

Single dose of rituximab in children with steroid-dependent minimal change nephrotic syndrome

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Abstract. Rituximab (RTX) can be used in children with nephrotic syndrome, particularly in those with steroid-dependent nephrotic syndrome (SDNS). However, at present there is no unified standard of how to use RTX, with regard to the amount of doses and frequency, in children with nephrotic syndrome. The study aimed to investigate the therapeutic efficacy of a single dose of RTX in children with steroid-dependent minimal change nephrotic syndrome (SD-MCNS). The patients with biopsy-proven minimal change disease (MCD) and clinical features of SDNS received a single dose of RTX (375 mg/m²). The toxicity and side effects of RTX were also observed. The study included 19 patients (10 males and 9 females). Follow-up of the patients was 1-50 months (28.1±16.6 months). B-cell depletion was achieved with RTX infusion (CD20<0.5%) and lasted 1-6 months (mean, 2.92±1.57 months). During follow-up, 10 patients remained in complete remission and did not relapse without administration of oral steroids or immunosuppressants for 4-50 months (mean, 30.1±12.6 months), despite recovery of the B-cell count. Nine patients relapsed in the process of reducing steroids, thus, treatment was maintained at a lower dosage (T=0, P<0.05) than prior to use of RTX. The number of relapses also decreased significantly (T=95, P<0.05). Five of the patients relapsed after stopping steroid for several months. At the end of follow-up, the efficacy of a single induction of RTX was 47.4% (9/19). There were no significant side effects associated with administration of RTX. In conclusion, RTX is a safe and effective alternative for children with SD-MCNS.

RTX is an effective treatment for the rapid induction of remission and reduces relapse and steroid dependency. A single dose of RTX for children with SD-MCNS is recommended for rapid induction of remission, reduction of long-term steroid dosage, and decrease in the number of relapses, as it has few side effects.

Introduction

Idiopathic nephrotic syndrome is one of the most common kidney diseases found in children, with a prevalence of 1-3 out of 100,000 in those younger than 16 years of age (1). Clinically, nephrotic syndrome is characterized by massive proteinuria, edema, hypoalbuminemia and hyperlipidemia with heterogeneous histological features ranging from minimal change disease (MCD), focal segmental glomerulosclerosis and mesangial proliferative glomerulonephritis (MPGN) (1). MCD is the most common pathological form of pediatric nephrotic syndrome (1). The epidemiological data from the International Study of Kidney Disease in Children (ISKDC) have shown that approximately 93% of patients with MCD respond well to steroids, with a relapse rate as high as 80-90% (2). Long-term steroid treatment and immunosuppressants, such as calcineurin inhibitors, have been successful in the management of these patients but result in severe side effects (3).

Monoclonal antibody, rituximab (RTX), is a 35-kDa protein highly expressed in B-lymphocytes from early to late B-cell stages, that inhibits CD20-mediated B-cell proliferation and differentiation (4). RTX was first introduced for the treatment of B-cell non-Hodgkin's lymphoma and was subsequently given to patients with autoimmune diseases, such as rheumatoid arthritis, lupus erythematosus, and immune complex-mediated glomerulonephritis (5). Previous findings showed that RTX is effective in maintaining remission in refractory steroid-dependent cases (6-10). Increased successful inductions of remission following RTX treatment in steroid-dependent nephrotic syndrome (SDNS) or frequently relapsing nephrotic syndrome (FRNS) than in steroid-resistant nephrotic syndrome were previously reported (6-7). Anecdotal studies have indicated the induction of RTX in MCD is superior to focal segmental glomerulosclerosis (8). In addition, it was recently demonstrated that the median relapse-free period was longer in the RTX group than the placebo group in patients

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with SDNS or FRNS (9). However, the patients received RTX four times, and 42% of the patients had severe side effects (9). Thus, whether a single dose of RTX for the patients with SDNS or steroid-resistance nephrotic syndrome with fewer side effects of RTX remained to be determined. Fujinaga *et al* showed that a single dose of RTX allowed for a decreased dose of steroids in the management of MCD (10).

The aim of the present study was to investigate the efficiency and side effects of a single dose of RTX in the management of pediatric SDNS with a histological diagnosis of MCD.

Materials and methods

Subjects. Patients with SDNS who were hospitalized in the Children's Hospital of Jiaotong University from October 2011 to December 2015 were enrolled in the study. The patients were diagnosed with SDNS according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines and ISKDC criteria with biopsy-proven MCD (11,12). All the patients had frequent relapses despite combined therapy with steroids and mycophenolate mofetil, cyclophosphamide or calcineurin inhibitors, tacrolimus (FK506) and cyclosporine A (CsA).

The patients with SDNS were excluded if they: i) Had no renal biopsy; ii) had renal biopsy but the pathology of renal was not MCD; and iii) were not administered with other immunosuppressants.

Diagnoses and outcomes of all the patients were according to the KDIGO guidelines and criteria (11): i) For nephrotic syndrome: Edema, urine protein/creatinine ratio (uPCR) $\geq 2,000$ mg/g (≥ 300 mg/mmol), or ≥ 300 mg/dl, or 3^+ protein on the urine dipstick, hypoalbuminaemia ≤ 2.5 g/dl; ii) complete remission: uPCR < 200 mg/g (< 20 mg/mmol) or $< 1^+$ of protein on the urine dipstick for 3 consecutive days; iii) partial remission: Proteinuria reduction of $\geq 50\%$ from the presenting value and absolute uPCR between 200 and 2,000 mg/g (20-200 mg/mmol); iv) no remission: failure to reduce urine protein excretion by 50% from baseline or persistent excretion uPCR 2,000 mg/g (200 mg/mmol); and v) relapse: uPCR $\geq 2,000$ mg/g (≥ 200 mg/mmol) or $\geq 3^+$ protein on urine dipstick for 3 consecutive days.

Patients with SDNS were defined as having at least two relapses during steroid tapering every other day or within 14 days after discontinuation according to the ISKDC criteria (12). RTX induced B-lymphocyte depletion was defined as a CD20 count $< 0.5\%$ of the total lymphocyte count (9,13). RTX efficiency was defined as complete remission lasting for ≥ 6 months after RTX until the end of follow-up without the administration of steroids or other immunosuppressants.

Protocol. A written consent form was obtained from all the patients for the indication and side effects of RTX. A single dose of RTX (375 mg/m²) was administered. Pheneregan and dexamethasone were administered as premedications prior to infusion. After RTX, the patients only taking steroids decreased rapidly after complete remission was achieved, and use of steroids ceased in 1-3 months depending on the various doses of steroids.

Follow-up. Follow-up on patients occurred at day 3, week 2, months 1, 3 and 6, and one year after RTX infusion.

Laboratory data including complete blood count, urinalysis, liver and kidney function tests, immunoglobulin levels, and lymphocyte fractionation were obtained prior to RTX infusion and at follow-up visits. All the patients were followed-up for ≥ 6 months.

Methods. Blood was collected in an EDTA-anticoagulation tube and tested immediately for CD20 (CD20 L27 and CD45-PC5; BD Biosciences, Franklin Lakes, NJ, USA) and lymphocyte fractionation (BD Multitest™ IMK kit; BD Biosciences) using a flow cytometer (BD FACSCalibur™; BD Biosciences). The blood count was tested using an automatic blood cell analyzer. Urinalysis was tested using a urine analyzer. Liver and kidney function tests were tested using an automatic biochemistry analyzer. Immunoglobulin was tested using the immune transmission turbidity method.

Statistical analysis. Data were presented as mean \pm standard deviation. Comparisons before and following RTX infusion were carried out using the Wilcoxon matched-pairs signed rank test. The correlation between different indices was studied using the Spearman's correlation analysis. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics. Nineteen patients (10 males and 9 females) with MCD, with an age range of 5-17 years (mean, 8.21 ± 2.99 years) were included in the present study. The maintenance dose of steroids was 6.82 - 32.1 mg/m²/day (13.7 ± 7.12 mg/m²/day). The course of disease prior to RTX was 18-108 months (52.7 ± 27.1 months). The patient follow-up was 1-50 months (28.1 ± 16.6 months). Pretreatment features of the patients are listed in Table I. Prior to RTX infusion, all the patients relapsed more than two times with steroids and immunosuppressants.

RTX infusion. Following RTX infusion, B-cell depletion ($CD20 < 0.5\%$) was achieved and lasted for 1-6 months (mean, 2.92 ± 1.57 months). The variability of B-cells is shown in Fig. 1. To the end of follow-up, 10 patients remained in complete remission and did not relapse following a single dose of RTX infusion for 4-50 months (mean, 30.1 ± 12.6 months) despite recovery of the B-cell (CD20) count. During steroid tapering, 9 patients relapsed within 2-21 months (mean, 7.67 ± 6.26 months) of RTX infusion, and 4 of them relapsed after steroids were ceased for several months. However, the maintenance dose of steroids and relapse rate within 12 months were less than those prior to RTX treatment ($T=0$, $P < 0.05$; $T=95$, $P < 0.05$). No correlation between relapses and B-cell count ($r = -0.194$, $P > 0.05$) was observed. Details of the 9 patients who relapsed are shown in Table II.

The efficacy of a single induction of RTX was 47.4% (9/19). Details of patients after RTX are presented in Table III.

Side effects of RTX. One patient developed a rash during the infusion of RTX with transient tachycardia (130 bpm) and tachypnea (35 times/min). The patient had no fever or anaphylaxis and the rash improved by retarding the infusion. Another patient complained of transient dizziness during the infusion.

Table I. Clinical characteristics of patients prior to RTX infusion.

Patient no.	Gender	Age (years)	Years since onset	Immunosuppressant before RTX	Relapse rate/year	Prednisone dose before RTX infusion (mg/kg/day)	Dependent-steroid dosage (mg/m ² /day)	Urine protein
1	F	6	4	MMF, CTX, FK506	3	0.5	17.5	+++
2	M	6	4.5	MMF, CTX	4	0.4	10.5	-
3	F	11	8	MMF, CTX, FK506	5	1.0	30.0	++
4	M	17	6	MMF, CTX, CsA	4	0.28	9.55	++
5	M	11	9	MMF, CTX	3	0.22	7.4	+++
6	F	8	3	CsA	3	0.23	8.45	+
7	M	9	7.5	CsA	2	0.43	13.5	+++
8	F	9	6	MMF	2	0.22	6.82	+++
9	M	8	3.5	CsA	3	0.35	12.1	+++
10	F	7	5	MMF, CTX, FK506	4	0.77	14.4	+++
11	F	6	3	CsA	2	0.78	8.89	++
12	M	5	4	MMF, CsA	3	0.69	8.77	+++
13	M	5	2	FK506	2	1.25	32.1	+++
14	M	7	4	CsA	2	0.35	11.5	-
15	M	10	2.5	MMF, FK506	4	0.41	18.2	+++
16	F	6.5	5	FK506, MMF	3	1.46	9.15	++
17	F	6.5	4.5	MMF, CsA	3	0.57	13.0	+++
18	F	6	2.5	CTX	2	0.78	19.5	++
19	M	12	10	FK506	2	0.39	8.93	-

RTX, rituximab; F, female; M, male; MMF, mycophenolate mofetil; CTX, cyclophosphamide; FK506, tacrolimus; CsA, cyclosporine A.

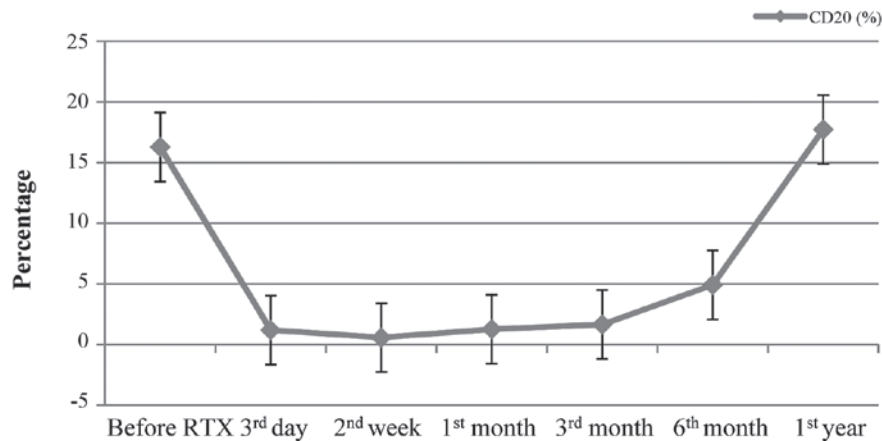


Figure 1. CD20 before and after infusion of RTX. The '3rd day', '2nd week', '1st month', '3rd month', '6th month' and '1st year' were all the days after the infusion of RTX. RTX, rituximab.

The remaining patients tolerated the infusion well without complications.

Studies available on RTX in children with SDNS or FRNS. There are several studies with regard to RTX administration in children (6,7,9,10,13-20). The information is presented in Table IV. The noted cases of steroid-sensitive nephrotic

syndrome relapsed more than two times so were classified as SDNS.

Discussion

Steroid dependency poses a challenge in the treatment of MCD in pediatric nephrotic syndrome. Long-term use and a

Table II. Patient relapse following RTX infusion.

Relapse	Patient no.								
	2	3	4	5	7	9	10	15	16
Relapse-free duration (months)	2	4	10	21	5	3	14	6	4
Cause of relapse	Infection	No	Infection	No	No	No	Infection	No	Infection
Steroid dosage on relapse (mg/kg/day)	5.26	1.88	3.05	No	No	2.02	No	No	0.13
Time to second relapse (months)	19	19	20	-	-	9	-	-	-
Cause of relapse	No	No	Rabies vaccine	-	-	Infection	-	-	-
Steroid dosage on relapse (mg/kg/day)	3.95	7.52	No	-	-	4.05	-	-	-

RTX, rituximab.

Table III. Clinical characteristics of patients following RTX infusion.

Patient no.	RTX dose	Prednisone dose (mg/kg/day)	Dependent-steroid dose (mg/m ² /day)	Urine protein	Relapse rate/year	Follow-up (months)	Drugs used now (mg/kg/day)
1	1	0	-	-	0	50	No
2	1	0.08	3.95	-	2	50	Pred 0.08
3	1	0.1	1.88	-	2	47	Pred 0.1
4	1	0.09	3.05	-	2	45	Pred 0.17
5	1	0	-	-	1	41	No
6	1	0	-	-	0	40	No
7	1	0	13.5	-	1	37	Pred 0.5, MMF
8	1	0	-	-	0	34	No
9	1	0.05	2.02	-	2	34	Pred 0.02
10	1	0	-	-	1	31	No
11	1	0	-	-	0	30	No
12	1	0	-	-	0	25	No
13	1	0	-	-	0	24	No
14	1	0	-	-	0	22	No
15	1	0.29	4.46	-	1	10	Pred 0.4
16	1	0.13	1.41	-	1	7	Pred 1.04
17	1	0	-	-	0	4	No
18	1	0.20	-	-	0	1	Pred 0.2
19	1	0.20	-	-	0	1	Pred 0.2

RTX, rituximab; Pred, prednisone; MMF, mycophenolate mofetil.

high dose of steroids and immunosuppressants cause severe side effects (3). Thus, oral agent-free treatment is an attractive therapeutic approach for patients with nephrotic syndrome (21).

The role of B lymphocytes in the pathogenesis of MCD, a T-cell, has been previously considered to play a key role (22-26). Previous findings have shown that CD23 increased in patients with nephrotic syndrome (22,23). Interleukin-13, a cytokine associated with type 2 T-helper cells, leads to antibody production and allergic reactions caused by immune responses involving B-cells in patients with nephrotic syndrome (24,25). B-cells are essential in CD4 T-cell activation for antigen presenting and

providing co-stimulation signals (26). Tokunaga *et al* (4) showed that RTX decreases CD40- and CD80-expressing cells in activated B-cells in patients with systemic lupus erythematosus and downregulates CD40L and CD69 on CD4-positive cells. The successful induction of remission following RTX treatment in some cases of MCD provides evidence supporting the hypothesis that the interference of B- and T-cells is a potential strategy for MCD treatment (8,10).

In our clinical study, patients receiving RTX treatment presented an outcome of fewer relapses, longer relapse-free periods and reduced maintenance doses of steroids. Patients

Table IV. Studies available on RTX administration in children with SDNS or FRNS.

Study (author, year)	No. of cases	Time of RTX	Follow-up	Co-drugs	Efficiency (%)	Refs.
Iijima <i>et al</i> , 2014	24 FRNS/SDNS	375 mg/m ² /time Once a week for 4 weeks	53 weeks	Pred	14/24 (58.3)	(9)
Sun <i>et al</i> , 2014	9 for SSNS 2 for SRNS	375 mg/m ² /time One or two times	4-16 months	Pred	5/9 (55.6)	(14)
Ravani <i>et al</i> , 2013	46 SDNS	375 mg/m ² /time One to five times	>3 years	Pred and CsA	22/46 (48.0)	(6)
Ito <i>et al</i> , 2013	53 SDNS/FRNS	375 mg/m ² /time One or more times	8-51 months	Pred or CsA	41/53 (77.0)	(15)
Tellier <i>et al</i> , 2013	18 SDNS	375 mg/m ² /time One to four times	Median 3.2 years	Pred	8/18 (44.5)	(16)
Sellier-Leclerc <i>et al</i> , 2012	30 SDNS	375 mg/m ² /time One to four times	>24 months	Pred or MMF or CsA	19/30 (63.3)	(17)
Kemper <i>et al</i> , 2012	29/37 SDNS	375 mg/m ² /time Once a week for 1 to 4 weeks	>24 months	Pred or CI or MPI	7/29 (24.1)	(18)
Ravani <i>et al</i> , 2011	54 SDNS	375 mg/m ² /time One or two times	>9 months	Pred and CsA	27/54 (50.0)	(19)
Fujinaga <i>et al</i> , 2010	10 MCD, SDNS	375 mg/m ² /time One time	17 months	CsA	5/10 (50.0)	(10)
Sellier-Leclerc <i>et al</i> , 2010	22 SDNS	375 mg/m ² /time One or two times	3.2-28.5 months	Pred or CsA	9/22 (41.0)	(20)
Prytuła <i>et al</i> , 2010	28 SDNS/FRNS	375 mg/m ² /time One to five times	1-16 months	Pred	10/28 (35.7)	(13)
Kamei <i>et al</i> , 2009	12 SDNS	375 mg/m ² /time One time	>12 months	Pred	3/12 (25.0)	(7)

RTX, rituximab; FRNS, frequently relapsing nephrotic syndrome; SDNS, steroid-dependent nephrotic syndrome; SSNS, steroid-sensitive nephrotic syndrome; SRNS, steroid-resistance nephrotic syndrome; MPA, mycophenolic acid; Pred, prednisone; CI, calcineurin inhibitors.

remained relapse-free despite the recovery of B-cell count, indicating that RTX treatment may regulate the immunity of patients and induce remission by inhibiting B-cells. B-cell depletion by RTX may block T-cell activation induced by B-cells or B-cell-derived factors resulting in a change of T-cell cytokine production responsible for the development of idiopathic nephrotic syndrome. B-cell depletion by RTX may also change regulatory T-cell functions, inducing changes in T- and B-cell cytokine production (18). Further studies are needed to confirm this hypothesis.

One to four doses of RTX were used to achieve and maintain complete remission in children with SDNS or FRNS in most clinical studies (6,7,9,10,13-20). The actual regimen of RTX may require adjustment in an individualized manner, depending on the response and actual clinical condition. In the present study, RTX efficacy on MCD in children with SDNS was 47.4% (9/19). Other studies showed efficacy to be between 25 and 77% with several doses of RTX. This result shows that a single dose of RTX can achieve a comparable outcome in the

management of pediatric MCD, with a favorable cost-benefit ratio and a decrease in side effects.

In conclusion, RTX is a safe and effective alternative for MCD forms of SDNS in children. For patients with severe side effects from steroid treatment or those who cannot tolerate immunosuppressants, RTX is an effective treatment in the rapid induction of remission, reducing relapses and steroid dependence. We recommend a single dose of RTX for children with steroid-dependent minimal change nephrotic syndrome for the rapid induction of remission, reduction on long-term steroid dose and decreasing the number of relapses, and having fewer side effects. Larger samples of randomized controlled clinical trials are required to justify the definite efficacy and safety of RTX in this group of patients.

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