Changing treatment paradigms for membranous nephropathies

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Membranous nephropathy (MN) is the most common cause of nephrotic syndrome (NS) in non-diabetic adult population. The immunopathogenesis of MN is mostly related to the presence of anti-phospholipase A2 receptor (PLA2R) antibodies (Ab), however, recent investigations have unveiled several new target antigens. The pathogenesis of MN primarily involves the formation and deposition of immune complexes, consisting of immunoglobulins and complement, leading to podocyte injury and disruption of the glomerular basement membrane (GBM) leading to proteinuria, often progressing to NS and, if persistent, to kidney failure. The latest KDIGO 2021 recommends that patients with a moderate to high risk of progression be treated with immunosuppressive (IS) therapy. (1) Options include calcineurin inhibitor (CNI), a combination of cyclophosphamide (CYC) and corticosteroids, and rituximab (RTX). However, the use of CNI is declining due to the increased risk of relapse and the combination of CYC and corticosteroids (cyclical therapy) is associated with increased risk of infection, osteoporosis, diabetes mellitus, weight gain, hemorrhagic cystitis and infertility. (3) In recent years, there has been significant interest in the use of RTX in the management of MN. Randomised clinical trials (RCT) like GEMRITUX and MENTOR have shown a favourable safety profile for RTX, positioning it as the preferred treatment for MN in the current era. (4,5) In the RI-CYCLO trial, the complete remission rate (CR) was lower in the RTX group compared to the modified ponticelli regimen (mPR) group (16% versus 32%) at 12 months. Despite the substantial response rates to RTX and mPR, 20–30% of cases have
resistant disease, with patients not responding to either treatment. Additionally, relapses are common, occurring in up to 30% of cases, stressing a need for more targeted and safer immunomodulatory drugs to improve long-term outcomes. Thus, the search for novel and specific therapies in MN management remains imperative.

*Rituximab and newer B-cell-targeted therapies*

B cells play a crucial role in autoimmune diseases, not only as precursors to pathogenic autoAb-producing cells but also via other mechanisms, such as by acting as antigen-presenting cells to start the autoimmune response. In addition, B cells can be a potent source of pro-inflammatory cytokines and can also initiate and/or sustain tertiary lymphoid tissues within tissues, which sustain inflammation and local production of Abs.

RTX is a chimeric anti-CD20 monoclonal antibody (mAb), it can lead to an overall remission rate of approximately 60%–70% in patients with MN. The main reason for treatment failure in RTX-treated cases remains unknown. However, several hypotheses have been proposed to explain RTX resistance in approximately one-third of the cases. These include insufficient B cell depletion, downregulation of CD20, complement depletion, resistance to antibody-dependent cellular cytotoxicity (ADCC) and apoptosis, lack of effect on CD20-negative plasmablasts and plasma cells (PCs) or their progenitors, and the development of anti-RTX antibodies. For MN cases resistant to RTX, second-generation anti-CD20 mAbs can offer a promising alternative. Obinutuzumab, a novel type II humanised mAb targeting CD20, has been engineered to enhance B-cell depletion and shows significant effects in lymphoid organs. It has been effective in inducing remission in MN with severe chronic kidney disease (CKD) and has shown success in refractory MN cases. In a recent trial of Obinutuzumab, 84.7% attained either total or partial remission (PR) with no significant adverse effects. (5) Ofatumumab targets a different CD20 epitope than RTX, potentially explaining its enhanced complement-dependent cytotoxicity. This difference helps reduce the number of autoreactive B-cells producing nephritogenic Ab. In these cells, alterations in the CD20 structure might have prevented RTX binding to B-cells. In a series of patients with MN and NS who were intolerant or unresponsive to RTX, ofatumumab was found to be efficacious. All RTX-intolerant patients achieved CR or PR, compared to only 3 of the 10 RTX-resistant patients. Levels of PLA2R Ab decreased in all patients. (6) B-cell activating factor (BAFF) is an important molecule involved in the regulation and maintenance of B-cell homeostasis. It promotes B-cell survival, maturation, and Ab production by binding to 3 specific receptors: BAFF-R, TACI, and BCMA. Belimumab, an IgG-Lambda mAb targeting soluble BAFF, shows potential in reducing PLA2R Ab and
inducing remission in PLA2R-positive MN patients, as evidenced in an open-label prospective trial where 64% (9/14) achieved CR or PR. (7) Ongoing trials are analysing the efficacy of Belimumab in MN. (NCT03949855)

A pilot trial combining RTX with CNI as induction therapy, followed by a second cycle of RTX showed higher rates of clinical CR and immunological response at 24 months compared to RTX or CNI alone. This suggests that the combination of CNI and RTX may be beneficial for patients who are refractory to RTX treatment.

Proteasome-inhibitor (PI)

PCs, the terminally differentiated end-product of B cell differentiation are primarily located in the bone marrow and secondary lymphoid tissues like the spleen and lymph nodes. PCs hold the ability to secrete high rates of Ab. In PLA2R-positive MN, long-lived PCs can be implicated in cases that do not respond to standard treatments, even after peripheral B-cell depletion. Given that PCs are terminally differentiated, they often show resistance to many standard IS treatments. PIs, such as bortezomib, induce apoptosis in Ab-secreting PCs by blocking the proteasome, leading to the accumulation of misfolded proteins and subsequent cell apoptosis involving ubiquitin-proteasome pathway. Bortezomib, which is already a frontline therapy for multiple myeloma, has shown promise in inducing apoptosis in high-turnover PCs and has been effective in treating refractory lupus nephritis. Moreover, there have been reports of its efficacy in severe cases of PLA2R-positive MN that have been resistant to various treatments, even after peripheral B-cell depletion. In a case series of MN patients with persistently elevated anti-PLA2R Ab levels and undetectable CD19+ B-cells despite several courses of RTX. (8) Treatment with a combination of bortezomib and dexamethasone for 6 cycles led to an immunological response and progressive renal improvement in most patients.

Anti-CD38 therapy

In addition to bortezomib, current research is ongoing into using anti-CD38 Ab therapies aimed at targeting long-lived PCs, a continuous source of Ab production. This approach may be beneficial in the treatment of PLA2R-associated MN. PCs in the spleen and bone marrow express high levels of CD38. Potential agents include daratumumab and felzartamab both of which decrease PCs numbers. Daratumumab is a humanised IgG1-κ mAb that triggers cell death through multiple mechanisms, such as complement-dependent cytotoxicity, ADCC, antibody-dependent cellular phagocytosis, and the induction of programmed cell death via Fc-gamma receptor-mediated cross-linking. Although case reports suggest their efficacy, formal
studies on refractory MN are lacking. However, there are ongoing open-label phase II trials, the efficacy and safety of anti-CD38 Ab (NCT04733040, NCT04145440).

Complement inhibitors

Activation of the complement pathway has been shown to be a key factor in proteinuria and kidney damage in both animal models and humans. The primary Heyman nephritis model of MN in rodents has indicated that the onset of proteinuria corresponds with complement-dependent changes in the interaction between nephrin and the actin cytoskeleton, leading to the disruption of podocyte slit diaphragm integrity. C3 deposits, often concurrently with pathognomonic IgG deposits, are frequently observed in MN and correlate with higher proteinuria levels. Analysis of differentially expressed genes in MN also reveals a significant association with complement cascade-related immune responses.

Evidence further links urinary levels of C5a to anti-PLA2R Ab titers and proteinuria levels, suggesting a connection between pathogenic Abs and complement-mediated tissue injury. (9) Mannose-binding lectin (MBL) and hypogalactosylated IgG are also emerging as crucial components of subepithelial deposits in primary MN.

Complement-directed therapies undergoing trials for various kidney diseases, including C3 glomerulopathy and IgA nephropathy, hold promise for adaptation to MN. Ongoing trials, such as those investigating BCX9930 (oral Factor D inhibitor), Iptacopan (factor B inhibitor) (NCT04154787), Narsoplimab (a mAb targeting MASP2) (NCT02682407), and Pegcetacoplan (APL-2; targeting C3, C3b), are anticipated for their potential to offer therapeutic roles in MN.

Other emerging therapies in MN

Crystallizable fragment receptor (FcRn) is important in trafficking immune complexes to the lysosome for proteolytic degradation and subsequent antigen presentation on MHC II, playing a pivotal role in adaptive immunity. (10) This function is being attempted to develop therapeutics for MN, such as Efgartigimod (Vyygart), an engineered Fc portion of human IgG1 devoid of antigen-binding regions. Similarly, Bruton’s tyrosine kinase (BTK), essential for B-cell receptor (BCR) signalling and subsequent B-cell proliferation, differentiation, and cytokine production, could also be a promising target in MN therapy. BTK inhibitors suppress BCR and myeloid Fc receptor-mediated signalling, inhibiting B-cell activation and Ab production. (Zanubrutinib: NCT05707377) Additionally, chimeric antigen receptor (CAR) T cells could be adapted as regulatory T cells (Tregs) to re-establish tolerance in autoimmune kidney diseases, including MN. The identification of specific antigens in MN might be helpful
for antigen-specific therapies such as CAR or chimeric autoantibody receptor T cell therapies in MN when autoimmunity is often driven by a single antigen. MN patients with a pro-inflammatory Th17 cytokine profile have increased relapse risk, and RTX does not affect Th17 pathways. Interferon-based therapies targeting Th17 cytokine production reduction are currently under investigation in MN, highlighting the ongoing expansion of targeted therapeutic strategies. (NCT05941845)

Figure 1 shows newer and emerging therapies in Membranous Nephropathy

SGLT2 inhibitors

SGLT2 inhibitors have shown promise in reducing CKD progression, but their efficacy in MN patients who are fully nephrotic or on immunosuppression lacks substantial data. However, for those achieving partial remission post-immunosuppression with persistent proteinuria from secondary segmental sclerosis, these agents, combined with RAAS blockade, may help mitigate proteinuria and slow CKD progression.

Indubitably, the management of MN is advancing rapidly, with the identification of several autoantigens in MN patients, paving the way for more targeted therapeutic strategies. However, current evidence does not provide clear guidance on selecting specific treatments for different MN profiles. The majority of new agents have not been sufficiently studied to offer definitive recommendations on their use and timing. Emerging B cell-targeted therapies, such as Ofatumumab and Obinutuzumab, show promise for patients who are intolerant or unresponsive to RTX. These therapies may also benefit those with multiple relapses requiring frequent RTX infusions, potentially maintaining prolonged remission. For severe cases of PLA2R-positive MN that are resistant to various treatments despite peripheral B-cell depletion and undetectable CD19+ B-cells, Anti-CD38 antibodies and proteasome inhibitors may be tried. Complement-directed therapies might be advantageous for patients at high risk of progression (indicated by very high PLA2R levels and high-grade proteinuria) as adjunctive or rescue therapies, especially when ongoing complement-mediated damage is evident. However, while serum or urinary markers, such as urinary C3dg and MAC titres, are being investigated to predict the clinical course and identify immune-mediated kidney damage, these biomarkers are not specific to MN and may be falsely elevated in other conditions and they are yet to be validated for MN. Innovative treatments involving CAAR (chimeric antigen receptor) cells, which target only the N-terminal region of autoantigens, may be effective in eliminating enough autoreactive B cells to alleviate the disease. Tailoring the CAAR strategy to the individual's epitope profile using domain-specific ELISAs could be
beneficial and can be used as an adjunctive therapy. Questions remain about the need to
generate memory CAR T cells, given that many patients achieve full remission over time. In
conclusion, while several promising therapies and biomarkers are under investigation, more
research is needed to guide individualized treatment strategies based on biomarkers and
immunological profiles.

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Figure 1: Newer and emerging therapies in Membranous Nephropathy

Ag: Antigen, BTK: Bruton's tyrosine kinase, BlyS: soluble B lymphocytes stimulator, BCR: B cell receptor, BAFF-R: B cell activating factor receptor, GC: Germinal cell, PLA2R: Phospholipase A2 receptor, CAAR: Chimeric autoantibody receptor