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Original Article

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Low Versus Standard Dose of Rituximab in Adult Patients with Relapsed or Refractory Primary Membranous Nephropathy: Does It Make Any Difference?

Şafak Mirioğlu[1,2], Arif Akyıldız[1], Ali Rıza Uçar[1], Ömer Uludağ[1], Yasemin Özlük[3], Ahmet Burak Dirim[1], Erol Demir[1], Özgür Akın Oto[1], Işın Kılıçaslan[3], Yaşar Çalışkan[1,4], Halil Yazıcı[1], Aydın Türkmen[1], Mehmet Şükrü Sever[1]

[1]Division of Nephrology, Department of Internal Medicine, İstanbul University, İstanbul School of Medicine, İstanbul, Türkiye
[2]Division of Nephrology, Department of Internal Medicine, Bezmialem Vakıf University, School of Medicine, İstanbul, Türkiye
[3]Department of Pathology, İstanbul University, İstanbul School of Medicine, İstanbul, Türkiye
[4]Division of Nephrology, Department of Internal Medicine, Saint Louis University, School of Medicine, MO, USA

ABSTRACT

Objective: Optimal dose of rituximab is still under debate in patients with primary membranous nephropathy, particularly who suffer from relapsed or refractory disease. We, therefore, analyzed the efficacy of low versus standard doses of rituximab in these patients.

Methods: Thirty-six consecutive patients with primary membranous nephropathy and characterized by proteinuria ≥3.5 g/24h despite at least 6 months of prior conservative and immunosuppressive therapy were included. Rituximab was administered in 2 different protocols: low dose (n = 20, 55.5%) (2 weekly doses of 375 mg/m^2) and standard dose (n = 16, 44.4%) (4 weekly doses of 375 mg/m^2). Primary outcome was defined as complete remission or partial remission.

Results: One patient who died due to sepsis caused by pneumonia shortly after rituximab and 1 who developed anaphylaxis during his first infusion were excluded from efficacy analyses. Overall, 34 patients were followed up for a median duration of 15.5 (interquartile range: 6-23.25) months after treatment. Nineteen (55.8%) patients experienced primary outcomes; among these, 12/18 (66.6%) were in low-dose group as compared to 7/16 (43.75%) in standard dose. The percentage of patients who underwent remission was similar in 24-month Kaplan–Meier analysis (P = .393). Five patients (27.7%) in low-dose group had a relapse, whereas no patients in standard dose group relapsed throughout the follow-up (P = .022). Carcinoma of the tongue developed in a patient, and 2 patients died due to sepsis caused by pneumonia.

Conclusion: Low and standard doses of rituximab showed similar efficacy in patients with relapsed or refractory primary membranous nephropathy, albeit lower doses were associated with more relapses.

Keywords: Clinical nephrology, glomerulonephritis, membranous nephropathy, nephrotic syndrome, proteinuria, rituximab

Corresponding author: Şafak Mirioğlu ✉ smirioglu@gmail.com

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INTRODUCTION

Primary membranous nephropathy (PMN), a frequent cause of nephrotic syndrome in adults, is a chronic disease characterized by a natural course of spontaneous remissions, expected almost in 30% of patients, and also frequent relapses.[1-3] Approximately 80% of cases with PMN are associated with the presence of circulating autoantibodies targeting podocyte antigens, such as M-type phospholipase A2 receptor (PLA2R), and rarely, thrombospondin type-1 domain containing 7A, neural EGF-like-1 protein, neural cell adhesion molecule 1, semaphorin 3B, and protocadherin 7.[4-6] Half of the affected patients, who do not go into remission, inexorably progresses to kidney failure over a period of 10 years; however, patients who reach even partial remission are characterized by an improvement in proteinuria and have quite favorable outcomes.[2] Therefore, it is imperative to aim for the remission of proteinuria with an effective treatment strategy to reduce the progression to kidney failure.

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According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, treatment of PMN should be initiated by supportive treatment, which includes dietary sodium restriction, renin-angiotensin system blockade, and diuretic use.[7,8] If no improvement is observed, immunosuppressive treatment is initiated in patients with nephrotic syndrome, which mostly included a regimen of corticosteroids and alkylating agents alternating every other month.[7,8] However, this quite successful regimen has been hampered by a high risk of toxicity profile which limits its widespread use.[9-11] Calcineurin inhibitors (CNIs) have been used in the treatment of PMN as well, whereas they are associated with frequent relapses once withdrawn.[12,13] Thus, new therapeutic options have been needed, especially when complicated by refractory or relapsing disease; therefore, the use of rituximab (RTX) has been considered.[14]

Rituximab, a monoclonal antibody-targeting CD20 on the surface of B cells, has been increasingly and successfully used over the decade in the treatment of PMN.[15] Several studies showed its efficacy across different populations;[16-19] however, the optimal dose of this agent is still under debate, and the results of various studies have been contradictory.[20-24] Therefore, in this study, we aimed to compare the efficacy of low dose versus standard dose of RTX in adult patients with relapsed or refractory PMN.

METHODS

Patients

Starting from May 2013, we have institutionally adopted a treatment protocol of RTX for adult patients suffering from relapsed or refractory biopsy-proven PMN, with a proteinuria level of ≥3.5 g/24h despite at least 6 months of prior supportive and immunosuppressive therapy. In this study, 36 consecutive patients fulfilling those criteria were included in the analysis. Patients who were suffering from membranous nephropathy attributable to other diseases, such as malignancies, systemic diseases (i.e., systemic lupus erythematosus), and infections (i.e., hepatitis B), were excluded.

Data on this retrospective cohort study were retrieved from the records of our weekly glomerulonephritis outpatient clinic. Demographic, clinical, and laboratory characteristics of the patients are shown in Table 1. Hypertension was defined as having systolic blood pressure (BP) ≥140 mmHg or diastolic BP ≥90 mmHg or using antihypertensive agents. The urinary protein-to-creatinine ratio in the first morning specimens was used to estimate proteinuria throughout the follow-up, and 24-hour urine collection was selectively used to solve any discrepancies arising from the spot urine assessment. Estimated glomerular filtration rates (eGFRs) were calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[25]

Histopathological Assessment

Adequate kidney biopsy specimens having at least 8 glomeruli were evaluated by using light and immunofluorescence microscopy. All histochemical and immunofluorescence stains were prepared by using 3-4 micrometer sections. About 0.4-0.6 cm unfixed tissue was frozen with liquid nitrogen for immunofluorescence staining of IgG, IgM, IgA, C1q, C3, and fibrinogen. Immunofluorescence staining was graded with a semiquantitative scale from 0 to 3 (0, negative; 1, weak; 2, moderate; and 3, strong staining). Remaining tissues were fixed in Hollande's fixative, embedded in paraffin, and processed routinely for light microscopic evaluation (hematoxylin and eosin, periodic acid-Schiff, methenamine silver-periodic acid, Masson trichrome, and Congo red). Interstitial fibrosis and tubular atrophy were also graded using a semiquantitative scale from 0 to 3: 0, normal; 1 (mild), <25% of interstitium; 2 (moderate), 25%-50%; and 3 (severe), >50%.[26]

Treatment and Follow-up

Supportive treatment included dietary interventions and administration of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers as long as they were tolerable. Corticosteroids or CNIs were used for immunosuppression according to the recommendations of KDIGO.[7,8] Mycophenolate mofetil (MMF) or mycophenolate sodium (MPS) were used as mycophenolic acid derivatives (MPA). Mycophenolate mofetil and MPS were administered at dosages of 2 g/day and 1440 mg/day, respectively. Corticosteroids with CNIs were selected as the initial therapeutic combination, and MPA derivatives were used as a second-line option in resistant cases. Patients with a relapsed or refractory disease were treated with RTX in 2 different protocols:

1. *Low-dose* (LDo) *group:* The patients were administered RTX infusions with a dosage of 375 mg/m^2 for 2 subsequent weeks. This group included 20 patients.
2. *Standard dose* (SDo) *group:* The same dosages of RTX were given 4 times on a weekly basis. There were 16 patients in this group.

In each case, the treatment protocol (LDo or SDo) was decided by the nephrologist after having the consent of the patient. The presence of anti-PLA2R antibodies was determined using indirect immunofluorescence assay or enzyme-linked immunosorbent assay at the time of diagnosis or anytime with an active disease state (defined as proteinuria level of ≥3.5 g/24 hours), when

MAIN POINTS

- The optimal dose of rituximab is still under debate in patients with primary membranous nephropathy, particularly who suffer from relapsed or refractory disease.
- Low and standard doses of rituximab showed similar efficacy in patients with relapsed or refractory primary membranous nephropathy and 56% of patients reached complete or partial remission.
- Lower doses were found to be associated with more relapses.

Table 1. Baseline Characteristics of Patients before Rituximab Administration

Characteristics	Low Dose (n = 20)	Standard Dose (n = 16)	*P*
Male/female	11/9	9/7	.940
Age (years), mean ± SD	39.9 ± 14.6	49.4 ± 10.1	.035
Time from diagnosis to first RTX infusion (months), median (IQR)	28 (14-62)	26.5 (5.25-78)	.464
Positivity for anti-PLA2R antibodies¶, n (%)	16/18 (88.8)	7/13 (53.8)	.028
Histopathological features			
Sclerotic glomeruli (%), median (IQR)	6.6 (0-17.9)	1.5 (0-17)	.418
Interstitial fibrosis, n (%)			
None	10 (50)	9 (56.25)	.443
Mild	10 (50)	6 (37.5)	
Moderate	0	1 (6.25)	
Tubular atrophy, n (%)			
None	8 (40)	7 (43.75)	.487
Mild	12 (60)	8 (50)	
Moderate	0	1 (6.25)	
Prior immunosuppressive medications, n (%)			
Corticosteroids	19 (95)	15 (93.75)	.871
Calcineurin inhibitors	18 (80)	16 (100)	.193
Mycophenolic acid derivatives	7 (35)	4 (25)	.517
Clinical and laboratory features			
eGFR (mL/min/1.73 m^2), mean ± SD	102.1 ± 35.6	81.2 ± 30.7	.073
Proteinuria (g/24 h), median (IQR)	6.94 (4.97-10.2)	6.39 (4.05-9.57)	.566
Serum albumin (g/dL), mean ± SD	2.73 ± 0.78	2.97 ± 0.73	.348
Hemoglobin (g/dL), mean ± SD	12.3 ± 1.8	12.4 ± 1.6	.917
Systolic BP (mmHg), median (IQR)	130 (120-130)	130 (125-130)	.986
Diastolic BP (mmHg), median (IQR)	80 (80-90)	80 (80-83.75)	.639

¶Presence of anti-PLA2R antibodies at the time of diagnosis or anytime with active disease was taken into consideration. The results of 5 patients could not be retrieved.
BP, blood pressure; eGFR, estimated glomerular filtration rate; IQR, interquartile range; PLA2R, phospholipase A2 receptor; RTX, rituximab; SD: standard deviation.

possible. Quantification of anti-PLA2R and B cell counts was not available for all patients; therefore, not taken into consideration.

Patients were evaluated periodically at the outpatient clinic, and all of the clinical and laboratory assessments performed at baseline were repeated at months 3, 6, 12, 18, and 24 after treatment with RTX. The follow-up period was calculated as the time interval between RTX administration and the last outpatient visit, experiencing a disease relapse after partial (PR) or complete remission (CR), initiation of kidney replacement therapies, or death. All patients evaluated in the final analysis had at least 6 months of follow-up.

Study Outcomes

The primary outcome was defined as complete or partial remission. Complete remission was assumed to be achieved when proteinuria level decreased to <0.3 g/24 hours with normal serum albumin and creatinine concentrations, whereas, partial remission was considered when proteinuria decreased to <3.5 g/24 hours or at least a 50% reduction in proteinuria with improvement or normalization of serum albumin concentration and a stable serum creatinine level were noted.[7,8] Patients not reaching any kind of remission were considered as non-responsive. Relapse was defined as the recurrence of ≥3.5 g/24h proteinuria after the achievement of a CR or PR.[2]

Secondary outcomes comprised changes over time in eGFR, proteinuria, and serum albumin levels. Infections requiring hospitalization, serious allergic reactions, malignancies, or death throughout the follow-up were recorded as serious adverse events. Associations of clinical features (age, sex, BP, eGFR, hemoglobin, albumin, and proteinuria) and histopathological

lesions (percentage of sclerotic glomeruli, interstitial fibrosis, and tubular atrophy) with primary outcome were also evaluated.

Statistical Analyses

Statistical analyses were performed by using Statistical Package for the Social Sciences version 21.0. (IBM SPSS Corp.; Armonk, NY, USA). Results were expressed as mean ± SD when normally distributed or as median [interquartile range (IQR)] otherwise. Comparisons of continuous variables between study groups were evaluated with *t*-tests or the Mann–Whitney *U* test where appropriate. Differences in the proportions of the groups were compared using the chi-squared or Fisher's exact test. Kaplan–Meier analyses were used to determine the probability of primary outcome, and survival time for each patient, and was computed from the baseline evaluation before RTX administration to partial remission or the last follow-up. Multivariate Cox regression analysis was carried out to determine predictors of remission. The results of this analysis were described as hazard ratios and 95% CIs. Kaplan–Meier curves were generated using MedCalc for Windows (MedCalc version 19.0, MedCalc Software, Ostend, Belgium). All analyses were 2-sided and a *P* value of .05 or less was considered as statistically significant.

Included patients provided informed consent to extract their data to our database. The study was approved by the local ethical committee in our institution (Date: November, 2018; Approval Number: 1541) and complied with the Declaration of Helsinki.

RESULTS

Baseline Characteristics of Patients

In total, 36 patients (20 males, 16 females) who were followed up for a median of 28 (10.5-62) months before RTX administration were included. The mean age was 44.1 ± 13.5 years. Study groups were comparable in terms of distribution of sex, serum albumin, level of proteinuria, and hemoglobin, as well as systolic and diastolic BP. Mean eGFR, mean serum albumin, and median proteinuria levels were 92.8 ± 34.7 mL/min/1.73 m^2, 2.83 ± 0.76 g/dL, and 6.39 (IQR: 4.4-9.87) g/24h, respectively. Twenty-three of the 31 patients (74.1%) were positive for serum anti-PLA2R antibodies, while anti-PLA2R status of 5 patients could not be retrieved from the records. More patients in LDo group were positive for serum anti-PLA2R antibodies when compared to patients in SDo group [16/18 (88.8%) vs. 7/13 (53.8%), *P* = .028].

Of the 36 individuals, 20 (55.5%) were treated with LDo regimen. These patients in LDo group were younger (39.9 ± 14.6 years) compared with SDo (n = 16, 44.4%) group (49.4 ± 10.1 years, *P* = .035). Baseline eGFR values were lower in SDo group (81.2 ± 30.7 mL/min/1.73 m^2 vs. 102.1 ± 35.6 mL/min/1.73 m^2); however, this difference was not statistically significant (*P* = .073).

In LDo and SDo groups, corticosteroids were used in 19 (95%) and 15 (93.75%) (*P* = .871), CNIs in 18 (80%) and 16 (100%) (*P* = .193), and MPAs in 7 (35%) and 4 (25%) (*P* = .517) patients, respectively. Histopathological evaluation revealed comparable amounts of sclerotic glomeruli (*P* = .418), interstitial fibrosis (*P* = .443), and tubular atrophy (*P* = .487). Characteristics of all patients before RTX administration are detailed in Table 1.

Study Outcomes

Two patients in the LDo RTX group were excluded from efficacy analyses; one of them died due to sepsis caused by pneumonia and the other one because of anaphylaxis during his first RTX infusion. These events were recorded as serious adverse events.

In total, 34 patients were followed up for a median duration of 15.5 (6-23.25) months after treatment, and 19 of them (55.8%) reached the primary outcome. Twelve patients (66.6%) in LDo group had PR or CR compared with 7 patients (43.75%) in SDo. The number of patients with primary outcome was comparable between study groups (*P* = .179), albeit LDo group had a longer follow-up period compared to SDo [19 (13.5-24) vs. 11 (6-16 months), respectively; *P* = .013]. Percentage of patients undergoing remission was similar in the 24-month Kaplan–Meier analysis, as well (*P* = .393 by log-rank test) (Figure 1). Remission was achieved over a median of 3 (3-6) months. Five patients (27.7%) in LDo group experienced a relapse, while no patients in the SDo group relapsed throughout the follow-up (*P* = .022). Outcomes of patients at 3, 6, 12, 18, and 24 months are described in Supplementary Table 1.

Secondary outcomes, which included mean eGFR, median proteinuria, and mean serum albumin levels, were generally comparable between study groups (Table 2). Estimated glomerular filtration rates values persistently decreased, though serum

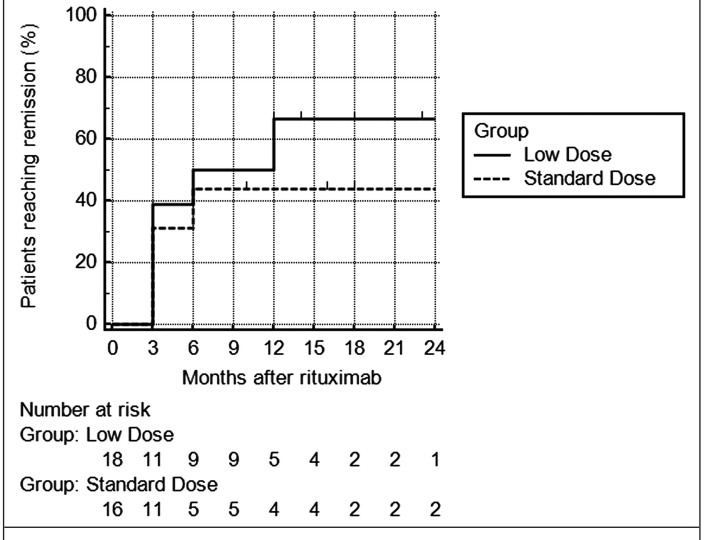

Figure 1. Kaplan–Meier analysis of patients undergoing partial remission in 24 months. Remission rates were similar in study groups (*P* = .393 by log-rank test).

Table 2. Estimated Glomerular Filtration Rate, Proteinuria, and Serum Albumin Values of Patients at 3, 6, 12, 18, and 24 Months after Rituximab Administration

Characteristics	Group	3 Months	6 Months	12 Months	18 Months	24 Months
eGFR (mL/min/1.73 m^2), mean ± SD	LDo	104.05 ± 31.11	99.82 ± 32.37	90.4 ± 35.08	82.57 ± 34.9	76.4 ± 22.24
	SDo	84.6 ± 24.26	73.74 ± 29.72	65.97 ± 31.89	60.75 ± 36.14	41.75 ± 30.78
	P	.074	.021	.116	.271	.110
Proteinuria (g/24h), median (IQR)	LDo	2.56 (1.7-4.96)	3.80 (1.63-6.1)	2.2 (1.17-3.76)	2.2 (0.78-3.7)	4.08 (0.7-4.4)
	SDo	3.9 (1.58-5.93)	2.80 (1.41-5.7)	1.8 (0.73-5.86)	4.2 (1.02-9.2)	4.52 (4.05-5)
	P	.722	.569	.821	.462	.557
Serum albumin (g/dL), mean ± SD	LDo	3.34 ± 0.68	3.48 ± 0.65	3.87 ± 0.57	3.89 ± 0.76	4.07 ± 0.5
	SDo	3.43 ± 0.80	3.47 ± 0.9	3.99 ± 0.75	3.63 ± 0.88	3.36 ± 0.43
	P	.738	.986	.671	.552	.117

eGFR, estimated glomerular filtration rate; IQR, interquartile range; LDo, low dose; SDo, standard dose; SD: standard deviation.

albumin levels demonstrated an increase over time in LDo and SDo groups. Proteinuria tended to decrease across 12 months in both groups; although there was a surge at 6 months in LDo group, mostly because of 2 patients with relapse. Proteinuria began to increase after 12 and 18 months in SDo and LDo groups, respectively (Supplementary Figure 1A-C).

Serious Adverse Events

Squamous cell carcinoma of the tongue developed in a patient in LDo group at 18 months after RTX. One patient each in LDo and SDo groups died at 2 weeks and 6 months after RTX due to sepsis induced by severe pneumonia, respectively. Another patient in SDo group suffered from pneumonia that necessitated hospitalization at 10 months after RTX and recovered. One patient did not get the assigned treatment because of anaphylaxis during the first RTX infusion.

Predictors of Primary Outcome

In multivariate Cox regression analysis, none of the variables, which included sex, age, disease duration at baseline before RTX administration, positivity for anti-PLA2R antibodies, eGFR, proteinuria, hemoglobin, systolic and diastolic BP, percentage of sclerotic glomeruli, interstitial fibrosis, tubular atrophy, and prior use of corticosteroids or MPAs, predicted the primary outcome (Table 3).

DISCUSSION

The use of RTX opened a new chapter in the treatment of patients with PMN. Before the RTX era, different regimens involving corticosteroids, alkylating agents, and CNIs have traditionally been used with somewhat established efficacy.[7,8] However, alkylating agents come with their unfavorable profile of adverse events, and withdrawal of CNIs has been associated with frequent relapses.[9-13] Efficacy and safety of RTX as a first- or second-line treatment option for PMN have been demonstrated previously,[15,18,19,27-29] yet the optimal dosing regimen is still unclear. The use of relatively high doses was common in the early days;[16,22,27,30] however high cost and a potential increase in the risk of infections have been a concern, which triggered the use of lower doses in the subsequent studies.[18,21,22] In this study, we compared low and standard doses of RTX in patients with relapsed or refractory PMN and showed that both regimens had the relatively same efficacy regarding remission, albeit patients in LDo group had more frequent relapses. Although it did not reach statistical significance, remission

Table 3. Multivariate Cox Regression Analysis with Regard to Primary Outcome in All Patients (n = 34)

Characteristics	HR (95% CIs)	*P*
Sex, male	3.484 (0.414-29.346)	.251
Age, years	1.037 (0.954-1.126)	.393
Disease duration at baseline	1.000 (0.977-1.023)	.970
Positivity for anti-PLA2R antibodies	0.416 (0.058-2.957)	.381
eGFR, mL/min/1.73 m^2	1.011 (0.976-1.047)	.551
Proteinuria, g/24h	0.935 (0.718-1.218)	.620
Serum albumin	0.481 (0.162-1.432)	.189
Hemoglobin	1.481 (0.891-2.464)	.130
Systolic BP	0.975 (0.912-1.043)	.469
Diastolic BP	1.074 (0.924-1.248)	.351
Percentage of sclerotic glomeruli	0.955 (0.897-1.018)	.158
Interstitial fibrosis	0.406 (0.065-2.526)	.334
Tubular atrophy	0.341 (0.049-2.387)	.279
Prior use of corticosteroids	4.214 (0.220-80.666)	.340
Prior use of mycophenolic acid derivatives	0.896 (0.178-4.523)	.894

Since 33 of 34 patients had used calcineurin inhibitors before rituximab, prior use of these agents was not included in the Cox regression model.
BP, blood pressure; CIs: confidence intervals; eGFR, estimated glomerular filtration rate; HR, hazard ratio; PLA2R, phospholipase A2 receptor.

rates were lower in SDo group. However, the 2 groups were not strictly comparable; since the patients in SDo group were older, had a lower rate of positivity for anti-PLA2R antibodies, and had numerically lower eGFR levels when compared to LDo group. Moreover, SDo group had a shorter median duration of follow-up, which might have caused an underestimation of both remission and relapse rates. Most patients started to go into remission at 6 months after RTX as previously described,[31] which may decrease the possible underestimation of remission rates.

Various non-randomized studies[16,18] and a recently published randomized trial, MENTOR,[19] demonstrated that RTX had a remission rate of approximately 60% in patients with PMN. In the MENTOR trial, the use of RTX was as successful as CNIs in inducing remission with fewer relapses.[19] As early as 2007, the efficacy of lower doses became a subject of debate in this population. It was demonstrated that titrating RTX based on peripheral B cell counts could reach the same efficacy as standard 4 weekly doses of 375 mg/m^2,[20] and this approach was found to be quite effective with a 65% remission rate in different cohorts.[18,22] However, a standard 4-dose regimen was associated with more effective B cell depletion,[29] and it was shown that 1 or 2 weekly doses had lower remission rates (44%).[21] Recently, delayed remission was reported with lower doses of RTX, despite an adequate B cell depletion.[23] In this study, we found an overall 55.8% remission rate, with 66.6% in LDo and 43.75% in SDo groups. Our cohort consisted of patients with relapsed or refractory disease which may have played a role in our relatively poor remission rates, as has been reported previously.[32] On the other hand, one might argue that SDo group had a lower median duration of follow-up (11 months), and more patients in this group might have reached the study outcome with a longer follow-up period. Probably, both scenarios may have significant roles in our lower remission rates. Also, the efficacy of RTX might have been overestimated in the literature, since negative results are usually underreported.

Most of the patients in this study reached only PR (91.1%). We defined remissions according to KDIGO guidelines, which described CR with a strict proteinuria level (<0.3 g/24h).[7,8] Patients with refractory or relapsed disease are expected to have some level of irreversible damage in glomerular and tubulointerstitial structures, which may have played a role in our patients' low rate of CR. Since protocol biopsies were not performed during this study period, we could not present any data to support this hypothesis.

Available data on the safety of RTX in patients with MN are quite limited, yet overall infection risk was similar between RTX and CNI groups in MENTOR trial.[19,24] All patients included in our study had been previously treated with immunosuppressive agents, which might have increased the risk of infections or malignancies. One of our patients developed squamous cell carcinoma of the tongue and 2 other patients died because of severe pneumonia, 1 of whom passed away just after 2 weeks of treatment. Thus, we speculate that cumulative immunosuppression associated with prior treatments and nephrotic syndrome rather than RTX might have contributed to these adverse effects. Nevertheless, a sound analysis of adverse events was not possible due to the lack of a control group.

Our study has several limitations. First, the sample size was relatively small. This limitation is not surprising if one considers the low number of patients with relapsed or refractory disease. Second, this study had a retrospective design, which was at the center of deficient data retrieval. Third, even though results for anti-PLA2R antibodies were available in most of the patients (86.1%), we had neither serial measurements nor quantitative levels of the antibodies. Fourth, B cell counts were not available in all patients, hence were not taken into consideration. Therefore, we do not have any concrete evidence whether our patients had effective B cell depletion after treated with RTX. Fifth, all patients had a relatively short duration of follow-up, which was less than 12 months in SDo group in particular. Both remission and relapse rates in this group could have been higher with a longer follow-up. Sixth, the dose choice of RTX was at the discretion of the treating senior physician, which may have caused a selection bias.

CONCLUSION

In conclusion, our data showed that low and standard doses of RTX had a relatively similar efficacy profile in patients with relapsed or refractory PMN, albeit lower doses were associated with a tendency for relapses. We believe that prospective studies including a higher number of patients and titrating RTX doses based on serial measurements of anti-PLA2R antibodies as well as B cell counts may be very useful to define the efficacy of targeted therapies.

Ethics Committee Approval: The study was approved by the İstanbul University İstanbul School of Medicine Ethical Committee (Date: November 12, 2018, Approval No:1541).

Informed Consent: Written informed consent was obtained from all patients included in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: Ş.M., H.Y.;Design: Ş.M., H.Y.; Supervision: M.Ş.S.; Materials: Ş.M., A.A., A.R.U., Ö.U., Y.Ö., A.B.D., E.D., Ö.A.O., I.K., Y.Ç., H.Y.,A.T.; Data Collection and Processing: Ş.M., A.A., A.R.U., Ö.U.;Analysis and Interpretation: Ş.M.; . Literature Review: Ş.M., A.A.; Writing: Ş.M.;Critical Review: H.Y., A.T., M.Ş.S.

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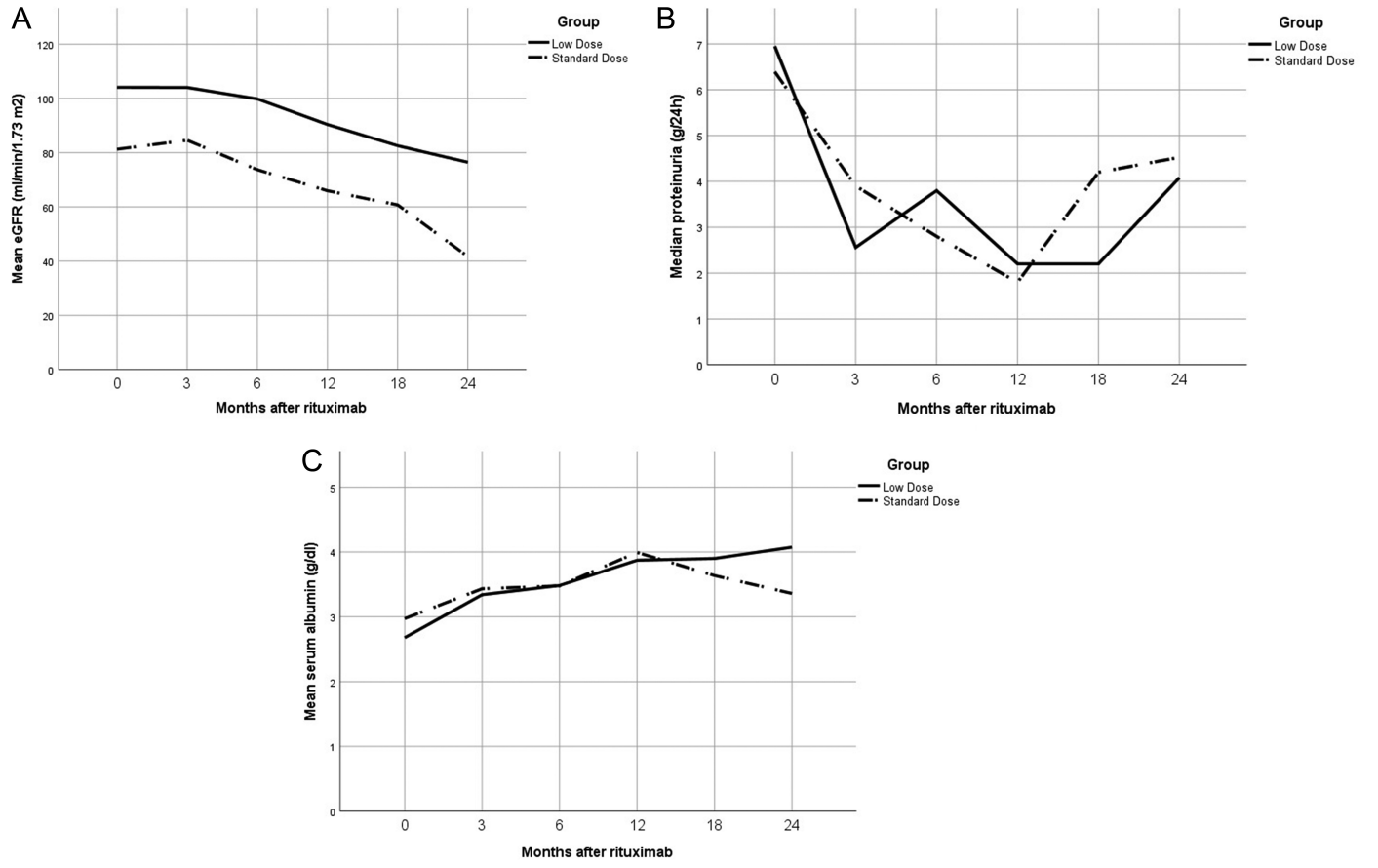
Supplementary Table 1. Outcomes of Patients at 3, 6, 12, 18 and 24 Months After Rituximab.

Time	Outcome	Low Dose (LDo)	Standard Dose (SDo)	*P*
3 months	Patients, n	17	13	.638
	Complete or partial remission, n (%)	8 (47)	5 (38.4)	
	Partial remission, n	8	5	
	Complete remission, n	-	-	
	No remission, n (%)	9 (53)	8 (61.5)	
6 months	Patients, n	18	16	.533
	Complete or partial remission, n (%)	6 (33.3)	7 (43.75)	
	Partial remission, n	6	7	
	Complete remission, n	-	-	
	No remission, n (%)	12 (66.6)	9 (56.25)	
	Relapse, n	2	-	
12 months	Patients, n	15	8	.645
	Complete or partial remission, n (%)	9 (60)	4 (50)	
	Partial remission, n	8	3	
	Complete remission, n	1	1	
	No remission, n (%)	6 (40)	4 (50)	
	Relapse, n	-	-	
18 months	Patients, n	11	5	.106
	Complete or partial remission, n (%)	7 (63.6)	1 (20)	
	Partial remission, n	5	-	
	Complete remission, n	2	1	
	No remission, n (%)	4 (36.3)	4 (80)	
	Relapse, n	1	-	
24 months	Patients, n	7	2	.257
	Complete or partial remission, n (%)	3 (42.8)	-	
	Partial remission, n	2	-	
	Complete remission, n	1	-	
	No remission, n (%)	4 (57.1)	2 (100)	
	Relapse	2	-	



Supplementary Figure 1. A. Slope of mean eGFR levels between study groups throughout the follow-up (eGFR: estimated glomerular filtration rate). B. Slope of median proteinuria levels between study groups throughout the follow-up. C. Slope of mean serum albumin levels between study groups throughout the follow-up.