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To study the effect of rituximab in patients with frequently relapsing/ steroid-dependent nephrotic syndrome

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ABSTRACT

Background: Corticosteroids have had a central role in the treatment of nephrotic syndrome. The management of these patients who become dependent on steroids is complex, involving different immunosuppressive drugs patterns. The monoclonal antibody anti CD20, Rituximab, is likely to have beneficial effects in cases of steroid-dependent nephrotic syndrome patients with no easy resolution, even when we cannot make a statement about the specific role in the impact. We bring our personal experience with pediatric patients treated with this medication during the last years, to provide a thorough overview and useful information about the role of Rituximab in this pathology.

Methods: Retrospective study in patients with steroid-dependent idiopathic nephrotic syndrome controlled in Dept. of Nephrology & renal Transplantation SCBMCH, Cuttack in those patients who had received at least one treatment cycle of Rituximab, at any moment along the evolution of the disease.

Results and Conclusion: In the Rituximab group more patients were 6-10 years old compared to the Control group and this was not statistically significant. The majority of patients were male in the Rituximab group compared to the Control group. This was not statistically significant. A higher proportion of patients had CR 6m in the control group compared to the Rituximab group but this was not statistically significant. The majority of patients who had CR 12m were found in the Rituximab group compared to the control group and this was not statistically significant.Only Rituximab group patients had PR 6m and this was also statistically significant.We observed that only Rituximab Group patients had NR at 12m and another side no patients had NR at 12m in the control group and this also was statistically significant.A higher number of age group patients were located in the control group compared to the Rituximab Group, but this was not statistically significant.More patients who had higher Se Creatinine at 0m were shown in the control group compared to the Rituximab Group this was also not statistically significant.

Key Words: Rituximab, steroid-dependent nephrotic syndrome, pediatric idiopathic nephrotic syndrome, pediatrics.

INTRODUCTION

Nephrotic syndrome is a serious chronic illness that affects children. In healthy youngsters, the annual incidence of nephrotic syndrome is estimated to be two to seven new cases per 100,000 children under the age of 18 [1]. In the great majority of cases of pediatric idiopathic nephrotic syndrome, steroid response is present (steroid-sensitive nephrotic syndrome, SSNS). Although initial prednisone (60 mg/m 2) treatment results in long-term remission in a small percentage

of individuals, up to 40%–60% will recur [2, 3]. This is a big issue in this condition, particularly in the event of steroid dependency (i.e., relapses during steroid treatment or shortly after termination). Despite the use of other medications such as levamisole, mycophenolic acid (MPA), and calcineurin inhibitors, some individuals acquire a resistant course [4].Repeated cytotoxic treatment is one option for these patients, but it can have serious long-term consequences [5]. As a result, SSNS is no longer considered a benign syndrome, because relapses continue throughout adulthood in refractory patients, and long-term treatment is linked with significant damage.

In the therapy of idiopathic NS, corticosteroids are the backbone (INS). Steroid sensitive NS (SSNS) is defined as a child who has completely resolved proteinuria after 6 weeks of daily prednisone (2 mg/kg/d or 60 mg/M2/d; maximum = 60 mg/d) [6, 7]. However, at least half may experience recurrent relapses and may develop steroid-dependent NS (SDNS; defined as two consecutive relapses during steroid tapering or within 14 days of medication termination) or frequently relapsing NS (FRNS; defined as at least four relapses per year or at least two relapses within 6 months of initial presentation) [8, 9, 10].

These SSNS patients, on the other hand, may develop steroid-dependent nephrotic syndrome (SDNS), which is defined as two consecutive relapses during tapering or within 14 days following steroid therapy termination [11, 12]. Fifty to sixty percent of FRNS children match the SDNS criterion. These definitions are based on criteria developed by the International Study of Kidney Disease in Children (ISKDC) [13]. Furthermore, steroid-resistant nephrotic syndrome (SRNS) affects 10–20 percent of individuals with idiopathic nephrotic syndrome, which is characterized as persistent proteinuria after a 4- to 8-week treatment of oral prednisolone [14].

Immunosuppressive drugs such as cyclophosphamide, chlorambucil, cyclosporine (CyA), tacrolimus, and levamisole are conventional therapies for FRNS/SDNS in children around the world, whereas CyA is the primary treatment for SRNS in children [15]. Calcineurin inhibitors with or without low-dose prednisone are used to treat the majority of individuals with SD and SR illness. However, calcineurin inhibitors produce partial rather than complete remissions, and relapse is prevalent when therapy is stopped in other patients [16]. Prolonged therapy is linked to hypertension, diabetes, aesthetic side effects, irreversible renal fibrosis, and chronic kidney disease in some patients.

Several data, including larger series from France, Japan, India, and an international investigation, highlight the role of anti-B-cell medication in the difficult-to-control steroid-dependent nephrotic syndrome (SDNS) [17, 18, 19]. Although 3 of 22 patients with SDNS did not respond in the trial by Sellier-Leclerc et al. [20], it appears that the majority, if not all, of patients with SSNS respond, and in many cases, a reduction in steroids and/or maintenance immunosuppression is conceivable. Ravani et al. [21] found that rituximab and a combination of a decreased dose of prednisone and calcineurin inhibitors were non-inferior in maintaining nephrotic syndrome remission in another newly published prospective research.

Long-term follow-up data, on the other hand, isn't available. This is troublesome since many individuals relapse after receiving rituximab during the first 9–12 months. In order to investigate the effect, complications, and long-term response following rituximab in SSNS, we developed a registry with the German Society of Paediatric Nephrology (GPN).

MATERIAL AND METHODS

From 2019 to 2021, a hospital-based study was conducted from the Srirama Chandra Bhanja Medical College and Hospital, Cuttack, Indiain the Department of Nephrology and Renal Transplantation. Patients ranging in age from 2 to 18 years old were enrolled in the study. Incomplete or partial disease remission, with a proven clinical history of Steroid-dependent nephrotic syndrome and an estimated creatinine clearance of more than 30 ml per minute per

1.73 m^2 of body-surface area, to receive intravenous CD 20 antibodies (rituximab) (four infusions, 375 mg/m^2 mg each week, with a follow-up dose at 6 months if partial response).

INCLUSION CRITERIA

1. Patient aged 2-18 years
2. Patient isin either complete or partial disease remission and with a proven clinical history of Steroid dependent nephrotic syndrome
3. Estimated creatinine clearance of more than 30 ml per minute per 1.73 m^2 of body-surface area
4. Blood Pressure <130/80 mm Hg
5. Post-menopausal females, or females surgically sterile or practicing a medically approved method of contraception (no birth-control pill)
6. Signed informed consent to participate in the study

EXCLUSION CRITERIA

1. Previous administration of Rituximab therapy
2. Patients with acute infections or chronic active infections
3. Positive serological screening test for HIV, B or C hepatitis
4. Positive immunological tests for antinuclear and anti-DNA antibodies
5. Usual contraindication to steroid or Rituximab
6. Immunosuppressed patients, patients with a severe immune deficit
7. Patients with hypersensitivity to a monoclonal antibody or biological agents
8. Patients with a known allergy to steroid and its excipients or to Rituximab and its excipients or to acetaminophen and its excipients or to cetirizine and its excipients or to the protein of murine origin
9. Patients with other uncontrolled diseases, including drug or alcohol abuse, severe psychiatric diseases, that could interfere with participation in the trial according to the protocol,
10. Patients who have a white blood cell count ≤4,000/mm3,
11. Patients who have platelet count ≤100,000/mm3,
12. Patients who have haemoglobinlevels<9g/dL,
13. Patients who have SGOT or SGPT or bilirubin levels greater than 3 times the upper limit of normal
14. Patients who have serum creatinine levels>150 µmol/l,
15. Patients with active cancer or recent cancer (<5 years),
16. Females of childbearing potential who don't have an effective method of birth control during the study and during the next 12 months after treatment stops
17. Women who are pregnant (positive βHCG at inclusion), or who plan to become pregnant whilst in the trial
18. Breastfeeding women
19. Severe heart failure (New York Heart Association Class III and IV) or severe, uncontrolled cardiac disease.

STATISTICAL ANALYSIS

Data were entered into a Microsoft Excel spreadsheet for statistical analysis and then analysed using SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5. For numerical variables, mean and standard deviation were used, whereas, for categorical variables, count and percentages were used. Independent samples or unpaired samples were used in two-sample t-tests for a difference in mean. Unpaired t-tests had less power than paired t-tests, which were a type of blocking. For numerical data, one-way analysis of variance (one-way ANOVA) was a technique used to compare the means of three or more samples (using the F distribution).When the null hypothesis is true, a chi-squared test (also known as a $\chi 2$ test) is any statistical hypothesis test in which the test statistic's sampling distribution is a chi-squared

distribution. The term 'chi-squared test' is frequently used as a shorthand for Pearson's chi-squared test without further qualification. The Chi-square test or Fischer's exact test were used to compare unpaired proportions. Statistical significance was defined as a P-value of less than 0.05.

RESULTS

Patients in the Control group ranged in age from 6 to 11, with 13 (65.0%) being 6 to 10 years old and 7 (35.0%) being ≥11 years old. Patients in the Rituximab group ranged in age from 6 to 11, with 15 (75.0%) being 6-10 years old and 5 (25.0%) being ≥11 years old. The age difference between groups was not statistically significant (p = 0.4901).

Table 1: Association between Age in group

Age in group	Control	Rituximab	Total
6-10	13	15	28
Row %	46.4	53.6	100.0
Col %	65.0	75.0	70.0
≥11	7	5	12
Row %	58.3	41.7	100.0
Col %	35.0	25.0	30.0
Total	20	20	40
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

In the Control group, 10 patients (50.0%) were female, and 10 patients (50.0%) were male. In the Rituximab group, 9 patients (45.0%) were female, and 11 patients (55.0%) were male. The gender vs. group relationship was not statistically significant (p = 0.7515).

Table 2: Association between Genders

Gender	Control	Rituximab	Total
Female	10	9	19
Row %	52.6	47.4	100.0
Col %	50.0	45.0	47.5
Male	10	11	21
Row %	47.6	52.4	100.0
Col %	50.0	55.0	52.5
Total	20	20	40
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

The mean age (mean ± s.d.) of the patients in the Control group was 9.7000 ± 2.0287. The mean age (mean ± s.d.) of patients in the Rituximab group was 9.0000 ± 1.8918. The difference in mean age between groups (p = 0.2662) was not statistically significant.

Table 3: Distribution of mean Age

		Number	Mean	SD	Minimum	Maximum	Median	p-value
Age	Control	20	9.7000	2.0287	6.0000	13.0000	9.5000	0.2662
	Rituximab	20	9.0000	1.8918	6.0000	12.0000	9.0000	

DISCUSSION

The primary outcome of this research was a 12-month composite of complete or partial proteinuria remission. According to Ravani et al. [21], steroid-dependent nephrotic syndrome (SDNS) is associated with a high risk of steroid or steroid-sparing drug toxicity. They looked for children aged 1 to 16 who had had SDNS in the previous 6–12 months and were kept in remission with high prednisone doses (≥0.7 mg/kg per day) [22]. Participants were given the option of continuing prednisone alone for one month (control) or adding a single intravenous infusion of rituximab (375 mg/m^2) (intervention). Patients in the Rituximab group were [15

(75.0%)] 6-10 years old on average, compared to [13 (65.0%)] in the Control group, however, this was not statistically significant (p=0.4901).

Rituximab (RTX) can be used in children with nephrotic syndrome, particularly those with steroid-dependent nephrotic syndrome, according to Niu et al. [23]. (SDNS). RTX toxicity and side effects were also investigated. There were 19 patients in the trial (10 males and 9 females). The patients were followed for 1-50 months (28.1 ± 16.6 months). RTX injection (CD20 < 0.5 percent) resulted in B-cell depletion that lasted 16 months (mean, 2.92 ± 1.57 months). Despite a recovery of the B-cell count, 10 patients maintained complete remission and did not relapse without the use of oral steroids or immunosuppressants for 4-50 months (mean, 30.1 ± 12.6).

In the Rituximab group, [11 (55.0 percent)] patients were more likely to be male than in the Control group [10 (50.0 percent)]. Statistically, this was not significant (p = 0.7515). The [9 (45.0 percent)] control group had a higher proportion of patients with CR 6m than the [6 (30.0 percent)] Rituximab group, although this was not statistically significant (p = 0.3271). The majority of patients with CR 12m were observed in the Rituximab group [14 (70.0 percent)] compared to the control group [13 (65.0 percent)], however, this was not statistically significant (p = 0.7356). Only patients in the Rituximab group had [10 (50.0 percent)] PR 6m, which was statistically significant (p = 0.0002). There were no PR 12m patients in the control group, and only [1 (5.0 percent)] patients in the Rituximab group. Statistically, this was not significant (p = 0.3111).

Childhood nephrotic syndrome is a difficult and often persistent kidney condition, according to Kallash et al. [24], and its prevalence varies by ethnicity and geography. They summarise recent studies on the efficacy and safety of rituximab in various types of childhood nephrotic syndrome, as well as the known and potential mechanisms of rituximab action, its potential complications and side effects, and the available and potential biomarkers of rituximab activity in this review.

We discovered that more patients in the control group had [1.8600 ± .2257] Se Albumin 0m than in the [1.7950 ± .3591] Rituximab group, although this was not statistically significant (p = 0.4972). The [3.2100 ± .4241] control group had more Se Albumin 6m than the [3.0250 ± .4951] Rituximab group, although the difference was not statistically significant (p = 0.2121). The [3.6650 ± .3048] control group had more Se Albumin 12m than the [3.5450 ± .6219] Rituximab group, although this was not statistically significant (p = 0.4432). Proteinuria, hypoalbuminemia, and dyslipidemia are all symptoms of nephrotic syndrome, as per Maratea et al [25].The standard of care is low-dose alternate-day steroid therapy. Steroid-sparing medications may be utilized in the event of a recurrence or serious side effects. The goal of this study was to see how effective and safe rituximab is for treating children with nephrotic syndrome.

More patients in the [6.7850 ± .9281] control group had 24-hour urine protein 0min than in the [6.1000 ± 1.2892] Rituximab group, although this was not statistically significant (p = 0.0613). We found that more patients in the Rituximab group had [1.8500 ± 1.8500] 24 hr urine protein 6m than in the [.6750 ± .6701] control group, which was statistically significant (p = 0.0092). The [1.1525 ± 1.6816] Rituximab group had the majority of patients with 24-hour urine protein 12m compared to the [.5965 ± .6702] control group, however, this was not statistically significant (p = 0.1776).

CONCLUSION

More patients in the Rituximab group were 6-10 years old than in the Control group, although this was not statistically significant. When compared to the Control group, the Rituximab group had a higher percentage of male patients. This did not have any statistical significance. The control group had a larger proportion of patients with CR 6m than the Rituximab group, however, this was not statistically significant. When comparing the Rituximab and control groups, the majority of patients with CR 12m were observed in the Rituximab group,

however,this was not statistically significant. Only patients in the Rituximab group had PR 6m, which was statistically significant.

Only patients in the Rituximab Group had NR at 12m, whereas no patients in the control group had NR at 12m, which was statistically significant. The control group had a higher number of patients in each age range than the Rituximab group, although this was not statistically significant. The control group had more patients with greater Se Creatinine at 0m than the Rituximab group, although this was not statistically significant. The majority of patients in the control group had higher Se Creat at 6m than those in the Rituximab group, although the difference was not statistically significant.

In the control group, more patients exhibited greater Se Creat 12m than in the Rituximab group, which was statistically significant. The control group had a lower number of patients with high T Cholesterol at one month than the Rituximab group. This was noteworthy from a statistical standpoint. The majority of patients in the control group had greater T Cholesterol at 6m than those in the Rituximab group, however, this was not statistically significant. The Rituximab group had a lower number of patients with elevated T Cholesterol at 12m than the control group, although this was not statistically significant.

We discovered that a greater number of patients in the control group had higher Se Albumin at 0 months than in the Rituximab group, although this was not statistically significant. The control group had more patients with greater Se Albumin at 6m than the Rituximab group, although this was not statistically significant. The control group had more patients with greater Se Albumin at 12m than the Rituximab group, although this was not statistically significant. The control group showed higher 24-hour urine protein at 0 months than the Rituximab group, although this was not statistically significant.When comparing the Rituximab and control groups, we found that the Rituximab group had greater 24-hour urine protein at 6m. This was noteworthy from a statistical standpoint. In the Rituximab group, the majority of patients had a greater value of 24-hour urine protein at 12m than in the control group, however, this was not statistically significant. The control group had higher relapses each year than the Rituximab group, however this was not statistically significant.

REFERENCES

1. Gipson DS, Massengill SF, Yao L, et al. Management of childhood onset nephrotic syndrome, Pediatrics, 2009, vol. 124 (pg. 747-757)
2. Van Husen M, Kemper MJ. New treatment options in steroid-sensitive and -resistant idiopathic nephrotic syndrome, Pediatr Nephrol, 2011, vol. 26 (pg. 881-892)
3. Dorresteijn EM, Kist-van Holthe JE, Levtchenko EN, et al. Mycophenolate mofetil versus cyclosporine for remission maintenance in nephrotic syndrome, Pediatr Nephrol, 2008, vol. 23 (pg. 2013-2020)
4. Hogg RJ, Fitzgibbons L, Bruick J, et al. Mycophenolate mofetil in children with frequently relapsing nephrotic syndrome: a report from the Southwest Pediatric Nephrology Study Group, Clin J Am Soc Nephrol, 2006, vol. 1 (pg. 1173-1178)
5. Hulton SA, Neuhaus TJ, Dillon MJ, et al. Long-term cyclosporin A treatment of minimal-change nephrotic syndrome of childhood, Pediatr Nephrol, 1994, vol. 8 (pg. 401-403)
6. Li X, Li H, Chen J, et al. Tacrolimus as a steroid-sparing agent for adults with steroid-dependent minimal change nephrotic syndrome, Nephrol Dial Transplant, 2008, vol. 23 (pg. 1919-1925)
7. Ueda N, Takahashi K, Akioka Y, et al. Beneficial effect of chlorambucil in steroid-dependent and cyclophosphamide-resistant minimal change nephrotic syndrome, J Nephrol, 2009, vol. 22 (pg. 610-615)
8. Kyrieleis HA, Levtchenko EN, Wetzels JF. Long-term outcome after cyclophosphamide treatment in children with steroid-dependent and frequently relapsing minimal change nephrotic syndrome, Am J Kidney Dis, 2007, vol. 49 (pg. 592-597)

9. Trompeter RS, Lloyd BW, Hicks J, et al. Long-term outcome for children with minimal-change nephrotic syndrome, Lancet, 1985, vol. 1 (pg. 368-370)
10. Niaudet P. Long-term outcome of children with steroid-sensitive idiopathic nephrotic syndrome, Clin J Am Soc Nephrol, 2009, vol. 4 (pg. 1547-1548)
11. Kyrieleis HA, Lowik MM, Pronk I, et al. Long-term outcome of biopsy-proven, frequently relapsing minimal-change nephrotic syndrome in children, Clin J Am Soc Nephrol, 2009, vol. 4 (pg. 1593-1600)
12. Shalhoub RJ. Pathogenesis of lipoid nephrosis: a disorder of T-cell function, Lancet, 1974, vol. 2 (pg. 556-560)
13. Kemper MJ, Meyer-Jark T, Lilova M, et al. Combined T- and B-cell activation in childhood steroid-sensitive nephrotic syndrome, Clin Nephrol, 2003, vol. 60 (pg. 242-247)
14. Benz K, Doetsch J, Rascher W, et al. Change of the course of steroid-dependent nephrotic syndrome after rituximab therapy, Pediatr Nephrol, 2004, vol. 19 (pg. 794-797)
15. Guigonis V, Dallocchio A, Baudouin V, et al. Rituximab treatment for severe steroid- or cyclosporine-dependent nephrotic syndrome: a multicentric series of 22 cases, Pediatr Nephrol, 2008, vol. 23 (pg. 1269-1279)
16. Fujinaga S, Hirano D, Nishizaki N, et al. Single infusion of rituximab for persistent steroid-dependent minimal-change nephrotic syndrome after long-term cyclosporine, Pediatr Nephrol, 2010, vol. 25 (pg. 539-544)
17. Kamei K, Ito S, Nozu K, et al. Single dose of rituximab for refractory steroid-dependent nephrotic syndrome in children, Pediatr Nephrol, 2009, vol. 24 (pg. 1321-1328)
18. Gulati A, Sinha A, Jordan SC, 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, vol. 5 (pg. 2207-2212)
19. Prytula A, Iijima K, Kamei K, et al. Rituximab in refractory nephrotic syndrome, Pediatr Nephrol, 2010, vol. 25 (pg. 461-468)
20. Sellier-Leclerc AL, Macher MA, Loirat C, et al. Rituximab efficiency in children with steroid-dependent nephrotic syndrome, Pediatr Nephrol, 2010, vol. 25 (pg. 1109-1115)
21. Ravani P, Magnasco A, Edefonti A, et al. Short-term effects of rituximab in children with steroid- and calcineurin-dependent nephrotic syndrome: a randomized controlled trial, Clin J Am Soc Nephrol, 201, vol. 6 (pg. 1308-1315)
22. Dumas De La Roque C, Combe C, Rigothier C. [Up to date of pathophysiology mechanism of idiopathic nephrotic syndromes: Minimal change disease and focal and segmental glomerulosclerosis]. Nephrol Ther. 2018 Dec;14(7):501-506. [PubMed]
23. Niu XL, Hao S, Wang P, Zhang W, Guo GM, Wu Y, Kuang XY, Zhu GH, Huang WY. Single dose of rituximab in children with steroid-dependent minimal change nephrotic syndrome. Biomedical reports. 2016 Aug 1;5(2):237-42.
24. Kallash M, Smoyer WE, Mahan JD. Rituximab use in the management of childhood nephrotic syndrome. Frontiers in pediatrics. 2019 May 10;7:178.
25. Maratea D, Bettio M, Corti MG, Montini G, Venturini F. The efficacy and safety of rituximab in treating childhood nephrotic syndrome: an Italian perspective. Italian journal of pediatrics. 2016 Dec;42(1):1-4.