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REVIEW

# Different Dosage Regimens of Rituximab in Primary Membranous Nephropathy Treatment: A Systematic Review

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**Abstract:** Primary membranous nephropathy (PMN) is one of the prevalent pathological types of adult primary nephrotic syndrome. Pathogenic autoantibodies targeting podocyte antigens such as phospholipase A2 receptor (PLA2R) lead to the disease. Patients frequently experience notable adverse effects when treated with conventional immunosuppressive therapies. Rituximab (RTX), a mouse/human monoclonal antibody, selectively depletes B cells and leads to a decrease in the antibody levels in the circulation, which helps to alleviate membranous nephropathy. Various RTX dosage regimens have been applied globally in the PMN treatment with satisfactory effects. Nevertheless, the optimal dosage of RTX has yet to be determined. This article reviews the application of different doses of RTX in the management of PMN so far.

**Keywords:** membranous nephropathy, nephrotic syndrome, rituximab, dosage

## Introduction

Primary membranous nephropathy (PMN) is a glomerulopathy caused by autoantibodies of unknown etiology. It is one of the prevalent pathological types of primary nephrotic syndrome and represents the most common etiology of nephrotic syndrome in adults worldwide.[1–3]

Pathogenic antigens and autoantibodies have been implicated in the disease.[4,5] Autoantibodies target podocyte antigens such as phospholipase A2 receptor (PLA2R) and, albeit less commonly, thrombospondin type-1 domain-containing 7A (THSD7A).[6] Approximately 70–80% of the patients exhibit circulating PLA2R antibodies.[7] At present, immunosuppressive therapy is advocated as the first-line therapy for patients diagnosed with PMN, involving glucocorticoids, alkylating agents, calcineurin inhibitors, etc.[8,9] Nevertheless, these regimens may not have the expected therapeutic effect across all patients, and patients frequently experience notable adverse effects during the treatment.[10]

It has been demonstrated that immunoglobulin deposition along the glomerular basement membrane is generated by B-cell-mediated responses, which increases disruption to the glomerular filtration barrier, resulting in proteinuria.[3] It is precisely this identification that has resulted in a shift in the treatment paradigm from non-specific immunosuppression treatment to B cell-targeted therapies. Rituximab (RTX), a small, engineered chimeric mouse/human monoclonal antibody, selectively depletes B cells by targeting the CD20 surface antigens on the cells.[11,12] After treatment with RTX, B cells are inhibited from proliferation and activation, and undergo apoptosis and lysis.[13] Ultimately, it leads to a decrease in the levels of anti PLA2R and THSD7A antibodies in the circulation, which helps to alleviate membranous nephropathy.

Since the initial experience with RTX treatment in eight patients with PMN was reported by Remuzzi et al in 2002, numerous studies have been conducted on RTX therapy for PMN, due to its superior short-term benefits and risks compared to traditional immunosuppressive medications.[14,15] Various RTX dosage regimens, ranging from a single dose

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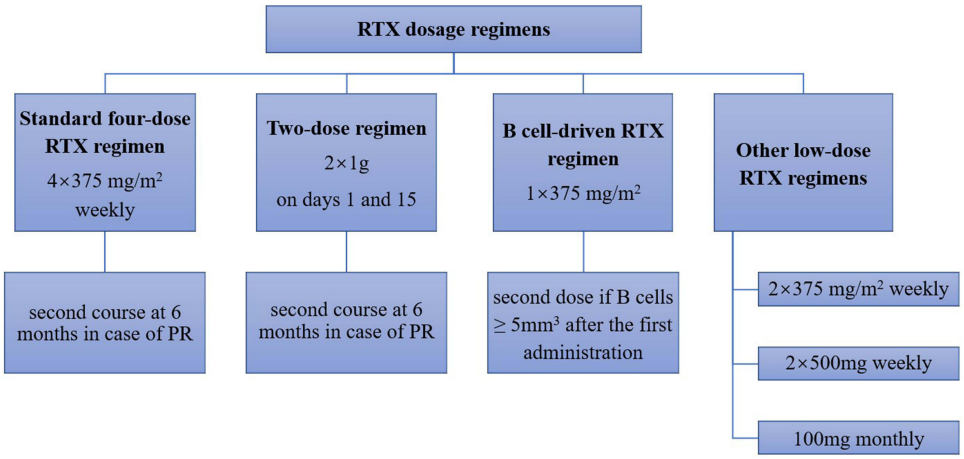


**Figure 1** Different RTX dosage regimens.
**Abbreviations**: RTX, rituximab; PR, partial remission.

of 375 mg/m² to four weekly doses of 375 mg/m², are employed by researchers globally in the management of PMN, as illustrated in Figure 1. Nevertheless, the optimal dosage of RTX for treating PMN has yet to be determined.[16] This article reviews the application of different doses of RTX in the management of PMN.

## Rituximab Doses in PMN Treatment

According to the 2021 Kidney Disease Improving Global Outcomes (KDIGO) guidelines, there are currently two types of RTX dosages that are mainly utilized in clinical practice. Firstly, standard four-dose therapy, RTX intravenous injection, 375 mg/m$^2$ each time, once a week, for a continuous 4-week course of treatment. Next is the intravenous injection of RTX, 1 g on Days 0 and 15.[6] For the aforementioned two ways of usage, at the sixth month following the initial course of treatment, the decision whether to administer RTX again is dependent on the patient's degree of B cell recovery, anti-PLA2R antibody level, and clinical remission. Afterwards, the evaluation is repeated every six months to determine whether to inject RTX again.[6] Additionally, there are several low-dose RTX infusion regimens, such as B-cell-driven RTX protocols, two doses of RTX (500 mg each), and two doses of RTX (375 mg/m$^2$ each), and so on, which have received comparatively less attention in both applications and research.[17–19] The detailed information regarding the studies on different dosing regimens of RTX discussed in this review is presented in Table 1.

### Standard Four-Dose RTX Regimen

As early as 2002, Remuzzi et al conducted a prospective, observational study to investigate the efficacy and safety of RTX in the treatments of PMN. A total of eight patients who had PMN with persistent nephrotic syndrome (NS) were administered with four weekly intravenous infusions of rituximab (375 mg/m$^2$). The patients were followed up for 20 weeks by Remuzzi et al, and then continued to be followed up until the twelfth month by Ruggenenti et al. At 1 and 12 months following the treatment, the urinary protein of patients decreased from mean 8.6 g/24h to 3.8 g/24h and 3.0 g/24h, respectively. By the twelfth month, the complete remission rate was 25%, and the partial remission rate was 37.5%. After the first dosage of RTX, CD20 B cells of all patients fell to undetectable levels and maintained greatly below normal levels until termination of the study. Three patients experienced infusion-related reactions, which were relieved after observation or glucocorticoids treatment. There were no serious drug-related incidents or significant changes in laboratory parameters in any of the participants. In terms of short- and long-term risk/benefit profile, rituximab seemed to outperform other traditional immunosuppressive medications for IMN treatment.[14,20] Roccatello et al conducted a prospective study involving 17 patients with MN, all of whom were treated with four weekly RTX doses of 375 mg/m², with a mean follow-up duration of 36.3 months. Proteinuria decreased from 5.6 (3.5–8) g/24h at 6 months to 2.4 (0.06–13) g/24h ($p < 0.05$), and by 12 months, it dropped to 1.3 (0.06–8) g/24h ($p < 0.01$). At the 6-month mark, 7 patients achieved complete remission (CR), while 4 patients achieved partial remission (PR). At the end of the follow-up period, 14 patients were in CR, 1 patient was in PR, and 2 patients were in no response (NR).[21] Similarly, in 2016, a prospective cohort study

**Table 1** Overview of Studies on Different RTX Dosing Regimens in This Review

| | Author | Year | Design | Total Subjects | Baseline Anti-PLA2R Level | Follow-up (Months) | Remission Rate (CR+PR) | Remission Rate (PR) |
|---|---|---|---|---|---|---|---|---|
| Four-dose RTX regimen (4 weekly 375 mg/$m^2$) | Remuzzi[14] Ruggenenti[20] | 2002 2003 | prospective, observational | 8 | – | 12 | 62% (end*) | 37% (end) |
| | Roccatello[21] | 2016 | prospective, observational | 17 | – | 36.3 (range 24–48) | 65% (6 months) 88% (end) | 23% (6 months) 6% (end) |
| | Fiorentino[22] | 2016 | prospective, observational | 38 | – | 15 (IQR 7.7–30.2) | 76% (end) | 37% (end) |
| Two-dose RTX regimen (1 g day 1 and 15) | Fervenza[23] | 2008 | prospective, observational | 15 | – | 12 | 57% (end) | 43% (end) |
| | Fervenza[12] | 2019 | RCT, open-label, multicenter | 65 (RTX group) 65 (cyclosporine group) | – | 24 | 60% (12 months) 60% (end) 52% (12 months) 20% (end) | 46% (12 months) 25% (end) 48% (12 months) 20% (end) |
| | Scolari[24] | 2021 | RCT, open-label, multicenter | 37 (RTX group) 37 (cyclic regimen group) | 73% positive 59% positive | 36 | 62% (12 months) 83% (24 months) 73% (12 months) 82% (24 months) | 46% (12 months) 41% (24 months) 41% (12 months) 39% (24 months) |
| B cell-driven RTX regimen | Cravedi[17] | 2007 | controlled, prospective, matched-cohort, single-center | 12 (B cell-driven protocol) 24 (four-dose protocol) | – | 12 | 67% (end) 66% (end) | 50% (end) 58% (end) |
| | van den Brand J[25] | 2017 | retrospective, observational | 100 | – | 40 (IQR 18–60) | 90% (end) | 64% (end) |

(*Continued*)


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**Table 1** (Continued).

| | Author | Year | Design | Total Subjects | Baseline Anti-PLA2R Level | Follow-up (Months) | Remission Rate (CR+PR) | Remission Rate (PR) |
|---|---|---|---|---|---|---|---|---|
| B cell-driven RTX regimen | Fenoglio[26] | 2021 | retrospective, case–control | 14 (B cell-driven protocol)<br>14 (four-dose protocol)<br>14 (Ponticelli protocol) | 100% positive<br>100% positive- | 24 | 93% (end)<br>93% (end)<br>86% (end) | 7% (end)<br>0% (end)<br>0% (end) |
| | Ramachandran[27] | 2021 | retrospective, observational | 25 (B cell-driven protocol)<br>21 (four-dose protocol)<br>63 (two-dose protocol) | 80% positive<br>60.7 (48,97) RU/mL<br>80% positive<br>111.3 (61,221.7) RU/mL<br>90% positive<br>126.8 (49.7,275) RU/mL | 19 (IQR 12–29) | 56% (12 months)<br>68% (end)<br>43% (12 months)<br>57% (end)<br>62% (12 months)<br>65% (end) | 44% (12 months)<br>28% (end)<br>33% (12 months)<br>38% (end)<br>38% (12 months)<br>40% (end) |
| | Moroni[28] | 2017 | prospective, observational | 34 | 71% positive<br>163.1±129.8 (remission) U/mL<br>464.2±460.2 (no response) U/mL | 12 | 44% (end) | 29% (end) |
| | Xin Wang[29] | 2018 | retrospective, observational | 36 | 94% positive<br>118±112 (remission) U/mL<br>345±357 (no response) U/mL | 12 (IQR 9–19.3) | 41.7% (end) | 36% (end) |
| | Dahan[19] | 2017 | RCT, multicenter | 37 (375 mg/m$^2$ RTX day 1 and 8)<br>38 (NIAT) | 73% positive<br>40.5 (0.0–275.5) RU/mL<br>74% positive<br>43.3 (0.0–457.5) RU/mL | 17 (IQR 12.5–24)<br>17 (IQR 13–23) | 35% (6 months)<br>65% (end)<br>21% (6 months)<br>34% (end) | – |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| RTX 500mg×2 weekly | Bagchi[18] | 2018 | retrospective, observational | 21 | – | 13.1 (IQR 10–23.9) | 62% (end) | 43% (end) |
| RTX 100mg monthly | Song Wang[30] | 2023 | retrospective, observational | 32 | 100% positive 160 (20–2659) RU/mL | 24 (IQR 18–38) | 84% (end) | 50% (end) |
| | Seitz-Polski[31] | 2019 | RCT | 28 (RTX 1g days 1 and 15) 27 (375 mg/m$^2$ RTX day 1 and 8) | 165.0 (67.0–245.5) RU/mL | 15 (IQR 11–19) | 64% (6 months) 86% (end) | 46% (6 months) 54% (end) |
| | | | | | 102.5 (36.1–672.5) RU/mL | 24 (IQR 22–25) | 30% (6 months) 67% (end) | 30% (6 months) 45% (end) |

**Notes:** *at the end of follow-up.

**Abbreviations**: RTX, rituximab; PR, partial remission; CR, complete remission; RCT, randomized controlled trial; IQR, interquartile range; NIAT, non-immunosuppressive antiproteinuric treatment.



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conducted by Fiorentino et al included 38 patients who were all treated with four weekly RTX doses of 375 mg/m², with a median follow-up duration of 15 months. The proportions of patients achieving CR and PR were 39.5% (15 patients) and 36.8% (14 patients), respectively. No significant adverse events were described during and after infusions.[22]

## Two-Dose Regimen (RTX 1 g, Intravenous on Days 1 and 15)

Fervenza et al prospectively treated 15 PMN patients with RTX 1 g intravenous on days 1 and 15 in 2007. Proteinuria was substantially reduced by around half at 12 months, with two patients achieving CR and six achieving PR at the end of follow-up.[23] Fervenza et al conducted a randomized controlled trial (MENTOR) in which 130 patients were randomly assigned to receive either RTX (two infusions, 1000 mg each, administered 14 days apart) or cyclosporine, with follow-up lasting approximately 24 months. At the 12-month and 24-month follow-ups, complete or partial remission both occurred in 60% of the patients in the RTX group. MENTOR identified that RTX was not inferior to cyclosporine in inducing complete or partial remission of proteinuria and was superior in sustaining proteinuria remission up to 24 months.[12] The Rituximab versus Steroids and Cyclophosphamide in the Treatment of Idiopathic Membranous Nephropathy (RI-CYCLO) trial compared two RTX infusions (1 g) two weeks apart to a regimen with corticosteroids and cyclophosphamide. At the 12 months and 24 months, patients achieving complete or partial remission accounted for 62% and 83%.[24] However, pharmacokinetic (PK) analysis revealed that drug exposure in the two-dose regimen (1 g, intravenous on days 1 and 15) may not have been ideal due to the presence of proteinuria, resulting in quicker B cell recovery in PMN patients.[23] The prospective study conducted by Fervenza et al demonstrated that CR or PR rate of patients treated with two doses of RTX in 12 months was 50%, which was consistent with previous work by Ruggenenti et al.[14,20,32] There was no significant difference in the response rate at 12 months between patients receiving two-dose RTX regimen and those treated with RTX 375 mg/m$^2$ × 4. However, it has been found that B cell depletion was more rapid and prolonged with four doses of RTX, while proteinuria reduction was comparable with the two-dose regimen. The latter has the advantage of decreasing the infusion frequency and cost.[20,23,32] In addition, participants who received four doses of RTX were less likely to develop human anti-chimeric antibodies (HACAs), which may be associated with more rapid RTX clearance, less effective B cell depletion, and an increased risk of side effects.[32]

## B Cell-Driven RTX Regimen

Previous studies have shown that B cells were fully depleted already after the first RTX infusion in PMN patients who were administered with four doses of RTX.[13,14] This finding indicated that a single dose of RTX may be adequate to completely inhibit the aberrant B cell clones. Cravedi et al first introduced the B cell-driven RTX regimen (a single dose of 375 mg/m$^2$ was initially administered, and the second dose of 375 mg/m$^2$ was given if ≥5 circulating B cells/mm$^3$ after the first administration) in 2007. Cravedi et al designed a matched-cohort, single-center, controlled study that compared the efficacy of the B cell-driven RTX regimen versus the standard four-dose RTX regimen in MN treatment.[17] At 12 months, the CR rate (2/12 17% versus 2/24 8%) or PR rate (6/12 50% versus 14/24 58%) was equivalent in both groups, and all patients achieved persistent B cell depletion. Only one patient received B cell-driven regimen required a second dose to achieve complete B cell depletion. Consequently, the hospitalizations and costs were substantially decreased in the B cell-driven RTX regimen group, allowing for more than €10,000 in savings per patient. Three repeated RTX doses following an initial 375 mg/m$^2$ administration did not seem to offer further benefits. Additionally, repeated exposure to RTX may stimulate the production of HACAs and weaken the safety profile of lymphocytolytic therapy.[17] Similarly, another two studies found that the two RTX treatment protocols above have virtually identical risk/benefit profiles, with the B cell–driven protocol providing significant cost reductions.[25,26] Recently, Ramachandran et al conducted a retrospective study of three dosing RTX regimens (Regimen 1: four doses of RTX; Regimen 2: 1 g on Days 0 and 15; Regimen 3: B cell-driven RTX regimen) and discovered that there was no difference in the remission rates among the different RTX regimens, while B cell-driven RTX regimen possibly hold greater economic significance especially in resource-limited settings.[27]

On the contrary, the multicenter prospective study of the low-dose RTX therapy by Moroni et al yielded unsatisfactory results, which revealed a much lower remission rate (less than 50% in 12 months) than four doses of RTX regimen or two doses of RTX regimen (1 g twice a month), though all patients had achieved complete B-cell depletion.[28,33] In their cohort, 41% patients had eGFR <60 mL/min/1.73 m$^2$, indicating more severe kidney injury and increased chronicity, which may explain why patients lack positive responses to immunosuppressive therapy.[7,33] In the study of Esposito et al, the remission and relapse rates of patients

treated with B cell-driven RTX regimen were undesirable, which was consistent with the findings of Moroni et al.[34] One possible reason was the limited number of patients included in the study, which was only four. In a Chinese cohort, Xin Wang et al also discovered a reduced remission rate among patients receiving low-dose RTX therapy in comparison to other researches.[29] The lower remission rate observed in this study compared to other research may be attributable to the inclusion of non-responsive MN patients, who might exhibit greater resistance to alternative immunosuppressive medications. Additionally, the majority of patients in this study had a mean serum creatinine level greater than 2 mg/dL.

Pharmacokinetics investigations of RTX have revealed considerable individual heterogeneity, related to either disease or genetic factors, may partially explain variations in therapeutic responses of patients.[35] Probably, higher dosages and longer treatments were likely required to induce and maintain a response, particularly in individuals with high anti-PLA2R antibody levels.[28] Even though B-cell depletion seemed very easy to achieve with low-dose RTX, inadequate dosage may postpone remission or expose the patient to a higher rate of relapse than those receiving higher dosage.[36,37] B-cell depletion alone may not be adequate to determine the appropriate dose of RTX. Roccatello et al considered that other mechanisms (such as T cell-related mechanisms of action), beyond the effect of B cells, might be implicated in explaining RTX action.[21] The therapeutic strategy should be determined by balancing the economic impact with the risk of long-term morbidity.

## Other Low-Dose RTX Regimens

Given that the quantity and activity of B lymphocytes in MN patients are significantly lower than those observed in lymphoma, the standard RTX dose may be oversaturated for B cell depletion in MN patients even with the urinary loss of RTX.[38,39] Higher dosing regimens of rituximab tend to be relatively expensive and may also increase the risk of infections, although the safety risk is relatively lower in comparison to other immunosuppressive agents.[12,40]

The Prospective Randomized Multicentric Open Label Study to Evaluate Rituximab Treatment for Idiopathic Membranous Nephropathy (GEMRITUX) trial, which was conducted by Dahan et al, compared RTX therapy (375 mg/m$^2$ intravenously RTX on days 1 and 8) with non-immunosuppressive antiproteinuric therapy (NIAT) in 75 patients.[19] They found that the difference in remission rates between the two groups at six months was not statistically significant. After a longer observation period (post–RCT observational phase, median follow-up was 17 months), the remission rate in RTX group was 65%, significantly higher than that of the NIAT group.[19] In a retrospective cohort research, 21 treatment-resistant PMN patients were administered with two doses of RTX (500 mg each) 7 days apart. Results showed that 61.9% of patients achieved remission with no severe adverse effects during a median follow-up of 13 months.[18] Recently, Song Wang et al assessed the efficacy of monthly mini-dose RTX therapy in PMN patients.[30] All patients received RTX 100 mg infusion monthly for at least 3 months, until either remission or a minimum serum anti-PLA2R titer < 2 RU/mL was achieved. Eighty-four percent of the patients achieved remission during a median follow-up of 24 months. Patients were classified into high-titer (≥150 RU/mL) and low-titer groups (<150 RU/mL) based on anti-PLA2R titer. The baseline anti-PLA2R concentrations were 62 ± 39 RU/mL in the low-titer group and 611 ± 637 RU/mL in the high-titer group, respectively ($p = 0.005$). Furthermore, they found that compared to the low anti-PLA2R titer group (<150 RU/mL), the cumulative RTX dose (960 ± 387 vs 694 ± 270 mg) was higher, and the complete remission rate (13% vs 53%) was lower in the high-titer group at 18 months.[30] Monthly mini-dose RTX therapy appears to be more suitable for patients with low anti-PLA2R titers compared to those with high antibody titers. Additionally, patients exhibiting low anti-PLA2R titers require a lower RTX dosage to achieve remission.[30]

Seitz-Polski et al compared the efficacy of RTX regimens in GEMRITUX cohort with the NICE cohort (RTX 1 g, intravenous on days 1 and 15). At six months, the remission rate in the NICE cohort was 64%, while the remission rate in the GEMRITUX cohort was 30%. It had been discovered that NICE cohort presented lower CD19 counts at month 3 and month 6, higher residual RTX levels at month 3, and a more substantial reduction in anti-PLA2R antibody levels at month 6, which might explain the fact that higher cumulative dosages of RTX induced earlier remission and higher rate of remission at month six.[31] However, further study revealed that remission was correlated with residual RTX levels at 3 months, serving as an effective predictor for achieving remission.[41,42] Consequently, maintaining residual RTX levels over an extended period may be more effective for remission. In 2024, Hao Liang et al established the first population pharmacokinetic and pharmacodynamic (PPK/PD) model for RTX treatment in MN. Simulation of a novel regimen consisting of six monthly doses of RTX 100 mg demonstrated comparable efficacy and enhanced duration of CD20+ B cell depletion relative to the standard dosage

while significantly reducing both the cumulative dosage and associated safety risks. This study provided evidence to support the RTX dosage optimization based on monthly mini-dose in MN treatment.[43]

The existing evidence for RTX administration comes from trials examining different treatment schedules and doses. However, lower doses have not been adequately explored in long-term randomized clinical trials (RCT). And the question of whether low-dose RTX is equally efficacious in MN treatment remains a subject of debate.

## Conclusion

It has been fully demonstrated that both the standard four-dose and two-dose (1 g on Days 0 and 15) regimens can effectively induce remission of proteinuria and achieve complete B-cell depletion. High-dose regimens have been associated with higher remission rates, shorter median times of remission, and more complete B-cell depletion, which is particularly important for patients with elevated circulating anti-PLA2R antibody titers. In contrast, low-dose regimens aim to optimize the overall dose of RTX, reduce treatment costs, decrease the frequency of hospitalizations, and potentially minimize adverse reactions and infection risks. However, several studies investigating the therapeutic efficacy of low-dose regimens have produced conflicting results, suggesting that low-dose regimens may be more suitable for patients with low anti-PLA2R titers. The question of whether low-dose RTX regimen is equally effective in MN treatment remains a topic of debate. To determine the optimal RTX dosage and regimen for various patient populations, it is essential to conduct multi-center large-scale RCTs to further explore the risks and benefits associated with different RTX administration regimens in the treatment of PMN.

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## References

1. Cattran DC, Brenchley PE. Membranous nephropathy: integrating basic science into improved clinical management. *Kidney Int*. 2017;91(3):566–574. doi:10.1016/j.kint.2016.09.048
2. Couser WG. Primary membranous nephropathy. *Clin J Am Soc Nephrol*. 2017;12(6):983–997. doi:10.2215/cjn.11761116
3. Ronco P, Beck L, Debiec H, et al. Membranous nephropathy. *Nat Rev Dis Primers*. 2021;7(1):69. doi:10.1038/s41572-021-00303-z
4. Hayashi N, Okada K, Matsui Y, et al. Glomerular mannose-binding lectin deposition in intrinsic antigen-related membranous nephropathy. *Nephrol Dial Transplant*. 2018;33(5):832–840. doi:10.1093/ndt/gfx235
5. Sethi S. New 'Antigens' in membranous nephropathy. *J Am Soc Nephrol*. 2021;32(2):268–278. doi:10.1681/asn.2020071082
6. Rovin BH, Adler SG, Barratt J. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. 2021;100(4s):S1–s276. doi:10.1016/j.kint.2021.05.021
7. Beck LH, Bonegio RG, Lambeau G, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *New Engl J Med*. 2009;361(1):11–21. doi:10.1056/NEJMoa0810457
8. Rovin BH, Adler SG, Barratt J, et al. Executive summary of the KDIGO 2021 guideline for the management of glomerular diseases. *Kidney Int*. 2021;100(4):753–779. doi:10.1016/j.kint.2021.05.015
9. Dantas M, Silva LBB, Pontes BTM, Dos Reis MA, de Lima PSN, Moysés Neto M. Membranous nephropathy. *Jornal Brasileiro de Nefrologia*. 2023;45(2):229–243. doi:10.1590/2175-8239-JBN-2023-0046en
10. Lu W, Gong S, Li J, Luo H, Wang Y. Efficacy and safety of rituximab in the treatment of membranous nephropathy: a systematic review and meta-analysis. *Medicine*. 2020;99(16):e19804. doi:10.1097/md.0000000000019804
11. So BYF, Yap DYH, Chan TM. B cells in primary membranous nephropathy: escape from immune tolerance and implications for patient management. *Int J Mol Sci*. 2021;22(24):13560. doi:10.3390/ijms222413560
12. Fervenza FC, Appel GB, Barbour SJ, et al. Rituximab or cyclosporine in the treatment of membranous nephropathy. *New Engl J Med*. 2019;381(1):36–46. doi:10.1056/NEJMoa1814427
13. Del Vecchio L, Allinovi M, Rocco P, Brando B. Rituximab therapy for adults with nephrotic syndromes: standard schedules or b cell-targeted therapy? *J Clin Med*. 2021;10(24):5847. doi:10.3390/jcm10245847
14. Remuzzi G, Chiurchiu C, Abbate M, Brusegan V, Bontempelli M, Ruggenenti P. Rituximab for idiopathic membranous nephropathy. *Lancet*. 2002;360(9337):923–4. doi:10.1016/s0140-6736(02)11042-7
15. Gauckler P, Shin JI, Alberici F, et al. Rituximab in membranous nephropathy. *Kidney Int Rep*. 2021;6(4):881–893. doi:10.1016/j.ekir.2020.12.035
16. Cattran D, Brenchley P. Membranous nephropathy: thinking through the therapeutic options. *Nephrol Dial Transplant*. 2017;32(suppl_1):i22–i29. doi:10.1093/ndt/gfw404
17. Cravedi P, Ruggenenti P, Sghirlanzoni MC, Remuzzi G. Titrating rituximab to circulating B cells to optimize lymphocytolytic therapy in idiopathic membranous nephropathy. *Clin J Am Soc Nephrol*. 2007;2(5):932–937. doi:10.2215/cjn.01180307

18. Bagchi S, Subbiah AK, Bhowmik D, et al. Low-dose Rituximab therapy in resistant idiopathic membranous nephropathy: single-center experience. *Clin Kidney J*. 2018;11(3):337–341. doi:10.1093/ckj/sfx105
19. Dahan K, Debiec H, Plaisier E, et al. Rituximab for severe membranous nephropathy: a 6-month trial with extended follow-up. *J Am Soc Nephrol*. 2017;28(1):348–358. doi:10.1681/asn.2016040449
20. Ruggenenti P, Chiurchiu C, Brusegan V, et al. Rituximab in idiopathic membranous nephropathy: a one-year prospective study. *J Am Soc Nephrol*. 2003;14(7):1851–1857. doi:10.1097/01.asn.0000071511.35221.b3
21. Roccatello D, Sciascia S, Di Simone D, et al. New insights into immune mechanisms underlying response to Rituximab in patients with membranous nephropathy: a prospective study and a review of the literature. *Autoimmunity Rev*. 2016;15(6):529–538. doi:10.1016/j.autrev.2016.02.014
22. Fiorentino M, Tondolo F, Bruno F, et al. Treatment with rituximab in idiopathic membranous nephropathy. *Clin Kidney J*. 2016;9(6):788–793. doi:10.1093/ckj/sfw091
23. Fervenza FC, Cosio FG, Erickson SB, et al. Rituximab treatment of idiopathic membranous nephropathy. *Kidney Int*. 2008;73(1):117–125. doi:10.1038/sj.ki.5002628
24. Scolari F, Delbarba E, Santoro D, et al. Rituximab or cyclophosphamide in the treatment of membranous nephropathy: the RI-CYCLO randomized trial. *J Am Soc Nephrol*. 2021;32(4):972–982. doi:10.1681/asn.2020071091
25. van den Brand J, Ruggenenti P, Chianca A, et al. Safety of rituximab compared with steroids and cyclophosphamide for idiopathic membranous nephropathy. *J Am Soc Nephrol*. 2017;28(9):2729–2737. doi:10.1681/asn.2016091022
26. Fenoglio R, Baldovino S, Sciascia S, et al. Efficacy of low or standard rituximab-based protocols and comparison to Ponticelli's regimen in membranous nephropathy. *J Nephrol*. 2021;34(2):565–571. doi:10.1007/s40620-020-00781-6
27. Ramachandran R, Nayak S, Kumar V, et al. Rituximab in primary membranous nephropathy: a comparative study of three dosing regimens. *Nephrol Dial Transplant*. 2021;36:1352–1354. doi:10.1093/ndt/gfab037
28. Moroni G, Depetri F, Del Vecchio L, et al. Low-dose rituximab is poorly effective in patients with primary membranous nephropathy. *Nephrol Dial Transplant*. 2017;32(10):1691–1696. doi:10.1093/ndt/gfw251
29. Wang X, Cui Z, Zhang YM, et al. Rituximab for non-responsive idiopathic membranous nephropathy in a Chinese cohort. *Nephrol Dial Transplant*. 2018;33(9):1558–1563. doi:10.1093/ndt/gfx295
30. Wang S, Deng Z, Wang Y, et al. Monthly mini-dose rituximab for primary anti-PLA2R-positive membranous nephropathy: a personalized approach. *BMC Nephrol*. 2023;24(1):146. doi:10.1186/s12882-023-03206-1
31. Seitz-Polski B, Dahan K, Debiec H, et al. High-dose Rituximab and early remission in PLA2R1-related membranous nephropathy. *Clin J Am Soc Nephrol*. 2019;14(8):1173–1182. doi:10.2215/cjn.11791018
32. Fervenza FC, Abraham RS, Erickson SB, et al. Rituximab therapy in idiopathic membranous nephropathy: a 2-year study. *Clin J Am Soc Nephrol*. 2010;5(12):2188–2198. doi:10.2215/cjn.05080610
33. Ruggenenti P, Cravedi P, Chianca A, et al. Rituximab in idiopathic membranous nephropathy. *J Am Soc Nephrol*. 2012;23(8):1416–1425. doi:10.1681/asn.2012020181
34. Esposito P, Grosjean F, Mangione F, Domenech MV, Rampino T. Rituximab in primary membranous nephropathy: beyond a B-cell-centered paradigm? *Clin Exp Nephrol*. 2018;22(1):208–209. doi:10.1007/s10157-017-1437-2
35. Hartinger JM, Kratky V, Hruskova Z, Slanar O, Tesar V. Implications of rituximab pharmacokinetic and pharmacodynamic alterations in various immune-mediated glomerulopathies and potential anti-CD20 therapy alternatives. *Front Immunol*. 2022;13:1024068. doi:10.3389/fimmu.2022.1024068
36. Fogueri U, Cheungapasitporn W, Bourne D, Fervenza FC, Joy MS. Rituximab exhibits altered pharmacokinetics in patients with membranous nephropathy. *Ann Pharmacother*. 2019;53(4):357–363. doi:10.1177/1060028018803587
37. Fenoglio R, Sciascia S, Beltrame G, et al. Rituximab as a front-line therapy for adult-onset minimal change disease with nephrotic syndrome. *Oncotarget*. 2018;9(48):28799–28804. doi:10.18632/oncotarget.25612
38. Teisseyre M, Cremoni M, Boyer-Suavet S, et al. Advances in the management of primary membranous nephropathy and rituximab-refractory membranous nephropathy. *Front Immunol*. 2022;13:859419. doi:10.3389/fimmu.2022.859419
39. Bensalem A, Cartron G, Specks U, et al. The influence of underlying disease on rituximab pharmacokinetics may be explained by target-mediated drug disposition. *Clin Pharmacokinet*. 2022;61(3):423–437. doi:10.1007/s40262-021-01081-3
40. Kaegi C, Wuest B, Schreiner J, et al. Systematic review of safety and efficacy of rituximab in treating immune-mediated disorders. *Front Immunol*. 2019;10:1990. doi:10.3389/fimmu.2019.01990
41. Boyer-Suavet S, Andreani M, Cremoni M, et al. Rituximab bioavailability in primary membranous nephropathy. *Nephrol Dial Transplant*. 2019;34(8):1423–1425. doi:10.1093/ndt/gfz041
42. Teisseyre M, Cremoni M, Boyer-Suavet S, et al. Rituximab immunomonitoring predicts remission in membranous nephropathy. *Front Immunol*. 2021;12:738788. doi:10.3389/fimmu.2021.738788
43. Liang H, Deng Z, Niu S, et al. Dosing optimization of rituximab for primary membranous nephropathy by population pharmacokinetic and pharmacodynamic study. *Front Pharmacol*. 2024;15:1197651. doi:10.3389/fphar.2024.1197651