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Role of Rituximab as First Line Immunosuppressant in Primary Glomerulonephritis

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ABSTRACT

Background: Primary glomerulonephritis remains a significant cause of chronic kidney disease, often requiring immunosuppressive therapy. Rituximab, a monoclonal anti-CD20 antibody, has emerged as a potential first-line immunosuppressant. However, its efficacy across different histopathological subtypes remains unclear. This retrospective study evaluated the clinical and biochemical response to rituximab in patients with primary glomerulonephritis. **Methods:** This retrospective review analyzed medical records of patients treated with rituximab at the Nephrology Department of Lahore General Hospital from 2019 to 2023. A total of 18 patients with biopsy-proven primary glomerulonephritis who received rituximab as first-line immunosuppressive therapy were included. Patient data were retrieved, including baseline demographics, renal function tests, proteinuria, histopathological findings, and treatment response over six months. The primary outcomes were changes in serum creatinine, eGFR, and proteinuria at six months. **Results:** The study population included six patients with membranous nephropathy, four with FSGS, three with lupus nephritis, two with MPGN, and one each with MCD and IgA nephropathy. Proteinuria significantly decreased in patients with eGFR >30 mL/min/1.73m² ($p<0.0001$), while those with eGFR <30 mL/min/1.73m² showed no improvement ($p=0.9$). Histopathological response varied, with 35.7% of patients with mild fibrosis achieving complete remission, while none with moderate or severe fibrosis achieved full remission. **Conclusion:** Rituximab effectively reduces proteinuria in patients with preserved renal function, but its impact on eGFR remains limited. Histopathological severity correlates with treatment response, with poorer outcomes observed in patients with advanced fibrosis. Larger retrospective studies are needed to further evaluate rituximab's role as a first-line therapy in primary glomerulonephritis.

INTRODUCTION

Primary Glomerulonephritis is a key determinant of renal impairment, contributing to 14 - 20 percent of cases of end stage renal disease [1]. Risk of advancement to ESRD is determined by various factors including type of Glomerulonephritis with maximum for Focal Segmental Glomerulosclerosis (FSGS) and least in minimal change disease. Despite the availability of different forms of therapeutic regimens including immune-suppressants to plasma exchange therapy; treatment of glomerulonephritis still remains a therapeutic challenge to nephrologists worldwide. Rituximab offers an important alternative therapy in various forms of primary glomerulonephritis [2].

Rituximab is a chimeric monoclonal antibody against CD-20, cell surface receptors found on B-Cells but not on plasma cells. Up till now, it is an approved drug therapy for B cell lymphoma, CLL as well as rheumatoid arthritis, granulomatous polyangiitis and microscopic polyangiitis [3]. Because of its multifactorial mechanisms of causing immune modulation[4], for the last decade; rituximab has been increasingly used by nephrologists worldwide in treatment of various forms of primary glomerulonephritis ranging from nephrotic syndromes as MCD or FSGS and membranous nephropathy to proliferative immune-mediated glomerulonephritis as idiopathic MPGN, refractory lupus nephritis, cryoglobulinemic glomerulonephritis, antibody mediated renal allograft rejection and recurrent glomerular diseases in renal allograft with long term successful outcomes as proven in various Randomized Controlled Trials(RCTs) [5,6].

Novel data has provided the efficacy of rituximab in maintaining prolonged remission with the use of

rituximab as a first line therapy in primary glomerulonephritis particularly membranous and HCV related cryoglobulinemic vasculitis [7,8] while paucity of data for the utilization of rituximab as first line agent in various other forms of glomerulonephritis needs to be elucidated. This study retrospectively analyzed the role of rituximab in inducing and maintaining long-term remission as an alternative to conventional agents such as steroids, cyclophosphamide, and calcineurin inhibitors, based on previously treated cases.

MATERIAL AND METHOD

The study was executed at Nephrology Department of Lahore General Hospital (LGH) after obtaining Institutional Review Board (IRB) approval (IRB # 00-155-2023). This retrospective analysis was based on a review of medical records of patients who had received rituximab for treatment of primary glomerulonephritis. Informed consent was not required, as data were extracted from existing patient records, ensuring confidentiality and ethical compliance.

The study included 18 patients aged 14 to 56 years, both male and female. Only those patients who had received rituximab as first-line immunosuppressive treatment and had complete follow-up data available were included. Patients with a history of prior immunosuppressive therapy, active infections such as tuberculosis or hepatitis B, malignancy, or any other immunosuppressive treatment for their renal pathology were excluded from study. Data were retrieved from hospital records regarding patient demographics, clinical presentation, laboratory investigations, and treatment details.

Renal biopsy findings, previously analyzed by a renal pathologist, were recorded, including histopathological features and immunofluorescence results. Baseline laboratory investigations at the time of rituximab administration, as documented in patient files, were collected, including CBC, serum albumin, renal function tests, urine complete examination, and 24-hour urinary protein and creatinine levels. Autoimmune profiles such as ANA, anti-dsDNA, C3, and C4 levels were reviewed. Additionally, chest X-ray findings, hepatitis B and C serology, and pANCA and cANCA results (where applicable) were noted. Vaccination records for influenza and pneumonia were also reviewed for documentation of pre-treatment immunization status.

Patients had received rituximab therapy at a dose of 375 mg/m² (BSA) weekly for 4 weeks, as per documented treatment protocols. Body surface area was calculated using the Du Bois formula. Pre-medication with methylprednisolone (250–500 mg) was administered 30 minutes prior to rituximab infusion, and infusion-related reactions were monitored as per hospital protocols. For the first dose, patients were observed for 24 hours post-infusion, while for subsequent doses, they were monitored for at least six hours. Follow-up data were retrospectively collected from patient medical records. Monthly follow-up evaluations were recorded, including clinical assessments and laboratory investigations. Serial measurements of 24-hour proteinuria, serum creatinine and estimated glomerular filtration rate (eGFR), computed via the Modification of Diet in Renal Disease (MDRD) equation, were documented. Any recorded adverse effects or complications related to rituximab therapy were also noted. The primary outcome was proportion of patients achieving complete/partial remission at six months, based on documented clinical and laboratory data. Complete remission was defined as a reduction in 24-hour proteinuria to <500 mg per day, with eGFR >60 mL/min/1.73m² or stabilization within 10–15% of baseline. Partial remission was defined as 24-hour proteinuria between 500 mg/day and 3.5 g per day, with at least a 50% reduction from baseline and eGFR stabilization within 15–25% of baseline or a value between 30–60 mL/min/1.73m². Non-responders were defined as patients who failed to show a reduction in proteinuria or whose eGFR declined by >25% from baseline. Patients requiring renal replacement therapy were classified as having advanced to ESRD.

Statistical Analysis

Data analysis was carried out using SPSS version 26 and GraphPad Prism 8.4.3. Descriptive statistics compiled patient characteristics and clinical outcomes. Normally distributed quantitative variables were reported as mean ± standard deviation (SD), while non-normally distributed data were reported as median with interquartile range (IQR). The independent-samples t-test compared quantitative variables between two groups. Categorical variables were expressed as frequencies and percentages, with comparisons conducted using the chi-square (χ^2) test or Fisher's exact test, depending on sample size. Statistical significance was set at $p \leq 0.05$.

Results

Out of the 18 patients, 12 (66.67%) were males and six were females (33.37%), with mean age of 28±12.06 years (Table 1)

Table 1

Baseline Characteristics of Patients Receiving Rituximab for Primary Glomerulonephritis

Parameter	All Patients (n=18)	Membranous (n=6)	FSGS (n=4)	Lupus Nephritis (n=3)	MCD (n=1)	MPGN I (n=2)	IgA (n=1)
Mean Age (years)	28.89 ± 12.06	35.75 ± 14.9	28.5 ± 9.19	26.33	18	44	28

Gender (M/F)	M: 12, F: 6	M: 5, F: 1	M: 3, F: 1	M: 0, F: 3	M: 0, F: 1	M: 1, F: 1	M: 1, F: 0
Mean BMI (kg/m²)	20.58 ± 5.71	23.02 ± 1.09	21.08 ± 2.02	16.80 ± 4.04	18.4	24.0	22.0
Mean Serum Creatinine at Presentation (mg/dL)	2.02 ± 1.38	1.75 ± 0.83	1.18 ± 0.54	2.40	0.90	1.75	3.2
Mean eGFR at Presentation (ml/min/1.73m²)	53.33 ± 27.69	54.0 ± 48.83	55.0 ± 52.24	30.02	71	31	16
Mean 24-Hour Urinary Protein at Presentation (g/day)	7.04 ± 3.3	6.87 ± 3.61	7.40 ± 0.42	6.7	4.7	15	4.4
Mean Spot Urinary Protein:Creatinine Ratio	7.74 ± 2.32	10.44	7.56	5.8	4.67	11.39	4.45
Mean Serum Albumin (g/dL)	2.51	2.65	1.60	3.00	2.20	3.10	3.50

Based on e GFR at the time of rituximab administration, we divided the study population in two groups; one with e GFR >/= 30ml/min/1.73m^2 consisting of 13 patients (72%) and other with e GFR < 30ml/min/1.73m2 which included 5 patients (28%). Average time from clinical presentation and renal biopsy to the administration of rituximab therapy in both e GFR groups was less than 3 months with patients having acute or subacute decline in renal function. Statistically significant improvement was seen in e GFR > 30ml/min/1.73m^2 group both in terms of proteinuria (p value 0.0001) and serum creatinine (p value 0.01) compared to patients having e GFR <30ml/min/1.73m^2 at time of presentation (p value:0.9) (Figure 1).

Figure 1

The different Glomerulonephritis included in the study.

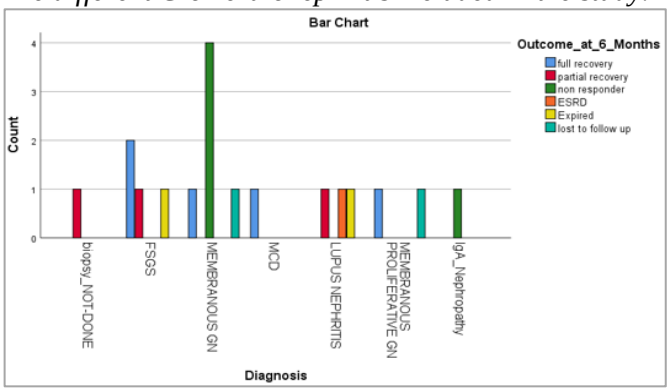
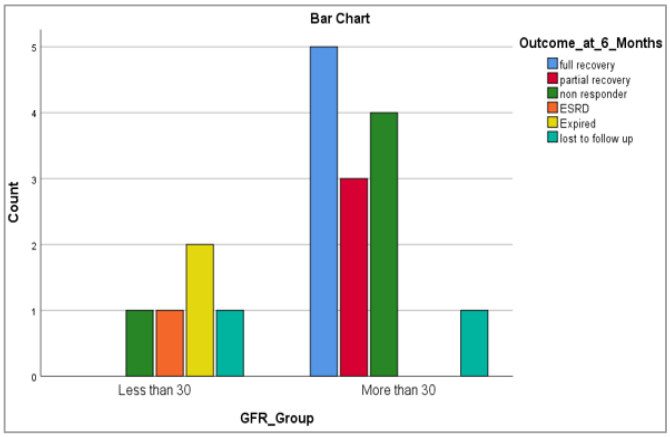


Figure 2

clinical outcomes at 6 months in patients having e GFR >30 and <30ml/min/1.73m2 at rituximab administration.



Our retrospective analysis included 18 patients, with membranous nephropathy being the most common diagnosis (n=6, 33.3%). The average age of patients with membranous nephropathy was 35.75 ± 14.9 years (95% CI: 20–56 years), and the average serum creatinine at presentation was 1.75 ± 0.83 mg/dL (95% CI: 0.7–2.66 mg/dL). The baseline eGFR was 54 ± 48.83 mL/min/1.73m², and the 24-hour urinary protein excretion was 6.87 ± 3.61 g/day (95% CI: 3.50–10.01 g/day). At six months, the average S/creatinine was 1.98 ± 1.15 mg/dL (95% CI: 0.61–3.30 mg/dL, p=0.4), and proteinuria had decreased to 3.94 ± 2.99 g/day (95% CI: 0.40–6.40 g/day, p=0.7). One out of six patients (16.7%) achieved complete remission, four (66.7%) were non-responders and 1 patient (16.7%) was lost to follow-up.

FSGS was second frequent diagnosis, comprising 22.2% (n=4) of the study population. The average age of patients with FSGS was 28.5 ± 9.19 years (95% CI: 22–35 years). Three patients (75%) had an eGFR >30 mL/min/1.73m², with a average creatinine of 1.18 ± 0.54 mg/dL at the time of biopsy, while one patient (25%) had an eGFR <30 mL/min/1.73m². By six months, 2 patients (50%) achieved complete remission, 1 (25%) showed partial remission (p <0.0001), and one patient (25%) with baseline eGFR <30 mL/min/1.73m² developed severe respiratory tract infection and expired.

Three patients with lupus nephritis were included, two with class V (membranous lupus nephritis) and one with class IV-A (diffuse proliferative lupus nephritis). None of these patients had received prior immunosuppressive therapy. All three were ANA-positive, with two showing low C3 and C4 levels. Among the 2 patients with membranous lupus nephritis, 1 (50%) achieved partial remission, while the other expired. The patient with class IV lupus nephritis did not benefit from therapy and progressed to ESRD (p=0.9).

Two patients with idiopathic immune complex-mediated membranoproliferative glomerulonephritis (MPGN I) were included. The patient with baseline eGFR >30 mL/min/1.73m² achieved complete remission by six months, while the other patient was lost to follow-up (p=0.5). A single patient with minimal change disease (MCD) received rituximab as a first-line agent without a prior trial of steroids and achieved complete remission

by six months. One patient with IgA nephropathy presented with rapidly worsening renal function over three months. Renal biopsy showed mesangial IgA deposits with an MEST-C score of M1S1E1T2C2. After discussing the risks and benefits, rituximab was administered; however, no improvement in proteinuria or eGFR was observed by six months, and the patient was classified as a non-responder.

Table 2

Change in Proteinuria Over Six Months in Patients Receiving Rituximab

Group	Proteinuria at Presentation (g/day) (Mean ± SD)	Proteinuria at 1 Month (g/day) (Mean ± SD)	Proteinuria at 2 Months (g/day) (Mean ± SD)	Proteinuria at 3 Months (g/day) (Mean ± SD)	Proteinuria at 4 Months (g/day) (Mean ± SD)	Proteinuria at 5 Months (g/day) (Mean ± SD)	Proteinuria at 6 Months (g/day) (Mean ± SD)	p-value
All Patients (17)	7.04 ± 3.30	4.75 ± 3.88	4.10 ± 3.30	3.64 ± 2.79	3.30 ± 3.12	3.21 ± 2.97	3.40 ± 3.49	0.01
Patients with eGFR >30 mL/min/1.73m² (13)	7.09 ± 3.35	3.71 ± 2.31	3.20 ± 2.45	2.79 ± 2.13	2.44 ± 2.42	2.30 ± 2.35	2.26 ± 2.40	<0.0001
Patients with eGFR <30 mL/min/1.73m² (4)	6.80 ± 3.75	8.89 ± 6.62	7.68 ± 4.40	7.03 ± 2.81	6.86 ± 3.44	6.83 ± 2.64	8.00 ± 3.78	0.9
Membranous Nephropathy (MN) (6)	5.99 ± 3.13	4.90 ± 2.24	4.64 ± 2.67	3.81 ± 2.25	3.85 ± 2.67	3.89 ± 2.67	4.05 ± 2.60	0.7
Focal Segmental Glomerulosclerosis (FSGS) (4)	7.46 ± 0.55	1.46 ± 1.19	1.11 ± 1.81	0.64 ± 0.66	0.41 ± 0.49	0.41 ± 0.51	0.58 ± 0.85	<0.0001
Minimal Change Disease (MCD) (1)	4.70 ± 0.00	1.80 ± 0.00	2.40 ± 0.00	3.50 ± 0.00	0.09 ± 0.00	0.10 ± 0.00	0.07 ± 0.00	N/A
Membranoproliferative GN Type 1 (MPGN I) (2)	5.50 ± 0.00	5.02 ± 3.25	4.10 ± 3.98	3.67 ± 3.67	5.00 ± 5.37	4.36 ± 4.80	4.85 ± 4.85	0.5
Lupus Nephritis (LN) (3)	8.63 ± 2.73	11.0 ± 7.07	9.11 ± 4.08	7.75 ± 3.18	7.01 ± 2.66	6.00 ± 2.44	7.57 ± 6.56	0.9
IgA Nephropathy (IgAN) (1)	3.80 ± 0.00	2.90 ± 0.00	3.90 ± 0.00	6.23 ± 0.00	4.55 ± 0.00	3.98 ± 0.00	4.90 ± 0.00	N/A

Table 3

Change in eGFR from Baseline to Six Months in Patients Receiving Rituximab

Group	n	Baseline eGFR (mL/min/1.73m²) (Mean ± SD)	eGFR at 6 Months (mL/min/1.73m²) (Mean ± SD)	p-value
All Patients	17	86.0 ± 27.4	122.9 ± 67.3	0.01
Patients with eGFR >30 mL/min/1.73m²	13	61.8 ± 23.0	106.5 ± 52.9	0.01
Patients with eGFR <30 mL/min/1.73m²	4	17.0 ± 4.3	16.4 ± 9.9	0.9
Membranous Nephropathy (MN)	6	59.2 ± 27.9	85.6 ± 84.1	0.4
Focal Segmental Glomerulosclerosis (FSGS)	4	51.7 ± 31.4	71.9 ± 51.5	0.4
Minimal Change Disease (MCD)	1	71.0 ± 0.0	129.0 ± 0.0	N/A
Membranoproliferative GN Type 1 (MPGN I)	2	35.5 ± 19.0	34.7 ± 44.2	0.9
Lupus Nephritis (LN)	3	30.0 ± 23.8	60.5 ± 77.1	0.5
IgA Nephropathy (IgAN)	1	25.0 ± 0.0	15.08 ± 0.0	N/A

Table:4 (below) shows the response to rituximab therapy relative to the degree of histopathological changes in terms of glomerulosclerosis, interstitial fibrosis and tubular atrophy. Mild changes were defined as having these chronic changes less than 25% of the total biopsy specimen, moderate being 25 to 50 % and severe as more than 50 %. In our study 77.78% patients were in the mild category of histological changes and 16.67% were in the moderate changes group while only one patient i.e 5.56% was of severe histological category.

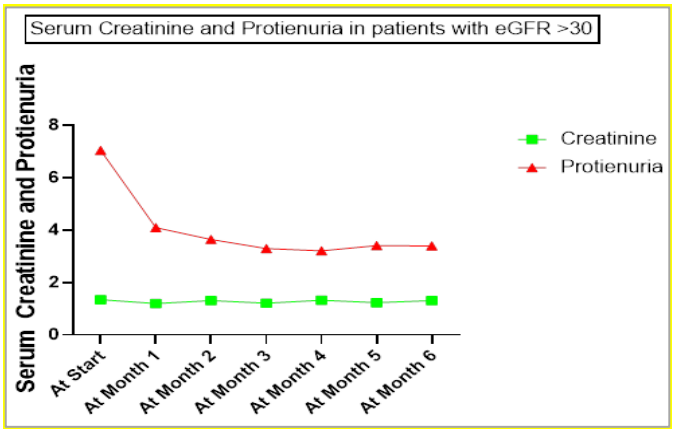
Table 4

Rituximab Response according to the degree of histo-pathological changes

Degree of glomerulosclerosis and interstitial fibrosis	Total patients	Complete remission	Partial remission	No response
Mild <25%	14	05	01	08
Moderate 25-50%	03	0	02	01
Severe >50%	01	0	01	01

Figure 3

monthly serum creatinine and proteinuria in patients with e GFR more than 30 ml/min/1.73m2.



DISCUSSION

Rituximab as an immunosuppressive therapy in various forms of treatment naive glomerulonephritis have shown variable results in our study. Because of its multiple mechanisms of action ranging from modulating B cell immune response and causing defective antibody mediated cell cytotoxicity to alteration in the process of antigen presentation, rituximab have shown effective outcomes in various glomerulonephritis from minimal change disease to proliferative glomerulonephritis [9].

Large number of clinical trials done so far including MENTOR Trial [8], GEMRITUX study [10] have shown rituximab superior to other therapies like cyclosporine and Ponticelli regimen (including steroids and alternating cyclophosphamide) in inducing long term remission in primary membranous nephropathy. Based on the fact that various auto antibodies as M type phospholipase A2 Receptor antibodies (anti-PLA2R antibodies) and Thrombospondin type 1 domain containing 7 (anti TSHD7A) along with newly discovered antibodies against Neural Epidermal growth factor like 1 (NELL-1) and anti semaphorin 3B autoantibodies, rituximab is now being considered as first line immunosuppression in primary membranous as per KDIGO guidelines (7). However, in our study only one patient of membranous nephropathy showed complete remission while 4 patients showed no response. This finding can be attributed to the fact that our follow up study period for this study was only 6 months while the majority clinical trials favoring rituximab therapy in membranous nephropathy have shown treatment response over 13 to 24 months after rituximab administration. To overcome this limitation, we expanded our followup duration which is still ongoing.

Role of rituximab in various podocytopathies like MCD and FSGS have been well studied. This is due to the direct effect of rituximab on podocyte receptors as sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b) [11]. Though the use of rituximab in adult MCD and FSGS is largely being studied as steroid and other immunosuppressant sparing agent but our study has shown beneficial outcomes in terms of complete remission with rituximab as first line immunosuppression in both adult MCD (100%) and FSGS (75%) patients not previously treated with steroids or other immunosuppressive drugs at 6 months. However, at present no randomized clinical trial is available comparing the effects of rituximab alone to other currently used agents as cyclophosphamide, cyclosporine and mycophenolate mofetil. To establish the role of rituximab in steroid-naive patients of MCD and FSGS studies on large population are required.

Recent advances in lupus nephritis treatment as Bliss LN study and AURORA-IV trials have shown Belimumab and Voclosporin respectively as an emerging therapy in class IV A lupus along with second generation of anti CD 20 antibodies such as Ofatumumab, Rituximab has been approved only for refractory lupus nephritis [12]. Our data showed a 50% response rate among membranous lupus nephritis(Class 5) while no response was seen with rituximab as an induction agent in the treatment- naive patients of diffuse proliferative lupus nephritis (class IV). Though our data was limited in lupus patients and larger clinical trial is required to study the outcomes of rituximab as an induction therapy In lupus nephritis. Likewise, among patients of immune complex mediated membrano-proliferative glomerulonephritis (idiopathic), a single patient showed full recovery in terms of proteinuria and creatinine improvement. This finding can be explained by the fact that B cells have a significant role in modulating immune complex mediated MPGN (idiopathic) [13,14].

Role of immunosuppression in patients of IgA nephropathy has always been a controversy among nephrologists. Recent KDIGO guidelines for IgA have shown beneficial effects of corticosteroids given for 6 months in patients of IgA having persistent proteinuria >1g/day and e GFR more than 50ml/min.1.73 m2, with few studies done on Asian population showing role of MMF. While patients of rapidly progressive glomerulonephritis are treated with steroids and cyclophosphamide [7,15]. Considering the fact that our study enrolled patient had features of crescentic IgA nephropathy **M1S1E1T2C2,** we administered rituximab along-with steroids but no response was seen at 6 months both in terms of GFR or proteinuria improvement.

Largely, our study data showed rituximab as effective in reducing proteinuria and stabilizing e GFR in patients having GFR of more than 30ml /min/m2 at the time of rituximab administration and lesser degree of glomerulosclerosis and interstitial fibrosis on biopsy, while no significant outcome was seen in patients of less than 30 ml/min/1.73m2 GFR group.

CONCLUSION

This study suggests beneficial effects of rituximab as first line immunosuppression in various primary forms of Glomerulonephritis particularly with baseline e GFR of more than 30ml/min/1.73m^2. However, larger and long term randomized controlled trials are required in various glomerular diseases to establish its therapeutic efficacy and safety compared to conventional immunosuppressant.

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