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Anti-Rituximab Antibodies in Idiopathic Nephrotic Children Treated with Rituximab: A Prospective Single Centre Study

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Abstract: Corticosteroids have been the main treatment of nephrotic syndrome (NS) for decades however many patients fail to respond. In such children, alternative immunosuppressive medications such as rituximab is used to maintain remission of NS. However, antibodies to rituximab develops during treatment reduces its efficacy. Therefore, this study aimed to measure anti-rituximab antibody (ARA) levels and efficacy of rituximab in children treated for NS. This prospective observational study was conducted among children with difficult to treat nephrotic syndrome. After baseline assessment, patients received single dose of intravenous infusion of 375 mg/m^2 rituximab. ARA levels were determined at base line, 3-month, 6-month, and 12-month interval. Thirty-four patients with a mean age of 7 years were evaluated in this study. During follow up visits five patients developed ARA; two patients detected ARA of 23.7 IU/ µL at 3-month, one patient had ARA level of 53.2 IU/µL at 6-month and during last follow up visit (at 12 month) two patients had mean ARA level of 24.1 IU/µL. The number of relapses per person year before rituximab was 1.5 (Incidence density) which changed to 0.14 per person year after the rituximab administration in the study subjects. Twenty-Nine patients became relapse-free during rituximab treatment. Out of five patients with ARA, one had relapse during follow up. There was no major adverse effect observed during and post-rituximab therapy. In conclusion, the study demonstrated ARA levels in few patients who were treated with rituximab having sustained clinical outcomes without any major adverse events.

Keywords: Anti-Rituximab Antibody, Rituximab, CD-19, Nephrotic Syndrome, Relapse

1. Introduction

Idiopathic nephrotic syndrome (NS), the most common chronic glomerular disease in children primarily involves immune dysregulation. It is characterized by several clinical conditions including but not limited to severe proteinuria, hypoalbuminemia, edema, infection, venous thromboembolism and increased risk of acute kidney injury. Based on the ethnicity and geographical location, the prevalence of idiopathic NS ranges from 1·15–16·9 per 100 000 children [1].

Treatment of NS is often challenging due to drug dependency, side effects, severe toxicity and frequent relapses. Although most patients initially respond favorably to corticosteroid therapy, more than 25% relapse or become steroid dependent requiring further treatment with other immunosuppressive drugs such as cyclophosphamide, calcineurin inhibitors (CNI) (cyclosporine or tacrolimus), and/or mycophenolate mofetil [2]. Steroid and/or CNI dependence are associated with several side effects including fibrosis with kidney failure, impaired growth, osteoporosis, obesity and hirsutism [3].

Rituximab, a chimeric monoclonal antibody that acts

against CD20-mediated B-cell proliferation and differentiation are accepted as successful therapy to treat idiopathic NS in children. Studies have demonstrated a reduction in dose and number of immunosuppressive drugs with rituximab usage. It has good efficacy and tolerability with no major side effects and has the ability to limit relapses in steroid- and/or CNI-dependent idiopathic NS in the short term [4-6]. However, all chimeric monoclonal antibodies carry the theoretical risk of inducing the development of anti-drug antibodies, including human anti-chimeric antibodies (HACA). The development of anti-drug antibodies and/or HACA against rituximab has previously been described in patients with various diseases [7, 8]. The appearance of anti-rituximab antibody (ARA) directed against therapeutic rituximab can affect efficacy [9]. Case reports of the development of ARA have been reported which indicates an association between ARA and decreased efficacy of rituximab in idiopathic NS [8]. However, no specific clinical trial has been conducted which measures ARA level in relation to altered efficacy of rituximab in idiopathic NS.

To the best of our knowledge, to date, there is no data reporting the development of ARA in children with idiopathic NS in the Indian context. The primary objective of the present study was to monitor the development of ARA in patients with NS who were treated with a single dose of rituximab.

2. Methods

2.1. Study Design

This is a single-center prospective observational study conducted at SVP Post Graduate Institute of Pediatrics, Cuttack during the period December 2018 to December 2020. This study enrolled pediatric patients with frequently relapsing nephrotic syndrome (FRNS) and steroid-dependent nephrotic syndrome (SDNS) treated with single dose of rituximab.

2.2. Definition

FRNS is defined as ≥ 2 relapses in 6 months or ≥ 4 relapses in 12 months and SDNS is defined as relapse on alternate day or within 2 weeks stoppage of steroid (Prednisolone).

2.3. Study Population

Children between 2 and 14 years diagnosed with FRNS and SDNS who had received at least ≥ 2 steroid sparing agents (cyclosporine, levamisole, cyclophosphamide, tacrolimus or mycophenolate mofetil) were included in the study.

Patients who have already received rituximab, having infantile onset of NS (<1 year), secondary causes of NS and any contraindication to rituximab (such as presence of active infection, Hepatitis B, hepatitis C or human immunodeficiency virus infection) were excluded from the study.

2.4. Treatment

Injection Rituximab was given as a single dose of 375 mg/m^2 infusion after ensuring stage of remission. Patients were prospectively followed up for 12 months and the development of ARA level was determined by enzyme-linked immunosorbent assay (ELISA) method and assessed the correlation between ARA and altered efficacy of rituximab. Demographics, medical history and physical examination, laboratory variables of enrolment were noted at baseline and at 3, 6 and 12-months follow-up visits.

2.5. Method of Anti-Rituximab Antibodies (ARA) Measurement

Two ml of venous blood was drawn from the cubital vein, allowed to clot and then centrifuged. Serum was collected from and assessed for anti-rituximab antibodies (ARA). The ARA was measured by sandwich ELISA as per the manufacturers protocol. Calibrators, controls and diluted serum samples were added to the ELISA wells coated with rituximab, mixed and incubated for sixty minutes at room temperature. Then after washing the wells with wash buffer, HRP conjugate was added so as to bind to Rituximab antibodies captured by Rituximab on the well surface. Following incubation for one hour at room temperature, the wells were washed and TMB substrate was added to it. After twenty minutes of incubation stop solution was added and absorbance (OD) was read at 450nm with reference wavelength of 650nm in an ELISA reader.

Calibration curve was drawn using OD of calibrators in Y axis and concentration of calibrators in X axis. Concentration of samples were read directly from the curve and the value was multiplied by the dilution factor.

Confirmation test was done for positive samples. The samples were diluted with confirmation reagent and incubated for 60 minutes. The test was repeated as for the samples done earlier.

Interpretation of true and false positives were done by calculating the inhibition% from the formula: OD sample-OD sample with confirmatory reagent/ OD sample × 100. If inhibition is ≥ 25%, the result is said to be true positive.

2.6. Ethical Conduct of Study

This study was conducted in accordance with the principles laid by the latest version of the Declaration of Helsinki and followed the guidelines for Good Epidemiology Practice. The study protocol was approved by the institutional ethics committee at the study site and followed ICH E6 guideline for good clinical practices. All the eligible patients were identified by the principal investigator (PI) or Co-PI and enrolled after obtaining informed consent from the parent/guardian by reading the consent document with them.

2.7. Statistical Analysis

Continuous variables were summarized by the mean,

standard deviation (SD), minimum, median and maximum. Categorical variables were summarized using counts and percentages. All data were included in the data listings. Data from unscheduled visits were not summarized. Detection of ARA and its correlation with efficacy of rituximab were analyzed with appropriate statistical test. Statistical analyses were performed using IBM SPSS-20 (Statistical Package for Social Scientist) free version.

3. Results

In total, 50 patients were enrolled in the study, of which 16 patients did not complete the study due to lost to follow-up and withdrawal of consent. Thus, 34 patients were evaluated and completed the study with 12 months follow-up (Figure 1).

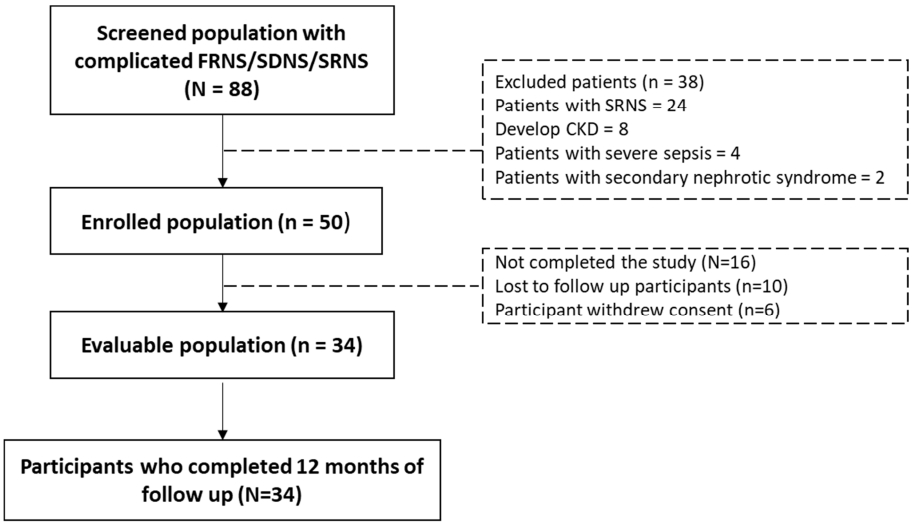

Figure 1. *Patient disposition.*

CKD, chronic kidney disease; FRNS, frequently relapsing nephrotic syndrome; NS, nephrotic syndrome; SDNS, steroid-dependent nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome.

Table 1. *Demographic and baseline characteristics of patients.*

Characteristics	Male (n=24)	Female (n=10)	Total (N=34)
Age (years)	6.8	7.4	7 (2.9)
Weight (kg)	24.65	23.3	24.2 (11.2)
Height (cm)	114.8	112	114 (15.1)
Age at first attack	2.8	2.25	1 (1.9)
Number of relapses	6.5	7.7	6.8 (2.8)
Pulse rate	103	104	103 (10.7)
Respiration rate	23.04	23.5	23.1 (3.6)
Blood Pressure, n (%)			
50^{th}-90^{th} Percentiles	18 (75.0)	6 (60.0)	24 (70.6)
90^{th} Percentiles	2 (8.3)	2 (20.0)	4 (11.8)
95^{th} Percentiles	4 (16.7)	1 (10.0)	5 (14.7)
99^{th} Percentiles	-	1 (10.0)	1 (2.9)
Cushingoid features, n (%)	2 (8.3)	3 (30.0)	5 (14.7)
CD-19 change, cells/µL			
Baseline	1196.4	835.6	1090 (162.8)
3 months	222.2	70.6	177.6 (348.7)
6 months	474.8	319	429 (439.0)
12 months	1048.8	739.6	957 (721.0)
Absolute lymphocyte count (ALC), (x 10^9/L)			
Baseline	21.6	20.2	21.2 (10.7)
3 months	5.21	3.1	4.4 (5.8)
6 months	109.9	12.6	81.3 (315.0)
12 months	24.3	21	23.3 (10.5)
Serum creatinine (mg/dL)			
Baseline	0.50	0.52	0.51 (0.18)
3 months	0.50	0.46	0.49 (0.16)
6 months	0.51	0.53	0.51 (0.17)
12 months	0.48	0.50	0.49 (0.19)

Data presented as mean (SD), unless specified.

Table 1 describes the gender wise demographics and baseline characteristics of the study participants (N=34). Majority of participants were males (n=24). The mean age of the patients was 7±2.9 years with a mean weight of 24.2±11.18 kg and the mean height was 114±15.1 cm. The number of relapses in each of the study participants varied, with a mean of 6.8±2.82 attacks. The majority of the patients (70.6%) had blood pressure in the 50th to 90$_{th}$ percentile and only 17.6% of the patients had their baseline blood pressure greater than 95th percentiles. Cushingoid features were present in five patients (14.7%), of them, three were girl.

The baseline mean CD-19 level was 1090 cells/µL (males, 1196.4 cells/µL; females, 835.6 cells/µL). Over a period of 3 months, the CD-19 levels dropped to 177.6 cells/µL and again elevated for the next 9 months (males, 1048.8 cells/µL; females, 739.6 cells/µL). The baseline mean of absolute lymphocyte count (ALC) was 21.2 x 109/L that dropped to 4.4 after a period of 3 months and again elevated for the next 9 months with mean levels of 81.3 and 23.3 at 6 months and 12 months (Table 1). The change in mean CD-19 over a period of 3 months and 12 months was statistically significant when compared with baseline and 6 months periods ($p<0.05$). Likewise, the mean ALC change over the first 3 months period was significant ($p<0.05$) but in the second period of 6 months, the observed change was not significant.

Table 2. *Characteristics of patients who developed ARA after rituximab injection.*

A	B	C	D	E	F	G	H	I	J
1	M	2.5	4	SDNS	MCD	5	Cyclosporin, MMF	12	1
2	F	7	2.5	FRNS	FSGS	10	Cyclosporin, MMF	6	-
3	M	8	3	FRNS	MCD	10	Tacrolimus, MMF	12	-
4	M	8	6	FRNS	MCD	6	Tacrolimus, MMF	3	-
5	M	9	6	FRNS	MCD	10	Cyclosporin, Tacrolimus, MMF	3	-

A: Patient number; B: Sex; C: Age (years); D: Age of onset (years); E: Diagnosis; F: Renal biopsy; G: Number of relapses before rituximab; H: Drugs taken before Rituximab; I: Time of appearance of antibody (months); J: Number of relapses after rituximab. M: male, F: female; SDNS, steroid-dependent nephrotic syndrome.; FRNS, frequently relapsing nephrotic syndrome, MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis; MMF, mycophenolate mofetil;

At the baseline, none of the patients had recorded levels of ARA. During follow up, two patients had elevated ARA (23.8 IU/µL) at month-3. Both these cases were FRNS requiring more than two steroid sparing drugs. During the second follow-up, one patient had ARA level of 53.2 IU/µL at month-6. This patient was a case of FRNS who has previously received tacrolimus and mycophenolate mofetil. However, during last follow up visit (at 12 month) the mean ARA level of 24.1 IU/µL was observed in two patients. Out of the two patients, one was a case of SDNS and the other one was a case of FRNS. In most of the patients, the ARA level was not present in all the follow-up visits (Figure 2).

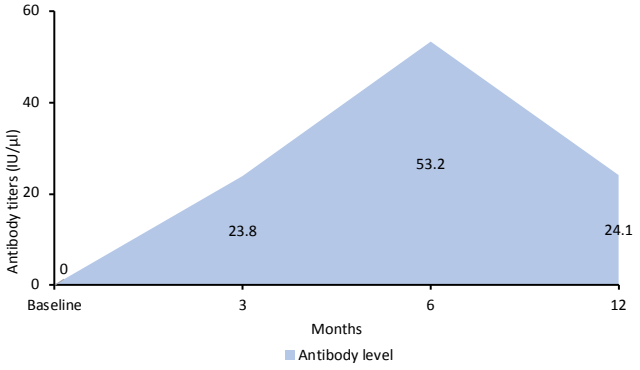

Figure 2. *Changes in the anti-rituximab antibody (ARA) level as observed from the baseline to the 3rd follow up period at 12 months.*

Out of the 34 patients followed up for 1 year, only five patients (males, n=4; females, n=1) developed ARA during the follow up period, constituting 14.7% in total. However, out of these five patients only one patient had detectable ARA level of 6.3 IU/µL at 12 months follow up visit (Table 2).

The number of relapses per person year before rituximab is (233/147) 1.5 (Incidence density) which has been changed to The number of relapses per person year before rituximab was 1.5 (Incidence density), reduced to (5/34) 0.14 per person year after the rituximab administration in the study. Twenty nine patients (85%) became relapse-free during rituximab treatment.

Among five patients who had anti-rituximab antibodies only one patient had relapse during follow up (Table 2). There was no significant difference between the relapse and the Antibody level (p=0.74) as per this study.

Table 3. *Association between the patients with ARA and without ARA.*

Parameters	Antibody +	Antibody -
Relapse	1 (2.9)	4 (11.7)
No-relapse	4 (11.7)	25 (73.7)

Data shown as n (%).

There was no major adverse effect observed during and immediately after rituximab injection. However, two patients had delayed complications. One patient developed severe varicella infection secondary to immunosuppression by injection rituximab. She responded well to intravenous acyclovir and supportive care. Another patient developed acute lung injury (ALI) following rituximab injection and treated successfully.

4. Discussion

This is the first Indian study to date to prospectively

evaluate the development of ARA post rituximab therapy in a pediatric cohort with idiopathic NS. In this study, the patients showed higher levels of CD19-positive B cells at baseline that dropped at 3 months after the rituximab doses and elevated at 6 and 12 months. Similarly, ALC levels dropped to a very high extent and elevated at 6 months and again at 12 months interval, the levels dropped to similar levels as a baseline. At baseline, none of the patients showed ARA while, only five patients showed a recorded level of ARA during a period of 12 months follow up. There were no major adverse events observed with rituximab injection except for two patients who experienced delayed complications.

The mean age of pediatric patients in the present study was 7 years. Several clinical trials and observational studies in children as well as adults encompassing a wide range of age group from 2.9 to 34.3 years having different types of NS and treated with rituximab have been reported [4, 10, 11]. However, these studies do not report the development of ARA in these patients. Few case reports have demonstrated ARA levels in children and adults with NS [8, 12]. Although, there are studies reporting ARA or HACA in other several diseases such as lymphoma, rheumatoid arthritis, systemic lupus erythematosus with diverse incidences [13-15]. The present study is one such study reporting the development of ARA levels in Indian pediatric patients with NS. The probable reason for the scarcity of this data might be a low incidence of ARA/HACA in NS. Among the 34 patients in this study, only five patients (14.7%) developed ARA. In a multicenter study by Ruggenenti et al [11] all the patients were Caucasian, with the exception of one Indian patient. Lastly, the majority of patients with NS receive rituximab concomitantly with cytotoxic or immunosuppressive drugs, which might lead to a decreased incidence of HACA. It is interesting to note that a study by Boyer-Suavet et al. that included 44 patients with membranous nephropathy, detected ARA in 23.0% of patients treated with rituximab [16]. Previous retrospective study evaluating 13 children with SDNS who developed infusion reaction during the second or subsequent rituximab reported higher incidence of ARA (38.0%) [17]. Additionally, development of severe infusion reaction in an ARA positive child with SDNS was associated with fourth infusion of rituximab [18]. Therefore, it was concluded that rituximab would lead to immunogenicity due to repeated infusions by the production of ARA, leading to severe infusion related infection in patients receiving additional rituximab treatments. Moreover, Albert et al. reported that the development of ARA was correlated with poor B cell depletion which results into early NS relapse after rituximab (< 6 months) [19].

Ahn et al. reported two cases belonging to age 3 and 6 years, one of them was diagnosed with NS 15 months before enrolment in the study [8]. It can be seen even up to 20 years of age as shown in an Italian multicentered clinical study [11]. The incidence density of relapses in the enrolled patients before injection rituximab was 1.5 per person year which reduced to 0.14 after a single dose of rituximab. In contrast, 22 relapses were reported by Ruggenenti et al. after rituximab therapy [11]. Ahn et al. [8] also reported several consecutive relapses after the rituximab therapy. However, both these studies reported a drop in the relapse rate after rituximab administration as compared to without rituximab therapy.

Some previous studies [14, 15] report that the development of HACA or ARA after rituximab therapy does not affect the safety or efficacy of further courses of treatment. On the contrary, several other studies demonstrated a decreased efficacy or treatment failure due to the presence of HACA or ARA [9]. In the present study, five patients with ARA (14.7%) did not exhibit declining clinical efficacy or therapeutic failure. Similar to the previous study rituximab was safe without any treatment related adverse events during or after the rituximab therapy [11]. Only one patient had relapse after 12 months of rituximab therapy. Nevertheless, post-treatment monitoring is recommended because serious adverse events such as progressive multifocal leukoencephalopathy have been reported [20]. Likewise, delayed complications such as varicella infection and cystic lesions in lungs have been reported in two patients in this study. Both cases with ARA reported by Ahn et al. exhibited incomplete B-cell depletion after the second course of rituximab therapy. An additional dose after 2 weeks did not impact B cell count but caused a severe infusion reaction [8]

In the present study, it was clearly evident that the mean CD-19 change showed a dip at 3 months period and further elevated at 6 and 12 months. However, mean ALC showed fluctuations during the 12 months period with an initial dip at 3 months period, then showed an intensive elevation and again decreased. Nevertheless, only five patients showed ARA levels; two at 3 months, one at 6 months and again two at 12 months. The number of relapses were also low (6.8). Thus, no clear relationship between change in CD-19 and ALC and ARA levels may be established. Though the values of the CD-19 have been taken in continuous scale, the values of the ARA as per the provided ELISA kit is in non-continuous manner. Hence a correlation could not be established through this research. An open-label pilot trial of rituximab therapy in a series of 15 patients with severe NS found no relationship between response and time to B-cell recovery, the development of ARA and B-cell count in renal tissue, nor the degree of tubular interstitial damage present [21]. Conversely, a series of case reports (n=8) demonstrated neutralization of rituximab activity in 80% of patients. However, the participants were French adult patients with primary membranous nephropathy. Of these, four patients developed ARA who were refractory to rituximab and hence, were treated with obinutuzumab or ofatumumab. The remaining four patients did not develop ARA and responded efficiently to repeated rituximab therapy [12]. However, randomized clinical trials are needed to establish therapeutic interventions based on ARA levels and to evaluate the efficacy and tolerability of rituximab in patients with NS who develop ARA.

This study is limited by a small sample size presented at a single center. Hence, these results cannot be extrapolated to patients belonging to other geographical regions and ethnicity. Thus, additional studies encompassing a larger sample

population with multiple doses of rituximab are warranted to determine the incidence of ARA in pediatric patients with NS, and its clinical implication. Additionally, prospective studies evaluating the long-term safety and efficacy outcome of concomitant immunosuppressant therapy in patients with ARA are needed. Large cohort studies will provide robust data that will enable to define the correlation between ARA levels and efficacy and safety of rituximab therapy.

5. Conclusion

In conclusion, the study demonstrated de novo ARA levels in few patients who were treated with rituximab having sustained clinical outcomes without any severe adverse events. The results do not indicate any clear relationship between the clinical efficacy and ARA levels. The number of relapses per person year which has been reduced after injection of single dose of Rituximab. However, our study is limited by a small sample size and estimating ARA level following single dose of rituximab therapy. It is prudent to estimate ARA levels in children requiring repeated rituximab injections.

Conflict of Interest

All the authors do not have any possible conflicts of interest.

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Author's Contributions

SN and SKP designed and drafted the study. RT did the ARA study by ELISA kit and assisted in data collection.

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