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REVIEW ARTICLE

Rituximab: What do we expect from difficult-to-treat nephrotic syndrome?

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Abstract

Background: In the treatment of idiopathic nephrotic syndrome (INS) rituximab (RTX) as a chimeric CD20 blocker has been widely used. However, its efficacy in steroid-resistant nephrotic syndrome (SRNS) is debated. In this study, we assessed the response to RTX in INS as well as the predicting factors in relapse-free time and outcome.

Method: This study has been carried out on 38 patients under 22 years old with INS. The study commenced in 2014, in Isfahan, Iran. The primary endpoint was a relapse-free period for 1 year or achieving a GFR of less than 70 ml/min. RTX protocol was 375mg/m2 /dose/4 times. Biochemical and urinary parameters were measured before the first and after the last dose of RTX. Further, Immunoglobulin G (IgG), CD19, and CD20 levels were assessed after the first and the last dose.

Results: The mean age was 12.86± 4.5 years. Histopathology of focal and segmental glomerular sclerosis was predominant. Following patients after 1 year demonstrated that 42% (n=16) of them were still in remission, and 34% (n=13) were in partial remission. However, 24% (n=9) of the participants achieved chronic renal failure (CRF) even after 4 doses of RTX. Neither the absolute CD20 level at the time of the first course nor its level after stopping RTX was a predictor of the final 24-hour urine protein and the final GFR (P> 0.05). Further, GFR ($p< 0.05$, $R^2= 0.56$) and age of

diagnosis ($p< 0.05$, $R^2= 0.591$) were the predictors of final 24-hour urine protein ($p< 0.05$). Response to steroids (SDNS, FRNS) had a positive effect on final GFR ($p< 0.05$).

Conclusion: RTX is an effective monoclonal antibody in keeping INS patients in remission. Although its efficacy in CNI-unresponsive SRNS is not as equal to SDNS, RTX may sustain a major proportion of INS in complete or partial remission.

Keywords: nephrotic syndrome; rituximab; children; recurrence

Introduction

Idiopathic nephrotic syndrome (INS), one of the most prevalent glomerular diseases in children, is characterized by nephrotic range proteinuria, hypoalbuminemia, peripheral edema, and hypercholesterolemia. The worldwide incidence of the disease varies in different ethnicities from 2 to 16.9 per 100,000 children [1]. Minimal change disease (MCD) followed by focal and segmental glomerular sclerosis (FSGS) is the most common histopathology reported in INS.

Thus far, the steroid is the mainstay and the first step of treatment. However, a considerable percentage of patients will be steroid-dependent (SDNS) or steroid-resistant (SRNS) and or will experience frequent relapses (FRNS).

Consequently, a few immunosuppressive agents focused on the T-cell-mediated nature of the disease such as calcineurin inhibitors (CNI) have been proposed as the second line of treatment.

During the last decades, the role of some circulating factors and B-cells has been discussed widely. An elevated memory B-cell level has been reported in steroid-sensitive nephrotic syndrome (SSNS) not only at the onset of the disease but also during the subsequent relapses [2].

Regarding the possible mechanisms of disease, rituximab (RTX) a chimeric anti-CD20 monoclonal antibody has been introduced to treatment regimens since 2004 [3]. Based on the published data, RTX was more successful in the treatment of SDNS and FRNS than SRNS [4-8].

Nonetheless, diversity of ethnicity, duration of disease before commencing RTX, histopathology, continuing treatment with immunosuppressives after RTX, times of RTX prescription and so many factors may change the response to treatment either in nephrotic syndrome or other diseases such as rheumatoid arthritis, idiopathic thrombocytopenic purpura, and non-Hodgkin lymphoma [9-12]. Considering the response to RTX, the mechanism of complement-dependent cytotoxicity and a correlation between CD20 level and response to RTX in lymphoma has been reported [13, 14]. However, there is no consensus on whether CD20 level correlates with response to treatment in INS. We assessed not only the response to RTX in our patients with INS, especially in difficult-to-treat nephrotic syndrome, but also the changes in the level of CD20 and CD19 in both responders and non-responders to the medication.

Participants and methods

This cross-sectional prospective study has been carried out on 38 children and adolescents aged under 22 years old diagnosed with INS who have been referred to Imam Hossein Children's Hospital (affiliated with Isfahan University of Medical Sciences). The study has been carried on between December 2014 and June 2020. The research proposal was approved by the Ethics Committee of Isfahan University of Medical Sciences. The written consent form was taken from parents/caregivers and children older than 6 years.

The primary endpoint was a relapse-free period for at least 1 year or achieving a GFR of less than 60 ml/min.

Kidney biopsy has been proposed for patients under the following circumstances:

- Early in the course of the disease for steroid-resistant patients.
- Before commencing calcineurin inhibitors.
- Re-doing biopsy in patients with rapid progression to low GFR

According to the response to steroids, patients have been divided into 3 groups:

- “Steroid-dependent nephrotic syndrome (SDNS):

Two consecutive relapses while receiving prednisolone on alternate days, or within 15 days of its discontinuation.

- Frequent relapsing nephrotic syndrome (FRNS):

> 2 Relapses within 6 months after initial therapy or > 4 relapses in any 12 months

- Steroid-resistant nephrotic syndrome (SRNS):

Lack of remission despite 4–8 weeks of therapy with daily prednisolone at a dose of 60mg/m2 or 2mg/kg (maximum 60–80mg) per day” [15].

Inclusion criteria

➢ Aged under 22 years old at the time of diagnosis.

➢ SRNS, FRNS, or SDNS based on past medical history.

➢ Received the RTX protocol once or more.

➢ Glomerular filtration rate≥ 60 ml/min at the time of prescribing RTX.

➢ Patients with Iranian ethnicity (to omit the role of ethnicity in response to RTX).

Exclusion Criteria

➢ Secondary nephrotic syndrome (based on history, physical examination, and/or histopathology.

➢ Histopathology other than minimal change disease, focal and segmental glomerulosclerosis, and mesangial proliferation nephrotic syndrome

➢ Positive results of serology in favor of a diagnosis of autoimmune diseases such as systemic lupus erythematosus.

➢ Poor compliance with follow-up.

A questionnaire containing demographic data, medications profile, kidney biopsy report, and biochemical results has been filled out for every patient.

RTX protocol was 375mg/m2 /dose/4 doses. The first 4 doses have been prescribed weekly. The fifth dose has been given 6-12 months after the first course.

Biochemical parameters including urea, creatinine, serum albumin, urine analysis, and 24-hour urine protein were measured before the first dose and after the last dose of RTX. Further, Immunoglobulin G (IgG), CD19, and CD20 levels were assessed after the first and the last dose.

We divided patients into 3 groups according to the time of RTX prescription:

- Early prescription: RTX has been prescribed after no response or partial response to corticosteroid or in steroid-dependent patients.
- Late prescription: RTX has been prescribed after no response or partial response to one of the following immunosuppressive medications: cyclophosphamide, cyclosporine, CellCept, and tacrolimus.
- Very late prescription: RTX has been prescribed after decreasing glomerular filtration rate (GFR) or after no response to all immunosuppressive medications.

In addition, we recorded the elapsed time between the first course of RTX and the second course of prescription (redosing).

All patients have been followed at least for 12 months after remission. Those patients who did not achieve complete remission were under concise management and regular every-other-month visit.

Results

The ratio of male to female ratio was 28/10 (2.8). The mean age was 12.86± 4.5 years. The mean duration of the disease was 8.3± 3.9 years, and the maximum age of disease presentation was 15.5 years (4.55± 2.78 y). Twenty-nine out of 38 participants (76.3%) had hypertension.

The results of biochemical and CBC parameters before and after the last dose of RTX have been shown in table I.

Parameter	Before treatment(Mean± SD)	After treatment(Mean± SD)	P-value
WBC (White blood cell)	13015.31 (±14197.52)	14936.36 (2892.25)	> 0.05
Neutrophil (percent)	58.46 (±14.55)	58.429(19.62)	> 0.05
Hemoglobin	15.92 (±18.39)	12.76 (1.94)	> 0.05
Platelet	306545.45 (±128025.65)	281031.25 (±122059.34)	> 0.05
Albumin (g/dl)	2.95 (±1.001)	3.22 (±1.06)	> 0.05
Blood urea nitrogen(mg/dl)	24.65 (±26.40)	30.12 (±2.82)	> 0.05
Creatinine(mg/dl)	0.84 (±0.52)	1.14 (±1.25)	> 0.05
24-hours urine protein (mg)	981(±1066.42)	686.36 (±1354.64)	> 0.05
CD 19	0.75 (±2.22)	7.16 (±18.38)	> 0.05
CD 20	0.63 (±1.94)	5.20 (±13.20)	> 0.05

Table I: Biochemical and CBC parameters before and after treatment

Results of Kidney biopsies revealed a higher percentage of FSGS in 22 patients (57.9%) in comparison to 15 (37.5%) patients with histopathology of MCD. Only one patient showed mesangial proliferation in his kidney biopsy.

According to the response to steroids, the following results have been achieved: 26% (n=10) SDNS, 42% (n=16) FRNS, and 34% SRNS (n=12).

Approximately 42% of the patients were receiving more than one immunosuppressant medication at the time of RTX prescription.

More than half of the patients (55.4%) received 4 doses of RTX. Nevertheless, 28.9% of the participants received 3 doses; 7.9% received 2 doses and 7.9% had medication for 5 doses (one dose 9-12 months after the first 4- doses course). All patients who received less than 4 doses, achieved remission.

RTX's side effects, including mild skin rash, itching, and low-grade fever, have been reported in 7 out of 38 patients (18%). No patient had a severe reaction or prophylaxis.

Based on the time of the RTX prescription, it has been revealed that only 5 patients (13%) received RTX in the early course of the disease. Twenty-six participants received RTX lately (68%) and the remaining (7 patients= 19%) received RTX very late in the course of the disease.

Following patients after 1 year demonstrated that 42% (n=16) of them were still in remission, and 34% (n=13) were in partial remission. However, 24% (n=9) of the participants achieved GFR less than 60ml/min even after 4 doses of RTX.

Comparing patients based on histopathology (MCD and FSGS) showed that the final 24-hour urine protein was significantly higher in FSGS patients than in MCD patients (919.0± 767.62 mg/day vs 298.93± 428.20 mg/day; p< 0.05), table II.

Variable	**Histopathology**MCD (N)=15FSGS (N)= 22	**Mean± Std**	**P-value**
Age (year)	**MCD**	13.86± 4.43	> 0.05
	FSGS	12.18± 4.62	
Disease duration (year)	**MCD**	8.93± 3.89	> 0.05
	FSGS	7.72± 4.05	
Age of diagnosis (year)	**MCD**	4.96± 3.24	> 0.05
	FSGS	4.40± 2.46	
Months of being in complete/partial remission after 4 doses	**MCD**	10.00± 1.85	> 0.05
	FSGS	6.72± 2.97	
Albumin (g/dl)	**MCD**	3.81± .70	> 0.05
	FSGS	3.24± .72	
Creatinine (mg/dl)	**MCD**	.72± .1	> 0.05
	FSGS	1.49± 1.09	
GFR (ml/min)	**MCD**	108.6± 9.27	> 0.05
	FSGS	82.22± 33.13	
24h urine protein (mg/day)	**MCD**	298.93± 428.20	**< 0.05**
	FSGS	919.0± 767.62	

Table II: Comparing different parameters based on histopathology (MCD and FSGS)

Also, we found that the age of complete responders was higher in comparison with partial responders ($p< 0.05$). In addition, relapse-free time was more prolonged in complete responders ($p< 0.05$), table III.

	RTX ResponseComplete remission: n=16Partial remission: n=13	Mean± SD	P-value
Disease Duration(Year)	Complete	9.12± 4.12	> 0.05
	Partial	6.76± 3.48	
Age (year)	Complete	13.62± 4.25	**< 0.05**
	Partial	10.69± 3.30	
Diagnosis age(year)	Complete	4.50± 1.68	> 0.05
	Partial	3.92± 1.94	
Time of Relapse after RTX (month)	Complete	10.12± 2.15	**< 0.05**
	Partial	7.15± 2.33	
RTX times	Complete	3.87± .71	> 0.05
	Partial	3.69± .63	
Serum Albumingm/dl	Complete	3.87± .71	**< 0.05**
	Partial	3.69± .63	
GFRml/min	Complete	111.18± 6.37	**< 0.05**
	Partial	88.61± .56	

Table III: Comparing response to RTX and demographic data between complete and partial responders

Applying correlation analysis demonstrated a positive significant correlation between final GFR and relapse-free time after RTX ($p= 0.002$, $r= 0.48$) and a negative correlation with 24-hour urine protein ($p=0.001$, $r=-0.496$).

Final GFR was significantly lower in CNI-unresponsive SRNS in comparison to SDNS (69.0± 39.26 VS 109.0± 13.43 ml/min; $p<0.05$) and FRNS (69.0± 39.26 VS 101.87± 9.81ml/min; $p<0.05$). By using a multivariate generalized linear model, we found that the mean of GFR was significantly different between complete and no responders ($p=0.0001$) and between complete and partial responders ($p=0.04$). Nevertheless, no significant difference in 24-h urine protein was seen between SRNS with other groups ($p> 0.05$).

Relapse-free time was significantly longer in SDNS and FRNS in comparison to SRNS, $P< 0.05$. Further, relapse-free time had a negative correlation with response to steroids ($P< 0.05$; $r= -0.4$).

The final GFR, final proteinuria and the outcome had no significant correlation with the number of RTX applications ($p> 0.05$).

Applying tests between subject effects demonstrated that response to steroids (SDNS, FRNS) had a positive effect on final GFR ($p< 0.05$).

All patients had low levels of CD19 and CD20 after the first dose and 2-4 weeks after terminating the treatment protocol, table IV.

CBC parameter	Mean± SD	P-value
Absolute CD20after the first course	5.58± 3.75	> 0.05
Absolute CD202-4 weeks after terminating the course	14.90± 25.36	
Absolute lymphocyte countafter the first course	3713.02± 3378.00	> 0.05
Absolute lymphocyte count2-4 weeks after terminating the course	5100.46± 6209.45	

Table IV: Comparing CD20 levels during different stages of treatment

Low IgG level has been documented in 28.9% (n=11) of patients at the time of commencing the treatment protocol. 7 out of 11 patients with low IgG levels, had a protocol regimen including mycophenolic acid (MMF). In addition, all patients who had low IgG levels were in the partial or no remission group.

Linear regression analysis showed that GFR ($p< 0.05$, $R^2= 0.56$) and age of diagnosis ($p< 0.05$, $R^2= 0.591$) were the predictors of final 24-hour urine protein ($p< 0.05$). Furthermore, relapse-free time after RTX was the predictor of not only final GFR ($P< 0.05$; $R^2 =0.23$) but the final 24-hour urine protein ($p< 0.05$; $R^2 = 0.24$).

Using a regression linear model analysis revealed that neither the absolute CD20 level at the time of the first course nor its level after stopping RTX was a predictor of the final 24-hour urine protein and the final GFR ($P> 0.05$). The same results have been achieved for CD19.

Discussion

We evaluated the effectiveness of RTX on proteinuria, GFR, IgG, CD19, and CD20 levels in INS children. Most of our patients were cases of SRNS or difficult-to-treat NS with FSGS histopathology.

INS is not an uncommon glomerular disease among children. While most of them respond to steroids, a majority will experience relapses [16]. However, FSGS histopathology has been more frequently accompanied by steroid -resistance than MCD [17]. Thus far, considering resistance to steroids a variety of immunosuppressants focusing either on T-cell function or depleting immune competent cells has been introduced such as cyclophosphamide, cyclosporine, tacrolimus, and mycophenolate mofetil [18].

After affirming the role of memory B-cells in relapsing cases of INS, RTX a chimeric CD-20 blocker has been brought into treatment protocols of INS [2,4,7].

Further experiments on $CD20^+$ CEM cells showed that complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity have complementary action in response to RTX [14].

The results of the response to RTX in SDNS differed from SRNS [19,20]. In addition, the response rate to RTX in idiopathic thrombocytopenic purpura (ITP) varies among different ethnicities [10]. Genetic factor such as FCGR3A polymorphism has been discussed in response to RTX in non-Hodgkin lymphoma [11]. Therefore, various rates of responses to RTX in INS are not unpredictable among different ethnicities.

A recent study on INS children demonstrated a longer relapse time and higher remission rate in those who received RTX in comparison to the steroid-cyclosporin group [6]. A meta-analysis of 6 RCT studies by Gao et al showed a significantly lower relapse rate in children on the RTX treatment protocol [20].

By the above-mentioned results, Ravani et al proposed a longer median relapse-free time in patients receiving RTX compared to steroids [4]. Lijima et al evaluated 52 children with INS and found similar results and a longer relapse-free period in children who

received RTX than in the placebo group [5].

Sinha et al demonstrated that SDNS patients had a longer duration of relapse-free time compared with SRNS after receiving RTX [21]. Further, they found that SRNS (mostly with FSGS histopathology) had an unfavorable outcome and lesser response to RTX.

A review on INS in children by Kemper et al showed a lesser effectiveness of RTX in CNI- unresponsiveness SRNS [22].

Approximately, 42% of our patients had a relapse-free period of at least one year and 34% were in partial remission even after one year. Since we enrolled difficult-to-treat patients and CNI-unresponsive SRNS along with SDNS and FRNS in the study, the percentage of patients with relapse-free periods was lesser than the similar studies.

In adult patients with SRNS and elevated levels of Soluble Urokinase-Type Plasminogen Activator Receptor (SU-PAR), RTX was not effective in inducing remission and could not prevent reaching end-stage renal disease (ESRD) [23].

Our study demonstrated a positive correlation between final GFR and relapse-free time and a negative correlation with final proteinuria. In addition, relapse-free time was the predictor of final GFR. We did not find that the RTX application could prevent decreasing GFR.

According to the results of our study, the number of RTX applications was not a predictor of the final GFR and or relapse-free time. The same results have been suggested by Kemper et al [24]. However, they found that relapse-free time was shorter in patients who received 1-2 times RTX in comparison with 3-4 times. A review by Chan et al proposed that no differences between the 2-doses protocol and more have been expected [9].

RTX as a CD20 blocker and B-cell-depleting drug with an inhibitory effect on $CD8^+$ T cells has raised concerns about its serious side effects [25, 26]. As a monoclonal antibody, infection, and hypogammaglobulinemia during and after treatment are predictable [27]. However, having a malignant disease in comparison to a non-malignant disease was associated with more serious side effects [27].

Lower levels of IgG at the baseline and having MMF before RTX prescription have been accompanied by prolonged hypogammaglobulinemia [27]. In patients with neuroinflammatory diseases who received long-term RTX, hypogammaglobulinemia has been reported in approximately 50% of the patients while serious infection has been seen in 10% [28].

We determined that 28.9% of our patients had low levels of serum IgG even at the time of commencing the RTX protocol. Most of them did not have any period of complete remission before changing treatment protocol to the RTX regimen. Therefore, prolonged uncontrolled proteinuria may be a responsible factor in occurring hypogammaglobulinemia. Approximately, 63% of patients with low IgG levels had a medical history of having MMF in their treatment protocols before starting RTX. This finding was compatible with the results of the study by Christou et al [27]. During the following-up, no serious infection has been documented.

Regarding the mechanism of RTX in blocking CD20 receptors, monitoring of CD20 level has been recommended during RTX prescription. CD20 monitoring has an important role in the prescription of the next doses of RTX in diseases such as Rheumatoid arthritis, Hodgkin lymphoma, and myasthenia gravis [29-31]. Even though low levels of CD20 have been widely reported in INS who received RTX, it has been debated if its level has a prognostic role in achieving remission [32,33].

Our results did not support any significant correlation between CD19 and CD20 levels after the first and the last dose of RTX with final GFR, proteinuria, and relapse-free time. Furthermore, the levels of CD19 and CD20 after the first and the last dose were not significantly different.

Conclusion

RTX is an effective monoclonal antibody in keeping INS patients in remission. Although its efficacy in CNI-unresponsive SRNS is not as equal to SDNS, RTX may sustain a major proportion of INS in complete or partial remission.

However, RTX-based treatment protocol should be considered before a marked decrease in GFR. Serial measuring of CD20 and CD19 predicting predicting predicting does not help predict relapse-free time. Nonetheless, in patients with either a history of non-remission or having mycophenolate mofetil, IgG level should be measured before RTX prescription.

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