

## CKJ REVIEW

# Future landscape for the management of membranous nephropathy

Fernando Caravaca-Fontán <sup>1</sup>, Federico Yandian<sup>2</sup>  
and Fernando C. Fervenza <sup>3</sup>

<sup>1</sup>Department of Nephrology, Instituto de Investigación Hospital “12 de Octubre” (imas12), Madrid, Spain,

<sup>2</sup>Department of Nephrology, Hospital de Clínicas “Dr Manuel Quintela”, Montevideo, Uruguay and <sup>3</sup>Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA

Correspondence to: Fernando Caravaca-Fontán; E-mail: [fcaravaca@gmail.com](mailto:fcaravaca@gmail.com)

## ABSTRACT

Among all glomerular diseases, membranous nephropathy (MN) is perhaps the one in which major progress has been made in recent decades, in both the understanding of the pathogenesis and treatment. Despite the overall significant response rates to these therapies—particularly rituximab and cyclical regimen based on corticosteroids and cyclophosphamide—cumulative experience over the years has shown, however, that 20%–30% of cases may confront resistant disease. Thus, these unmet challenges in the treatment of resistant forms of MN require newer approaches. Several emerging new agents—developed primarily for the treatment of hematological malignancies or rheumatoid diseases—are currently being evaluated in MN. Herein we conducted a narrative review on future therapeutic strategies in the disease. Among the different novel therapies, newer anti-CD20 agents (e.g. obinutuzumab), anti-CD38 (e.g. daratumumab, felzartamab), immunoabsorption or anti-complement therapies (e.g. iptacopan) have gained special attention. In addition, several technologies and innovations developed primarily for cancer (e.g. chimeric antigen receptor T-cell therapy, sweeping antibodies) seem particularly promising. In summary, the future therapeutic landscape in MN seems encouraging and will definitely move the management of this disease towards a more precision-based approach.

**Keywords:** belimumab, felzartamab, iptacopan, obinutuzumab, resistant membranous nephropathy

## INTRODUCTION

Membranous nephropathy (MN) represents a histologic pattern of glomerular injury characterized by an accumulation of electron-dense deposits in the subepithelial region of the glomerular basement membrane, composed of immunoglobulins and complement components [1, 2]. MN is one of the most common causes of nephrotic syndrome in adults. According to the classically described natural history of MN, if left untreated up to 5%–30% may go into spontaneous complete remission at 5 years [3–5]; 25%–40% may go into spontaneous

partial remission (proteinuria  $\leq 2$  g/day) at 5 years [3–5]; whereas kidney failure may occur in 14% of patients with persistent nephrotic syndrome at 5 years, 35% at 10 years and 41% at 15 years [3–6]. However, this is not true for patients with high levels of anti-phospholipase A2 receptor (PLA2R) antibodies, since high baseline or increasing PLA2R antibody levels associate with nephrotic syndrome and progressive loss of kidney function [7]. A recent meta-analysis shows that patients with MN who are PLA2R positive have a lower rate of spontaneous remission when compared with seronegative patients [8].

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Among all glomerular diseases, MN is perhaps the one in which major strides have been made over recent decades, in both the understanding of the pathogenesis and treatment. A myriad of culprit antigens/biomarkers have been identified so far: phospholipase A2 receptor (PLA2R) [9], thrombospondin type 1 domain-containing 7A (THSD7A) [10], exostosin 1/exostosin 2 (EXT1/EXT2) [11], neural epidermal growth factor-like 1 protein (NELL-1) [12, 13], semaphorin 3B (SEMA3B) [14], protocadherin 7 (PCDH7) [15], protocadherin FAT1 (FAT1) [16], neural cell adhesion molecule 1 (NCAM-1) [17], Transforming Growth Factor Beta Receptor 3 (TGFBR3) [18], high temperature recombinant protein A1 (HTRA1) [19], contactin-1 (CNTN1) [20] and netrin G1 (NTNG1) [21]. This broad repertoire of target antigens has led to the proposal of a new antigen-based classification system [22].

On the other hand, the results from latest clinical trials on MN have sparked renewed interest in its management among nephrologists [23]. Briefly, the GEMRITUX (Evaluate Rituximab Treatment for Idiopathic Membranous Nephropathy) trial evaluated the rates of complete or partial remission at 6 months between rituximab (RTX) and placebo [24]. No significant differences were observed in this primary endpoint, although in the follow-up beyond 6 months, the remission rate was significantly greater with RTX. The MENTOR (membranous nephropathy trial of rituximab) trial compared RTX versus cyclosporine in a large multicentric cohort comprising 130 patients, 74% of whom were PLA2R positive [25]. The primary endpoint was an intention-to-treat analysis of complete or partial remission at 24 months. At 6 months, immunological remission rates were higher in the RTX arm (52% vs 28%). At 12 months, no significant differences were observed in the rate of complete or partial remissions between RTX and cyclosporine (60% vs 52%). However, at 24 months a significantly greater number of patients remained in remission in the RTX arm (60% vs 20%), mostly due to a large number of relapses after the discontinuation of the calcineurin inhibitor. Thus, RTX was found to be non-inferior to cyclosporine for induction of remission at 12 months, but statistically superior at 24 months in terms of maintenance of remission (35% vs none) [25]. The STARMEN (Sequential Treatment with Tacrolimus-Rituximab versus Steroids Plus Cyclophosphamide in Patients with Primary Membranous Nephropathy) trial compared a sequential regimen of tacrolimus followed by RTX, with a cyclical alternating treatment with corticosteroids and oral cyclophosphamide [26]. Likewise, the primary endpoint was the rate of complete or partial remission at 24 months. Treatment with corticosteroids–cyclophosphamide induced more complete or partial remissions at 24 months, as compared with tacrolimus–RTX (84% vs 58%). In addition, the rate of complete remissions was significantly greater in the former as compared with the latter (60% vs 26%). Remarkably, the number of relapses were also lower in the group of patients treated with corticosteroids–cyclophosphamide. Thus, the STARMEN trial failed to support the hypothesis that the tacrolimus–RTX regimen was superior to corticosteroids–cyclophosphamide [26]. Results of the STARMEN can be explained by the time-lag in anti-PLA2R antibodies reduction of 6 months on the tacrolimus arm versus the first cyclophosphamide–glucocorticoids dose, which together with the low rituximab dose used limited its efficacy. Finally, the RI-CYCLO (Rituximab or Cyclophosphamide in the Treatment of Membranous Nephropathy) trial aimed to evaluate the effect of RTX compared with corticosteroids–cyclophosphamide for induction of remission [27]. At 12 months, the number of patients with complete remission was lower in the RTX arm as compared with corticosteroids–cyclophosphamide (16% versus 32%), while at 24 months, in which 77% of the initial population

was assessed, complete remission and relapses were 35% vs 42%, and 22% vs 13% for cyclophosphamide–glucocorticoids and rituximab, respectively, the difference no longer significant [27].

Despite the overall significant response rates to these therapies, particularly RTX and corticosteroids–cyclophosphamide, cumulative experience over the years has shown, however, that 20%–30% number of cases may confront resistant disease. The 2021 Kidney Disease: Improving Global Outcomes (KDIGO) Guideline for the Management of Glomerular Diseases [28] acknowledges that there is no accepted definition for resistant disease. In patients with circulating PLA2R antibodies, we consider that persistence of nephrotic syndrome despite immunosuppression, or persistence/increments, of proteinuria in the presence of unchanged or increasing antibody levels after 3 months of appropriate immunosuppression therapy (e.g. zero CD19/20<sup>+</sup> B cell counts following RTX) are highly suggestive of resistant disease [7]. Therefore, patients should be carefully evaluated on an individual basis taking into the account the presence of detectable antibody levels and their response to immunosuppression therapy, and in patients with PLA2R-associated MN, a profile of antibody levels needs to be taken into consideration when ascertaining response versus resistance to immunosuppression therapy. A comprehensive algorithm for the management of resistant MN is proposed in the KDIGO 2021 guideline, based on the previous immunosuppressive regimen received and the trends in kidney function (Fig. 1). For patients who do not respond to either RTX or cyclophosphamide, the guideline recommends enrollment of patients in ongoing trials with new experimental therapies [28].

Therefore, there are still multiple unmet challenges in the treatment of resistant forms of MN which require newer approaches. Fortunately, several emerging new agents—developed primarily for the treatment of hematological malignancies or rheumatoid diseases—are currently being evaluated in MN. This narrative review aims to summarize what the future holds for MN and the rationale behind these potential new therapies (Table 1).

## NEWER ANTI-CD20

B-cell lymphocytes have been shown to play a key role in the pathogenesis underlying MN [5]. CD20 is a transmembrane phosphoprotein highly expressed on the cell surface of B cells and, even though its biological function is poorly understood, evidence suggests that it is involved in the T-cell-independent antibody response [29, 30].

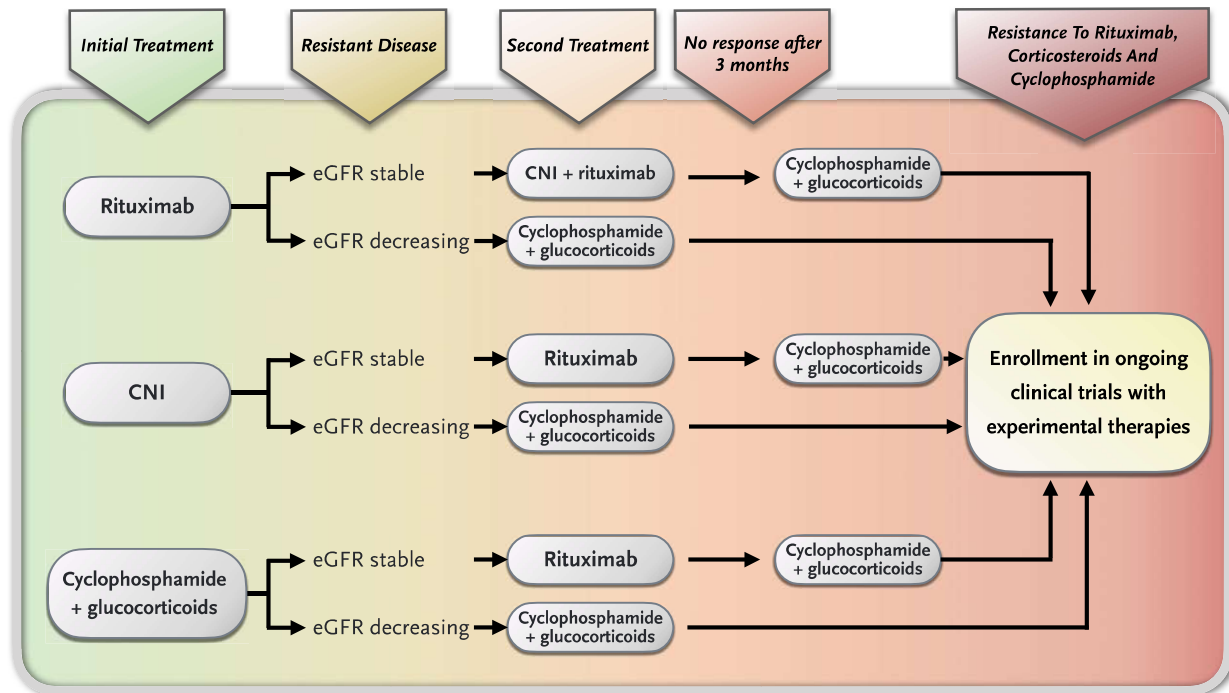
CD20 is composed of four membrane-spanning domains with the amino- and carboxyterminal domains located within the cytoplasm (Fig. 2). The extracellular part of CD20 consist of two loops formed between position 72–80 and 142–182, and represent the main targets of anti-CD20 monoclonal antibodies [31–33].

The introduction of RTX, a chimeric immunoglobulin G1- $\kappa$  (IgG1- $\kappa$ ) against CD20, dramatically improved the management of several B-cell malignancies [34], and also demonstrated efficacy in MN in the aforementioned studies [24, 25]. RTX can induce B-cell death through complement-mediated cytotoxicity, antibody-dependent cellular cytotoxicity or by triggering apoptosis [35–37]. However, up to 35%–40% may show treatment failure with RTX [25, 38], further raising the need for more potent alternative therapies. Moreover, patients may become sensitized to the murine portion of the drug, and delayed serum sick syndrome or hypersensitivity reactions may contraindicate further infusions of RTX [39].

Table 1: Summary of potential future therapeutic approaches in resistant MN and ongoing trials with these novel agents.

| Drug class or technology | Generic name (brand)                                                | Type                                                                  | Mechanism of action                                                                                                                                                                      | Rationale on MN                                                                   | Clinical trials on MN/status                                                                                                               |
|--------------------------|---------------------------------------------------------------------|-----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Anti-CD20                | Ofatumumab (Arzerra® , Kesimpta®)                                   | Type I (first generation) fully human IgG1 mAb                        | Binding to the CD20 molecule. More potent direct cell death; minimal complement dependent cytotoxicity; potent antibody-dependent cellular cytotoxicity; antibody-dependent phagocytosis | B-cell depletion                                                                  | Obinutuzumab (NCT04629248, NCT05050214)/ongoing                                                                                            |
| Proteasome inhibitors    | Obinutuzumab (Gazyva®)                                              | Type II (second generation) non-fucosylated, fully humanized IgG1 mAb |                                                                                                                                                                                          |                                                                                   |                                                                                                                                            |
|                          | Bortezomib (Velcade®); carfilzomib (Kyprolis®); ixazomib (Ninlaro®) | Boronic acid peptide                                                  | Inhibition of proteasome is a proteinase complex responsible for most of intracellular protein degradations                                                                              | Target antibody-producing plasma cells                                            | N/A                                                                                                                                        |
| Anti-CD38                | Daratumumab (Darzalex®)                                             | Humanized IgG1-κ mAb                                                  | Plasma cell death through complement-dependent cytotoxicity; antibody-dependent cell-mediated cytotoxicity; antibody-dependent cellular phagocytosis; apoptosis                          | Target long-lived plasma cells responsible for sustained production of antibodies | Felzartamab (NCT04733040, NCT04145440, NCT04893096)/ongoing                                                                                |
| Anti-BlyS                | Isatuximab (Sarclisa®)<br>Felzartamab<br>Belimumab (Benlysta®)      | Chimeric IgG1-κ mAb<br>Humanized IgG1-λ mAb<br>Humanized IgG1-λ mAb   | Blocks the binding of soluble BlyS, a B-cell survival factor, to its receptors on B cells                                                                                                | Inhibition of autoreactive B cells                                                | Belimumab (NCT01610492)/completed; belimumab (NCT03949855)/ongoing<br>Iptacopan (NCT04154787)/ongoing<br>Narsoplimab (NCT02682407)/ongoing |
| Anti-complement          | Iptacopan<br>Narsoplimab                                            | Oral selective inhibitor of factor B<br>Humanized IgG4-λ mAb          | Alternative complement pathway blockade<br>Inhibition of MASP-2                                                                                                                          | Complement system blockade                                                        |                                                                                                                                            |
| Immunoadsorption         | Peptide GAM immunoadsorption (Globafin® Fresenius Medical Care)     | Immunoadsorption                                                      | Specific removal of IgG, in particular IgG1, IgG2 and IgG4 (and to a lesser extent IgG3)                                                                                                 | Extracorporeal treatment to remove nephritogenic antibodies                       | Peptide GAM immunoadsorption (NCT03255447)/completed                                                                                       |
| CAAR-T cell therapy      | N/A                                                                 | Genetic engineering of T cells                                        | Allows modified autologous T cells to target specific antigens (e.g. domains of PLA2R) with T-cell receptor, leading to their lysis                                                      | Target B cell                                                                     | N/A                                                                                                                                        |
| Sweeping antibodies      | N/A                                                                 | Genetic engineering of IgG                                            | Active elimination of soluble antigens from circulation                                                                                                                                  | Bind nephritogenic antibodies and facilitate lysosomal degradation                | N/A                                                                                                                                        |

CD: cluster of differentiation; mAb: monoclonal antibody; N/A: no information available.



**Figure 1:** Algorithm for management of patients with treatment-resistant MN (adapted from [26]). When initial treatment fails, second treatment is dependent on the severity of kidney function. When rituximab is chosen as second treatment, response should be evaluated after 3 months. For patients who do not respond to either rituximab or cyclophosphamide, enrollment of patients in ongoing trials with new experimental therapies is recommended. Note that for patients with PLA2R-associated MN, profile in antibody levels needs to be taken into consideration when ascertaining response versus resistance to therapy. eGFR: estimated glomerular filtration rate; CNI: calcineurin inhibitor.

These challenges, together with the improvement in the understanding of the biology of monoclonal antibodies, have led to the development of novel drugs during the last decade [40]. One such agent is ofatumumab (OFA), a type I humanized monoclonal antibody that binds CD20 through the Fab domain at a distinct epitope compared with RTX [41]. OFA recognizes both small and large loops of CD20, whereas RTX only binds to the large loop of the distal epitope [42]. Furthermore, OFA has a binding site for C1q, which results in improved complement-mediated cytotoxicity [43]. The efficacy of OFA in MN was reported in a patient with a multiple relapsing disease requiring repeated infusions of RTX, in whom rescue treatment with OFA achieved a persistent remission of nephrotic syndrome for 2 years [44]. In another study from the same group, B-cell depletion induced by OFA followed by double-filtration plasmapheresis accelerated PLA2R antibody depletion, in three patients with nephrotic syndrome and high PLA2R antibody titers [45].

Obinutuzumab (OBI), a highly potent type II humanized monoclonal antibody against CD20, was primarily designed to overcome several postulated mechanisms of RTX resistance [46]. OBI is an IgG1- $\kappa$  antibody that recognizes epitopes different from those of RTX, and also has a glycosylated Fc portion which confers specific *in vitro* activities [34]. OBI has been found to induce reduced complement-dependent cytotoxicity, lysosome-dependent cell death, increased antibody-dependent cellular cytotoxicity and phagocytosis [34]. These B-cell depletion mechanisms contrast with the complement-dependent cytotoxicity of RTX [47]. In addition, OBI has demonstrated superiority in the depletion of B cells in whole blood samples, and also triggers a deeper depletion of B cells in spleen and lymph nodes, compared with RTX [48]. All these characteristics provide a strong

pathophysiological rationale for its use in resistant MN patients aimed at preventing the production of antibodies against certain podocyte antigens, and the deposition of immune complexes [47, 49, 50]. Currently there are two ongoing trials with OBI in MN (NCT04629248, NCT05050214), which will likely shed light and further evidence on the effectiveness of this agent in the disease.

## PROTEASOME INHIBITORS

The proteasome is a proteinase complex responsible for most of intracellular protein degradations, and this process is primarily mediated by the ubiquitin–proteasome pathway [51]. Several proteins involved in the process of cell growth and differentiation are degraded through the proteasome [51]. Thus, the inhibition of the proteasome ultimately leads to an accumulation of misfolded proteins inducing cell apoptosis. Antibody-secreting plasma cells are particularly susceptible to this mechanism, which explains why these agents have great efficacy in plasma cell malignancies [52].

Bortezomib is a first-in-class proteasome inhibitor that was initially approved by the United States Food and Drug Administration for the treatment of multiple myeloma, although it is currently used also for certain types of lymphoma or light-chain amyloidosis, among others. The rationale for the potential use of proteasome inhibitors in resistant MN lies in the ability to target antibody-producing plasma cells. However, the frequent treatment-related side effects—particularly herpes zoster infection and peripheral neuropathy—are an important area of concern, and often lead to discontinuation when prescribed for hematological-related diseases. Second generation proteasome

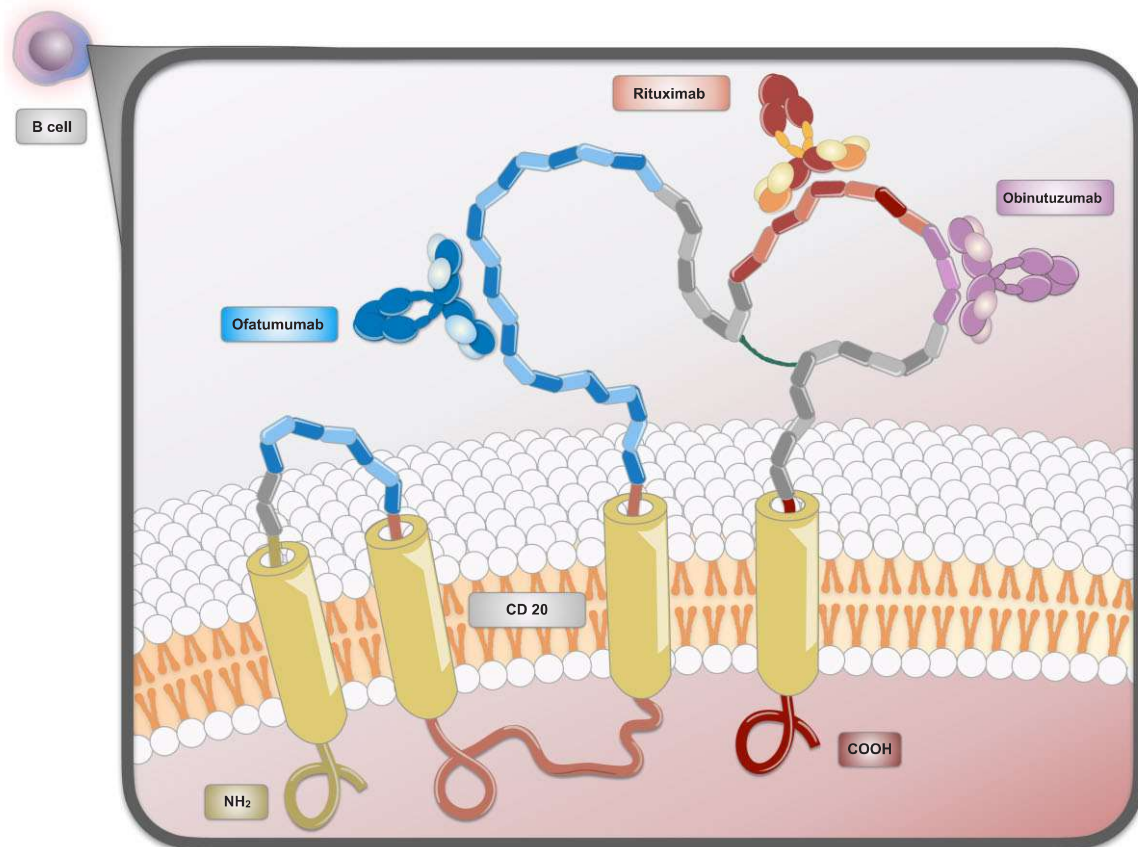


Figure 2: Schematic representation of CD20 with the corresponding binding epitopes of ofatumumab (blue), rituximab (red) and obinutuzumab (purple).

inhibitors, such as carfilzomib, ixazomib or delanzomib, have been developed.

Successful use of bortezomib in MN has been reported in the literature [53–55], including an early recurrence after kidney transplantation refractory to RTX [56]. To our knowledge, there are no planned or ongoing clinical trials with proteasome inhibitors in MN and therefore, further investigation on this promising therapeutic strategy is warranted.

## ANTI-CD38

Long-lived plasma cells play a major role in the sustained production of antibodies in autoimmune diseases [57]. As such, targeting them represents a therapeutic challenge because, unlike short-lived plasmablasts ( $CD19^+CD20^-$ ), long-lived plasma cells ( $CD19^-CD20^-CD38^+CD138^+$ ) reside in survival niches in inflamed tissue and bone marrow [58]. Current therapeutic strategies based on immunosuppression might only reduce the number of long-lived plasma cells that reside in secondary lymphoid organs and thus, the elimination of these cells requires different approaches [58].

Splenic and bone marrow plasma cells highly express CD38 and therefore, the use of anti-CD38 agents represents an attractive option in autoimmune diseases [59, 60] (Fig. 3). One such agent is daratumumab, a humanized monoclonal IgG1- $\kappa$  antibody that induces cell death through a wide variety of mechanisms including complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and antibody-

dependent cellular phagocytosis, together with the induction of programmed cell death via Fc-gamma receptor-mediated cross-linking [61]. Daratumumab is currently approved for the treatment of refractory multiple myeloma, either as monotherapy or combined with other agents [61]. The use of daratumumab in MN has recently been reported in a PLA2R-positive patient with multi-resistant disease, although the patient eventually reached kidney failure [62].

In addition to daratumumab, anti-CD38 drugs have been developed, such as isatuximab (chimeric IgG1- $\kappa$  antibody) or felzartamab (humanized IgG1- $\lambda$  antibody). In fact, felzartamab is currently being evaluated in MN in ongoing trials (NCT04733040, NCT04145440, NCT04893096). Preliminary results presented in abstract form showed: 5/7 patients treated with felzartamab for  $\geq 4$  weeks had a  $>50\%$  reduction from baseline in anti-PLA2R antibody, whereas 2/7 patients had reductions from baseline of  $-16.8\%$  and  $-5.0\%$ . The drug was well tolerated and B-cell counts were not markedly changed from baseline. However, longer follow-up will be required to assess felzartamab safety and efficacy in this population.

## BELIMUMAB

Another novel therapeutic strategy assessed in MN is the inhibition of autoreactive B cells by targeting B-lymphocyte stimulator (BLyS), which promotes its apoptosis and prevents the differentiation and survival of B cells [63].

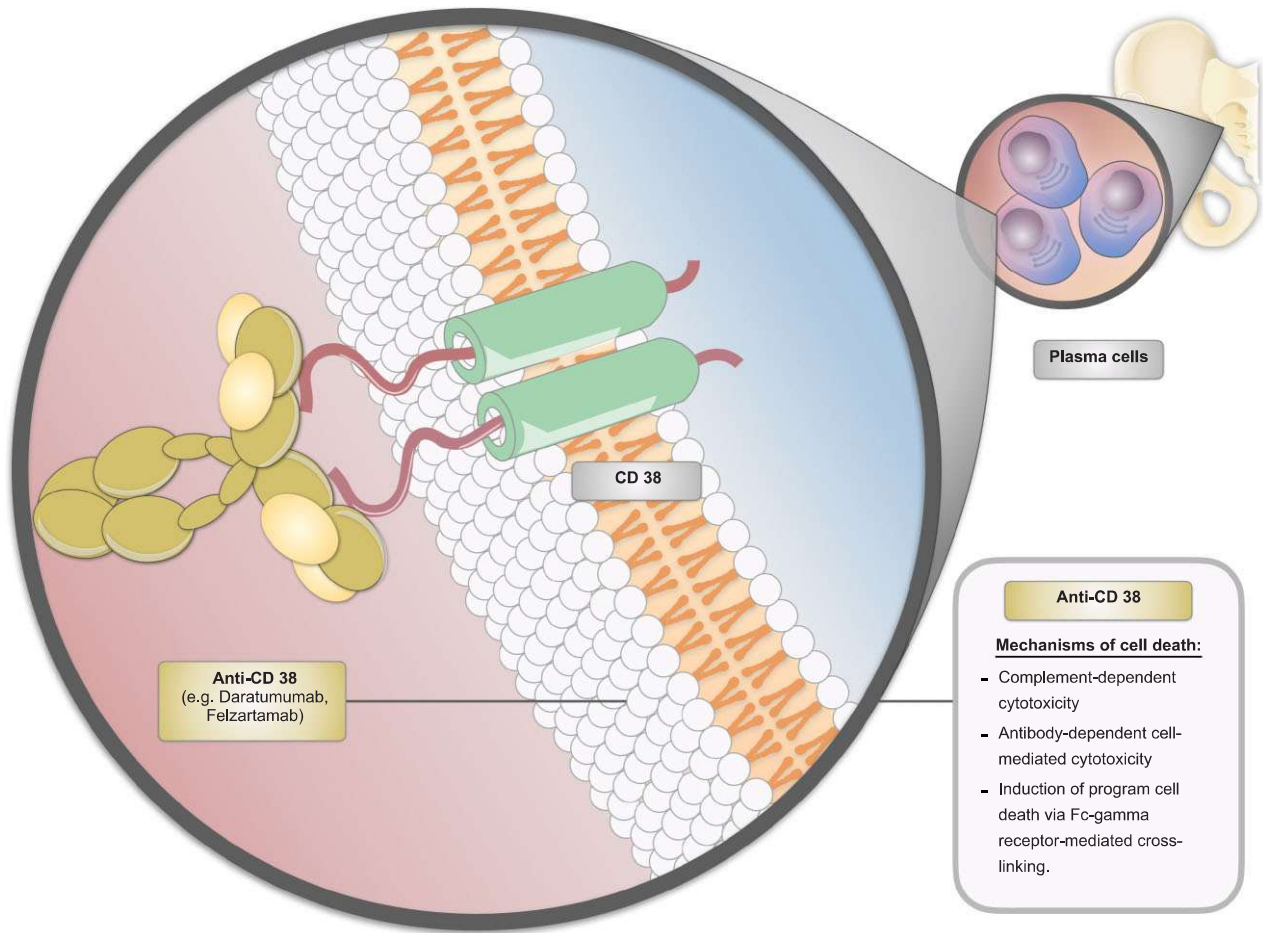


Figure 3: Schematic representation of CD38 and the mechanisms of cell death of anti-CD38 antibodies (e.g. daratumumab, felzartamab).

Belimumab is an IgG1- $\lambda$  monoclonal antibody targeting BlyS, which has shown efficacy in patients with systemic lupus erythematosus [64, 65].

A small, prospective, single-arm study evaluated the effect of belimumab on proteinuria in 11 patients with PLA2R-positive MN [66]. Patients received belimumab monotherapy (10 mg/kg intravenously every 4 weeks). Eight patients completed treatment, three interrupted it before 16 weeks, one patient interrupted because of remission at week 64, and two discontinued after 16 weeks because deteriorating kidney function or persisting hypogammaglobulinemia. The authors found in the intention-to-treat analysis a reduction of proteinuria at 7 months and at 2 years, together with a reduction of PLA2R antibody titers. Eight participants achieved partial remission and one case complete remission.

Currently, there is an ongoing trial that will evaluate the effectiveness of belimumab combined with RTX, compared with RTX alone, in achieving complete remission in MN (NCT03949855).

## ANTI-COMPLEMENT THERAPIES

Evidence for complement system activation in MN patients is well acknowledged by the frequent finding of C3 and C5b-9 components in kidney biopsies [67–70]. In addition, in some cases, kidney biopsies from MN patients stain positive for C1q, which

binds to immune complexes containing IgG or IgM, leading to activation of the classical pathway [71]. However, the specific role and clinical impact of the individual activation of each pathways in MN are still poorly understood [71]. The classic and lectin pathways merge at the level of C3 convertase (C4b2a), and the proteolytic degradation of C3b leads to the formation of C4d, which is a strong histologic marker in kidney biopsy [72, 73]. On the other hand, the alternative complement pathway has also been found to be active in MN by the presence of low levels of factor B, properdin, together with complement factor H and complement factor H-related proteins [70, 74]. More recently, another study investigated the role of C3a and C3a receptor in the pathogenesis of MN [75]. Plasma C3a levels were elevated in all study patients and there was an increased expression of the C3a receptor on podocytes, which correlated with serum creatinine and proteinuria [75]. When the investigators used a C3a receptor antagonist a reduction in proteinuria was observed, thus supporting the notion that anaphylatoxin C3a is a major effector of complement-mediated podocyte damage in MN [75].

All this evidence makes the use of complement system blockers an attractive therapeutic target in MN. Currently there are two ongoing trials that will evaluate the efficacy of two anti-complement drugs in the disease. The first drug is iptacopan, a highly potent oral selective inhibitor of factor B, which is an important component of the alternative complement pathway [76]. This randomized, two arm, parallel group study will evaluate the efficacy of iptacopan compared with RTX in subjects at

high risk of disease progression defined on the basis of PLA2R antibody titers and proteinuria (NCT04154787).

The other agent is narsoplimab, a humanized IgG4- $\lambda$  monoclonal antibody inhibiting mannan-binding lectin serine protease 2 (MASP-2), a serine protease responsible for cleavage of the complement components C2 and C4. The ongoing trial with this drug aims to assess the safety of the drug in patients with MN and other glomerular diseases (NCT02682407).

## IMMUNOADSORPTION THERAPY

Immunoadsorption is a selective apheresis technique for the removal of specific antibodies—particularly efficient in the removal of all IgG subclasses—and other molecules from the blood. The use of immunoadsorption as an ancillary technique in the management of nephrotic syndrome was reported back in 1999 [77]. Among diverse etiologies, four patients had MN and underwent treated with Immuno-sorba® processing 2–2.5 plasma volumes, achieving a reduction in proteinuria after treatment [77].

Since the discovery and characterization of disease-specific antibodies in MN, there is a plausible rationale for performing extracorporeal treatment to remove nephritogenic antibodies, while combining with immunosuppression to have a prolonged effect on new production [78]. The efficacy of immunoadsorption was reported in two patients with THSD7A-positive MN in the setting of active tumor disease, which disqualified them for standard immunosuppression [79]. This treatment was associated with a reduction of THSD7A antibody titers and reduction in proteinuria [79].

A single-arm prospective pilot study was carried out (NCT03255447) to evaluate the efficacy of selectively removing PLA2R antibody using immunoadsorption in 12 adult patients with biopsy-proven MN [80]. The authors used peptide GAM immunoadsorption technology, which specifically removes IgG1, IgG2 and IgG4, and to a lesser extent IgG3. Each patient underwent daily immunoadsorption for 5 days, showing a median reduction in PLA2R antibody titer by 87% at the end of the treatment week, followed by an increase over follow-up. However, this treatment had no significant impact on outcomes [80], suggesting that patients may need repeated treatments to completely remove and/or keep anti-PLA2R antibody levels low.

## BRUTON'S TYROSINE KINASE INHIBITORS

Bruton's tyrosine kinase (BTK) is a member of the tyrosine kinase family and it is found in different hematopoietic cell types, such as B cells, mast cells or neutrophils, among others [81]. However, neither T cells nor natural killer cells express BTK [82]. This kinase plays a crucial role in both the development, survival and activation of B cells, and it is also involved in several B-cell functions such as antigen presentation or production of antibodies by B-cell receptor [83].

Ibrutinib is an agent that irreversibly binds to BTK, thereby inhibiting B-cell proliferation. This drug is approved for the treatment of several B-cell malignancies and overall tolerability is good, with upper respiratory infections or diarrhea being its main side effects [84, 85]. Several new BTK inhibitors have been developed over recent years, such as fenebrutinib, elsabrutinib, evobrutinib or zanubrutinib, among others. The mechanism of action of these agents provide rationale for its potential use in autoimmune diseases such as MN. Experimental studies in mice showed efficacy of BTK inhibitors in collagen-induced arthritis, lupus models or antibody-mediated glomerulonephritis [86–88].

This notion has further been supported by various human studies with patients with pemphigus vulgaris or rheumatoid arthritis [89]. There are currently ongoing trials in systemic lupus erythematosus and rheumatoid arthritis, but no planned or ongoing trials on MN. Therefore, this potential strategy requires further investigation.

## CHIMERIC AUTOANTIBODY RECEPTOR T-CELL THERAPY

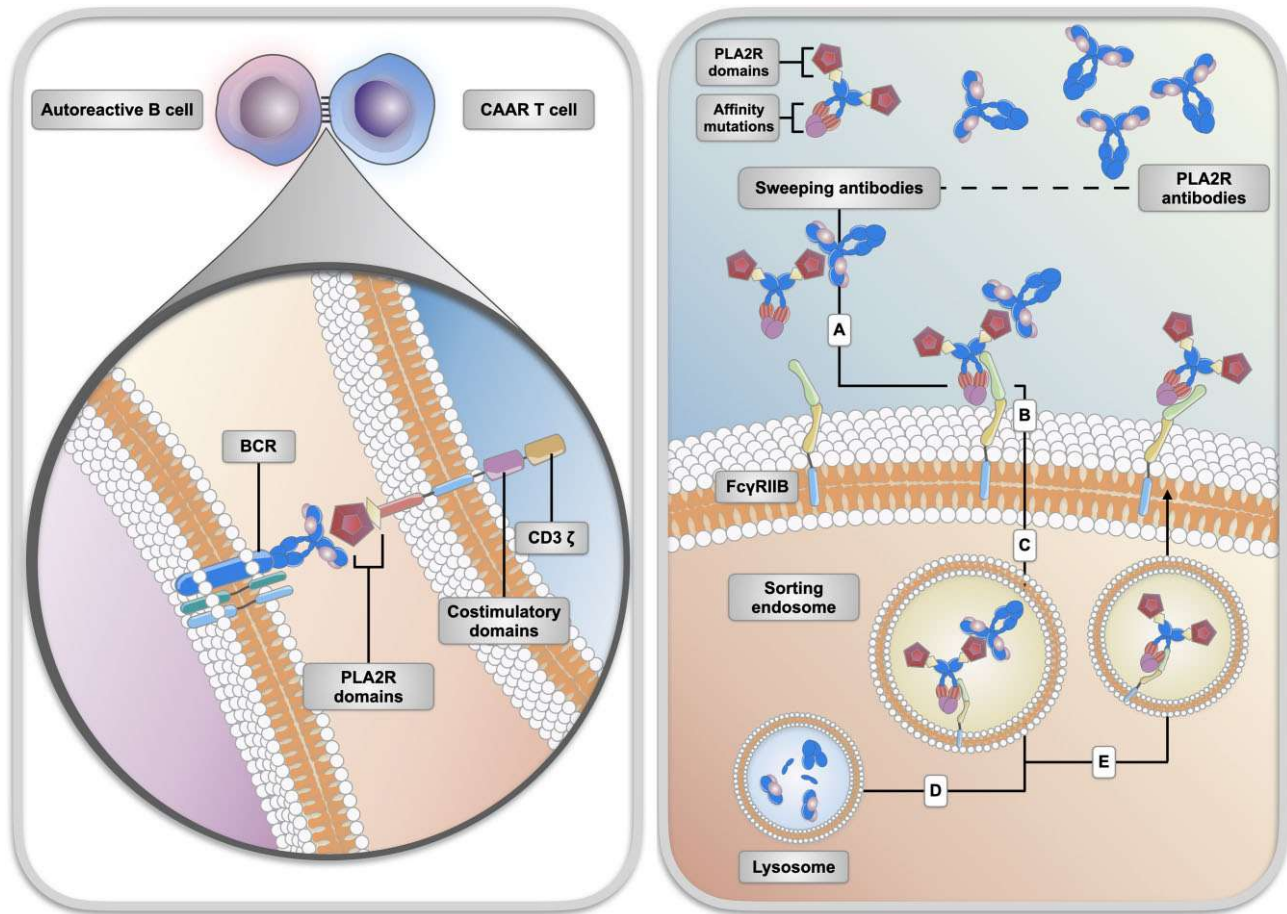
Over the last decade, groundbreaking innovations have been made in Onco-Hematology, which have brought new hopes for cancer therapies. For instance, genetic engineering of immune cells through chimeric antigen receptor-T (CAR-T) cell therapy has improved the prognosis of B cell malignancies that are refractory to conventional therapies [90, 91]. Briefly, this technology allows modified autologous T cells to target specific tumor antigens with T-cell receptor (TCR), leading to their lysis. Mononuclear cells from peripheral blood are isolated with leukapheresis and then genetically engineered *in vitro* to express chimeric antigen receptor (e.g. the antigen-binding domain of an anti-CD19 antibody fused to a transmembrane and several intracellular signaling domains in B-cell malignancies) [92, 93]. Thus, CAR-T cells gain the ability to recognize specific antigens on tumor cells without antigen processing and presentation. Once genetically modified, CAR-T cells undergo extensive proliferation *in vitro* and, after treatment with lymphodepleting chemotherapy, then these cells are reinfused into the patient [92]. The advantage of this therapy is the opportunity to develop long-term memory CAR-T cells, which offers sustained efficacy against newly produced target cells, without needing repetitive dosing [93].

The positive results shown with this therapy in Onco-Hematology have opened up the possibility of applying this technology to autoimmune diseases. Indeed, the effectiveness of this therapy has recently been reported in a series of five patients with refractory systemic lupus erythematosus [94].

One major modification is required in order to apply this therapeutic strategy in antibody-mediated diseases: the antigen-binding domain of a conventional CAR should be replaced by a part of the autoantigen of interest, which results in a chimeric autoantibody receptor (CAAR) [93] (Fig. 4). Thus, the resulting CAAR-T cell will bind and erase B cells that express the corresponding B-cell receptor, a membrane-anchored immunoglobulin that matches with the autoantibody produced by the clone [93].

The potential application of CAAR-T cell strategy in MN has been hypothesized [93]. Accordingly, in order to achieve an optimal intermembrane distance of the immunologic synapse, it would seem reasonable to fuse smaller fragments of the target antigen to the chimeric receptor, which would likely be sufficient to erase a significant number of autoreactive B cells [93].

Despite the promising results with this state-of-the-art therapy, enthusiasm does not preclude caution, as there are also several potential drawbacks. On one hand, development of personalized CAAR-T cells is complex, expensive and time-consuming. On the other hand, several potential serious adverse events may occur, such as the cytokine release syndrome, caused by the activation of CAR-T cells and subsequent production of proinflammatory cytokines [93, 95]. Therefore, weighing overall benefits and risks, it is likely that only a minor proportion of patients with MN would potentially benefit for this treatment once implemented, although more evidence is needed before firm conclusions can be drawn.



**Figure 4:** Schematic representation of mechanism of action of CAAR-T cell therapy and sweeping antibody technology (inspired by Köllner et al. [93]). Left hand side: the CAAR is composed of PLA2R domains (cysteine-rich and fibronectin type II domains), a transmembrane domain, a costimulatory domain and the CD3 $\zeta$  domain (which contain three immunoreceptor tyrosine-based activation motifs). The CAAR binds to a B cell, expressing the corresponding B-cell receptor (BCR), a membrane-anchored IgG corresponding to the autoantibody that is produced by the B cell. The interaction between CAAR-T cell to pathogenic B cell leads to release of granzyme B, which eliminates the target B cell. Right hand side: sweeping antibody contains PLA2R domains (cysteine-rich and fibronectin type II domains) and affinity enhancing mutations in Fc portion. (A) After injection, sweeping antibody bind PLA2R antibodies in circulation; (B) scavenger cells that express Fc $\gamma$ RIIB bind the circulating immune complex; (C) immune complexes are internalized and transported to the sorting endosome, where pH is about 6; (D) subsequently, the autoantibody is released from the immune complex and degraded inside the lysosome; (E) the sweeping antibody is returned to cell surface which allows binding of new circulating autoantibodies, thus causing the "sweeping" effect.

## SWEEPING ANTIBODY TECHNOLOGY

Under physiological conditions, antibodies are non-specifically internalized by endothelial cells and transported to the sorting endosome, where pH is about 6 [96]. Inside sorting endosomes, antibodies are captured by neonatal Fc receptor (FcRn) and are preferentially directed toward recycling pathways in the extracellular space, thus preventing their lysosomal degradation [97]. In contrast, at neutral pH, IgGs are released from the FcRn back into circulation, and this mechanism has been shown to prolong their half-life in circulation by approximately 30 days [98]. As a result, this continuous recirculation of antigen-antibody complexes from endothelial cells back into circulation can profoundly increase also the half-life of an antigen [97] (Fig. 4).

A novel therapeutic modality termed sweeping antibodies is being developed, which allows active elimination of soluble antigens from circulation [99]. Two antibody engineering technologies are combined: variable region engineering which enables the antibody to bind to an antigen in

plasma and then dissociate from the antigen in endosome; on the other hand, constant region engineering increases the cellular uptake of the antibody-antigen complex into endosome [99]. Consequently, the recirculation of the therapeutic sweeping antibody leads to further removal of antigens from circulation [93].

Animal models have demonstrated that the sweeping antibody method can be used for the elimination of antigen-specific antibodies. Based on this experience, it has been hypothesized that the sweeping antibody concept could also be applied in MN patients [93]. Theoretically, sweeping antibodies with the Fab region substituted for the cysteine-rich domain of PLA2R antibody, would bind nephritogenic antibodies. The resulting immune complex would be taken up by the liver or endothelial cells, leading to lysosomal degradation of the autoreactive antibodies and potential recirculation of the therapeutic sweeping antibody. To summarize, this promising yet complex therapeutic strategy would facilitate the elimination of pathogenic autoantibodies through endogenous degradation systems.

## CONCLUSIONS

Recent years have witnessed dramatic improvements in the understanding of the pathogenesis of MN, along with a paradigm shift in its therapeutic management, which have impacted its prognosis. Despite this, a number of patients may confront resistant MN in clinical practice, which requires alternative therapeutic approaches. Herein, we conducted a comprehensive review on future therapeutic strategies on MN. Among the different novel therapies described, novel anti-CD20, anti-CD38 and complement inhibitors seem to be particularly promising approaches. Nonetheless, the therapeutic landscape in MN seems encouraging and the technologies and innovations developed primarily for cancer (e.g. CAR-T cell, sweeping antibody) will definitely move the management of this disease towards a more precision-based approach.

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