent nephrotic syndrome: multicentric report. Clin J Am Soc Nephrol. 2010;5(12):2207-12.
16. Nakagawa T, Shiratori A, Kawaba Y, Kanda K, Tanaka R. Efficacy of rituximab therapy against intractable steroid-resistant nephrotic syndrome. Pediatr Int. 2016;58(10):1003-1008.
17. Basu B, Mahapatra TK, Mondal N. Mycophenolate mofetil following rituximab in children with steroid resistant nephrotic syndrome. Pediatrics 2015;136:e132-39.

18. Gurcan HM, A review of current use of rituximab in autoimmune diseases. Int Immunopharmacol 2009;9(1):10-25.

19. Cohen SB, Emery P, Greenwald MW, Dougados M,Furie RA, Genovesi MC et al. REFLEX Trial Group (2006), Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty four weeks. Arthritis Rheum 54(9):2793-2806.

20. Sellier-Lecleric AL, Baudoin V, Kwon T, Macher MA, Guerin V, Lapillonne H et al. Rituximab in steroid dependent nephrotic syndrome in childhood- follow-up after CD19 recovery. Nephrol Dial Transplant. 2012;27(3): 1083-9

21. Kamei K, Ogura M, Sato M, Ito S, Ishikura K. Infusion reactions associated with rituximab treatment for childhood-onset complicated nephrotic syndrome. Pediatr Nephrol. 2018;33(6):1013-1018.

22. Kamei K, Takahashi M, Fuyama M, Saida K, Machida H, Sato M, et al. Rituximab-associated agranulocytosis in children with refractory idiopathic nephrotic syndrome: case series and review of literature. Nephrol Dial Transplant. 2015;30(1):91-6.

23. Sato M, Ito S, Ogura M, Kamei K, Miyairi I, Miyata I, et al. Atypical Pneumocystis jiroveci pneumonia with multiple nodular granulomas after rituximab for refractory nephrotic syndrome. Pediatr Nephrol. 2013;28(1):145-9.