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Original Article

Rituximab in steroid resistant nephrotic syndrome

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Abstract

Background Nephrotic syndrome (NS) is one of the most common glomerular disease in children, characterized by massive proteinuria, hypoalbuminemia, dyslipidemia and edema. Steroid-resistant nephrotic syndrome (SRNS) and steroid-dependent nephrotic syndrome (SDNS) present challenges in pharmaceutical management. Patient need several immunosuppressant for optimal control, each of which has significant side effects and difficult to get desired results. Rituximab (RTX) is a monoclonal antibody that targets B cells and has been shown to be effective for patients with SRNS and SDNS.

Objective To see efficacy of RTX in pediatric patients with SRNS.

Method This retrospective study took place in Pediatric Nephrology Department of Bangabandhu Sheikh Mujib Medical University from July 2017 to June 2019. Patients diagnosed with SRNS who were treated with RTX and followed up for 6 months were enrolled in this study. Primary endpoint was achievement of remission after rituximab infusion; secondary endpoint was relapse-free survival rate in 6 months period following rituximab infusion.

Results Total 7 patients were recruited in this study. Among them 4 were male. Clinical and lab parameters of all patients before and after RTX were compared. Complete remission achieved in 4/7 patients, partial remission in 2/7 patients and no response in 1/7 patient. Mean number of relapse in 3 patients before RTX infusion was 3.67 (SD 0.57) and after 0.33 (SD 0.00) (P=0.038).

Conclusion RTX is a biological agent that is effective and promising drug in children with SRNS. Rituximab is useful to induce and maintain remission. **[Paediatr Indones. 2019;59:175-82; doi: http://dx.doi.org/10.14238/pi59.4.2019.175-82]**.

Keywords: *nephrotic syndrome; Rituximab; steroid resistant*

Idiopathic nephrotic syndrome (INS) is one of the most common kidney disease in children and characterized by massive proteinuria, hypoalbuminemia, dyslipidemia, and edema. Idiopathic nephrotic syndrome affects 2 to 7 new children per 100,000 children per year in Western countries, with a prevalence of 15 per 100,000 under 16 years of age.[1] In Asia, the incidence is higher, 9 to 16 cases per 100,000 children per year and 10% of INS resistant to conventional oral prednisolone.[2] Disease mechanism in INS is poorly understood, but thought to include different genetic and pathologic variants,[3-5] with polymorphic podocyte injury as a unifying feature.[6-8] All described phenotypes are considered part of a pathological continuum, from minimal lesions (minimal change disease) to podocyte depletion and glomerulosclerosis (focal and segmental glomerular sclerosis).[8]

Prednisolone is the cornerstone therapy for INS, generally induce remission within 4 weeks in approximately 90% of cases. A significant portion of steroid-

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sensitive patients are likely to relapse frequently or become dependent on steroids and develop a high risk of steroid toxicity; like hypertension, growth disturbance and glucose intolerance.[9] However, 10-20% of these patients do not respond to steroids (steroid-resistant) and have a high risk of developing end-stage renal disease.[10] In cases of such intractable NS, drugs such as cyclophosphamide, levamisole, mycophenolate mofetil, cyclosporine and tacrolimus are used to reduce steroid toxicity or overcome steroid resistance. However, many of these drugs have significant side effects and are not always effective.

Rituximab (RTX) is a genetically-engineered, chimeric, monoclonal antibody directed against the CD20 antigen on the surface of B lymphocytes, inhibits B cell proliferation and differentiation. Rituximab was first introduced in clinical practice for the treatment of Hodgkin lymphoma and autoimmune diseases.[11-14] In the past 10 years, RTX has been used to treat patients with steroid-dependent or resistant NS.[10,15-17] *The 2012 Kidney Disease Improving Global Outcomes Clinical Practice Guidelines* introduced RTX as a treatment option for steroid-dependent NS.[18] The objective of this study was to see the effectiveness of RTX in steroid-resistance nephrotic syndrome.

Methods

The subjects in this study were pediatric patients with SRNS who were treated with RTX and followed up for 6 months at a tertiary care center of Pediatric Nephrology Department of Bangabandhu Sheikh Mujib Medical University from July 2017 to June 2019. Steroid-resistant nephrotic syndrome was defined as no response after 4 weeks of steroid in adequate doses (60 mg/m^2/day) plus 3 pulses intravenous methylprednisolone at 30 mg/kg/dose. Complete remission was defined as bed side urine albumin (BSUA) nil for 3 consecutive days; partial remission was defined as BSUA (+) or trace or intermittent proteinuria. Infusion reaction was defined as all adverse events occurring within 24 hours of rituximab infusion. Initial resistance was defined as absence of remission despite 4 weeks of initial steroid treatment. Late resistance was defined as an initial response but subsequent steroid resistance. Mendoza protocol consists of methylprednisolone (30 mg/kg intravenously), administered every other day for 2 weeks, weekly for 8 weeks, every other week for 8 weeks, monthly for 9 months and then every other month for 6 months, with oral prednisolone.

Before RTX administration, patients underwent following assessments: complete blood counts, biochemical parameters (albumin, serum creatinine, liver function, electrolytes, C-reactive protein, etc.), hepatitis B and C virus titer, chest X-ray. Patient got 2-4 doses of rituximab, depending on their condition, with minimum 14 days interval between doses. Rituximab (RTX) was administered at a dose of 375 mg/m^2. To minimize the risk of infusion reaction, patient received oral acetaminophen (15 mg/kg; maximum 1 gm), intravenous hydrocortisone (8 mg/kg; maximum 500 mg) and intravenous diphenhydramine (1 mg/kg; maximum 50 mg) 30 minutes prior to RTX infusion. Rituximab was diluted to 1 mg/mL with saline and administered to patients at initial dose of 5 mL/hour and increased by 5 mL every 30 min, as tolerated with monitoring of blood pressure (BP), heart rate (HR), respiratory rate (RR) and oxygen saturation (SPO_2). Maximum infusion rate was 50 mL/hour. In the event of an infusion reaction, the attending physician decreased or stopped the infusion rate according to the severity of symptom, until symptoms disappeared. The physician also administered medical intervention, such as oxygen inhalation and anti-hypertensive medications, as clinically indicated.

Patients were followed up for at least 6 months from the initial administration of rituximab. During this period, patients' complete blood count, biochemical parameters were measured and urine analysis were performed to confirm relapse and remission. A patient was considered to have relapse if proteinuria 3+ or more for 3 consecutive days. The primary endpoint was achievement of remission after rituximab infusion and secondary endpoint was relapse-free survival rate in 6 months following administration of rituximab. Number of relapses were compared before and after administration of rituximab.

Data were collected retrospectively from patients' medical records and include patients' sex, age at diagnosis, age at starting treatment, duration of disease, immunosuppressant used at start of treatment, renal histology and number of relapses. The data were analyzed with appropriate statistical test (Pearson

correlation test, Wilcoxon signed rank test or paired T-test). Statistical significance was established at P value < 0.05.

This study was approved by the Institutional Review Board (IRB), Bangabandhu Sheikh Mujib Medical University.

Results

Table 1 shows demographic characteristics of seven patients. Patients are ordered from youngest to oldest at the time of RTX treatment. Among seven patients, 4 were male. Three patients were diagnosed as SRNS in their first attack. Two patients (no. 6 and 7) did not get calcineurine inhibitor(CNI) before RTX administration due to raised serum creatinine but they got immunosuppressant other than CNI before RTX treatment. Renal biopsy was not done in 1 patient (no. 3) due to massive ascites.

Table 2 and **3** show clinical and laboratory parameters of 7 patients before and after RTX. One patient (no.3) died 3 days after RTX due to septicemia. All patients had 3+ or 4+ proteinuria before RTX. After giving RTX it was absent in 4 patients, 1+ in 1 patient, 2+ in 1 patient (P<0.001) (**Figure 1**). All

Table 1. Demographic characteristics of patients received RTX

Patient number	Age, years	Gender	Age of disease onset, years	Duration of disease before rituximab, years	Age of onset of RTX, years	Immunosuppressants before RTX	Duration of CNI, months	Number of RTX infusion
1	3	Female	2	0.5	2.5	CNI with others	1	2
2	4	Male	0.66	2.5	3	CNI with others	1	4
3	5.5	Male	4.5	1	5.5	CNI with others	1	1
4	9.5	Male	8.75	0.25	9	Others	0	2
5	10.5	Female	3	7	10	CNI with others	1.5	2
6	11.5	Female	9.5	1.5	11	Others	0	2
7	12.5	Male	9	1.5	12	Others	0	2

Table 2. Clinical and laboratory parameters before RTX

Patient number	Proteinuria	Hematuria	Hypertension	Serum creatinine, mg/dL	Albumin, g/L	Cholesterol, mg/dL	24 hrs urinary total protein, g/m^2/day
1	+++	-	+	0.2	11	614	2.8
2	+++	-	+	0.4	15	340	2.2
3	+++	+	+	1.2	14	890	2.5
4	+++	+	+	1.2	19	225	1.2
5	+++	-	+	0.5	20	254	2.0
6	+++	+	+	5	22	384	3.2
7	+++	-	+	1.4	16	549	2.2

Table 2. Clinical and laboratory parameters after RTX infusion

Patient number	Proteinuria	Hematuria	Hypertension	Serum creatinine, mg/dL	Albumin, g/L	Cholesterol, mg/dL	24 hrs urinary total protein, g/m^2/day
1	Absent	-	-	0.2	42	350	0
2	Absent	-	-	0.2	38	220	0
3							
4	+	+	+	0.6	30	210	0.5
5	Absent	-	-	0.4	36	180	0
6	++	+	+	3.8	28	340	0.8
7	Absent	-	-	0.5	40	300	0

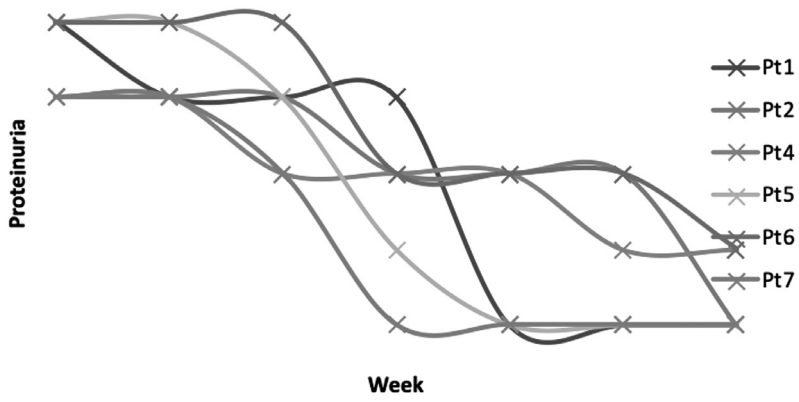

Figure 1. Status of proteinuria after RTX therapy (P ≤ 0.001) - Pearson correlation test

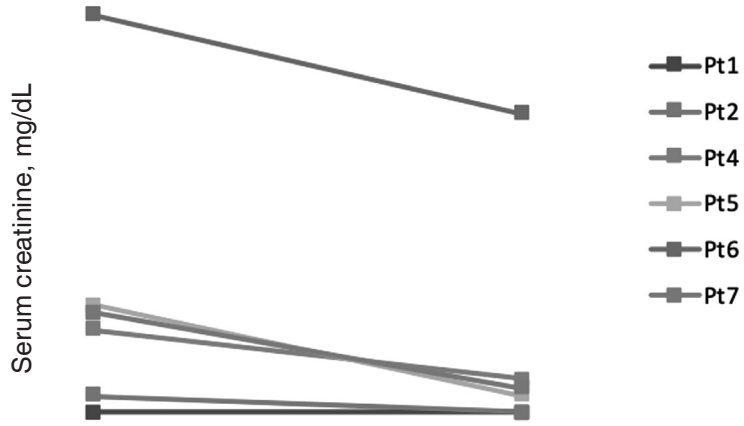

Figure 2. Pre- and post-RTX serum creatinine (P = 0.043 : Wilcoxon signed rank test)

patient had hypertension before RTX that resolved in 4 patients during follow-up period. Hematuria was present in 3 patients before RTX but it did not resolve after RTX therapy. Four patients (no. 3, 4, 6, and 7) had raised serum creatinine before RTX which became normal in 2 patients (no. 4 and 7) and decreased in 1 patient (no. 6) (P=0.043) (**Figure 2**) after RTX. Regarding renal histology, 2 patient had minimal change disease (MCD) (no. 1 and 6), 2 had mesangial proliferative glomerulonephritis (MesPGN) (no. 4 and 5), 1 had focal segmental glomerulosclerosis (FSGS) (no. 7), 1 had membranoproliferative glomerulonephritis (MPGN) (no. 2).

Figure 3 shows the primary endpoints: 4/7 patients achieved complete remission, 2/7 achieved partial remission, 1/7 showed no response (no.3) who died due to septicemia 3 days after infusion of first dose.

Table 4 shows infusion reaction (IR) during and after RTX administration. The severity of IR was categorized as grade 1-5, using the *Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0*.[19] Four patients required neither decreased nor discontinuation of RTX infusion. No patients experienced CTCAE grade 1 events. The CTCAE grade 2 events occurred in 4 patients and required non-invasive intervention such as anti-hypertensive agents and oxygen supplementation. No patients experienced grade 3-5 events and all patients completed their RTX infusion.

Table 5 shows adverse effect of RTX administration. Granulocyte count decreased in 1 patient, so granulocyte colony stimulating factor (GCSF) was given to that patient. One patient developed septicemia and died 3 days after RTX administration.

Table 4. Infusion reaction of RTX administration (n=7)

Reaction	RTX administration			
	1st dose infusion	2nd dose infusion	3rd dose infusion	4th dose infusion
Fever	0	0	0	0
Cough	0	0	0	0
Rash	0	0	0	0
Shivering	0	0	0	0
Headache	0	0	0	0
Dyspnea	2	1	0	0
Desaturation	0	1	0	0
No reaction	5	5	1*	1*

*Only 1 patient (patient no. 2) got 4 doses of RTX

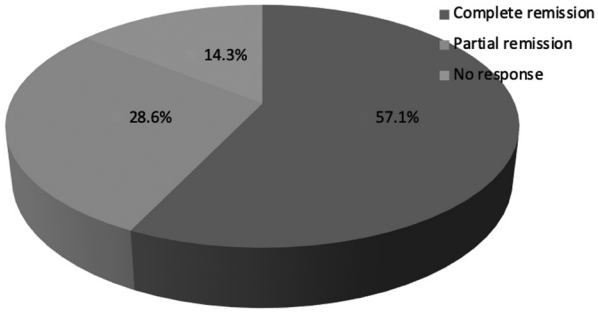

Figure 3. Effect of RTX administration

One patient developed pneumonia just after the 2nd dose of RTX infusion and clinical condition did not improve. However after 7 days that patient achieved partial remission.

Figure 4 shows secondary endpoint . Secondary endpoint was relapse-free survival rate after RTX administration. Six months after RTX administration, remission was sustained in 6 patients (patient no. 3 died 3 days after RTX therapy) either complete or partial remission with different post-RTX immunosuppressant protocol. The mean number of relapse in 3 out of 7 patient (as 3 patient was diagnosed SRNS and got RTX during their first attack, 1 patient died 3 days after RTX therapy) was 3.67 (SD 0.57) before RTX administration and 0.33 (SD 0.00) after RTX administration (P=0.038) (**Table 6**).

Table 5. Adverse effects after RTX administration

Adverse effects	Number of patients
Agranulocytosis	0
Reduced granulocyte count	1
Infection	2
Exacerbation of atopic condition	0

Table 6. Relapse-free survival rate pre-RTX and post-RTX (n=3)

	Pre-RTX	Post-RTX	P value
Mean number of relapse (SD)	3.67 (0.57)	0.33 (0.00)	0.038

Paired T-test

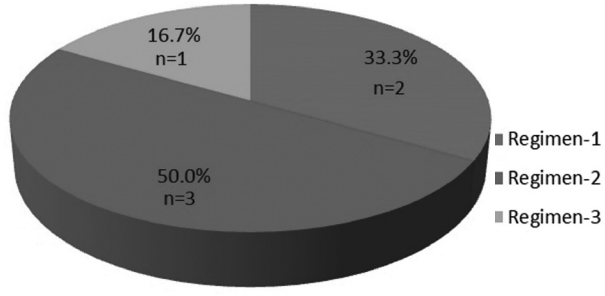

Figure 4. Patients maintaining remission over 6 months with immunosuppresant following RTX administration
Regimen-1 : Calcineurin inhibitor (CNI) + oral prednisolone
Regimen-2 : Mycophenolate mofetil (MMF) + Mendoza protocol + monthly cyclophosphamide
Regimen-3 : Calcineurin inhibitor (CNI) + Mendoza protocol + monthly cyclophosphamide

Discussion

Rituximab is considered a treatment option for SDNS and SRNS. Rituximab interacts with regulatory elements of the cytoskeleton[20] and in this way, directly modify podocyte structure. Rituximab affects regulatory elements of CD20 B cells that are implicated in innate immunity and affects Th17 cell.[21-22]

In this study, 3 patients were initialy steroid resistant and 4 patients were late steroid-resistant. All patients got 2 doses of rituximab 14 days apart (375 mg/m^2) except 1 who died 3 days after 1st infusion of rituximab. Four patient went into complete remission within 1 month of giving rituximab. This is a remarkable result in a situation where rituximab was used as a rescue therapy in patients who did not respond to immunosuppresant like prednisolone, methylprednisolone, cyclophosphamide, livamisole, MMF or CNI.

Multiple case reports support the efficacy of rituximab in inducing and/or sustaining remission of nephrotic syndrome.[23] Bagga *et al.* studied the response rate to rituximab in five pediatric patients with NS (two with MCNS and three with FSGS) who were resistant to treatment with high-dose steroids, alkylating agents and CNI. Four of these patients had a complete remission and one had partial remission. The complete remission was maintained in three patients.[16] An international, multicenter report comprising 28 patients with SDNS, 27 patients with SRNS, and 15 with post-transplant recurrence of nephrotic syndrome provided satisfactory data on efficacy and safety of rituximab.[24] Guigonis *et al.*, in a multicenter report (from France), examined the efficacy of rituximab in 22 patients with SDNS or SRNS. They included a heterogeneous group of patients receiving concomitant treatment with prednisone, calcineurin inhibitors, or MMF. At a median follow-up of 9.5 months, 19 (86.3%) patients had a beneficial effect with sustained remission or reduction of proteinuria.[15] Gulati *et al.* assessed the efficacy of RTX in 33 pediatric patients with SRNS (24 with initial resistance and 9 with late resistance). Treatment consisted of 4 weekly doses of RTX (375 mg/m^2 each). Nine patients (27.2%) achieved complete remission, 7 patients (21.2%) achieved partial remission, and 17 patients (51.5%) had no response. The median time to response was 32 days (range 8 to 60) after the last dose of RTX. At the 6 months follow up, all 16 patients remained in remission (complete or partial). The remission rate was higher in patients with minimal change disease (64.7%) than in those with FSGS (31.2%; P=0.08).25 In our study, we found 1 patient with FSGS who underwent complete remission after rituximab but 1 of 2 MCD patients had partial response and 1 had complete remission. However, a previous randomized study conducted by Magnasco *et al.* showed no benefit from RTX therapy.[26] Alaifan *et al.* showed beneficial effect of RTX in SDNS in reducing relapse rate, but they concluded that RTX is less effective in SRNS.[27]

In our study, 3 patients with late SRNS went into remission following rituximab infusion and relapse significantly reduced (P=0.038) in 6-month follow-up period. Only 1 patient had 1 relapse in a year after rituximab infusion. That patient was treated successfully with re-infusion of single dose rituximab. Several studies showed rituximab is a promising agent for maintaining remission in SDNS.[28-31]

A literature review of rituximab for difficult pediatric nephrotic syndrome 32 included 9 published studies and showed RTX is relatively safe in children with nephrotic syndrome. The main adverse events were related to infusion reactions. In our study, 3 patients developed dyspnea, 1 patient developed desaturation. Reaction was mild, so infusion was continued. One of our patient developed decreased granulocyte count, so granulocyte colony-stimulating factor (GCSF) was given. But the patient was concurrently treated with IV cyclophosphamide, so it was not clear that decreased granulocyte count was an isolated effect of RTX. One patient died 3 days after rituximab infusion, as disease course worsened with severe anasarca, raised serum creatinine & urea during infusion of rituximab.

Our study has some limitation such as sample size was small and it was done in a single center. We gave rituximab only to patients with SRNS refractory to MMF, alkylating agent and CNI, as treatment with rituximab is very expensive in contrast to our economic condition. So, these sample size could be considered as an important enrollment. Moreover, study follow-up period was short, so we could not rule out delayed complication of RTX like lung fibrosis. In addition, all our patients concurrently got other immunosuppressant like prednisolone, MMF, CNI. Thus, effects of these drugs could not be ruled out.

In our small study, RTX is an effective and promising drug in children with SRNS. It is safe with mild infusion reaction. Rituximab helps to induce and maintain remission. Although there was a trend toward better response in patients with MCD, in this report, we could not identify any histological finding that predicted the response to rituximab. There is a need for randomized controlled trials with larger population to further define the role of rituximab in idiopathic childhood onset NS.

Conflict of Interest

None declared.

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