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CKJ REVIEW

Newer B-cell and plasma-cell targeted treatments for rituximab-resistant patients with membranous nephropathy

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ABSTRACT

Membranous nephropathy is the most common cause of nephrotic syndrome in adults. While spontaneous remission occurs in approximately one-third of cases, another one-third of patients receiving immunosuppressive therapy demonstrate treatment resistance. This resistance, coupled with persistent proteinuria, significantly increases the risk of kidney failure. Alternative therapies, including B-cell and plasma-cell targeted treatments have been explored in isolated cases and case series. In this review, we examine the available evidence on the treatment of resistant and relapsing membranous nephropathy with a particular focus on B- and plasma-cell directed therapies.

Keywords: glomerulonephritis, membranous nephropathy, plasma-cell targeted, rituximab, treatment

INTRODUCTION

Primary membranous nephropathy (MN) is a leading cause of nephrotic syndrome in adult non-diabetics, accounting for 20%–30% of cases overall and up to 58% among individuals over 65 years of age [1, 2]. Over the past two decades, significant advancements in our understanding of MN have been driven by the identification of mostly podocyte autoantigens, along with their circulating antibodies. Phospholipase A2 receptor 1 (PLA2R1) has been implicated in ~70% of cases, and ongoing research continues to reveal additional target antigens, thereby expanding our diagnostic and therapeutic options [3–6].

B-cell depletion with rituximab has emerged as a first-line therapy for primary MN in most patients without severe risk factors. While it has proven effective, data from large observational cohort studies indicate a failure rate approaching 35%, with recurrence rates of up to 27% [7, 8]. Treatment with calcineurin inhibitors (tacrolimus, cyclosporine), is associated with a high relapse rate of up to 40%–50% on withdrawal. Additionally, cyclophosphamide, while effective, is linked to adverse events [9–11]. These findings underscore the need for alternative therapies. In this review, we discuss the available data on the treatment of rituximab-resistant and -relapsing MN with particular consideration of B-cell and plasma-cell therapies.

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Current standard of treatments

Spontaneous remission is relatively common in MN. Therefore, assessing the risk of progressive kidney function loss is crucial before initiating therapy [12]. According to the KDIGO 2021 guidelines [13], all patients should receive optimal supportive care regardless of their risk profile. This includes interventions such as dietary salt restriction, blood pressure control (<120/80 mmHg), dyslipidemia management, renin–angiotensin–aldosterone system blockade, and, more recently, the incorporation of SGLT-2 inhibitors into supportive care [13–15]. Although specific randomized controlled trials investigating SGLT-2 inhibitors in MN are lacking, their use is becoming increasingly prevalent [16].

Immunosuppressive therapy is recommended for patients with primary MN who are at moderate to very high risk for progressive disease or with severe consequences of nephrotic syndrome. Treatment options include rituximab, cyclophosphamide combined with alternate-month glucocorticoids for 6 months, or CNI-based therapy for at least 6 months. The choice among these options should be guided by a comprehensive risk assessment. Patients should be monitored using proteinuria, serum albumin, and estimated glomerular filtration rate (eGFR); in cases associated with PLA2R1, serum anti-PLA2R1 levels should also be quantified. Notably, immunologic remission—characterized by a reduction or disappearance of PLA2R autoantibodies—often precedes clinical remission by several months [17]. Clinicians must recognize this characteristic delay between immunologic and clinical response and should not hastily modify treatment plans if patients achieve immunologic improvement without a significant short-term reduction in proteiuria.

In many parts of the world rituximab has now become the treatment of choice for nephrotic patients with MN. In most of these, rituximab induces a full or partial remission, but 35%–40% of the patients fail to respond and among those initially responding, relapse rates of up to 33% have been observed upon cessation of the therapy [18–21]. The reasons accounting for primary non-response remain unclear but are likely multifactorial. Rituximab targets CD20 on immature, naive, and memory B cells; however, as B cells differentiate into plasmablasts and plasma cells—both responsible for antibody production—they lose CD20 expression and become hypo- or nonresponsive to rituximab [22, 23]. Furthermore, a significant proportion of patients (23–43%) may develop anti-rituximab antibodies that can diminish drug efficacy [24, 25]. Finally, good biomarkers to guide rituximab therapy are still lacking. While B-cell depletion in peripheral blood is frequently used as a surrogate, this may not accurately reflect the total autoreactive B-cell burden, as most B cells reside in lymphoid tissues [26, 27].

In addition to monotherapy with rituximab, combination therapy with calcineurin inhibitors (CNIs) is also effective for selected patients [13, 16, 18, 28]. Although the STARMEN trial demonstrated a lower remission rate with rituximab plus cyclosporine compared to cyclophosphamide plus glucocorticoids, the therapy was effective and associated with a reduced rate of side effects [28]. It is worth noting, however, that rituximab was administered 6 months after disease onset in this trial.

Importantly, it is important to emphasize that the current KDIGO guidelines do not unconditionally endorse rituximab as the first-choice immunosuppressant. Instead, for patients in the very-high-risk category, cyclophosphamide is preferred over rituximab [13]. Additionally, some experts also recommend the use of cyclophosphamide in patients with very high PLA2R1 antibody titers (>150 RU/ml) based on available data [29, 30].

Therapeutic options for resistant and relapsing MN

Resistant MN presents a complex clinical challenge characterized by persistent disease activity despite standard first-line therapies. While there is no universally accepted definition, cases are typically identified by the continued presence of nephrotic syndrome alongside sustained or elevated levels of podocyte autoantibodies, in particular PLA2R1-antibodies, despite immunosuppressive treatment for a sufficient time. It is important to note that moderate proteinuria alone does not indicate resistance, as it can persist for up to 12 months following immunologic remission [31]. Conversely, low-grade, persistent proteinuria accompanied by normalized serum albumin levels and reduced, or absent autoantibody levels may suggest alternative pathomechanisms, such as the development of secondary focal segmental glomerulosclerosis (FSGS) or other etiologies.

The optimal management strategy for patients with resistant MN remains uncertain. Generally, it is recommended that these patients be referred to specialized centers with expertise in treating MN. As patients with persistent nephrotic syndrome exhibit a 40% risk of progression to kidney failure within 10 years, there is urgent need for novel therapeutic approaches [16].

At present, experts and the current KDIGO guideline on glomerular diseases recommend, in cases of rituximab resistance, in addition to reviewing patient compliance and conducting close monitoring of therapy-efficacy (e.g. B-cell counts, serum albumin, anti-rituximab antibodies, IgG titers if available), either attempting a second cycle of rituximab or modifying the immunosuppressive regimen [13, 29]. According to the guidelines, in patients with preserved eGFR, CNIs in combination with rituximab may be considered, while in patients with declining eGFR, cyclophosphamide plus glucocorticoids is suggested [13]. Some experts generally recommend cyclophosphamide due to its strong data support and efficacy [13, 28, 29, 32–35].

Although cyclophosphamide combined with glucocorticoids is a highly potent alternative immunosuppressant, its use is limited by side effects (e.g. increased malignancy risk, myelotoxicity, septic infections) [11]. It is important to emphasize that the toxicity of cyclophosphamide is strongly dose-dependent, and modified or shortened, or even individualized protocols, should be considered over the standard regimen (e.g. modified Ponticelli regimen) [36–39]. For instance, in the STARMEN trial, many patients achieved immunological remission within just 3 months [28].

Relapse is defined as a return of proteinuria to ≥3.5 g/day after an initial complete or partial response to immunosuppressive therapy. In patients with a prior partial remission, relapse also requires a ≥50% increase in proteinuria from the nadir, in addition to proteinuria ≥3.5 g/day. For patients with relapsing MN, requiring further immunosuppressive therapy the choice of agent depends on the initial regimen [13].

In addition to the established therapies mentioned before, several new treatment strategies have been explored in case series and reports of patients with resistant MN (Table 1). Agents such as obinutuzumab and ofatumumab, both targeting CD20 to deplete B cells, have shown promise. Furthermore, bortezomib, felzartamab, and daratumumab, i.e. agents targeting plasma

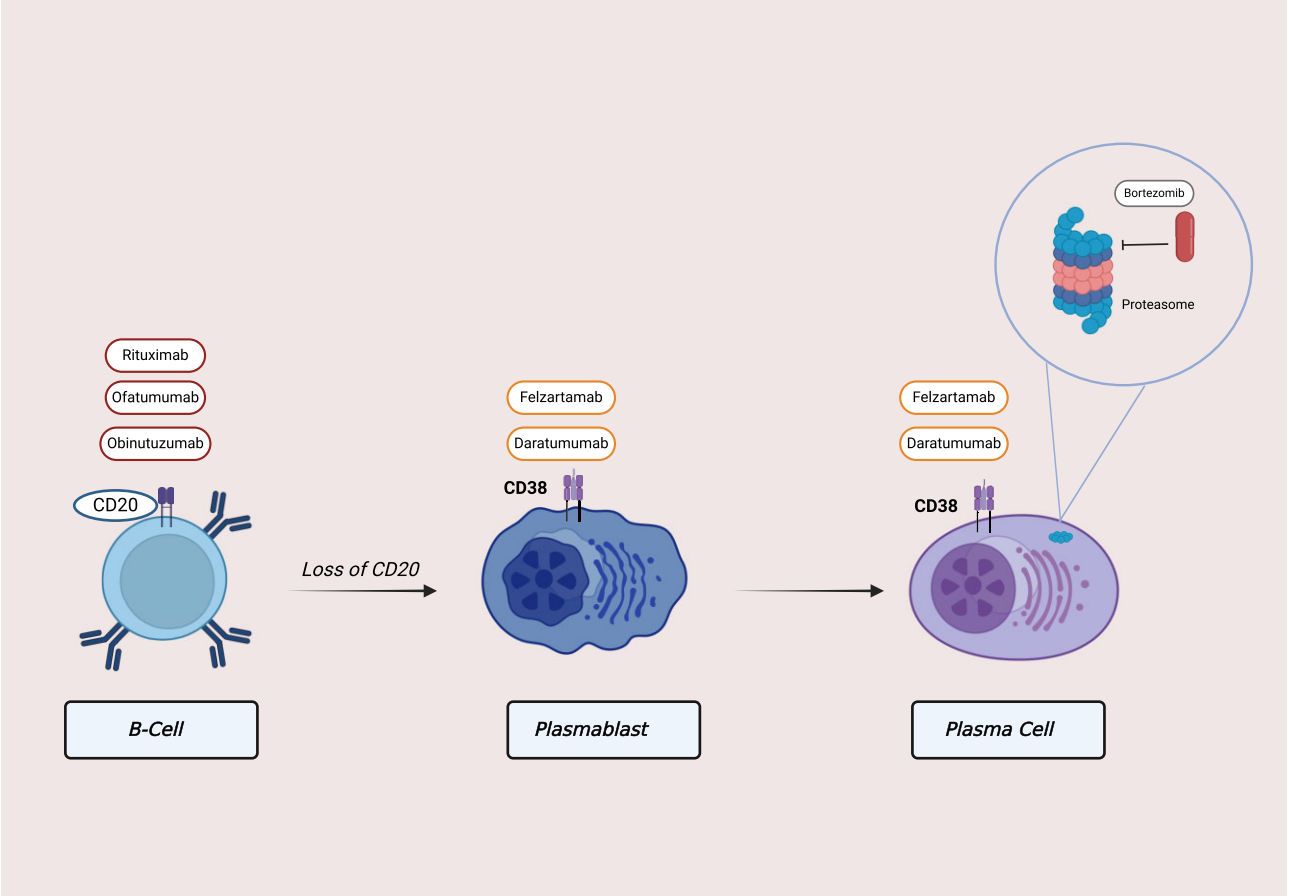

Figure 1: Overview of available treatments for resistant and relapsing MN and their mechanisms of action. B-cell targeted therapies, including obinutuzumab and ofatumumab, function as anti-CD20 monoclonal antibodies that deplete B cells, thereby reducing autoantibody production. Plasma-cell-directed therapies, such as bortezomib—a proteasome inhibitor—and felzartamab and daratumumab, which target CD38-expressing plasma cells, all contribute to lowering pathogenic autoantibody levels. (Created with BioRender.com.)

Table 1: Overview of drug mechanisms targeting resistant MN.

Drug name	Target	Mechanism of action
Obinutuzumab	CD20	Depletes B cells
Ofatunumab	CD20	Depletes B cells
Bortezomib	Proteasome	Induces apoptosis in high-turnover plasma cells
Daratumumab	CD38	Targets plasma cells
Felzartamab	CD38	Targets plasma cells

cells, are being investigated for their potential efficacy in this challenging population (Fig. 1).

B-cell-depleting therapeutic approaches obinutuzumab

Obinutuzumab is a humanized, type II anti-CD20 antibody that exhibits enhanced CD20 depletion and greater efficacy compared to rituximab in certain hematologic malignancies [40–43]. Its advantages over rituximab include: (i) a reduced likelihood of triggering immune responses due to its humanized structure, (ii) binding to a different CD20 epitope that increases cytotoxicity and induces B-cell apoptosis, and (iii) a higher affinity for the Fcγ-RIII, which enhances cellular phagocytosis and toxicity [44].

Obinutuzumab has primarily been studied in patients with resistant MN, often after prior treatment with rituximab, cyclophosphamide, CNIs, and corticosteroids. Most patients exhibited anti-PLA2R1 positivity and moderate chronic kidney disease (CKD stages 1–3) [45–48]. Typical regimens involved cumulative doses ranging from 2 to 4 g, with some studies reporting up to 6 g (Table 2). More than half of the patients achieved complete remission of their nephrotic syndrome with disappearance of circulating PLA2R1-antibodies [45, 47, 49, 50]. Partial or complete remission was induced by obinutuzumab in 82% of rituximab-resistant cases in the studies conducted thus far (Table 3). Additionally, most treated patients experienced seroconversion (i.e. became autoantibody-negative). However, it should be noted that most of the patients studied had only moderately reduced eGFR values, and there are a lack of data regarding its efficacy in patients with more severely impaired kidney function.

Side effects associated with obinutuzumab were generally mild to moderate and self-limiting, most commonly involving infusion-related reactions and mild infections, such as urinary tract and upper respiratory tract infections [35–41]. However, during the early COVID-19 pandemic, a higher incidence of severe COVID-19 pneumonia was observed among patients treated with obinutuzumab compared to those receiving standard therapies [51]. It is important to note that no effective vaccine against the virus was available at that time.

Table 2: Obinutuzumab in resistant MN.

Study	Prior treatment	No. of patients	CKD stage	Anti-PLA2R1 before obinutuzumab	Dosage	Remission outcomes	Anti-PLA2R1 after obinutuzumab	AEs	Follow-up duration (months)
[46]	RTx	7	III	3	2 × 1 g	4 CR (57%); 2 PR (29%); NR1 (14%)	negative (5/5)	IRR, neutropenia, infections[a]	9–24 m
[49]	RTx, CNI, CS, Cyc,	1	NR	1	3 × 2 g	PR (100%)	positive		12
[45]	RTx	14	I–III	10	1–4 × 1 g	3 CR (21%); 6 PR (43%); NR 5 (36%)	NR	IRR, neutropenia, infections	9
[47]	RTx, CNIs, CYC, CS	3	NR	3	1–2 × 1 g	1 CR (33%); 2 PR (67%)	2 patients negative, 1 patient titer 5 RU/ml	Herpes zoster	17
[88]	RTx, Cyc, and CS	2	IV/V	1	2 × 1 g	1 CR (50%) 1 PR (50%)	1 patient negative, 1 with decreasing titer (2.55 RU/ml)	NR	14
[48]	RTx	12[b]	NR	5	1–4 × 1 g	8 CR (67%); 4 PR (33%)	2 negative; 3 decrease in titer	infection, itching, 2 severe COVID-19 cases	13.6
[50]	CS, CNIs, RTX	1	NR	Semaphorin	1 × 0,5g	relapse	light decrease		
[89]	RTx, CNIs, CYC, CS	2	II	1	2 × 1 g	2 CR (100%)	negative		13.5
[51]	CS, CNIs, RTX, Cyc	18	I—IIIb	18	1–2 × 1 g	6 CR (33%), 8 PR (44%); NR 4 (22%)	15 patients negative	17/18 serious COVID infection	12

[a]Respiratory infections, urinary tract infection.
[b]11 rituximab-resistant and 1 with adverse events, IRR infusion-related reaction, NR not reported, CS corticosteroids, Cyc cyclophosphamide, RTx rituximab, CR complete remission, PR partial remission.

Table 3: Clinical outcomes of obinutuzumab in resistant MN [45–51, 88, 89].

	Number of patients (%)
Prior treatments	
• Rituximab	60 (100%)
• CNI	25 (42%)
• Cyclophosphamide	26 (43%)
CKD stages	
• Stage I–III	41 (68%)
• Stage IV	2 (3%)
• unknown	17 (28%)
Remission rates	
• Complete remission	25 (42%)
• Partial remission	24 (40%)
• No response	10 (17%)
• Relapse	1 (1%)
Anti-PLA2R1 status	
• (+) before treatment	53 (88%)
• (−) after treatment	26 (43%)
• (+) after treatment	12 (20%)
• unknown	14 (23%)

Overall, obinutuzumab represents a highly potent agent for cases resistant to rituximab. Larger studies evaluating the efficacy and safety of obinutuzumab in MN are currently underway (NCT04629248, NCT05050214), with initial results anticipated by mid-2025.

Ofatumumab

Ofatumumab is a fully human monoclonal antibody that targets a distinct epitope of CD20 that is closer to the basement membrane and explains better complement-dependent cytotoxicity [52]. It has been approved by both the FDA and EMA for the treatment of chronic lymphocytic leukemia [53, 54]. Additionally, ofatumumab has shown efficacy in managing autoimmune diseases such as rheumatoid arthritis and autoimmune thrombotic thrombocytopenic purpura, making it valuable when rituximab is contraindicated, particularly due to anaphylaxis [55–60].

Data on ofatumumab in MN are limited [61–63]. A case series of 17 male MN patients with CKD stages 1–3 included seven patients intolerant to rituximab due to severe infusion reactions, and 10 with treatment resistance, defined as the lack of remission 9 months post-rituximab. Ofatumumab (50–300 mg, single intravenous infusion) was administered using a regimen designed to reduce infusion-related reactions. Within 5 months, complete or partial remission was achieved in seven (7/10) rituximab-resistant and three (3/7) rituximab-intolerant patients. Among the 12 anti-PLA2R1-positive patients, seven achieved immunologic remission with undetectable antibody levels (three rituximab-intolerant, four rituximab-resistant). B-cell depletion occurred within 1 week, while reconstitution varied, often 3 months after infusion [63]. Additionally, a case report further illustrates ofatumumab's efficacy in a frequently relapsing MN patient who was intolerant to rituximab (serum-sickness). This patient went into a prolonged remission

Table 4: Ofatumumab in resistant MN.

Study	Prior treatment	No. of patients	CKD stage	Anti-PLA2R1 before	Dosis	Remission (Proteinuria)	Immunological remission	AEs	FU
[63]	RTx	17 (10 RTx-resistant + 7 RTx-intolerant)	1–3b	14 (+) in disease history; 12 (+) at start of the study	50–300 mg	RTx-resistant: 7 Pts.; RTX-intolerant: 3 Pt.	7 of 12 patients	14 events (9 patients): IRR (mild to moderate)	24 months

Note. RTx rituximab, IRR infusion-related reaction, FU follow-up duration.

Table 5: Bortezomib in resistant MN.

Study	Prior treatment	No. of patients	CKD stage	Anti-Pla2R1 before	Dosage	Remission outcomes	Anti-Pla2R1 after Bortezomib	AEs	FU
[69]	RTx, CNI, Cyc, Apheresis	1	Not reported	+	1× cycle	CR (100%)	negative	Not reported	21m
[70]	RTx	1	Not reported	+	14× cycles	CR (100%)	negative	Not reported	34m

Note. RTx rituximab, Cyc cyclophosphamide, AEs; adverse events, FU follow-up duration.

comparable to between-treatment intervals (17.4 ± 4.2 months) seen with rituximab [62] (Table 4).

Ofatumumab has also been tested in patients with nephrotic syndrome caused by minimal change disease or FSGS. In these cases, it was well tolerated and induced remission in patients either resistant to or intolerant of rituximab due to severe or delayed infusion reactions [64, 65].

In summary, like obinutuzumab, ofatumumab also offers a promising alternative for patients with MN who are either resistant to or intolerant of rituximab. Further comprehensive studies are needed to fully establish its safety and efficacy in this patient population.

Plasma-cell therapies

As B cells shed the CD20 surface marker during their differentiation into plasma cells, therapies targeting CD20-negative plasma cells may prove beneficial in overcoming resistance observed with rituximab [22].

Bortezomib

Bortezomib is a proteasome inhibitor that blocks the 26S proteasome subunit, preventing the breakdown of damaged proteins. This disruption triggers signaling pathways and activates caspases, leading to cell cycle arrest and apoptosis [66]. Because highly active B cells generate more cellular waste, bortezomib relatively selectively targets high-turnover plasma cells for destruction [66, 67].

Data on bortezomib in resistant MN are limited to a few case reports [68–70]. In one report complete remission was induced in a 66-year-old patient with MN who had previously been treated with prednisolone, tacrolimus, cyclophosphamide, plasmapheresis, and four cycles of rituximab. The patient achieved immediate immunologic remission after treatment with bortezomib (Table 5). However, proteinuria persisted at >4 g/g over the observation period. Antibodies remained undetectable during the 21-month follow-up period [68].

Another study suggested using bortezomib in combination with dexamethasone. A 63-year-old patient with PLA2R1-positive MN exhibited persistent nephrotic proteinuria and a progressive decline in eGFR despite four cycles of rituximab. After 34 months of treatment with a total of 14 cycles of bortezomib (1.3 mg/m², subcutaneously) and dexamethasone (4 × 20 mg), the patient achieved complete immunological remission (no detectable antibodies), with normalized renal function, proteinuria, and serum albumin levels (Table 5) [70].

While bortezomib has shown promise, its use requires caution due to potential side effects in particular severe neuropathy, which occurs in 28%–54% of cases and can limit its utility. The incidence is lower with subcutaneous administration compared to intravenous forms [71, 72].

While these findings are encouraging, larger studies are needed to fully establish the efficacy and safety of bortezomib in treating resistant MN.

CD38 antibodies: daratumumab and felzartamab

Daratumumab targets CD38 on plasma cells, which are largely responsible for producing autoantibodies [73]. Daratumumab has been successfully used in patients with refractory MN. A notable case involved a 16-year-old patient who developed MN after graft-versus-host disease and failed to respond to rituximab, tacrolimus, and steroids. After receiving daratumumab, her nephrotic syndrome resolved, and she achieved near-complete remission of her kidney disease [74]. Short-term success with daratumumab was also noted in a 38-year-old patient with multidrug-resistant, aPLA2R1-refractory MN, supporting its potential in challenging cases [75]. Finally, a patient unresponsive to multiple therapies, including mycophenolate mofetil, rituximab, cyclophosphamide, and bortezomib/dexamethasone was switched to daratumumab (16 mg/kg weekly), which rapidly reduced aPLA2R1 levels and improved clinical outcome. Extending dosing intervals led to aPLA2R1 rebound, but reintroducing rituximab then resulted in sustained improvement and partial remission after 7 months [74]. More comprehensive studies are required to validate daratumumab's long-term efficacy and safety.

Felzartamab was evaluated in the phase 1a/2b M-PLACE study, which involved 31 patients with anti-PLA2R1-positive primary MN. The study included patients with newly diagnosed or relapsed MN (Cohort 1) and those refractory to immunosuppressive therapy (Cohort 2). Participants received a nine-dose course of intravenous felzartamab over 6 months. A ≥50% reduction in anti-PLA2R1 titers was achieved in 77% of patients, with responses observed as early as week 1 in 44%. By the end of the study, 54% maintained this response. Partial proteinuria remission, defined as a ≥50% reduction in UPCR to <3.0 g/g with stable kidney function, was seen in 35% of patients, with better outcomes in Cohort 1 (47%) compared to Cohort 2 (18%). Additionally, 77% showed increased serum albumin levels at the end of the study. The treatment was generally well tolerated. However 87% experienced treatment-emergent adverse events (TEAEs), including infusion-related reactions (29%), hypogammaglobulinemia (26%), peripheral edema (19%), and nausea (16%). Serious TEAEs, in particular grade ≥3 infusion-related reaction, grade ≥3 type 1 hypersensitivity reaction and grade 4 neutropenia, occurred in 16% of patients but resolved in all cases [76]. In conclusion, felzartamab showed limited efficacy in therapy-resistant cases and was associated with notable side effects. Notably, another study indicated that patients treated with felzartamab showed a humoral response to COVID-19 vaccination comparable to that in healthy individuals, suggesting immune responses to vaccinations are preserved during treatment, a major advantage over rituximab [77].

The MONET phase 2 trial is currently underway to assess the efficacy and safety of felzartamab in patients with refractory MN (NCT 04893096; conclusion of the trial anticipated in February 2025).

Other therapies

Further innovative approaches to B-cell depletion include chimeric autoantibody receptor (CAAR) natural killer (NK) cells. Unlike chimeric antigen receptor (CAR) T-cells, which incorporate a single-chain variable fragment and therefore target surface markers (e.g. CD20) in a relatively nonspecific manner [78]—affecting all CD20-positive cells—CAAR-NK-cells are equipped with specific fragments of the target antigen on their chimeric receptor [79]. In the case of MN these fragments can be derived, for example, from PLA2R1 or THSD7A. A connection between the target B-cell and the CAAR-NK-cell can be established because B cells express an immunoglobulin on their surface that matches the antibodies they produce, such as those directed against PLA2R1 or THSD7A [80]. Once an immunological synapse is formed, the CAAR-NK-cell releases granzyme B, leading to the destruction of the B-cell [79]. This approach appears promising due to its highly selective depletion of autoreactive B cells while sparing 'normal' B cells. *In vitro* studies have already demonstrated the successful production of such CAAR-NK-cells and validated their highly selective activity [81]. However, these studies are currently still in the basic research stage.

Further upstream in the development of autoreactive B cells, the interleukin-4 (IL-4) antibody dupilumab represents another promising therapeutic strategy. IL-4 plays a critical role in B-cell differentiation, antibody-class switch, and the development of autoreactivity [82, 83]. Elevated levels of IL-4 have been associated with breaking immune tolerance [83]. In two case reports, dupilumab was successfully used in patients with therapy-refractory MN (previously treated with cyclophosphamide, steroids, or rituximab), effectively reducing proteinuria and anti-PLA2R1 titers [84]. Both cases achieved sustained complete remission. Interestingly, these patients also had comorbid atopic dermatitis, which improved under dupilumab therapy. No adverse effects associated with dupilumab were reported [84].

Apart from autoreactive antibodies and B cells, the complement system also plays a role in the pathogenesis of MN [85–87]. However, studies on complement-inhibition have thus far been unconvincing. Trials investigating eculizumab (C5-inhibitor), iptacopan (CFB-inhibitor, NCT04154787), and BCX9930 (factor D-inhibitor, NCT05162066) were terminated by the sponsors due to a lack of therapeutic benefit. A further study evaluating narsoplimab (MASP2 inhibitor, NCT02682407) for the inhibition of the lectin pathway is currently in an unknown status.

CONCLUSION

The management of rituximab-resistant MN remains a challenge, with rituximab's limitations underscoring the need for innovative therapeutic strategies. Despite the potent therapeutic alternatives of cyclophosphamide (and combination therapy with CNI plus rituximab), these options are not universally applicable and are significantly limited by their associated side effects. Emerging treatments such as obinutuzumab and ofatumumab, which target B cells, and bortezomib, daratumumab, and felzartamab, which target plasma cells, offer promising alternatives. These novel approaches have shown encouraging results in achieving remission and reducing autoantibody levels, potentially transforming the treatment landscape for MN. However, further research is crucial to validate their long-term efficacy and safety.

Among the therapies discussed here, obinutuzumab stands out as the most extensively researched option, demonstrating significant efficacy in inducing remission in rituximab-resistant MN. Other B-cell therapies, such as ofatumumab, also show promise, although more evidence is needed. Plasma-cell-directed therapies like bortezomib and daratumumab are highly potent but require further investigation, particularly for daratumumab monotherapy. Conversely, felzartamab has shown limited efficacy in therapy-resistant cases and was associated with a notable incidence of adverse effects.

The primary goal of any therapeutic strategy should be the elimination of pathogenic antibodies. From a pathophysiological perspective, combined B- and plasma-cell depletion strategies appear particularly promising, as they target all antibody-producing cells. However, careful consideration must be given to the potential side effects and increased immunosuppression associated with combination therapies.

DATA AVAILABILITY STATEMENT

No new data were generated or analyzed in support of this research.

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CONFLICT OF INTEREST STATEMENT

J.F. is the Editor-in-Chief of *Clinical Kidney Journal*.

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