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Original Research Article

Efficacy and Safety of Treatment with Rituximab for Steroid-Resistant and Dependent Nephrotic Syndrome

Acharya A[1], Naik H[2], Rout S[3]

[1]Assistant Professor, Department of Nephrology, SCB Medical College, Cuttack, Odisha, India

[2]Assistant Professor, Department of Surgery, SCB Medical College and Hospital, Cuttack, Odisha, India

[3]Professor and HOD, Department of Nephrology, SCB Medical College and Hospital, Cuttack, Odisha, India

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Corresponding author: Dr. Aruna Acharya

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Abstract

Background: Rituximab is considered to be a promising drug for treatment of patients with nephrotic syndrome (NS). However, the efficacy and safety of rituximab remain inconclusive.
Objective: To investigate the efficacy and safety of rituximab in patients with steroid resistance/ dependent nephrotic syndrome (SRNS/SNS).
Methods and materials: This prospective observational study was conducted among patients with NS during January 2018 to December 2020. Patients with SRNS or SDNS treated with intravenous rituximab were included in this study. Demographic details included age, immunosuppressant therapy at the time of rituximab, duration of remission, and post-treatment complications were obtained and recorded.
Results: Out of 13 patients, eight patients had SRNS, and the remaining five had SDNS. In SRNS group, the proportion of male patients was higher than female patients (62.5% vs. 37.5%). The mean protein to creatinine ratio was higher in patients with SDNS than SRNS (8.1 vs. 6.9 mg/mmol). The median 24 h albumin level was comparable between the two groups (500.0 mg/24 h). After rituximab therapy, the remission observed was comparable in both the SRNS and SDNS groups (22.0 months). Three patients with SRNS had some post-treatment complications such as chicken-pox, convulsions, and massive pleural effusion (n = 1, each).
Conclusion: Rituximab may be an effective and relatively safe alternative which is well-tolerated in patients with minimal side-effects and reduced relapse incidences.

Keywords: Protein to creatinine ratio, remission, safe, SRNS.

Introduction:

Nephrotic syndrome (NS) is one of the most prevalent manifestations of kidney disease. It has a global prevalence of about 1.15-16.9 new cases per 100,000 adults [1]. In India,

childhood NS has an overall incidence of about 90-100 per million population [2]. It can be of two types, primary mainly due to kidney disease and secondary mainly due to some systemic disorder such as diabetes mellitus [3]. The most common causes of NS are minimal change disease (MCD), membranous neuropathy, and focal segmental glomerulosclerosis (FSGS) [4].

The patients of NS who develop resistance to immunosuppressants are defined as steroid resistance nephrotic syndrome (SRNS). Steroid dependent nephrotic syndrome (SDNS) is defined as steroid-sensitive nephrotic syndrome with 2 or more consecutive relapses during tapering steroids therapy [5].

The treatment of NS mainly includes fluid and sodium restriction, oral diuretics, and angiotensin-converting enzyme inhibitors. The corticosteroid treatment may benefit some patients [6]. In order to avoid steroid toxicity, steroid-sparing agents like calcineurin inhibitors (CNIs) are used. however, therapeutic options are limited in patients with SRNS as they show resistance against CNIs and alkylating agents. Hence, these patients are more prone to the complications associated with this disease. They require longer immunosuppressive therapy and are at the higher risk of developing progressive renal injury thus they require some alternative treatments [7]. Currently, rituximab has shown efficacy for SDNS and frequently relapsing NS [8]. Hence, it is an effective treatment modality to induce or prolong clinical remission in patients with NS.

However, the efficacy and safety of rituximab remain inconclusive in patients SRNS and SDNS, thus the present study particularly focuses on the use of rituximab for NS. The present study was aimed to evaluate the efficacy of rituximab as a treatment modality in patients with SRNS/SDNS.

Material and methods

Study design and participant criteria

This was prospective observational study conducted among patients with NS recruited from the department of Nephrology at SCB medical college and hospital, Odisha, India during January 2018 to December 2020. The study was conducted in accordance with ethical principles that are consistent with the Declaration of Helsinki. The study protocol was approved by Institutional Review Board/ Ethics Committee. Written informed consent was obtained from all the patients. The inclusion criteria were patients of either sex, with a confirmed diagnosis of NS. Exclusion criteria were as follows: patients with pregnancy, severe medical conditions, including uncontrolled hypertension, cardiovascular, pulmonary disease, neutropenia or thrombocytopenia.

Treatment protocol

The medical treatment consisted of a combination of intravenous rituximab (375 mg/m^2; maximum of 500 mg), steroids and/or CNIs, whereas patients in the control group were treated steroids and/or CNIs. As long as remission was maintained, oral corticosteroids was reduced to 40 mg/m^2 and were given as a single dose on alternate days for 4 weeks. After 4 weeks of treatment the dose was tapered by 25% for 3 months. Patients continued their pre-enrolment treatment with rituximab, steroids and CNIs once remission was achieved, the steroid dose was reduced by 25% every 4 weeks, followed by CNIs tapering.

Data collection

Demographic details included age, sex, renal histology, duration of biopsy and NS, previous immunosuppressive therapy, biochemical parameters, and urine analysis

were recorded. Immunosuppressant at the time of rituximab, duration of remission, and post-treatment complications were obtained and recorded.

Statistical analysis

Data were analysed using Statistical Package for The Social Sciences (SPSS) software, version 22.0. Qualitative data was presented as number and percentages, while quantitative data was presented as mean (standard deviation [SD]) or median (range), depending on the normal or skewed distribution of data.

Results

Baseline characteristics of patients with SRNS and SDNS

A total of 13 patients were included in this study. Out of this, eight patients had SRNS, and the remaining five had SDNS. The average age of the patient was comparatively higher in SRNS group than in SDNS (17.0 vs. 14.0 years). In SRNS group, the proportion of male patients was higher than female patients (62.5% vs. 37.5%). In SDNS group, the proportion of female patients was higher than male patients (60.0% vs. 40.0%). The most frequently seen histological finding on the renal biopsy was MCD in six and two patients, respectively from SRNS and SDNS group. Single patient from SDNS group noted FSGS in renal histology. The longer disease duration was observed among patients with SDNS than SRNS (9.0 vs. 6.5 years). Prednisolone was administered to eight and five patients respectively from SRNS and SDNS group, respectively. Only one patient with SDNS, received rituximab and three patients with SRNS and single patient with SDNS, were administered tacrolimus (Table 1).

Biochemical parameters

The mean systolic pressure was slightly higher in patients with SDNS than patients with SRNS (132 vs. 123.8 mmHg). Similarly, the mean diastolic pressure was slightly higher in patients with SDNS than patients with SRNS (82.0 vs. 76.3 mmHg). The mean protein to creatinine ratio was higher in patients with SDNS than SRNS (8.1 vs. 6.9 mg/mmol). The median 24 h albumin level was comparable between the two groups (500.0 mg/24 h), as reported in urine analysis (Table 1).

Table 1: Baseline characteristics of patients with steroid-resistant and steroid-dependent nephrotic syndrome

Parameters	**SRNS (n = 8)**	**SDNS (n = 5)**
Age (years)	17.0 (8.0-48.0)	14.0 (8.0-17.0)
Sex, n (%)		
Men	5 (62.5)	2 (40.0)
Women	3 (37.5)	3 (60.0)
Age at onset (years)	8.0 (2.5-44.0)	3.0 (2.5-4.0)
Renal histology, n (%)	[n = 6]	[n = 3]
MCD	6 (100.0)	2 (66.7)
FSGS	-	1 (33.3)
Duration of biopsy (years)	14.0 (12.0-44.0)	9.0 (5.0-10.0)
Duration of NS (years)	6.5 (4.0-10.0)	9.0 (6.0-10.0)

Parameters	SRNS (n = 8)	SDNS (n = 5)
Previous immunosuppressive therapy, n (%)		
Prednisolone	8 (100.0)	5 (100.0)
Rituximab	-	1 (20.0)
Tacrolimus	3 (37.5)	1 (20.0)
Levamisole	1 (12.5)	-
MMF	-	1 (20.0)
Cyclosporine	-	1 (20.0)
Biochemical parameters, mean (SD)		
SBP (mmHg)	123.8 (22.0)	132.0 (11.0)
DBP (mmHg)	76.3 (17.7)	82.0 (4.5)
Pulse rate (beats per min)	91.8 (36.3)	81.2 (5.0)
Protein-to-creatinine ratio (mg/mmol)	6.9 (3.0)	8.1 (3.0)
Serum urea (mmol/L)	32.3 (10.8)	30.6 (9.5)
Serum creatinine (mg/dL)	1.0 (0.4)	0.8 (0.2)
Albumin (mg/dL)	2.3 (0.3)	2.6 (0.2)
Urine analysis		
Albumin (mg/24 h)	500.0 (200.0-3050.0)	500.0 (500.0-3050.0)
Pus cells, n (%)		
≤5	6 (75.0)	5 (100.0)
6-15	2 (25.0)	-

Data shown as median (range) unless otherwise specified.
DBP, diastolic blood pressure; FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; MMF, mycophenolate mofetil; NS, nephrotic syndrome; SBP, systolic blood pressure; SDNS, steroid-dependent nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome

Immunosuppressant at the time of rituximab

In patients with SRNS, prednisolone and tacrolimus were administered in five (62.5%) and two (25.0%) patients, respectively. In SDNS, prednisolone, tacrolimus, and cyclosporine was given to three (60.0%), one (20.0%), and one (20.0%) patient, respectively (Table 2).

Remission

After rituximab therapy, the remission observed was comparable in both the SRNS and SDNS groups [22.0 months] (Table 2).

Side-effects

Three patients with SRNS had some post-treatment complications such as chicken-pox, convulsions patient, and massive pleural effusion (n = 1, each). No post-treatment side-effects were reported in SDNS group of patients. None of the patients had any other serious infection or adverse event on follow-up (Table 2).

Table 2: Intra-and post-treatment characteristics of patients

Parameters	SRNS (n = 8)	SDNS (n = 5)
Immunosuppressant at the time of rituximab		
Prednisolone	5 (62.5)	3 (60.0)
Tacrolimus	2 (25.0)	1 (20.0)
Cyclosporine	-	1 (20.0)

Remission [months], median (range)	22.0 (2.0-42.0)	22.0 (4.0-96.0)
Post-treatment complications		
Chickenpox	1 (12.5)	-
Convulsion	1 (12.5)	-
Massive pleural effusion	1 (12.5)	-
Data shown as n (%), unless otherwise specified. SDNS, steroid-dependent nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome.		

Discussion

This prospective study aimed at establishing rituximab as a treatment modality in patients with SRNS and SDNS. There were impressive results achieved as the trial concluded the potential role of therapy with rituximab in patients with SDNS and SRNS. The key findings were; the proportion of male patients with SRNS was higher than female patients; the urine analysis of patients reported pyuria in patients with SRNS; after rituximab therapy, the remission observed was comparable in both the SRNS and SDNS groups; mild infusion-related reactions were seen in SRNS patients

Male predominance in patients with SRNS observed in this study is in concordance with the previous studies [9,10]. The previous study by Ye et al. noted, a maximum number of male populations (69.2 vs. 30.8%) [11]. A retrospective study that included patients with SRNS from China revealed the male preponderance (71.4%) [12]. Imbusi et al. reported male predominance, with a male to female ratio of 4.2:1 [13]. Hammad et al. and Shah et al also reported higher number of their SRNS patients were male. However, there was no significant difference regarding sex (P = 0.057) [14,15].

Urine analysis of NS is characterized by a large amount of pus cells. A case study report by Kumar et al. reported 5-8 pus cells/high power field (HPF) in patients with SRNS. Pyuria (pus cells >10 per HPF) was observed in 48.0% and 52.0% of patients with SRNS in an earlier study by Kumar et al. and Aodedoyin et al [16,17]. Another case report by Dhingra et al reported pus cells of 4-6/HPF in patients with SRNS [18]. On the parallel line, the present study also revealed in patients with SRNS.

In two recent studies evaluating efficacy of rituximab in patients with SRNS/SDNS noted relapse-free survival in 50-70% and 41%-46% of SRNS and SDNS patients, respectively. The mean time to relapse was found to be 9.6 and 14.6 months [19,20]. Kamei et al. reported that the single dose of rituximab had a higher rate of relapse (75.0%) than those receiving 3-4 doses [21]. Kallash et al. studied the efficacy of rituximab in 15 patients with NS who have received one dose of rituximab. The results concluded that patients had significantly lower risk of relapse rate at 6 months, 1, and 2 years after treatment (P<0.01) and the median time to relapse was 18 months [8]. Liu D et.al, the evaluated the efficacy of rituximab and corticosteroid in patients with NS. The combined therapy which was proven to be effective in inducing remission rate with fewer side effects [22]. In parallel to this study present study revealed similar median relapse time of 22 months in patients with SRNS/SDNS.

Rituximab is generally well-tolerated in most published studies. The most common adverse events are mild infusion-related reactions however the risk of side effects and long-term safety attributed to rituximab is not fully known. Serious complications associate with rituximab therapy were arthritis, neuropathy, lung injury, serum sickness, and inflammatory bowel disease [23-25].

Previous multicenter study by Guigonis et al. evaluated the safety of rituximab in treatment of patients with SDNS. The authors concluded that rituximab as an efficient therapy for treatment for NS with no relapse of proteinuria and an increase in other immunosuppressive drugs [26]. A recent retrospective cohort study of 102 patients with NS who were treated with rituximab. In accordance with the present study the authors found that rituximab was associated with a longer remission time and fewer side effects than cyclophosphamide [27]. In this study, mild infusion-related reactions were seen in 23.0% of patients without any serious adverse events. However, physicians must also be aware of potentially life-threatening side effects, including multifocal leukoencephalopathy and acute lung injury.

The main limitation of this prospective study was that the small sample size which might lead to misinterpretation of results. The present study suggests performing multicenter randomized controlled study for analyzing the efficacy of rituximab in patients with SRNS and SDNS. Due to limited information, the relapse rates and post-treatment urine analysis were not evaluated in this study. This study did not record B-lymphocyte antigen CD-20 of the patients which could have added valuable data while inferring the observations.

Conclusion

It is quite evident that rituximab treatment was safe and well tolerated in patients, and it effectively reduced the incidence of relapses and need for maintenance immunosuppressive therapy in adults with difficult-to-treat SRNS and SDNS. In summary, by pooling results of current prospective studies, rituximab may be an effective and relatively safe alternative for most adult with SRNS/SDNS, to replace calcineurin inhibitors or prednisone in the standard treatment. It is well-tolerated in patients with minimal side-effects which was accompanied by reduced relapse incidences.

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