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Pro/Con Debate

PRO/CON DEBATE

The place of cyclical therapy for the treatment of membranous nephropathy in the era of rituximab

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ABSTRACT

Primary membranous nephropathy (MN) is the most frequent cause of nephrotic syndrome in adults, due to a variety of autoantibodies, most frequently against phospholipase A2 receptor (PLA2R). In severe cases or when spontaneous remission is not achieved, immunosuppression is required. Cyclical therapy, based on glucocorticoids and cyclophosphamide on alternate months for 6 months, has proven effective to induce remission and reduce the risk of end-stage renal disease. Since the early 2000s, rituximab (RTX) has emerged as a key player in the management of MN, showing overall comparable effectiveness and likely better safety compared with the cyclical regimen, despite the lack of adequately powered trials comparing the two approaches head to head. For these reasons, RTX is now considered the agent of choice for most patients with MN. However, there are still uncertainties. Around 20–40% of patients are resistant to RTX, especially in the setting of high anti-PLA2R levels, and this drug remains relatively unexplored in patients with the most severe disease. In these scenarios, although the expanding therapeutic armamentarium is probably going to provide further options, the cyclical regimen still plays a key role as a safety net. The aim of this article is to illustrate the role of cyclical therapy in the RTX era.

Keywords: cyclical therapy, cyclophosphamide, membranous nephropathy, nephrotic syndrome, rituximab

Primary membranous nephropathy (MN) is an autoimmune disease caused by the deposition of immune complexes in the subepithelial space of the glomerulus [1]. It is the most frequent cause of nephrotic syndrome in adults and the disease course may be variable, with around one-third of patients entering spontaneous remission [2]. If remission is not achieved, deterioration of renal function can occur, up to end-stage renal disease (ESRD). Furthermore, persistent nephrotic syndrome exposes patients to significant complications, such as fluid overload, thrombosis and infections. Once secondary forms are ruled out, immunosuppression may be required in patients not achieving spontaneous remission or presenting with severe manifestations of nephrotic syndrome or kidney function deterioration.

The first immunosuppressive approaches employed in the 1970s and 1980s were based on alkylating agents or glucocorticoids. The studies comparing these treatments with placebo provided conflicting evidence, with remission rates ranging from ≈20 to 65% [3–6]; of note, even when effective, sustained remission was not achieved. Importantly, when the alkylating agent employed was chlorambucil, an increased risk of cancer was observed [7]. A revolution in disease management was achieved when glucocorticoids (intravenous pulses, followed by oral administration) and alkylating agents (oral cyclophosphamide or chlorambucil) were combined in the so-called cyclical regimen. This approach was based on the administration of these drugs on alternate months for an overall treatment

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course of 6 months. The cyclical regimen proved to be more effective than supportive treatment alone in inducing remission in three randomised controlled trials, with response rates ranging from 62 to 72% [8–11]. The benefit of this approach was also confirmed in the long-term, leading to a reduced 10-year risk of ESRD or death (8% in the cyclical regimen group versus 40% in the untreated group [10]), as well as ESRD alone (11% in the cyclical regimen versus 35% with supportive treatment alone [11]). Of note, when a cyclophosphamide- and chlorambucil-based cyclical regimen were compared in a randomised controlled trial enrolling 83 patients, clinical outcomes were similar across the two groups, both in terms of remission rates (55% and 56%, respectively) and relapse rates (30% and 25%, respectively). However, the chlorambucil-based approach was less tolerated, with six patients withdrawing treatment due to side effects compared with two in the cyclophosphamide arm [12]. Despite the effectiveness of cyclical therapy, concerns regarding the toxicity of such an approach drove researchers to explore other options, ranging from calcineurin inhibitors (CNIs) to mycophenolate mofetil and adrenocorticotropic hormone [13]. Of note, among these therapies, CNIs have proven effective in different contexts, however, their use has been limited by safety concerns, especially in patients with a decreased glomerular filtration rate (GFR), and by a high relapse risk at the time of their withdrawal [13].

A cyclophosphamide-based cyclical regimen became the recommended initial therapy in primary MN for several years, and this was also the recommendation of the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) glomerulonephritis guidelines [14]. Importantly, the rationale for such an approach became stronger when the autoimmune nature of primary MN was confirmed with the 2009 report by Beck *et al.* [15] showing that autoantibodies directed towards the podocyte antigen M-type phospholipase A2 receptor (PLA2R) were detectable in 70% of patients and played a key pathogenetic role. In the following years, the list of putative autoantigens in MN rapidly expanded, including thrombospondin type-1 domain-containing 7A (THSD7A) [16] and neural epidermal growth factor-like 1 (NELL-1) [17]. This resulted in a smaller and smaller proportion of patients with no detectable antibodies, currently being ≈5–10% [18]. Whether antigen specificity can affect the response to immunosuppression remains unclear, with the heterogeneity and rarity of individual autoantigens hindering adequately powered studies. Overall, the recognition that primary MN is an autoantibody-mediated disease significantly supports a role for therapeutic approaches targeting B-cells [19].

The first report of rituximab (RTX) use in MN was published in 2002 [20], and several retrospective studies in the early 2010s supported its effectiveness in this context [21–24]. In 2017–2019, two randomised controlled trials (RCTs), GEMRITUX (NCT01508468) [25] and MENTOR (NCT01180036) [26], confirmed the efficacy of RTX in different settings. The GEMRITUX study showed that RTX was superior to placebo, both in terms of immunological remission at 6 months and clinical remission after a median follow-up of 17 months (65% versus 34%) [25]. The MENTOR trial compared RTX with a 12-month course of cyclosporine, showing equivalence of the two approaches at 12 months but superiority of RTX at 24 months (60% versus 20% remission rate) [26].

Interestingly, a direct comparison between the cyclical regimen and RTX had to wait until 2020. One study, STARMEN (NCT01955187), compared the cyclical regimen to a tacrolimus-based regimen for 6 months, tapered by month 9, plus RTX 1 g at day 180 [27]. Response to therapy was assessed at 24 months from baseline. A higher proportion of combined complete and partial remissions was observed with the cyclical regimen compared with the tacrolimus–RTX regimen (36/43 versus 25/43; $P = .002$). Of note, adverse events were more frequent in patients who received the cyclical regimen, although the rate of serious events was similar. The remission rate in the tacrolimus–RTX arm of this study (58%) was similar to those reported in other prospective studies using RTX, while the remission rate in the cyclical therapy arm (84%) was unusually high [28]. This may reflect several potential biases in the STARMEN cohort: prognostically relevant features were not equally balanced across treatment groups at baseline, possibly favouring the cyclical therapy group (more males, higher PLA2R antibody titres and more severe nephrotic syndrome in the RTX–tacrolimus arm). This, together with the lower RTX dose used compared with other trials, urges caution in the interpretation of results.

The second RCT comparing RTX and a cyclical regimen was RI-CYCLO (NCT03018535), a pilot study aimed at providing preliminary results to design a bigger trial [29]. This study included 74 patients randomized to either RTX (1 g 2 weeks apart) or cyclical therapy. No significant differences were detected in terms of combined complete and partial remission at 12 months (62% and 73%, respectively), time to remission and relapse rates at the intention-to-treat analysis. However, at the per-protocol analysis, the rate of complete remission at month 12 was lower in the RTX arm than in the cyclical regimen arm [4/32 versus 13/38 patients; odds ratio 0.28 (95% confidence interval 0.08–0.95)]. No differences in terms of safety emerged. Of note, in four cases RTX had to be discontinued for infusion reactions.

Overall, the prospective trials performed, although limited by small sample sizes, seem to support a largely similar effectiveness of cyclical therapy and RTX, with possibly some hints of a marginally higher efficacy of the cyclical regimen and a better safety profile for RTX. The possible advantages of RTX in terms of safety are supported by a large retrospective study with a 5-year follow-up: compared with 103 patients receiving steroids and cyclophosphamide, the 100 patients treated with RTX experienced fewer events (63 versus 173; $P < .001$), both serious (11 versus 46; $P < .001$) and non-serious (52 versus 127; $P < .001$) [30]. However, this study has to be cautiously interpreted for several reasons: its retrospective nature; the possibility of 'centre effects', with subsequent biases, due to the fact that the RTX and steroids–cyclophosphamide groups were enrolled in two different centres (in Italy and The Netherlands, respectively); and the fact that the steroids–cyclophosphamide group received corticosteroids for 5 months and cyclophosphamide for up to 1 year, resulting in significantly higher steroid exposure and cyclophosphamide cumulative doses (up to 36 g) than the regimen commonly employed. Despite these uncertainties, it has to be stressed that the safety profile of RTX is now well established in different contexts, even after long-term follow-ups [31]. All these findings clearly support the role of RTX as a first-line therapeutic option for the majority of patients with idiopathic MN, in line with the most recent KDIGO guidance [32]. Now the question is: is there still room for cyclical therapy?

To answer that, we need to consider several factors. To begin with, it is important to underline that a non-negligible proportion of patients with MN do not respond to RTX: this is the case for ≈20–40% of patients according to the data generated so far. Several reasons can underlie resistance to RTX. First, a significant loss of RTX in the urine can occur in the setting of nephrotic syndrome [33], especially in patients with higher proteinuria and lower serum albumin; this subgroup shows lower residual serum RTX levels 3 months after administration and lower response

rates [34]. In this context, a way to overcome RTX resistance may be an increase in dosing. Some retrospective data suggest that higher doses of RTX can induce faster and improved remission rates [35]. RTX dosing may be relevant, especially in the setting of high anti-PLA2R antibody titres. An observational study showed that in patients with elevated levels of anti-PLA2R [defined as >152 relative units (RU)/ml], a cyclophosphamide-based regimen (1.5 mg/kg/day, duration 8–24 weeks) was more effective than RTX (cumulative dose 1.5–2 g) in inducing immunological remission [36]. Importantly, rituximab redosing was shown to be a successful strategy in this group of patients [37].

A second mechanism of RTX resistance may be the presence of neutralising antibodies directed towards RTX itself. In a cohort of 44 patients, 10 (23%) showed anti-RTX antibodies at 6 months after treatment [38]. These antibodies were associated with faster B-cell reconstitution at 6 months, higher proteinuria at 12 months (despite similar remission rates) and a higher relapse rate. Patients with anti-RTX antibodies may benefit from different anti-CD20 monoclonal antibodies, such as the humanised one, obinutuzumab [39].

A third mechanism of RTX resistance may reflect the biology of the B-cell clones that sustain the production of anti-PLA2R antibodies. In most cases of MN, autoantibodies are likely produced by short-lived plasma cells, derived from memory B-cells that express CD20 on their surface and are therefore targeted by RTX [40]. It has been hypothesized that in some cases of RTX resistance, long-lived plasma cells instead may be driving autoantibody production. This has been demonstrated to be the case in the setting of idiopathic thrombocytopenic purpura refractory to anti-CD20 [41]. Long-lived plasma cells are CD20 negative and therefore intrinsically resistant to RTX and other anti-CD20 agents [42, 43]. Relative resistance to RTX due to insufficient B-cell depletion in immunological niches, such as the bone marrow, lymph nodes and tissues, may play a role as well [44]. In these settings, therapeutic approaches with synergistic and broader mechanisms of action, such as cyclophosphamide and glucocorticoids, may play a role to overcome RTX resistance [40]. Although the effect of cyclophosphamide in targeting plasma cells is unclear and largely unexplored, this drug seems to be potentially effective on plasma cells, but with long-lived plasma cells being more refractory [45, 46].

The impact of glucocorticoids on the B-cell compartment also remains unknown to a great extent. High-dose glucocorticoids (especially dexamethasone) affect plasma cells and have been widely employed in multiple myeloma [47]; they also exert broad effects on B-cell activation and, to a lesser extent, proliferation [48]. Notably, the impact of high-dose glucocorticoids on the B-cell compartment is definitely not negligible, as further underlined by the observation that the risk of hypogammaglobulinemia in RTX-treated patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis increases in parallel with the glucocorticoid dose employed at induction [49].

Taken together, these observations suggest that RTX, cyclophosphamide and glucocorticoids may act synergistically on the B-cell compartment, leading to speculation that a multitarget approach may be of potential interest. Prospective studies of such an approach in MN are not available at the moment. A retrospective study reported 60 patients with primary MN treated with a combination of low-dose oral cyclophosphamide (2.5 mg/kg for 1 week then 1.5 mg/kg for 7 weeks), a prednisone taper (60 mg/day withdrawn in 28 weeks) and a 2-year course of high-intensity RTX (1 g every 4 months) [50]. Remarkably, all patients achieved immunological remission by 6 months and clinical remission by 2 years, with complete remission in 83%. No significant safety concerns emerged.

How all these scanty preclinical data and observational studies focused on clarifying the mechanisms of RTX resistance in MN should be translated to guide clinical practice is still unclear. For sure, while the identification of the mechanisms of RTX resistance may inform alternative emerging therapeutic strategies, there may be a rationale for employing cyclical therapy, since the mechanisms of RTX resistance do not apply to this therapeutic regimen.

Beside RTX resistance, another important point is the management of patients with severe MN, namely the ones with severe manifestations of nephrotic syndrome and/or deteriorating kidney function. In this setting, data on the use of RTX are very scarce, while one RCT explored the role of the cyclical regimen in patients with deteriorated kidney function. This RCT included 108 patients with reduced kidney function [at least a 20% decline in estimated GFR (eGFR) in the 2 years before study entry, with creatinine <300 μmol/L (3.4 mg/dl)] [51]. The risk of further decline of kidney function was significantly lower in the 33 patients treated with cyclical therapy than in the ones treated with cyclosporine or supportive care alone. Importantly, adverse events (mainly haematological) were more frequent in the cyclical therapy arm (61% of the patients) compared with the other two (49% with cyclosporine and 42% with supportive care).

The preference, based on available evidence, for the cyclical regimen in the most severe cases of MN is reflected also in the recently published KDIGO 2021 guidelines for the management of glomerular diseases [32]. According to these guidelines, personalization of treatment according to the individual risk profile is key: RTX and CNIs may be the first-line approaches for patients at moderate risk of progressive loss of renal function (defined as normal and stable eGFR after diagnosis), while RTX, a cyclical regimen or CNIs with RTX are recommended for patients at high risk (decreased eGFR, proteinuria >8 g/day, normal eGFR associated with serum albumin <25 g/L or PLA2R antibodies >50 RU/ml) and, importantly, only the cyclical regimen is advised for patients at very high risk (life-threatening nephrotic syndrome or rapid deterioration of kidney function).

With potential toxicity being one of the major concerns regarding cyclical therapy, it has also been suggested that intravenous dosing of cyclophosphamide, instead of oral, may provide benefits in this respect, while retaining therapeutic efficacy, similar to other glomerular diseases like ANCA-associated vasculitis [52] or systemic lupus erythematosus [53]. Some small, retrospective cases series have reported encouraging outcomes with such modifications of the cyclical regimen, alone [54] or in combination with reduced dosing of corticosteroids, avoiding intravenous pulses [55–57]. However, more robust data are needed before these approaches can be widely recommended.

In conclusion, the therapeutic armamentarium for idiopathic MN is rapidly expanding, however, there is still light to be shed. While RTX is now rightly considered the therapeutic of choice for the great majority of patients, cyclical therapy still plays a central role in the management of this disease, especially in high-risk patients with deteriorating kidney function or severe manifestations of nephrotic syndrome, and in cases resistant to RTX. Early reports on multidrug approaches are very promising, offering a proof of concept that the combination of drugs with synergistic mechanisms of action can induce very high rates of immunological remission. Despite the reassuring available data, the safety of these combined regimens remains an important

concern, especially in light of the relapsing course that MN often presents.

Future studies are needed to discover clinically relevant molecular endotypes and identify biomarkers predictive of treatment response, embracing the challenges of developing a precision medicine approach in MN.

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AUTHORS' CONTRIBUTIONS

FA, FM and FS drafted and reviewed the article.

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REFERENCES

1. Ronco P, Beck L, Debiec H *et al*. Membranous nephropathy. *Nat Rev Dis Primers* 2021;**7**:1–23. https://doi.org/10.1038/s41572-021-00303-z
2. Polanco N, Gutiérrez E, Covarsí A *et al*. Spontaneous remission of nephrotic syndrome in idiopathic membranous nephropathy. *J Am Soc Nephrol* 2010;**21**:697–704. https://doi.org/10.1681/ASN.2009080861
3. Donadio JV, Holley KE, Anderson CF *et al*. Controlled trial of cyclophosphamide in idiopathic membranous nephropathy. *Kidney Int* 1974;**6**:431–9. https://doi.org/10.1038/ki.1974.129
4. A controlled study of short-term prednisone treatment in adults with membranous nephropathy—collaborative study of the adult idiopathic nephrotic syndrome. *N Engl J Med* 1979;**301**:1301–6. https://www.nejm.org/doi/full/10.1056/NEJM197912133012401
5. Cattran DC, Delmore T, Roscoe J *et al*. A randomized controlled trial of prednisone in patients with idiopathic membranous nephropathy. *N Engl J Med* 1989;**320**:210–5. https://doi.org/10.1056/NEJM198901263200403
6. Cameron J, Healy M, Adu D. The Medical Research Council trial of short-term high-dose alternate day prednisolone in idiopathic membranous nephropathy with nephrotic syndrome in adults. *Q J Med* 1990;**74**:133–56. https://doi.org/10.1093/oxfordjournals.qjmed.a068422
7. Lagrue G, Bernard D, Bariety J *et al*. Treatment with chlorambucil and azathioprine in primary glomerulonephritis. Results of a "controlled" study. *J Urol Nephrol (Paris)* 1975;**81**:655–72.
8. Ponticelli C, Zucchelli P, Imbasciati E *et al*. Controlled trial of methylprednisolone and chlorambucil in idiopathic membranous nephropathy. *N Engl J Med* 1984;**310**:946–50. https://doi.org/10.1056/NEJM198404123101503
9. Ponticelli C, Zucchelli P, Passerini P *et al*. A randomized trial of methylprednisolone and chlorambucil in idiopathic membranous nephropathy. *N Engl J Med* 1989;**320**:8–13. https://doi.org/10.1056/NEJM198901053200102
10. Ponticelli C, Zucchelli P, Passerini P *et al*. A 10-year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy. *Kidney Int* 1995;**48**:1600–4. https://doi.org/10.1038/ki.1995.453
11. Jha V, Ganguli A, Saha TK *et al*. A randomized, controlled trial of steroids and cyclophosphamide in adults with nephrotic syndrome caused by idiopathic membranous nephropathy. *J Am Soc Nephrol* 2007;**18**:1899–904. https://doi.org/10.1681/ASN.2007020166
12. Ponticelli C, Altieri P, Scolari F *et al*. A randomized study comparing methylprednisolone plus chlorambucil versus methylprednisolone plus cyclophosphamide in idiopathic membranous nephropathy. *J Am Soc Nephrol* 1998;**9**:444–50. https://doi.org/10.1681/ASN.V93444
13. Scolari F, Alberici F, Mescia F *et al*. Therapies for membranous nephropathy: a tale from the old and new millennia. *Front Immunol* 2022;**13**:789713. https://doi.org/10.3389/fimmu.2022.789713
14. Kidney Disease: Improving Global Outcomes Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl* 2012;**2**:139. https://doi.org/10.1038/kisup.2012.9
15. Beck LH, Bonegio RGB, Lambeau G *et al*. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med* 2009;**361**:11–21. https://doi.org/10.1056/NEJMoa0810457
16. Tomas NM, Beck LH, Meyer-Schwesinger C *et al*. Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. *N Engl J Med* 2014;**371**:2277–87. https://doi.org/10.1056/NEJMoa1409354
17. Sethi S, Debiec H, Madden B *et al*. Neural epidermal growth factor-like 1 protein (NELL-1) associated membranous nephropathy. *Kidney Int* 2020;**97**:163–74. https://doi.org/10.1016/j.kint.2019.09.014
18. Sethi S, Madden B. Mapping antigens of membranous nephropathy: almost there. *Kidney Int* 2023;**103**:469–72. https://doi.org/10.1016/j.kint.2023.01.003
19. Rojas-Rivera JE, Carriazo S, Ortiz A. Treatment of idiopathic membranous nephropathy in adults: KDIGO 2012, cyclophosphamide and cyclosporine A are out, rituximab is the new normal. *Clin Kidney J* 2019;**12**:629–38. https://doi.org/10.1093/ckj/sfz127
20. Remuzzi G, Chiurchiu C, Abbate M *et al*. Rituximab for idiopathic membranous nephropathy. *Lancet* 2002;**360**:923–4. https://doi.org/10.1016/S0140-6736(02)11042-7
21. 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**:2188–98. https://doi.org/10.2215/CJN.05080610
22. Michel PA, Dahan K, Ancel PY *et al*. Rituximab treatment for membranous nephropathy: a french clinical and serological retrospective study of 28 patients. *Nephron Extra* 2011;**1**:251–61. https://doi.org/10.1159/000333068
23. Ruggenenti P, Cravedi P, Chianca A *et al*. Rituximab in idiopathic membranous nephropathy. *J Am Soc Nephrol* 2012;**23**:1416. https://doi.org/10.1681/ASN.2012020181
24. 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**:337–41. https://doi.org/10.1093/ckj/sfx105
25. 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**:348–58. https://doi.org/10.1681/ASN.2016040449

26. Fervenza FC, Appel GB, Barbour SJ *et al*. Rituximab or cyclosporine in the treatment of membranous nephropathy. *N Engl J Med* 2019;**381**:36–46. https://doi.org/10.1056/NEJMoa1814427
27. Fernández-Juárez G, Rojas-Rivera J, van de Logt AE *et al*. The STARMEN trial indicates that alternating treatment with corticosteroids and cyclophosphamide is superior to sequential treatment with tacrolimus and rituximab in primary membranous nephropathy. *Kidney Int* 2021;**99**:986–98. https://doi.org/10.1016/j.kint.2020.10.014
28. Ronco P, Plaisier E, Debiec H. Advances in membranous nephropathy. *J Clin Med* 2021;**10**:607. https://doi.org/10.3390/jcm10040607
29. 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**:972–82. https://doi.org/10.1681/ASN.2020071091
30. van den Brand JAJG, Ruggenenti P, Chianca A *et al*. Safety of rituximab compared with steroids and cyclophosphamide for idiopathic membranous nephropathy. *J Am Soc Nephrol* 2017;**28**:2729–37. https://doi.org/10.1681/ASN.2016091022
31. 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. https://doi.org/10.3389/fimmu.2019.01990
32. Kidney Disease: Improving Global Outcomes Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int* 2021;**100**(Suppl):S1–276. https://doi.org/10.1016/j.kint.2021.05.021
33. Boyer-Suavet S, Andreani M, Cremoni M *et al*. Rituximab bioavailability in primary membranous nephropathy. *Nephrol Dial Transplant* 2019;**34**:1423–5. https://doi.org/10.1093/ndt/gfz041
34. Teisseyre M, Cremoni M, Boyer-Suavet S *et al*. Rituximab immunomonitoring predicts remission in membranous nephropathy. *Front Immunol* 2021;**12**:738788. https://doi.org/10.3389/fimmu.2021.738788
35. 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**:1173–82. https://doi.org/10.2215/CJN.11791018
36. van de Logt AE, Dahan K, Rousseau A *et al*. Immunological remission in PLA2R-antibody–associated membranous nephropathy: cyclophosphamide versus rituximab. *Kidney Int* 2018;**93**:1016–7. https://doi.org/10.1016/j.kint.2017.12.019
37. Dahan K, Johannet C, Esteve E *et al*. Retreatment with rituximab for membranous nephropathy with persistently elevated titers of anti-phospholipase A2 receptor antibody. *Kidney Int* 2019;**95**:233–4. https://doi.org/10.1016/j.kint.2018.08.045
38. Boyer-Suavet S, Andreani M, Lateb M *et al*. Neutralizing anti-rituximab antibodies and relapse in membranous nephropathy treated with rituximab. *Front Immunol* 2019;**10**:3069. https://doi.org/10.3389/fimmu.2019.03069
39. Basu B, Angeletti A, Islam B *et al*. New and old anti-CD20 monoclonal antibodies for nephrotic syndrome. Where we are? *Front Immunol* 2022;**13**:805697. https://doi.org/10.3389/fimmu.2022.805697
40. Schrezenmeier E, Jayne D, Dörner T. Targeting B cells and plasma cells in glomerular diseases: translational perspectives. *J Am Soc Nephrol* 2018;**29**:741–58. https://doi.org/10.1681/ASN.2017040367
41. Mahévas M, Patin P, Huetz F *et al*. B cell depletion in immune thrombocytopenia reveals splenic long-lived plasma cells. *J Clin Invest* 2013;**123**:432–42. https://doi.org/10.1172/JCI65689
42. Radbruch A, Muehlinghaus G, Luger EO. Competence and competition: the challenge of becoming a long-lived plasma cell. *Nat Rev Immunol* 2006;**6**:741–50. https://doi.org/10.1038/nri1886
43. Hiepe F, Radbruch A. Plasma cells as an innovative target in autoimmune disease with renal manifestations. *Nat Rev Nephrol* 2016;**12**:232–40. https://doi.org/10.1038/nrneph.2016.20
44. Wallin EF, Jolly EC, Suchánek O *et al*. Human T-follicular helper and T-follicular regulatory cell maintenance is independent of germinal centers. *Blood* 2014;**124**:2666–74. https://doi.org/10.1182/blood-2014-07-585976
45. Dörner T, Jacobi AM, Lipsky PE. B cells in autoimmunity. *Arthritis Res Ther* 2009;**11**:247. https://doi.org/10.1186/ar2780
46. Hoyer BF, Moser K, Hauser AE *et al*. Short-lived plasmablasts and long-lived plasma cells contribute to chronic humoral autoimmunity in NZB/W mice. *J Exp Med* 2004;**199**:1577–84. https://doi.org/10.1084/jem.20040168
47. Sharma S, Lichtenstein A. Dexamethasone-induced apoptotic mechanisms in myeloma cells investigated by analysis of mutant glucocorticoid receptors. *Blood* 2008;**112**:1338–45. https://doi.org/10.1182/blood-2007-11-124156
48. Cupps TR, Gerrard TL, Falkoff RJ *et al*. Effects of in vitro corticosteroids on B cell activation, proliferation, and differentiation. *J Clin Invest* 1985;**75**:754–61. https://doi.org/10.1172/JCI111757
49. Podestà MA, Mescia F, Ricchiuto A *et al*. Predictors of hypogammaglobulinemia in ANCA-associated vasculitis after a rituximab-based induction: a multicentre study. *Rheumatology (Oxford)* 2022;keac716. https://doi.org/10.1093/rheumatology/keac716.
50. Zonozi R, Laliberte K, Huizenga NR *et al*. Combination of rituximab, low-dose cyclophosphamide, and prednisone for primary membranous nephropathy: a case series with extended follow up. *Am J Kidney Dis* 2021;**78**:793–803. https://doi.org/10.1053/j.ajkd.2021.04.014
51. Howman A, Chapman TL, Langdon MM *et al*. Immunosuppression for progressive membranous nephropathy: a UK randomised controlled trial. *Lancet* 2013;**381**:744–51. https://doi.org/10.1016/S0140-6736(12)61566-9
52. de Groot K, Harper L, Jayne DRW *et al*. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med* 2009;**150**:670–80. https://doi.org/10.7326/0003-4819-150-10-200905190-00004
53. Houssiau FA, Vasconcelos C, D'Cruz D *et al*. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum* 2002;**46**:2121–31. https://doi.org/10.1002/art.10461
54. Luzardo L, Ottati G, Cabrera J *et al*. Substitution of oral for intravenous cyclophosphamide in membranous nephropathy. *Kidney360* 2020;**1**:943–9. https://doi.org/10.34067/KID.0002802020
55. Mathrani V, Alejmi A, Griffin S *et al*. Intravenous cyclophosphamide and oral prednisolone is a safe and effective treatment option for idiopathic membranous nephropathy. *Clin Kidney J* 2017;**10**:450–4. https://doi.org/10.1093/ckj/sfw152

56. Kanigicherla DAK, Hamilton P, Czapla K *et al*. Intravenous pulse cyclophosphamide and steroids induce immunological and clinical remission in new-incident and relapsing primary membranous nephropathy. *Nephrology* 2018;**23**:60–68. https://doi.org/10.1111/nep.12955

57. Ștefan G, Zugravu A, Stancu S. Intravenous cyclophosphamide as an alternative to the oral cyclophosphamide modified Ponticelli regimen for high-risk PLA2R-positive membranous nephropathy. *J Nephrol* 2023;**36**:293–5. https://doi.org/10.1007/s40620-022-01426-6