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Original Article

To determine the Safety and Efficacy of Rituximab in Children with Steroid-Resistant Nephrotic Syndrome- A Hospital-based Prospective observational study from Kolkata

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ABSTRACT

Purpose: This study evaluates the safety and efficacy of Rituximab (RTX) as a second-line immunosuppressive therapy for children with difficult steroid-resistant nephrotic syndrome (SRNS). **Procedures:** A prospective observational study was conducted at IPGME&R, Kolkata, between January 2015 and December 2016. The cohort included 14 patients (aged 1–16 years) with SRNS who were calcineurin inhibitor (CNI) resistant or dependent. Patients received RTX (375 mg/m² weekly for four doses), with a second course administered at six months if no response was achieved. Primary outcomes were complete (CR) and partial remission (PR) rates at 12 months. **Findings:** At the 12-month follow-up, 42.8% (n=6) of patients achieved remission, consisting of four cases of CR (28.57%) and two cases of PR (14.28%). Proteinuria levels significantly decreased from a baseline mean of 3584.33 mg/24h to 315.50 mg/24h at 12 months (p=0.039) in the responding group. Infusion-related reactions occurred in 42.8% of cases, including one case of anaphylactoid reaction and one mortality attributed to cumulative clinical severity. **Conclusions:** Rituximab provides a reasonable treatment option for a subset of children with difficult SRNS, offering a potential steroid-sparing benefit and remission where other therapies have failed.

Keywords*: Rituximab, Nephrotic Syndrome, Steroid-Dependent, frequently relapsing, Steroid-Sparing Agents.*

INTRODUCTION

Childhood Onset Nephrotic Syndrome is the most common chronic glomerular disease in children. It includes Minimal change disease (MCD), Focal segmental glomerulosclerosis (FSGS) and Diffuse mesangial disease. Majority of these patients, up to 90%, respond to initial corticosteroid therapy. Of these children have 80–90% chance of having one or more relapses.[1,2] Half of those that relapse have infrequent relapses and can be managed with short courses of prednisone. The remaining children have FRNS or SDNS[1,2]. Five to ten percent of these patients do not respond to steroid and they are considered to have Steroid resistant nephrotic syndrome(SRNS). SRNS generally, and FSGS specifically, is associated with a 50% risk for ESRD within 5 years of diagnosis, if patients do not achieve a partial or complete remission.[3]

While treating these patients first issue is to attain remission, and second issue is to reduce the therapeutic side effects. [4] Cyclosporine has been most widely studied for treatment of SRNS. Tacrolimus has been compared to cyclosporine in one study with 41 total participants [5] and showed no significant difference in control of proteinuria. Relapse in up to 70% of

those responding to CNI therapy has been documented after discontinuation of 6- and 12-month courses of therapy. Extension of therapy beyond 12 months to prevent relapse is common practice; however, the impact of this approach on relapse risk, long-term kidney function, and risk for nephrotoxicity has not been established. Cyclophosphamide is not indicated in patients with SRNS.[4] We have limited drugs to treat SRNS. So we are in search of molecules which can help patients with SRNS.

Multiple recent studies stressed the role of Rituximab in these cases. Recent metanalysis has suggested that Rituximab has reasonable role in these cases.[6] Rituximab is a monoclonal antibody against CD-20 marker that prevents proliferation and differentiation of B lymphocytes.[6] Rituximab has been used successfully in patients with non-Hodgkin lymphoma, Rheumatoid Arthritis, Systemic Lupus Nephritis, Vasculitis. Recently its role has been included in the treatment of Difficult Nephrotic Syndrome.[7]

The present study will be done to assess the safety and efficacy of Rituximab in treatment of SRNS in children.

OBJECTIVES

1) To estimate the complete remission and partial remission rates with Rituximab in SRNS patients.
2) To determine the clinical toxicity of Rituximab.

MATERIALS AND METHODS

1. **STUDY AREA:** Department of Nephrology; IPGME&R; Kolkata
2. **STUDY POPULATION:** Patients with SRNS who were CNI resistant or CNI dependent and /or have serious side effects of CNI, attending Nephrology OPD/ admitted in nephrology wards of SSKM hospital.

3) **STUDY PERIOD:** January 2015 to December 2016
4) **STUDY DESIGN**: Hospital based prospective observational study
5) **SAMPLE SIZE:** 14
6) **PARAMETERS STUDIED:**

A) Biochemical

i. urine routine & microscopy
ii. 24 hour urine protein.
iii. Urine protein creatinine ratio OR urine albumin creatinine ratio
iv. Renal function test :
    a. Serum urea (GLDH Urea's Method by autoanalyser)
    b. serum creatinine (Alkaline picrate method of Jaffe's reaction)

GFR will be calculated using Schwartz formula.
Schwartz formula = kL / Serum creatinine.
L is height in cms, k is a constant. The value of k being as follows:

a) For term infants upto 1 year of age 0.45
b) For children and adolescent girls 0.5
c) For adolescent boys 0.7

v. Serum sodium/potassium/chloride (Flame photometry method)
vi. Serum calcium/phosphate: Direct calorimetry with complex agents
vii. Serum Alkaline Phosphatase: P-nitrophenyl Pyrophosphate method
viii. Serum Albumin: Dye binding Capacity buffer method
ix. ANA tested by**:** Enzyme immunoassay.
x. Anti ds-DNA tested by: ELISA (Chorus Trio System)
xi. C3 levels by: EIA
xii. FBS
xiii. Evidence of clinical toxicity of tacrolimus: Hypertension, tremors, new onset diabetes mellitus, renal impairment,
xiv. Complete hemogram
    a. Hemoglobin: Sahli's Method
    b. Total Leucocyte Count: Neuber's Chamber Method
    c. Differential Count: Blood film

B) Radiological

Ultrasound (USG) for kidney size, margin, corticomedullary differentiation, evidence of hydronephrosis, presence of calculus

C) Histopathological

Renal biopsy findings prior to Rituximab therapy.

INCLUSION CRITERIA:

0. Children aged 1- 16 years and adults diagnosed with SRNS
1. Patients with MCD, FSGS, and Diffuse mesangial disease on renal biopsy were in the study.

EXCLUSION CRITERIA:

0. Onset less than 1 year of age.
1. Patients with eGFR < 30 ml/min/1.73sq mt
2. Patients with MPGN or MN on renal biopsy
3. Patients with secondary cause of nephrotic syndrome.
4. History of inflammatory nephritis such as IgA nephropathy
5. History of serious infectious diseases such as Tuberculosis, fungal diseases
6. HCV, HBV and HIV infections
7. Live vaccine administration within 4 weeks of starting therapy
8. Uncontrolled hypertension with standard agents
9. Abnormal LFT Ex AST or ALT > 2.5 × upper normal limit
10. Presence or history of angina pectoris, myocardial infarction, serious arrhythmias
11. Presence or history of autoimmune diseases such as Hashimoto disease, Crohn's disease, Ulcerative Colitis, Rheumatoid Arthritis, SLE, Autoimmune Hemolytic Anemia, Scleroderma etc
12. Presence or history of cancer
13. History of Organ Transplantation
14. Hematological disorder such as WBC<2000/mcL,Neutrophil <1500/mcL, Plt < 50000/mcL
15. History of taking monoclonal antibody therapy in the past
16. Pregnant patients or patients who do not agree for contraception during the study period

METHODS

This was a prospective observational study with inclusion of retrospective cohort who were being treated with the same protocol since 2013.

All the SRNS cases enrolled since 2013 and managed as per my thesis protocol were followed up and the new cases were managed as per the thesis protocol.

Patients with difficult SRNS were treated with Rituximab at a dose of 375mg/m^2 once every week for four doses. SRNS patients who did not respond to first four doses received second course of Rituximab therapy at 6^{th} month. Second course included two doses of Rituximab at a similar dose.

Rituximab dissolved in normal saline at concentration of 2mg/ml was infused over 3-4 hrs. Premedications used were oral acetaminophen (15mg/kg) and oral diphenhydramine (0.5mg/Kg) 30 mins prior to Rituximab. Intravenous Hydrocortisone (4mg/Kg) was given prior to first dose of Rituximab. Patients were monitored for infusion related reactions and screened for infection at each visit.

Patients body surface area was calculated using following formula;
BSA = √Height in cms ×body weight in kg ÷3600

All the patients received ACE inhibitors or ARB, and other supportive therapy as required. The dose of Enalapril was 0.2-0.3mg/kg/day. If required for blood pressure control the dose of Enalapril was increased to 0.4-0.5mg/kg and Amlodipine 0.1-0.3mg/kg/day was added if needed. Patients intolerant to Enalapril were treated with Losartan at 0.7mg/kg/day and increased upto 1.4mg/kg/day if required for blood pressure control. Furosemide used for control of edema, if needed. Patients with blood cholesterol >130 mg/dl were treated with Atorvastatin.

The children were followed twice weekly initially for the first month, followed by monthly visits. They were subjected to a baseline assessment of standard biochemical parameters: serum glucose, serum creatinine, serum urea, serum electrolytes, serum albumin, serum cholesterol and complete blood count. Biopsy was done initially if not done previously or to diagnose CNI toxicity. 24 hour urine protein and uPCR/urine ACR was initially done, then once in 2 weeks till remission, then will be subsequently monitored with urine dipstick and uPCR/urine ACR for detection of relapse.

On follow up, each patient was subjected to clinical assessment including height, weight, blood pressure monitoring and signs of infection. Also a repeat urine dipstick, uPCR/urine ACR, blood glucose, serum protein, serum albumin, and serum cholesterol and serum creatinine estimation was done at each follow-up visit.

End Points:
1: The primary outcome measure was cumulative number of patients who experience complete remission (CR) or partial remission (PR).
2: The secondary outcome measures were time required for CR, cumulative number of sustained remissions, relapse rate, renal function during treatment and follow-up, steroid sparing effect, side effects.

PLAN FOR ANALYSIS OF DATA
Statistical analysis was done by statistical software SPSS. Continous data was expressed as means ± SD. The differences for normally distributed continuous variables between two groups were compared by an independent *t*-test. A paired *t*-test was performed to analyze changes within each group during therapy. The nonparametric variables were expressed as median and range and were compared using the Mann–Whitney test. The chi-square test was used to compare the cumulative proportion of patients who had complete or sustained remission with patients who had relapses. A *P* value of ≤ 0.05 was considered statistically significant.

RESULTS
Total of 14 cases were included in this study. Out of which, 6 cases were Primary SRNS and 8 cases were Secondary SRNS. Of the total cases, 6 cases were male and 8 cases were female. Histologically, 9 cases were FSGS and 5 cases were MCD. At the time of onset of nephrotic syndrome, 10 out of 14 cases were below the age of 18 yrs. At the time of treatment with Rituximab 9 cases were below the age of 18 yrs. Three cases had their onset of nephrotic syndrome before the age of 2 yrs. None of the cases received Rituximab prior to the age of 2 yrs. Seven cases were between the age of 2 - 18 yrs at the onset of nephrotic syndrome and 9 cases were between the age of 2-18 yrs at the time of Rituximab therapy. Five cases achieved partial remission at the end of 1st month and 3rd month. None of the cases were in complete remission till the end of 3rd month. Five cases achieved some remission at the end of 6th month. Two were in complete remission and 3 were in partial remission at the end of 6th month. By the end of 12th month, 6 cases out of 14 cases were in some remission. Among these 6 cases, 4 were in complete remission and 2 were in partial remission. At the end of study 4 out of 14 cases achieved complete remission and 2 out of 14 cases achieved partial remission. Eight out of 14 cases did not show any remission at any point of time.

Table 1- Characteristics of patients

SRNS PATIENTS CHARACTERISTICS		
NUMBER OF PATIENTS		14
AGE AT THE ONSET OF FIRST EPISODE OF NEPHROTIC SYNDROME	0- 2YRS	3
	3- 6 YRS	4
	7-10 YRS	1
	11- 14 YRS	0
	15. 18 YRS	2
	> 18 YRS	4
AGE AT THE TIME OF RITUXIMAB USAGE FOR SRNS	1- 2YRS	0
	4- 6 YRS	2
	7-10 YRS	3
	12- 14 YRS	1
	16. 18 YRS	3
	> 18 YRS	5
GENDER	MALE	6
	FEMALE	8
TYPE OF SRNS	PRIMARY SRNS	6
	SECONDARY SRNS	8
HISTOLOGY PATTERN	MCD	5
	FSGS	9
HISTOLOGY PATTERN IN PRIMARY SRNS	MCD	1
	FSGS	5
HISTOLOGY PATTERN IN SECONDARY SRNS	MCD	4
	FSGS	4

Table 1 shows the baseline clinical and demographic data of the SRNS study population. The cohort showed a slight female preponderance (57.1%, n=8) and a significant distribution of late-adolescent or adult patients, with 57% (n=8) aged 16 years or older at the time of Rituximab administration. Pathological evaluation revealed that **Focal Segmental Glomerulosclerosis (FSGS)** was the predominant histological pattern, accounting for 64.3% (n=9) of total cases, compared to **Minimal Change Disease (MCD)** at 35.7% (n=5). Notably, FSGS was highly prevalent in the **Primary**

SRNS subgroup, representing 83.3% of those cases (5 out of 6). In contrast, the **Secondary SRNS** subgroup displayed an equal distribution between FSGS and MCD (n=4 each). These baseline characteristics underscore the high-risk nature of the study group, particularly given the strong association between primary steroid resistance and FSGS histology

Table 2 -Total Remission rates attained at follow up of the SRNS patients.

Month of follow up	No Remission(%)	Partial Remission(%)	Complete Remission(%)	Total
1 month	9 (64.28)	5 (35.71)	0	14
3 months	9 (64.28)	5(35.71)	0	14
6 months	9(64.28)	3 (21.42)	2(14.28)	14
9 months	8(57.14)	2(14.28)	4 (28.57)	14
12 months	8 (57.14)	2(14.28)	4(28.57)	14
Chi-square 10	df 8	Probability= 0.65		

Table 2 shows the longitudinal response to Rituximab therapy over a 12-month observation period. At the 1-month and 3-month intervals, 35.7% (n=5) of patients achieved partial remission (PR), with no cases of complete remission (CR) recorded. The therapeutic response evolved by the 6-month mark, with the emergence of CR in 14.28% (n=2) of the cohort. By the end of the 12-month study period, the total response rate was 42.8%, comprising 28.57% (n=4) in CR and 14.28% (n=2) in PR. Statistical analysis using the Chi-square test (Chi-square: 10; df: 8; p=0.65) indicated that while the number of patients in remission increased over time, the distribution across follow-up intervals did not reach statistical significance. These findings suggest that while a subset of difficult SRNS patients benefits from Rituximab, the transition to complete remission is often delayed, occurring primarily between the 6th and 9th months of therapy.

Table 3-Comparison of mean proteinuria in SRNS patients who achieved Complete or partial remission during therapy (n=6)

24 hr urine protein	Mean	Std Dev	Minimum	Maximum	Median	p-value
Base line	3584.33	3446.932	762	10300	2250.00	p=0.039
1 month	2801.83	2734.488	690	8065	1648.00	
3 months	1978.17	1754.473	705	5463	1328.50	
6 months	1008.33	1379.427	152	3760	565.00	
9 months	271.33	239.691	85	681	176.00	
12 months	315.50	223.358	67	640	233.00	

Table 3 data indicates a significant clinical response among the six patients who achieved remission. There was a progressive and statistically significant reduction in 24-hour urine protein levels from a baseline mean of 3584.33 mg to 315.50 mg at the end of the 12-month follow-up period (p=0.039). The most substantial reduction was observed between the 6th and 9th months, where mean proteinuria dropped by approximately 73%, aligning with the timing of complete remission for four of these patients.

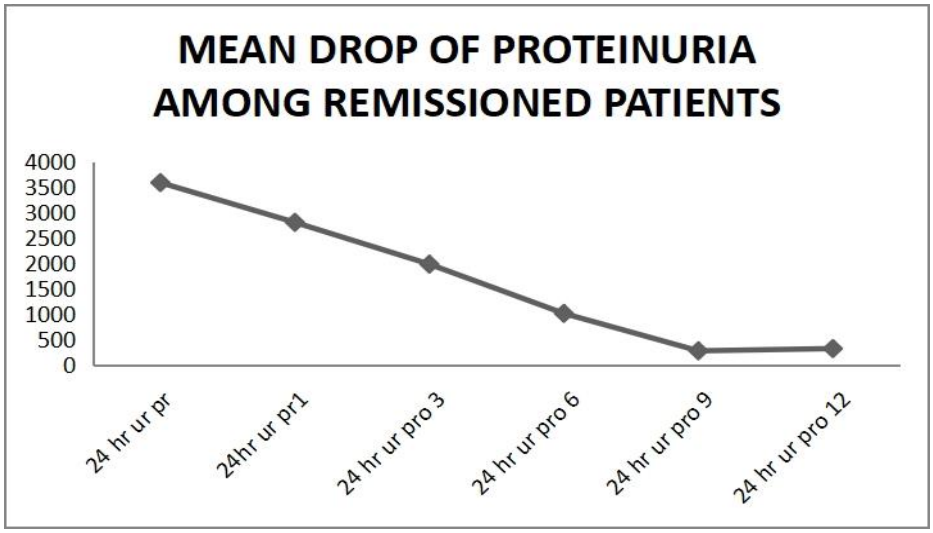

Figure 1- Mean proteinuria in SRNS patients who did not achieve Complete or partial remission during therapy (n=8)

In contrast to the responder group, the eight patients classified as non-responders showed persistent high-grade proteinuria throughout the study period. These patients failed to achieve either complete or partial remission at any point during the 12-month follow-up. This highlights that while Rituximab is effective for a subset of SRNS cases (42.8%), a significant proportion remains refractory to this therapy, emphasizing the need for alternative interventions or genetic screening to identify potential inherited causes.

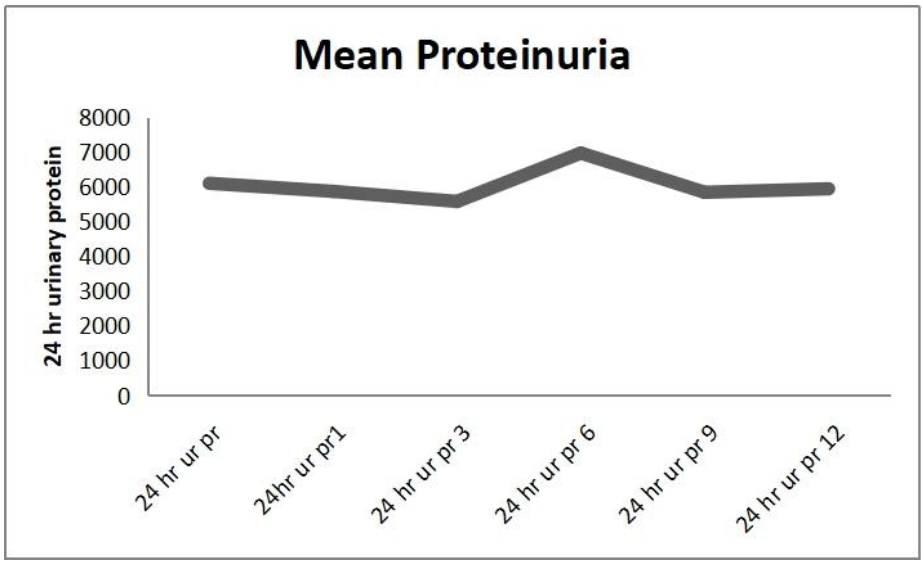

Figure 2

List of all the adverse events seen in study group.

Adverse events	Number of patients
Chills and rigors during infusion	3
Back pain during infusion	1
Chest pain during infusion	1
Oral candidiasis	1
Lower lobe pneumonia-Outpatient treatment	1
Suspected fungal septicemia- Treated	1
Anaphylactoid reaction after 2nd dose	1*
Death	1*

*These 2 cases were not included in the analysis as they received only one dose of Rituximab and second dose was terminated because of anaphylactoid reaction. They did not give consent for second challenge of drug.

DISCUSSION

In out study efficacy of Rituximab was mild to moderate; remission was achieved in 42.8% patients with SRNS. The patients reported here include mostly children (4 were adults) with SRNS who had either responded unsatisfactorily to treatment with multiple immunosuppressive agents including cyclophosphamide, levamisole, MMF, cyclosporine, and tacrolimus. Patients with Primary SRNS received only steroid and Calcineurin inhibitors. Because occurrence of remission is considered an important predictor of long-term outcome[8], the demonstration of complete or partial remission in 6 of 14 patients (42.8%) with SRNS, who were otherwise refractory to all proven therapies, is valuable. Secondary SRNS patients responded better but it was not statistically significant. Genetic tests were not done and hence some inherited nephrotic syndrome patients might be present in Primary SRNS group and it might have resulted in poor results in Primary SRNS. There was no statistical difference of treatment response between MCD and FSGS. In a study conducted by Gulati A et al, 33 patients with SRNS were studied. Six months after rituximab therapy, 9 (27.2%) patients with SRNS showed complete remission, 7 (21.2%) had partial remission, and 17 (51.5%) had no response. At 21.5±11.5 months, remission was sustained in 15(45%) (Complete: 7, partial: 8) patients[9]. Similarly Magnasco et al[10], Ito et al[11]and Prytula et al[12] reported complete remission in 18.7%, 31.6% and 22% of patients respectively. Ito et al[11] and Prytula et al[12] reported partial remission in 31.6% and 44% of patients respectively. Hence among these studies overall response rate ranged from 45% to 66%. Our result of 42.8% is quite comparable with these studies.

The risk of side effects attributed to Rituximab is variable. The multicentric French report found transient adverse effects in 45%, including one with P. carinii pneumonia[13]. Prytula et al.[12] reported acute reactions in 27% patients and a high incidence of severe side effects including anaphylaxis and serious infections. Another case series reported occasional cases of reversible cytokine shock and neutropenia, with no risk of severe infections[14]. In a study by Gulati A et al, mild

infusion-related reactions, none meriting discontinuation of therapy, were seen in 7% of patients; there were no serious adverse events. None of the patients had serious infections[9]. In our study both transient and serious side effects were seen. Infusion reactions were observed in 42.8% of cases. It included chills and rigors, chest pain, back pain and 1 cases of anaphylactoid reaction. Anaphylactoid reaction included angioedema and shock. Death occurred in a child with Primary SRNS after 5 days of first dose of Rituximab. Mortality is very high in any child with uncontrolled Nephrotic syndrome. However another study quoted significant fall in CD20 B cell count by 3rd day and hence it may be attributed to Rituximab.[15] Hence, physicians must be aware of potentially life-threatening side effects, including anaphylactoid reactions, infections.

LIMITATIONS

This report has multiple limitations, the main limitation being the lack of a control group. However, all patients had prolonged illnesses that were refractory to standard therapy, and apart from tapering doses of steroids, none of the patients did not receive any other concomitant therapies. Although it is unlikely that the observed impact of therapy with Rituximab was fortuitous, prospective controlled trials are necessary to confirm the efficacy of this agent. Second, sample size is small. Third, genetic studies were not done and hence inherited causes of nephrotic syndrome were not excluded. It might have under estimated efficacy of Rituximab in patients with SRNS. Fourth, CD19 and CD20 counts were not measured in our study. The number of doses of Rituximab used was thus based on experience rather than targeting specific CD19 and CD20 levels.

CONCLUSION

Although there might be a bias for reporting favorable outcomes, findings from this and previous studies suggest that therapy with Rituximab benefits a proportion of patients with Difficult SRNS. Future studies are needed to analyze clinical, histologic, and other features associated with a satisfactory response to Rituximab. Although therapy is expensive, Rituximab was safe and offers an acceptable second line option in immunosuppression for Difficult SRNS. Until then, treatment with Rituximab should be considered in patients with Difficult SRNS who are refractory to other medications or show evidence of calcineurin inhibitor side effects.

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