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Review

Anti-CD20 monoclonal antibodies in membranous nephropathy

Anticuerpos monoclonales anti-CD20 en la nefropatía membranosa

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ABSTRACT

Novel anti-CD20 monoclonal antibodies have been developed to optimize B-cell depletion. A key mechanism of action of these therapeutic monoclonal antibodies is the activation of immune cells via Fc receptors (FcγR). B-cell depletion with anti-CD20 monoclonal antibodies was initially developed for the treatment of B-cell lymphoma. Subsequently, its use was extended to autoimmune diseases. Rituximab has long been the main monoclonal antibody used to treat immune-mediated glomerulopathies. In glomerular diseases, rituximab was initially used to treat membranous nephropathy, demonstrating a better safety profile compared to conventional immunosuppressive therapies and a good treatment response. Therefore, other drugs targeting the same therapeutic receptor, anti-CD20, have been developed. This review aims to highlight, from a comprehensive perspective, the different anti-CD20 agents available to date.

Palabras clave:
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RESUMEN

Se han desarrollado nuevos anticuerpos monoclonales anti-CD20 para optimizar la depleción de células B. Un mecanismo de acción clave de estos anticuerpos monoclonales terapéuticos es la activación de las células inmunitarias a través de los receptores Fc (FcγR). La depleción de células B con anticuerpos monoclonales anti-CD20 se desarrolló inicialmente para el tratamiento del linfoma de células B. Posteriormente, su uso se extendió a las enfermedades autoinmunitarias. El rituximab ha sido durante mucho tiempo el principal anticuerpo monoclonal utilizado para tratar las glomerulopatías inmunomediadas. En las enfermedades glomerulares, el rituximab se utilizó inicialmente para tratar la nefropatía membranosa, demostrando un mejor perfil de seguridad en comparación con las terapias inmunosupresoras convencionales y una buena respuesta al tratamiento. Por lo tanto, se han desarrollado otros fármacos dirigidos al mismo receptor terapéutico, anti-CD20. Esta revisión tiene como objetivo destacar, desde una perspectiva integral, los diferentes agentes anti-CD20 disponibles hasta la fecha.

Introduction

Membranous nephropathy (MN) is a leading cause of nephrotic syndrome in adults and represents a prototypical autoimmune glomerular disease characterized by subepithelial immune complex deposition and podocyte damage.[1] The identification of autoantibodies directed against podocyte antigens, such as the M-type phospholipase A2 receptor (PLA2R) and thrombospondin type-1 domain-containing protein 7A (THSD7A), has transformed the understanding and management of MN, enabling antigen-based classification and more individualized therapeutic approaches via monitoring of autoantibody levels. Despite advances in the immunopathological characterization of MN, therapeutic management

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remains challenging, particularly in patients with refractory or relapsing disease following standard immunosuppressive therapy.[2]

Rituximab, a chimeric anti-CD20 monoclonal antibody, has become a cornerstone of MN management, demonstrating favorable efficacy and safety in inducing both immunological and clinical remission. However, a subgroup of patients exhibits incomplete or transient responses, resistance, or intolerance to rituximab, highlighting the need for alternative B-cell-targeted agents.[1,2] In this context, next-generation humanized and glycoengineered anti-CD20 monoclonal antibodies, such as obinutuzumab and ofatumumab, have emerged as promising options due to their enhanced antibody-dependent cellular cytotoxicity and sustained B-cell depletion.[3]

Recent studies have shown that obinutuzumab, a humanized type II anti-CD20 antibody, is effective in patients with rituximab-resistant or refractory PLA2R-associated membranous nephropathy.[2,3] Case series and routine clinical practice data have reported that obinutuzumab can induce clinical remission in these patients with acceptable tolerability profiles.[4,5] Similarly, ofatumumab, a fully human anti-CD20 antibody, has shown promising efficacy in rituximab-resistant or -intolerant membranous nephropathy, offering an alternative for patients at risk of hypersensitivity reactions due to the development of antichimeric antibodies.[5]

Furthermore, emerging evidence from tertiary hospital experience indicates favorable results with the use of novel anti-CD20 monoclonal antibodies in various immune-mediated glomerulopathies, including membranous nephropathy, reinforcing their potential in clinical practice.[5,6] These findings support a paradigm shift in the management of MN, emphasizing the potential of humanized and next-generation anti-CD20 antibodies as more effective and safer therapeutic alternatives for patients who do not respond to conventional therapy.

Methodology

A PubMed search was conducted using the terms “membranous nephropathy” and “anti-CD20”, “rituximab”, “obinutuzumab”, “ofatumumab”, “ocrelizumab”, “veltuzumab”, or “kidney disease”. The search was not limited by language or publication date. Seventy-two publications were identified. Of these, 5 reports provided information on membranous nephropathy and anti-CD20 therapies in the context of randomized controlled trials, 10 were clinical practice studies, and 12 were case reports. Additional references were found within the manuscripts identified in the search. In addition, “humanized anti-CD20 monoclonal antibodies” were searched on the EMA and FDA websites.

Membranous nephropathy: overview, epidemiology, clinical characteristics, and diagnosis

Membranous nephropathy is an immune-mediated glomerular disease characterized by the deposition of subepithelial immune complexes along the glomerular basement membrane, leading to diffuse thickening and podocyte damage. Primary MN, which accounts for approximately 70–80% of cases, is due to autoantibodies directed against podocyte antigens, primarily the M-type phospholipase A2 receptor, followed by thrombospondin type-1 domain-containing domain 7A (THSD7A) and other recently identified antigens, such as NELL-1 and protocadherin 7 (Fig. 1a and b). Secondary forms are associated with autoimmune diseases, chronic infections, malignancies, or certain drugs.[7,8]

From an epidemiological perspective, MN is the leading cause of nephrotic syndrome (NS) in non-diabetic adults, with an estimated incidence of 8–12 cases per million inhabitants per year in North America and Europe, and a higher incidence in individuals between 50 and 60 years of age. A consistent male predominance (ratio ~2:1) is observed. The global burden of the disease has increased in recent decades, partly reflecting improved serological detection and the aging of the population.[9]

Clinically, membranous nephropathy typically presents with nephrotic-range proteinuria, often accompanied by edema, hypoalbuminemia, and hyperlipidemia. Microscopic hematuria and mild hypertension may be present, though less frequently. Despite preserved renal function at onset, persistent nephrotic syndrome is associated with progressive renal deterioration and an increased risk of thromboembolic and cardiovascular events. Its natural history is heterogeneous: approximately one-third of untreated patients achieve spontaneous or partial remission, while 30–40% progress to renal failure within 5–15 years.[10] Diagnosis is based on the integration of clinical presentation, serological tests, and renal biopsy. The detection of circulating antibodies against PLA2R or THSD7A, or the accumulation of these antigens within immune deposits, confirms the autoimmune nature of the disease and provides both diagnostic and prognostic information. Renal histology demonstrates uniform thickening of the capillary wall, granular deposition of IgG (predominantly IgG4) and complement (C3) on immunofluorescence, and electron-dense subepithelial deposits with effacement of podocyte processes on electron microscopy.[7,8,10]

Classic treatment

Immunosuppressive therapy in patients with primary nephrotic syndrome (NS) has gone through different stages and treatment regimens throughout history. Classical treatment options include regimens based on cyclophosphamide, calcineurin inhibitors, and the chimeric anti-CD20 monoclonal antibody, rituximab.[11]

The selection of the immunosuppressive regimen should be based on risk stratification for progression according to KDIGO recommendations, primarily considering the presence of proteinuria in nephrotic syndrome, hypoalbuminemia, and the estimated glomerular filtration rate (eGFR).[9] In patients at moderate risk of progression, treatment with glucocorticoids and calcineurin inhibitors may be considered for 4 months, with discontinuation if no clinical response is observed. If treatment is continued, a dose reduction regimen is suggested after 12 months. In this group of patients, treatment with rituximab may be considered.[12]

Meanwhile, for patients at high risk of progression, it is suggested to start induction regimens with rituximab or cyclophosphamide in conjunction with systemic glucocorticoids, or the use of regimens that combine rituximab and calcineurin inhibitors, with which comparable partial and complete remission rates have been achieved, although with a better safety profile, compared to cyclophosphamide.[11,12]

Cyclophosphamide-based regimens have historically been the mainstay of immunosuppressive treatment for high-risk or very-high-risk primary membranous nephropathy, as well as in patients with secondary membranous nephropathy, due to their side effects. The historical data supporting the modified Ponticelli regimen are derived from older randomized cohorts originally reported by Ponticelli et al.[13,14] The cyclical regimen of oral cyclophosphamide (Modified Ponticelli) is administered during months 2, 4, and 6 of treatment, alternating with intravenous glucocorticoid doses during months 1, 3, and 5, and continuing with oral glucocorticoids for the remaining days. Alternatively, in settings where oral cyclophosphamide is unavailable or where therapeutic adherence may be compromised, a regimen of intravenous cyclophosphamide in conjunction with glucocorticoids has limited the cumulative cyclophosphamide dose throughout treatment. Observational studies have shown this to reduce gonado toxicity and the risk of neoplasia compared to the use of oral cyclophosphamide.[12,15]

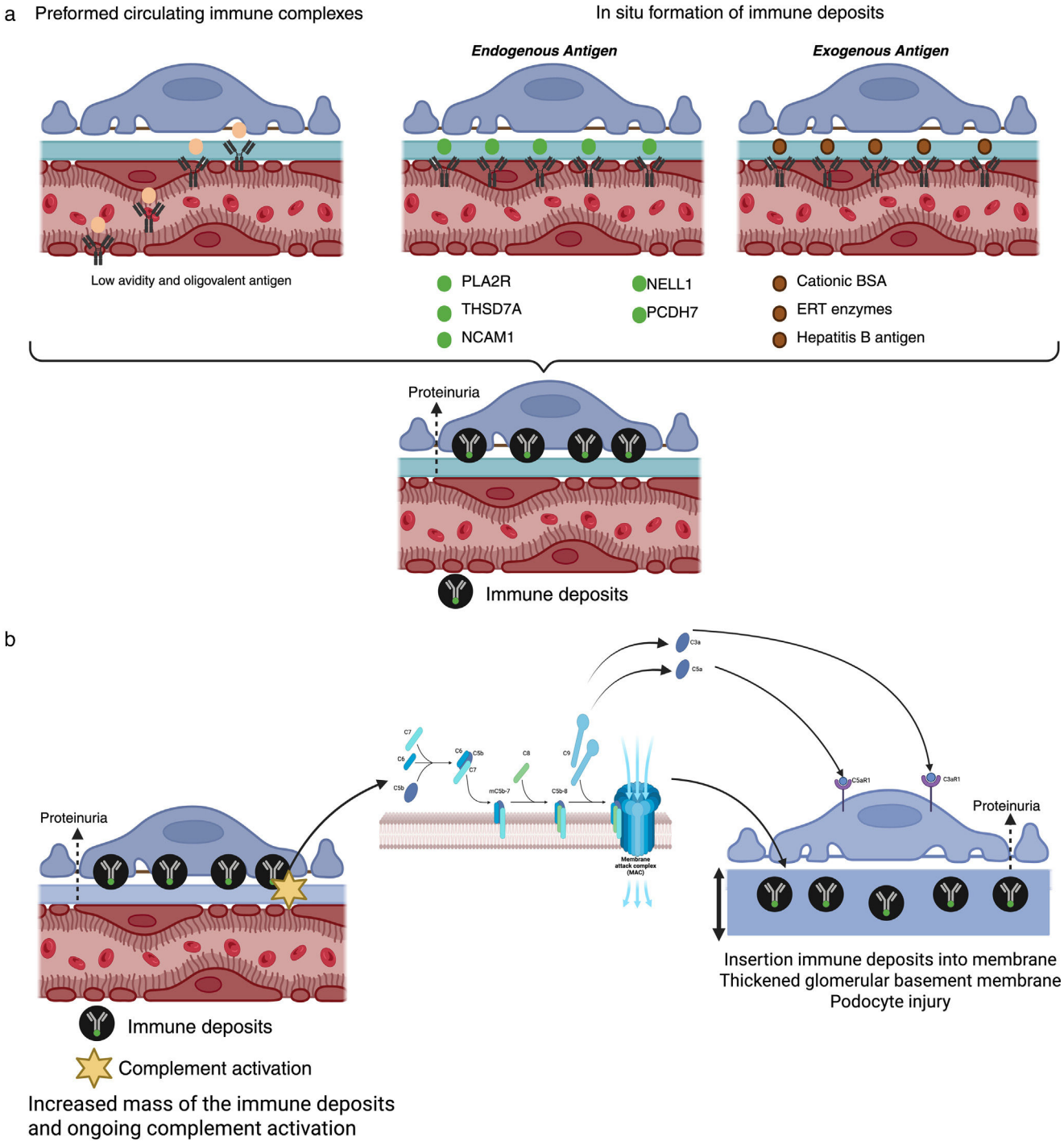

Fig. 1. Fig. a, b. Pathophysiology of membranous nephropathy. Primary membranous nephropathy is characterized by the formation of subepithelial immune deposits, composed of autoantigens and immunoglobulins, located beneath the podocyte basement membrane. The loss of self-tolerance to podocyte antigens, most frequently the phospholipase A2 receptor, likely reflects the interaction between genetic susceptibility, environmental factors, and dysregulated antigen expression. The binding of circulating autoantibodies to podocyte antigens initiates complement activation, leading to the formation of the membrane attack complex (C5b–9). This results in significant podocyte injury, increased calcium influx, cytoskeleton disruption, and loss of slit diaphragms. The lectin and alternative complement pathways appear to be the main mediators of the damage, while activation via the classical pathway is limited. Complement-derived mediators, such as C3a and C5a, further amplify podocyte injury through maladaptive signaling, culminating in proteinuria and progressive remodeling of the glomerular basement membrane.[49] Created in https://BioRender.com. BSA, cationic bovine serum albumin; ERT, enzyme replacement therapy; PLA2R, phospholipase A2 receptor; THSD7A, thrombospondin type-1 domain-containing protein 7A; NELL1, neural epidermal growth factor-like protein 1; PCDH7, protocadherin 7; NCAM1, neural cell adhesion molecule 1.

Because of the risk for cytopenias, patients should be monitored weekly after cyclophosphamide administration, and treatment should be discontinued if the total white blood cell count is <4000 cells/μL. Treatment can be restarted at half the previous dose once the cell count recovers to >4000 leukocytes/μL.[15]

The use of calcineurin inhibitors (tacrolimus and cyclosporine) for the treatment of MN, due to their effects on stabilizing the actin cytoskeleton of podocytes by inhibiting synaptopodin degradation and TRPC6 expression, has found its niche in combination with rituximab as a remission-induction regimen for primary MN. The decision to use

tacrolimus or cyclosporine should be based on availability, accessibility, cost and individualized safety profile for each patient, provided that adequate plasma concentrations of 125–175 ng/ml and 5–8 ng/ml are achieved for cyclosporine and tacrolimus, respectively.[15]

A network meta-analysis published in 2025 included the results of 21 randomized clinical trials with a total of 1396 patients to compare the efficacy and safety of rituximab, tacrolimus, cyclosporine, and cyclophosphamide, alone or in combination, in primary membranous nephropathy.[16] The overall response rate of the rituximab + tacrolimus combination was superior to cyclosporine (RR = 0.15, 95% CI 0.04–0.54), cyclophosphamide (RR = 0.09, 95% CI 0.03–0.31), and rituximab (RR = 7.06, 95% CI 2.29–21.80), with a SUCRA value of 93.5%. Regarding the reduction of proteinuria, the combination of rituximab and tacrolimus showed a SUCRA value of 99.4%, superior to rituximab, rituximab and cyclophosphamide, tacrolimus, cyclosporine, and cyclophosphamide alone. For the reduction of serum creatinine, it was also superior to tacrolimus alone. The combination of rituximab and cyclophosphamide showed a SUCRA value of 76.7% for the normalization of serum albumin, superior to cyclophosphamide alone. The incidence of adverse events was mostly associated with the use of cyclophosphamide.

Despite this, up to 30% of patients experience incomplete or transient responses, leading to the need for alternative agents targeting B cells (i.e., next-generation humanized and glycosylated anti-CD20 monoclonal antibodies) as promising therapies for this disease.[2]

CD20 physiology

Initially described in 1980, CD20 is a non-glycosylated transmembrane protein of approximately 33–37 kDa, belonging to the MS4A protein family (four-domain transmembrane protein family A), encoded by the *MS4A1* gene.[17] Most *MS4A* genes, including *MS4A1*, are located in a cluster on human chromosome 11q12[18]; the *MS4A1* gene is 16 kb long, consists of eight exons, and several CD20 mRNA transcripts have been described.[19] The CD20 protein consists of four hydrophobic transmembrane domains, one intracellular domain, and two extracellular domains (large and small loops), with the N- and C-terminal ends located in the cytosol. Three CD20 isoforms (33, 35, and 37 kDa) resulting from different phosphorylations have been identified.[20] CD20 is found on the surface of B lymphocytes as homodimeric and homotetrameric oligomers along with other membrane proteins, contributing to intercellular signal transduction.[21,22] CD20, which is considered an atypical tetraspanin, is known to form supramolecular complexes due to its proximity to other tetraspanin molecules such as CD53, CD81, and CD82, and it physically couples to the major histocompatibility complex (MHC) class II, the CD40 molecule, the B cell receptor, and the C-terminal Src kinase-binding protein, Csk.[23] Its expression is lost in plasmablasts and terminally differentiated plasma cells.[24] The lack of CD20 expression in early pro-B cells and hematopoietic stem cells allows anti-CD20 therapy to selectively eliminate mature and malignant B cells without depleting bone marrow stem cell reserves, thus ensuring repopulation after depletion.[25]

CD20 does not detach from the cell surface and is not internalized after antibody binding.[25,26] The CD20 antigen is not found free in the circulation; therefore, an agent that reacts with CD20 is not neutralized before binding to the target cell. Nor does it form antigen–antibody complexes in the plasma that could be deposited on bystander cells to activate the complement cascade and thus damage non-target cells. Its stable expression, restricted to mature B lymphocytes, makes it an ideal target for B cell depletion therapies.[26]

CD20 may function as a calcium channel subunit, based on the observation that CD20 ligation affects B cell activation, differentiation, and cell cycle progression.[27] Early experiments suggested its importance in regulating human B cell activation, proliferation, and Ca^{2+} transport; however, its function is not yet fully understood.[28] The function of CD20 has been studied in humans with CD20 mutations and in murine models. These studies in human and murine CD20-deficient B lymphocytes suggest that CD20 is necessary for both optimal T-independent humoral immunity and the response to T-dependent antigens.[29]

Overall, the relatively mild phenotype resulting from CD20 loss is somewhat surprising, given that CD20 has been described as physically and functionally coupled to MHC class II and CD40, both of which are essential for B-T cell interactions.[30]

Mechanism of action of anti-CD20 monoclonal antibodies

Anti-CD20 monoclonal antibodies are designed to bind to CD20+ cells and cause their depletion, with CD19+CD20+ B cells being the primary target[31] (Fig. 2).

Anti-CD20 monoclonal antibodies are classified into two distinct types: type I or II, depending on whether the antibody, when bound to CD20, induces the rearrangement of CD20 molecules into lipid rafts on the cell surface.[31,32] Lipid rafts are microdomains of lipids and proteins important for signal transduction through the colocalization of receptors and effector molecules.[32]

Type I: CD20 molecules accumulate in lipid rafts and allow the activation of the complement pathway. The clustering of CD20 with type I antibodies stabilizes CD20 in lipid rafts, leading to increased C1q binding and greater complement-dependent cytotoxicity (CDC), with limited induction of programmed cell death (PCD).[31–33]

Type II: CD20 molecules do not reorganize into lipid rafts, and CDC induction is minimal. However, type II antibodies can induce programmed cell death independently of complement activation.[32]

Anti-CD20 monoclonal antibodies induce lysis of target cells through different mechanisms: complement-dependent cytotoxicity, antibody-dependent cytotoxicity (ADCC), antibody-dependent phagocytosis (ADP), and programmed cell death/direct apoptosis. CDC and ADCC are considered the most common mechanisms of cell lysis mediated by anti-CD20 monoclonal antibodies.[31,33] CDC involves antibody-mediated activation of the complement pathway and occurs when IgG antibodies coat a target cell.[34] The Fc region of the anti-CD20 monoclonal antibody binds to C1q of the complement system, leading to the formation of the membrane attack complex and subsequent lysis of the target cell.[34,35] ADCC is independent of the complement system and is primarily mediated by interactions between the Fc region of the anti-CD20 monoclonal antibody and FcγRIIIa, an IgG-binding FcγR, on NK cells. This interaction initiates a series of signaling pathways in NK cells, including the release of cytolytic compounds such as granzyme B and perforin, leading to B cell lysis. In ADP, macrophage FcγRs bind to anti-CD20 monoclonal antibodies attached to target B cells, triggering antibody-dependent phagocytosis of B cells by macrophages; FcγRIIIa is considered the main FcR involved in macrophage-mediated ADP.[35] Finally, type II antibodies can induce direct cell death (i.e., PCD) by binding to CD20 independently of the Fc region. Interestingly, the relative contribution of complement-dependent cytotoxicity and antibody-dependent phagocytosis to B cell lysis varies depending on the specific anti-CD20 monoclonal antibody.[34]

The disparate characteristics of type I and II anti-CD20 monoclonal antibodies do not translate into differences in their ability to induce antibody-dependent cellular cytotoxicity or antibody-dependent phagocytosis. These immune responses are mediated by interactions between the Fc region of the antibody and FcγRIIIa molecules on the surface of immune effector cells[31–33] (Table 1).

Anti-CD20 therapies in membranous nephropathy

Clinical and observational trials with anti-CD20 agents have benefited from the ability to monitor anti-PLA2R levels, the causative

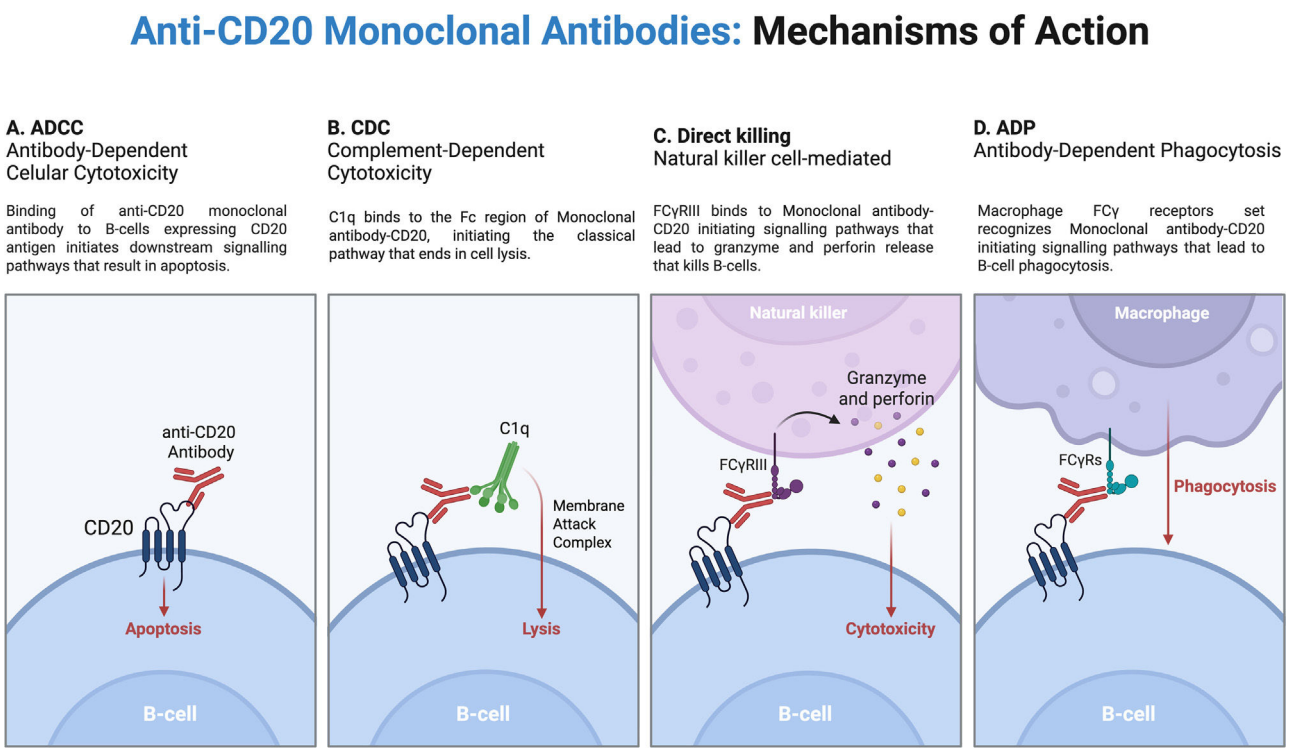

Fig. 2. Mechanism of action of anti-CD20 monoclonal antibodies. Created in https://BioRender.com.
CDC, Complement-dependent cytotoxicity; ADCC, Antibody-dependent cellular cytotoxicity; ADP, Antibody-dependent phagocytosis.

Table 1
Comparison of several commercially available anti-CD20 monoclonal antibodies.

Antibody	Rituximab	Obinutuzumab	Ofatumumab
Antibody type	I	II	I
IgG subclass	IgG1	IgG1	IgG1
Structure	Chimeric	Humanized	Fully human
Binding to the CD20 epitope	Large loop	Large loop	Large and small loop
Clustering into lipid rafts	+ +	–	+ + + +
Antibody-dependent cytotoxicity	+ +	+ + + +	+ +
Complement-dependent cytotoxicity	+ +	+	+ + + +
Direct cell death	+	+ + + +	+

Abbreviations: Ig, immunoglobulin.

autoantibody in the majority of primary MN cases. With effective treatment, anti-PLA2R declines and disappears (which is called "immunological remission") and is a necessary step before a full clinical remission can occur.

Rituximab

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen. It has emerged as an effective therapeutic option for primary membranous nephropathy, inducing remission in a substantial proportion of patients with persistent nephrotic syndrome, including those previously exposed to immunosuppressive therapy.[36,37]

In a large cohort of 100 high-risk patients, 65% achieved complete or partial remission during long-term follow-up, with associated stabilization or improvement in renal function, increases in serum albumin, and no serious treatment-related adverse events.[38] Complementary evidence from a larger study of 132 patients further reinforces the efficacy of rituximab, demonstrating remission in two-thirds of treated individuals and highlighting the central role of anti-PLA2R antibodies in therapeutic monitoring. In antibody-positive patients, lower baseline titers and complete antibody depletion at 6 months robustly predicted remission, with serologic improvement preceding clinical response by approximately 10 months, while antibody reappearance was strongly associated with relapse.[39]

The 2020 STARMEN study compared the effectiveness of a cyclic regimen of cyclophosphamide and glucocorticoids versus treatment with tacrolimus for 6 months followed by 1 g rituximab prior to tacrolimus taper in 86 patients diagnosed with primary MN. They reported a higher remission rate (partial or complete) at 2 years of follow-up in patients treated with cyclophosphamide and glucocorticoids (83.7% vs. 58.1%), as well as a higher rate of complete remission (60% vs. 26%). While immunological remission was higher in the cyclophosphamide group at 6 months, it was similar between both groups (83% vs. 86%) at the end of the follow-up period. The cyclophosphamide group showed a lower relapse rate (2.7% vs 12%). However, the rituximab dosage in this study was likely suboptimal; baseline anti-PLA2R titers were higher in the tacrolimus-rituximab group, and the time required to achieve antibody reduction was longer. Therefore, the response rate in this group may have been underestimated.[36]

The RI-CYCLO study compared the use of a cyclic regimen of cyclophosphamide and glucocorticoids with the use of rituximab on days 0 and 14 in 74 patients at moderate risk of progression, finding

no difference between groups in the primary outcome of achieving complete remission at 12 and 24 months. The relapse rate was lower in the rituximab-treated group at 2 years of follow-up (5% vs. 25%).[37]

The 2019 MENTOR study failed to demonstrate a difference between groups in terms of partial or complete remission rate at 1 year of follow-up between a cyclosporine treatment regimen (52%) and a rituximab regimen (60%). However, rituximab was superior at 2 years of follow-up, maintaining remission in 60% of patients, while remission was maintained in only 20% of patients treated with cyclosporine. Furthermore, there was a better safety profile in the group treated with rituximab.[40]

Current KDIGO recommendations establish the use of rituximab as a first-line treatment agent, achieving remission (more partial than complete remissions) in more than 80% of patients, with a dose of 1 g intravenously on days 0 and 14, or 375 mg/m^2 weekly in 1–4 doses.[9] However, in our experience, many of these cases required subsequent doses after the initial therapy. A study that included only 12 patients with primary MN and nephrotic syndrome compared the 4-weekly dose protocol with one guided by B-cell levels showed no differences between the two groups at 1-year follow-up in the proportion of patients who achieved remission criteria.[41]

The pursuit of personalized rituximab treatment suggests that monitoring plasma levels of anti-PLA2R antibodies and CD19+ B-cell depletion may safely guide the dosage and timing of this monoclonal antibody, improving its safety, efficacy, and cost-effectiveness compared to cyclophosphamide-based regimens, even in patients with high-risk and very-high-risk MN. Among these regimens, those with an initial dose of 375 mg/m^2 and the administration of the second dose when >5 B lymphocytes/mm^3 are detected have been proposed, demonstrating non-inferiority to traditional regimens and offering a better safety profile by reducing the cumulative rituximab dose.[42]

Even greater personalization and precision in rituximab dosing for the treatment of primary MN might be achieved through the use of artificial intelligence technologies. The iRITUX study proposes stratifying patients into three groups based on estimated underdosing (estimated underdosing <50%, 50–75%, and >75%) and administering adjusted doses of rituximab (1 g on days 0 and 14; 0, 14, and 30; or 0, 14, 30, and 45, respectively) to achieve the desired therapeutic effect.[43]

In cases of relapse of primary MN after rituximab use, treatment with a new course of rituximab is recommended. If the patient has been previously treated with cyclophosphamide plus glucocorticoids, reinduction with the same regimen may be considered, or treatment with rituximab or rituximab and a calcineurin inhibitor may be initiated.[44]

Multiple mechanisms of resistance to rituximab have been described. The most widely described is the generation of neutralizing anti-rituximab antibodies, predominantly through the recognition of epitopes in the murine-derived variable fragment (Fv) in 23–43% of patients.[44,45] These antibodies are capable of preventing the correct binding of rituximab to its therapeutic target, thereby decreasing its efficacy. The development of neutralizing anti-rituximab antibodies is a recognized mechanism of treatment resistance in membranous nephropathy and other autoimmune diseases. These antibodies can accelerate B-cell reconstitution, reduce serum rituximab concentrations, blunt clinical response, and are associated with higher rates of relapse and secondary loss of efficacy after rituximab exposure. In membranous nephropathy, the presence of neutralizing anti-rituximab antibodies has been shown to impair B-cell depletion and is linked to earlier relapse and increased need for retreatment.[45]

When neutralizing anti-rituximab antibodies are detected, repeating rituximab is generally ineffective due to antibody-mediated neutralization of the drug's activity.[45] In this scenario, the medical literature supports switching to alternative anti-CD20 agents, specifically humanized (obinutuzumab) or fully human (ofatumumab) monoclonal antibodies, which do not exhibit significant cross-reactivity with anti-rituximab antibodies and have demonstrated efficacy in patients with rituximab resistance.[46] Ofatumumab and obinutuzumab have been successfully used to achieve B-cell depletion and clinical response in patients with anti-rituximab antibodies, while ocrelizumab may show partial cross-reactivity and should be used with caution.[45,46]

In summary, the presence of neutralizing anti-rituximab antibodies should prompt a switch to an alternative anti-CD20 agent rather than further rituximab retreatment. This approach is supported by clinical and mechanistic data demonstrating restored efficacy and B-cell depletion with these agents in the setting of anti-rituximab antibody-mediated resistance.

Another well-described mechanism is the preservation of a reservoir of autoreactive B lymphocytes after rituximab use within lymphoid organs such as the spleen, generating resistance and causing the disease to recur despite appropriate treatment.[47] Mechanisms directly associated with the pathophysiology of primary MN have also been described, where the pharmacokinetics of rituximab are altered with increased clearance and a shorter half-life, related to proteinuria levels > 8 g/day or marked non-selective proteinuria.[48]

An important clinical challenge after B-cell-depleting therapy in membranous nephropathy is disease relapse following an initial remission induced by rituximab. Relapses occur in approximately 20–40% of patients during long-term follow-up and are frequently associated with B-cell reconstitution and the reappearance or increase of anti-PLA2R antibodies, suggesting renewed autoimmune activity. In this context, immunological monitoring has emerged as a valuable tool to anticipate disease recurrence and guide retreatment strategies.[7,40,49,50]

In many cases, re-exposure to rituximab is effective and can lead to renewed immunological and clinical remission and therefore remains the most commonly adopted strategy in clinical practice.[40] Current recommendations from KDIGO also support retreatment with anti-CD20 therapy in patients who relapse after an initial response, particularly when immunological activity persists or anti-PLA2R antibodies reappear.[9]

Nevertheless, the optimal management of relapses remains uncertain. Some patients exhibit incomplete B-cell depletion or reduced responsiveness to rituximab, potentially related to CD20 modulation, pharmacokinetic variability, or the development of anti-drug antibodies.[49] In these situations, alternative anti-CD20 monoclonal antibodies such as obinutuzumab or ofatumumab may provide deeper and more sustained B-cell depletion and encouraging results have been reported in small series of patients with rituximab-refractory membranous nephropathy.[21,51]

Additional strategies are currently being explored, including combination approaches targeting complementary immune pathways, such as therapies directed against plasma cells or other mechanisms involved in B-cell activation. Although clinical evidence remains limited, these approaches may be particularly relevant for patients with multiple relapses or persistent immunological activity despite conventional anti-CD20 therapy.

The development of new anti-CD20 monoclonal antibodies aims to offer these patients new treatment alternatives by combating rituximab resistance mechanisms.

Obinutuzumab

A significant proportion of patients do not achieve complete remission or relapse early after treatment with rituximab, prompting the evaluation of agents that allow for deeper and more lasting B-cell depletion. In this context, obinutuzumab, a second-generation, type II anti-CD20 antibody, has emerged as a promising option.[52–54]

Characteristics

Obinutuzumab is a genetically modified (glycoengineered) type II humanized anti-CD20 monoclonal antibody that has increased affinity for FcγRIIIa. Compared with type I antibodies, such as rituximab, obinutuzumab induces more potent antibody-dependent cell-mediated cytotoxicity and promotes direct B-cell apoptosis with less complement activation.[53,54] These pharmacodynamic differences result in deeper and more sustained B-cell depletion in peripheral blood and lymphoid tissues, a feature that may be particularly relevant in autoantibody-mediated diseases, such as primary MN.[32] In various experimental models and other autoimmune conditions, including lupus nephritis, obinutuzumab has demonstrated advantages over rituximab in reducing autoantibodies and preventing early B-cell repopulation.[55,56]

Available clinical evidence

Preliminary data are derived from small, well-documented case series in primary MN refractory to rituximab (Table 2a). In 2020, three cases of PLA2R-positive patients refractory to rituximab were reported in which obinutuzumab (1 g on days 1 and 15) achieved complete immunological remission in all three cases and partial clinical remission in two, supporting its utility as salvage therapy.[51] Since 2024, larger cohorts have documented the benefit of obinutuzumab as initial therapy and as an alternative in refractory disease, generally with a rapid decline in anti-PLA2R titers.[57] In a propensity-matched comparison of 63 patients, obinutuzumab was associated with a higher likelihood of clinical remission at 12 months than rituximab (95% vs 67%; odds ratio 10.00; 95% CI, 1.21–82.35; $p = 0.03$), possibly related to a higher rate of immunological remission at 6 months (92% [12/13] vs 64% [16/25]; $p = 0.06$); safety was similar.[58] In a retrospective cohort of 51 patients with cyclophosphamide- and calcineurin inhibitor-refractory disease, the response rate favored obinutuzumab over rituximab (90.0% vs 38.7%; $p < 0.001$) during a median follow-up of 24 months (IQR 10–34).[57] Additional studies in Chinese populations, conducted under real-world conditions, report high rates of clinical and immunological remission with an acceptable safety profile in both patients with previously untreated primary MN and those refractory to rituximab.[5,58]

Clinical trials ongoing

Currently, there are two registered and ongoing clinical trials of obinutuzumab in primary MN (Table 2b): one phase II study (ORION; NCT05050214), and the phase III MAJESTY trial (NCT04629248). MAJESTY randomly compares obinutuzumab with tacrolimus in patients with PLA2R-positive primary MN, with complete remission at week 104 as the primary endpoint; recruitment (approximately 142 participants) has ended, and results are pending.

Future perspectives

Current evidence supports obinutuzumab as an emerging option for primary membranous nephropathy, particularly in patients refractory to rituximab, with frequent relapses, or with persistently elevated anti-PLA2R titers. If ongoing trials confirm initial indications, obinutuzumab could be considered as first-line treatment in selected high-risk subgroups; however, further head-to-head, cost-effectiveness, and long-term safety data are still needed.

Ofatumumab

Ofatumumab is a fully human, type I anti-CD20 monoclonal antibody that binds to an epitope adjacent to the cell membrane (the small loop and part of the large loop of CD20). Its high affinity and slow dissociation promote potent complement-dependent cytotoxicity

Table 2a
Clinical studies with obinutuzumab in primary membranous nephropathy.

Author (year)	Population	Obinutuzumab regimen	Follow-up times	Main findings	Safety
Klomjit et al. (2020)[51]	PLA2R+ MN, rituximab-refractory	1 g IV on day 1 and day 15 (2 doses)	12 months	Complete immunologic remission 3/3; partial clinical remission 2/3	No serious adverse events reported
Sethi et al. (2020)[61]	PLA2R+ MN, rituximab-refractory	1 g IV on day 1 and day 15 (2 doses)	12 months	High immunologic response and proteinuria reduction in refractory cases	Well tolerated; mild infusion reactions
Hudson et al. (2022)[62]	PLA2R+ MN, rituximab-refractory	1 g IV ×2 (≈2 weeks apart)	12 months	Immunologic remission and clinical improvement in both cases	No serious adverse events reported
Su et al. (2024)[57]	PLA2R+ MN (initial therapy $n = 20$; second-line $n = 39$)	1 g IV on day 1 and day 15 (2 doses)	Median 9.4 months	84.7% CR/PR; anti-PLA2R decline; strong responses, even as initial therapy	Mostly infusion reactions; no new safety signals
Hu et al. (2024)[58]	PLA2R+ MN; propensity-matched (OBI $n = 21$ vs RTX $n = 42$)	1 g IV on day 1 and day 15 (2 doses)	12 months	Clinical remission 95% vs 67% at 12 months; higher 6-month immunologic remission	Similar safety to rituximab
Xu et al. (2025)[59]	Refractory PLA2R+ MN (OBI $n = 20$ vs RTX $n = 31$)	1 g IV on day 1 and day 15 (2 doses)	Median 24 months (IQR 10–34)	Response 90.0% with OBI vs 38.7% with RTX; higher immunologic remission at 3–6 months	Comparable safety between groups
Li H et al. (2025)[60]	PLA2R+ MN, rituximab-refractory	1 g IV on day 1 and day 15 (adjunct after RTX)	Assessments at 3–6 months (median time to remission ≈4.4 months)	High early remission rates; sustained B-cell depletion in a subset	No serious adverse events signaled
Li L et al. (2025)[64]	Refractory PLA2R+ MN ($n = 25$)	Individualized; mostly 1 g ×2	≥12 months	Clinical response 76%; complete immunologic remission 90.5% among PLA2R+	No severe adverse events
Xue Qi Li et al. (2025)[63]	PLA2R+ MN (initial therapy, retrospective)	1 g IV on day 1 and day 15 (2 doses)	≥6–12 months	Immunologic remission 76% (3 m) and 80% (6 m); high partial clinical remission early	Well tolerated; no major serious events
Cheng et al. (2025)[5]	PLA2R+ MN ($n = 55$; initial $n = 15$/rescue $n = 40$)	1 g IV on day 1 and day 15 (2 doses)	Median 13 months (IQR 10–18)	Clinical remission 83.6% (CR 43.6%); immunologic remission 92%	Infusion reactions; severe infections uncommon

Abbreviations: MN, membranous nephropathy; PLA2R, phospholipase A2 receptor; OBI, obinutuzumab; RTX, rituximab; IV, intravenous; IQR, interquartile range; *n*, number; CR, complete remission; PR, partial remission.

Table 2b
Obinutuzumab trials in primary membranous nephropathy.

Trial ID/Name	Phase and design	Population (key inclusion)	Arms/Dosing	Primary endpoint	Enrollment (planned/actual)
NCT04629248 (MAJESTY)	Phase III; randomized, open-label	Adults 18–75 with primary MN; UPCR ≥ 5 g/g after ≥3 mo BSC or ≥4 g/g after ≥6 mo; eGFR ≥40 mL/min/1.73 m^2	OBI 1000 mg IV Day 1, Weeks 2, 24, 26 vs tacrolimus 0.5 mg/kg BID up to 14 mo	Complete remission at Week 104 (UPCR ≤ 0.3 g/g with stable eGFR); key secondary: CR/PR at Week 104; CR at Week 76	142 (fully enrolled)
NCT05050214 (ORION)	Phase II; single-arm pilot (non-controlled)	Biopsy-proven pMN; rituximab-resistant, -dependent, or -intolerant; adults ≥18; typical inclusion: proteinuria > 3.5 g/24 h, eGFR ≥ 30	OBI total 3000 mg over 1 month (Day 1: 100 mg; Day 2: 900 mg; Day 15: 1000 mg; Day 29: 1000 mg)	Efficacy (remission of nephrotic syndrome) and safety (per registry); additional immunologic/PLA2R assessments	≈20 (planned)

Abbreviations: MN, membranous nephropathy; PLA2R, phospholipase A2 receptor; OBI, obinutuzumab; RTX, rituximab; IV, intravenous; IS, immunosuppression; IQR, interquartile range; *n*, number; CR, complete remission; PR, partial remission; UPCR, urine protein creatinine ratio; eGFR, estimated glomerular filtration rate.

(CDC), in addition to ADCC, which can result in effective B-cell depletion even when CD20 expression is low or in the presence of anti-rituximab antibodies.[65,66]

Available clinical evidence

Specific evidence for PLA2R-positive primary membranous nephropathy is limited but growing, primarily in patients with rituximab intolerance or resistance (Table 3):

- Podestà et al.[2]: Seven patients with rituximab intolerance and ten patients with rituximab resistance received a single intravenous infusion of ofatumumab (50–300 mg). After a median of approximately 5 months, 7 of 7 intolerant and 3 of 10 resistant patients achieved clinical remission (complete or partial); rapid B-cell depletion (approximately 1 week) and a decrease in anti-PLA2R antibodies were observed in most evaluable patients; infusion reactions were mild.
- Podestà et al.[67]: Multirelapsing PLA2R-positive primary membranous nephropathy complicated by rituximab-induced serum sickness; Intravenous administration of 300 mg of ofatumumab induced remission; the 100 mg dose was insufficient; retreatment with 300 mg restored remission without relevant toxicity.
- Chen et al.[68]: In one refractory patient and one relapsed patient, subcutaneous administration of ofatumumab resulted in anti-PLA2R seronegativity in one case and a reduction in proteinuria in both; no adverse events were reported during the short follow-up period.
- Teisseyre et al.[69]: In the presence of anti-rituximab antibodies, ofatumumab or obinutuzumab were more effective than rituximab in inducing clinical remission, supporting the use of alternative anti-CD20 antibodies when rituximab immunogenicity is present.

Future perspectives

Ofatumumab is a robust alternative in patients intolerant to rituximab (e.g., serum sickness or hypersensitivity) and shows evidence of benefit in primary resistance (particularly with intravenous doses ≥300 mg or with retreatment). The subcutaneous route is promising in selected cases; controlled studies with longer follow-up are needed to define its role compared with rituximab and second-generation anti-CD20 antibodies.

Other humanized anti-CD20 monoclonal antibodies

Ocrelizumab

Ocrelizumab is a recombinant humanized IgG1 monoclonal antibody directed against CD20. It binds to a CD20 epitope that is different but partially overlapping with that of rituximab, and its Fc fragment demonstrates enhanced binding affinity for low-affinity FcγRIIIa receptor variants on effector cells. Because these receptor variants are associated with reduced clinical response to rituximab, ocrelizumab may represent a valuable therapeutic alternative in conditions demonstrating rituximab resistance.[70] Moreover, as a humanized antibody, it carries a lower risk of treatment resistance because it is less susceptible to neutralizing anti-drug antibodies.[71]

To date, there are no clinical trials validating the efficacy of ocrelizumab in the treatment of primary MN. However, in 2021, a case report was published of a 52-year-old man diagnosed with multiple sclerosis and PLA2R-positive primary MN, treated with two 300 mg doses of ocrelizumab over 2 weeks, and 14 months later, a third 300 mg dose, with promising results, achieving sustained effects for up to 2 years.[72] Experience with the use of ocrelizumab in the treatment of other autoimmune diseases and proliferative lupus

Table 3
Clinical studies with ofatumumab in primary membranous nephropathy.

Author (year)	Population	Ofatumumab regimen	Design/*n*	Main findings	Safety
Podestà et al. (2024)[2]	pMN; rituximab-intolerant and rituximab-resistant	Single IV dose 50–300 mg	Case series/17	Clinical remission 7/7 (intolerant) and 3/10 (resistant); ↓ anti-PLA2R; rapid B-cell depletion	Mild infusion reactions
Podestà et al. (2020)[67]	PLA2R + multirelapsing pMN; rituximab-induced serum sickness	300 mg IV (response); 100 mg (failure); 300 mg retreatment (response)	Single case	Clinical remissions with 300 mg; rescue in RTX-sensitized patients	No serious AEs
Chen et al. (2025)[68]	pMN: one refractory, one relapsing	20 mg sc once a week for the first 3 weeks, followed by a maintenance dose of 20 mg monthly thereafter.	Two cases	Anti-PLA2R seronegativity (1/2) and ↓ proteinuria (2/2)	No AEs reported
Teisseyre et al. (2025)[69]	pMN with anti-rituximab antibodies	Ofatumumab or obinutuzumab vs rituximab	Observational (anti-RTX +)	Higher remission with alternative anti-CD20 vs RTX	Comparable safety

Abbreviations: MN, membranous nephropathy; PLA2R, phospholipase A2 receptor; RTX, rituximab; IV, intravenous; *n*, number; AEs, adverse events.

nephritis has shown similar effectiveness to the use of rituximab; however, a higher incidence of treatment-associated infections has been noted, which should be explored extensively in clinical trials in patients with primary MN.[73]

Veltuzumab

Like ocrelizumab, veltuzumab is a recombinant humanized IgG1 anti-CD20 monoclonal antibody, binding to an epitope similar to that targeted by rituximab, but with a 1-amino acid change in the Fv region that increases its binding affinity to CD20, triggering greater complement-mediated cytotoxicity. It has the advantage of being able to be administered subcutaneously or intravenously.[70]

It has been used in the treatment of primary immune thrombocytopenia with a good response and a suitable safety profile; however, experience in patients with MN and other glomerulopathies is currently limited.[73]

Zuberitamab

Zuberitamab (HS006) is a novel chimeric anti-CD20 monoclonal antibody that induces B-cell depletion primarily through antibody-dependent cellular cytotoxicity. In a recent observational study including 25 patients with primary membranous nephropathy treated with zuberitamab and a matched rituximab control cohort, treatment with zuberitamab was associated with a high overall remission rate at 12 months, with complete remission observed in 80% of patients. Moreover, significant reductions in proteinuria and anti-PLA2R antibody levels were observed, while no severe adverse events were reported during follow-up.[74] Although these results are encouraging, the evidence currently derives from small retrospective cohorts, and larger prospective studies will be necessary to define the role of zuberitamab in the therapeutic algorithm of membranous nephropathy.

Dosing strategies and repeated administrations of anti-CD20 antibodies

In membranous nephropathy, the use of anti-CD20 antibodies has become established as first-line therapy in patients with moderate or high risk of progression, displacing more toxic regimens.[75] Regarding dosing and the need for repeated administrations, there are three main strategies to guide treatment: autoantibody levels (anti-PLA2R, when available), peripheral B-cell reconstitution (CD19+), and clinical parameters such as proteinuria; in practice, a combination of these factors is typically employed.[76,77]

Autoantibody levels: A decline or disappearance of anti-PLA2R levels strongly predicts clinical remission, their titers correlate closely with disease activity and severity, and its reappearance or persistently elevated anticipates relapses.[78,79] Immunological remission precedes clinical remission by several months, and the persistence of antibodies after treatment is associated with a higher risk of relapse and increased risk of nonresponse.[76] Strengths: allows for a personalized approach and anticipates clinical response. Limitations: not all patients have detectable antibodies, and test availability may be limited.

Integrating autoantibody levels with clinical parameters, such as proteinuria, serum albumin, and renal function, enhances prognostic accuracy and guides individualized treatment decisions. The medical literature supports combining these markers for risk stratification and monitoring, as this approach outperforms reliance on proteinuria alone.[80,81]

Peripheral B-cell reconstitution: Monitoring CD19+ guides the need for retreatment, as the reappearance of B cells may precede immunological relapse. The timing of B-cell reappearance varies, but persistent depletion is generally associated with ongoing immunosuppression and, in some cases, sustained clinical remission.[82] However, the correlation between B-cell reconstitution and clinical response is not absolute, and some patients maintain clinical remission despite B-cell recovery.[75] This discordance is partly explained by the heterogeneity of B-cell subsets: memory B cells and plasmablasts may reappear earlier than naïve B cells and may be more relevant to disease activity.[83,84] Nonetheless, standardized protocols for subset monitoring are lacking, and most clinical practice still relies on total CD19+ enumeration. Recent research suggests that monitoring specific B-cell subsets, such as memory B cells (CD27+) and plasmablasts, may provide more precise information about immune activity and risk of relapse than total CD19+ counts alone.[85] In summary, peripheral B-cell reconstitution (CD19+) is a useful but imperfect biomarker for guiding anti-CD20 retreatment in membranous nephropathy. Its main strengths are accessibility and applicability to all patients, but its limitations include imperfect correlation with clinical and immunological outcomes. Integration with autoantibody levels and clinical parameters is recommended for optimal management.

Clinical parameters: Proteinuria reduction remains the primary goal and the most accessible marker of response. However, proteinuria decrease after anti-CD20 therapy may be delayed by months compared to immunological remission, and persistent proteinuria does not necessarily imply immediate therapeutic failure.[76,77] The medical literature consistently supports the use of proteinuria as a surrogate endpoint for clinical trials and therapeutic monitoring, but emphasizes the importance of combining it with immunological and biochemical parameters for optimal management.

In summary, the optimal strategy is to integrate autoantibody levels, B-cell reconstitution, and clinical evolution (proteinuria) to individualize anti-CD20 dosing and repetition, maximizing efficacy and minimizing toxicity.

Safety profiles of the anti-CD20 agents

Although anti-CD20 therapies are generally well tolerated in patients with membranous nephropathy, differences in safety profiles among available agents deserve consideration. Rituximab has the most extensive safety data and is generally associated with a favorable risk–benefit profile. Infusion-related reactions represent the most common adverse events and are usually mild and manageable. Nevertheless, B-cell depletion may predispose patients to infectious complications, particularly in those receiving repeated treatment cycles or concomitant immunosuppressive therapy.[49,40,86]

Another important concern is the development of hypogammaglobulinemia during prolonged B-cell depletion. Observational studies have demonstrated that repeated exposure to rituximab can lead to progressive reductions in serum immunoglobulin levels, which in some cases are associated with an increased risk of serious infections.[87] These findings support the recommendation to monitor immunoglobulin levels during long-term therapy, particularly in patients receiving multiple courses of treatment.

Second-generation anti-CD20 monoclonal antibodies, such as obinutuzumab and ofatumumab, may induce deeper and more sustained B-cell depletion due to differences in their mechanisms of action. While this property may potentially improve therapeutic efficacy in rituximab-refractory disease, it could theoretically increase the risk of infectious complications and hypogammaglobulinemia. However, clinical experience with these agents in membranous nephropathy remains limited and currently derives mainly from small case series.[49,51] Overall, available evidence suggests that anti-CD20 therapies maintain a relatively favorable safety profile, although careful patient selection and monitoring for infectious complications and immunoglobulin levels remain essential aspects of clinical management.

Role of B-cell-targeting therapies in post-transplant disease recurrence

In membranous nephropathy after kidney transplantation, recurrence can occur in up to 50% of recipients, generally within the first year post-transplant. The main determinant of recurrence is the presence of circulating anti-PLA2R antibodies at the time of transplantation. As observed in the non-transplant population, a significant proportion of recipients do not respond to conventional therapies or rituximab, ultimately losing the graft.[88]

The first report describing the use of Obinutuzumab (OBI) in kidney transplant recipients with membranous nephropathy was published in 2020. Four patients (three with recurrent primary membranous nephropathy and one with de novo membranous nephropathy) received OBI (total dose of 2000 mg) after failed treatment with tacrolimus or rituximab. During follow-up (between 9 and 24 months), all patients achieved remission (complete or partial), showing substantial improvements in the urine protein/creatinine ratio, serum albumin concentration, and circulating anti-PLA2R antibody levels. Overall, graft function remained stable.[60]

In a recent single-center case series from Australia, five patients with refractory or recurrent MN received OBI (100 mg on day 1, 900 mg on day 2, and 1000 mg on day 15) as salvage therapy. Among these patients was a kidney transplant recipient with recurrent MN. Three of the five subjects (specifically, those with PLA2R-associated MN) achieved complete clinical and immunological remission, with sustained anti-PLA2R antibody negativity. Despite OBI, the kidney transplant recipient showed no signs of remission and ultimately lost the graft due to recurrence.[89] The positive results observed in native kidneys support the use of OBI in the context of kidney transplantation, especially in cases of refractory membranous nephropathy or with frequent relapses and the presence of circulating anti-PLA2R antibodies; however, well-designed clinical trials are needed to confirm the role of OBI in kidney transplantation.

CAR-T cell-based therapies as potential treatment for refractory MN

Chimeric autoantibody receptor (CAAR) modified immune cells have demonstrated preclinical activity in a growing number of models, most recently anti-PLA2R and thrombospondin domain 7A-positive (THSD7A) membranous nephropathy.[90,91] A major challenge in the development of a CAAR T cell therapy (CAART) for PLA2R-mediated membranous nephropathy is the size and complexity of the PLA2R antigen. A previous study evaluated the preliminary potential of a PLA2R cysteine-rich (CysR) domain CAART design for PLA2R-associated membranous nephropathy and analyzed its activity by in vitro elimination of PLA2R-specific hybrid B cells, although in vivo efficacy and potential off-target effects were not investigated.[92] In another study, the feasibility of developing a CAART T cell therapy for PLA2R-specific B cell depletion in PLA2R-associated membranous nephropathy (PLA2R-CAART) was determined. The results demonstrated that both C17-CAART and C178-CAART were successfully expressed in primary T cells and exhibited specific cytotoxicity in vitro against anti-PLA2R B cell lines targeting the CysR, CTLD1, and CTLD7 epitopes, significantly reducing anti-PLA2R B cells and adsorbing between 69% and 97% of anti-PLA2R antibody reactivity from plasma. In in vivo studies, treatment with C17-CAART and C178-CAART resulted in a significant reduction in target cell growth, with a slight but consistent increase in cytotoxic activity observed with C17-CAART. Specificity testing, using comprehensive in vivo pathological analysis and high-throughput membrane proteome analysis, showed no significant nonspecific binding for either treatment (C17-CAART and C178-CAART). These findings establish a preclinical proof of concept for the therapeutic potential of antigen-specific B cell depletion by PLA2R-CAART,[93] however further studies are required to determine the clinical feasibility of PLA2R-CAART for the treatment of PLA2R-associated membranous nephropathy.

Conclusions

Membranous nephropathy remains a challenging glomerular disease with significant heterogeneity in clinical presentation and therapeutic response. The introduction of anti-CD20 monoclonal antibodies, particularly rituximab, has transformed management by providing an effective and safer alternative to conventional immunosuppression. However, a considerable subset of patients exhibits incomplete, transient, or refractory responses, underscoring the need for next-generation B-cell-targeted therapies.

New humanized and glycoengineered anti-CD20 agents such as obinutuzumab and ofatumumab demonstrate enhanced mechanisms of action, deeper B-cell depletion, and promising efficacy in rituximab-resistant cases, expanding the therapeutic armamentarium. Emerging clinical evidence, including ongoing randomized trials, supports their potential role as salvage treatments and possibly first-line options in selected high-risk patients.

Despite these advances, important challenges remain: optimizing patient selection, individualizing dosing guided by pharmacokinetics and biomarkers, ensuring long-term safety, and addressing access and cost-effectiveness within the Spanish and broader European health-care context. Further head-to-head comparisons and real-world data are needed to refine treatment algorithms and improve outcomes.

In summary, humanized anti-CD20 monoclonal antibodies represent an important evolution in membranous nephropathy therapy, promising improved disease control and quality of life for patients. Ongoing research and clinical experience will clarify their optimal use, paving the way toward more personalized and precise nephrology care.

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Conflicts of interest

The authors declare that they have no conflict of interest.

References

1. Ponticelli C. Membranous nephropathy. J Clin Med. 2025;14:761, http://doi.org/10.3390/jcm14030761
2. Podestà MA, Trillini M, Portalupi V, Gennarini A, Tomatis F, Villa A, et al. Ofatumumab in rituximab-resistant and rituximab-intolerant patients with primary membranous nephropathy: a case series. Am J Kidney Dis. 2024;83:340–9, http://doi.org/10.1053/j.ajkd.2023.08.010. e1.
3. Lin Y, Han Q, Chen L, Wang Y, Ren P, Liu G, et al. Obinutuzumab in refractory membranous nephropathy: a case series. Kidney Med. 2024;6100853, http://doi.org/10.1016/j.xkme.2024.100853
4. Su W, Li J, Men J, Zhong S, Wang Y, Zhang Y, et al. Obinutuzumab is effective for the treatment of rituximab-refractory PLA2R-associated membranous nephropathy. Clin Kidney J. 2025;18sfaf026, http://doi.org/10.1093/ckj/sfaf026
5. Cheng X, Zheng ZF, Qi Y, Cao X, Gao XQ, Fang YX, et al. Efficacy and safety of obinutuzumab in primary membranous nephropathy: a real-world retrospective study. Front Immunol. 2025;161650054, http://doi.org/10.3389/fimmu.2025.1650054
6. Zamora JI, López-Martínez M, Ramos N, Bermejo S, Agraz I, García-Carro C, et al. Experience with new anti-CD20 monoclonal antibodies for immune-mediated glomerulopathies in a tertiary hospital. Nefrologia. 2025, http://doi.org/10.1016/j.nefro.2025.501372
7. Beck LH Jr, Salant DJ. Membranous nephropathy: recent travels and new roads ahead. Kidney Int. 2010;77:765–70, http://doi.org/10.1038/ki.2010.34
8. Cattran DC, Brenchley PE. Membranous nephropathy: integrating basic science into improved clinical management. Kidney Int. 2017;91:566–74, http://doi.org/10.1016/j.kint.2016.09.048

9. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. Kidney Int. 2021;100(4S):S1–276, http://doi.org/10.1016/j.kint.2021.05.021
10. Sethi S, Fervenza FC. Antigens in membranous nephropathy: discovery and clinical implications. Nat Rev Nephrol. 2025;21:653–70, http://doi.org/10.1038/s41581-025-00980-z
11. Ponticelli C, Patrizia P, Del Vecchio L, Locatelli F. The evolution of the therapeutic approach to membranous nephropathy. Nephrol Dial Transplant. 2021;36:768–73, http://doi.org/10.1093/ndt/gfaa014
12. Peritore L, Labbozzetta V, Maressa V, Casuscelli C, Conti G, Gembillo G, et al. How to choose the right treatment for membranous nephropathy. Medicina (Kaunas Lithuania). 2023;59:1997, http://doi.org/10.3390/medicina59111997
13. Ponticelli C, Zucchelli P, Passerini P, Cagnoli L, Cesana B, Pozzi C, et al. A randomized trial of methylprednisolone and chlorambucil in idiopathic membranous nephropathy. N Engl J Med. 1989;320:8–13, http://doi.org/10.1056/NEJM198901053200102
14. Ponticelli C, Altieri P, Scolari F, Passerini P, Roccatello D, Cesana B, 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, http://doi.org/10.1681/ASN.V93444
15. Radhakrishnan Y, Zand L, Sethi S, Fervenza FC. Membranous nephropathy treatment standard. Nephrol Dial Transplant. 2024;39:403–13, http://doi.org/10.1093/ndt/gfad225
16. Cai N, Zhu S-Y, Huang J-J, Chen Y-X, Huang C, Qin X-H. Rituximab, tacrolimus, cyclophosphamide and cyclosporin in primary membranous nephropathy with nephrotic syndrome: comparison of safety profiles, effect on remission rate, 24-h urinary total protein, serum albumin, and serum creatinine levels using network meta-analysis. Int Urol Nephrol. 2025;57:3733–50, http://doi.org/10.1007/s11255-025-04549-4
17. Stashenko P, Nadler LM, Hardy R, Schlossman SF. Characterization of a human B lymphocyte-specific antigen. J Immunol (Baltimore Md: 1950). 1980;125:1678–85.
18. Eon Kuek L, Leffler M, Mackay GA, Hulett MD. The MS4A family: counting past 1, 2 and 3. Immunol Cell Biol. 2016;94:11–23, http://doi.org/10.1038/icb.2015.48
19. Tedder TF, Klejman G, Schlossman SF, Saito H. Structure of the gene encoding the human B lymphocyte differentiation antigen CD20 (B1). J Immunol (Baltimore Md: 1950). 1989;142:2560–8.
20. Tedder TF, Schlossman SF. Phosphorylation of the B1 (CD20) molecule by normal and malignant human B lymphocytes. J Biol Chem. 1988;263:10009–15.
21. Bubien JK, Zhou LJ, Bell PD, Frizzell RA, Tedder TF. Transfection of the CD20 cell surface molecule into ectopic cell types generates a Ca^{2+} conductance found constitutively in B lymphocytes. J Cell Biol. 1993;121:1121–32, http://doi.org/10.1083/jcb.121.5.1121
22. Polyak MJ, Li H, Shariat N, Deans JP. CD20 homo-oligomers physically associate with the B cell antigen receptor. Dissociation upon receptor engagement and recruitment of phosphoproteins and calmodulin-binding proteins. J Biol Chem. 2008;283:18545–52, http://doi.org/10.1074/jbc.M800784200
23. Szöllósi J, Horejsí V, Bene L, Angelisová P, Damjanovich S. Supramolecular complexes of MHC class I, MHC class II, CD20, and tetraspan molecules (CD53, CD81, and CD82) at the surface of a B cell line JY. J Immunol (Baltimore Md: 1950). 1996;157:2939–46.
24. Forsthuber TG, Cimbora DM, Ratchford JN, Katz E, Stüve O. B cell-based therapies in CNS autoimmunity: differentiating CD19 and CD20 as therapeutic targets. Therap Adv Neurol Disord. 2018;11, http://doi.org/10.1177/1756286418761697. 1756286418761697.
25. Glennie MJ, French RR, Cragg MS, Taylor RP. Mechanisms of killing by anti-CD20 monoclonal antibodies. Mol Immunol. 2007;44:3823–37, http://doi.org/10.1016/j.molimm.2007.06.151
26. Maloney DG, Liles TM, Czerwinski DK, Waldichuk C, Rosenberg J, Grillo-Lopez A, et al. Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. Blood. 1994;84:2457–66.
27. Tedder TF, Engel P. CD20: a regulator of cell-cycle progression of B lymphocytes. Immunol Today. 1994;15:450–4, http://doi.org/10.1016/0167-5699(94)90276-3
28. Smith MR. Rituximab (monoclonal anti-CD20 antibody): mechanisms of action and resistance. Oncogene. 2003;22:7359–68, http://doi.org/10.1038/sj.onc.1206939
29. Kuijpers TW, Bende RJ, Baars PA, Grummels A, Derks IA, Dolman KM, et al. CD20 deficiency in humans results in impaired T cell-independent antibody responses. J Clin Investig. 2010;120:214–22, http://doi.org/10.1172/JCI40231
30. Uchida J, Lee Y, Hasegawa M, Liang Y, Bradney A, Oliver JA, et al. Mouse CD20 expression and function. Int Immunol. 2004;16:119–29, http://doi.org/10.1093/intimm/dxh009
31. Marshall MJE, Stopforth RJ, Cragg MS. Therapeutic antibodies: what have we learnt from targeting CD20 and where are we going? Front Immunol. 2017;8:1245, http://doi.org/10.3389/fimmu.2017.01245
32. Boross P, Leusen JH. Mechanisms of action of CD20 antibodies. Am J Cancer Res. 2012;2:676–90.
33. Klein C, Lammens A, Schäfer W, Georges G, Schwaiger M, Mössner E, et al. Epitope interactions of monoclonal antibodies targeting CD20 and their relationship to functional properties. mAbs. 2013;5:22–33, http://doi.org/10.4161/mabs.22771
34. Bondza S, Marosan A, Kara S, Lösing J, Peipp M, Nimmerjahn F, et al. Complement-dependent activity of CD20-specific IgG correlates with bivalent antigen binding and C1q binding strength. Front Immunol. 2020;11609941, http://doi.org/10.3389/fimmu.2020.609941
35. VanDerMeid KR, Elliott MR, Baran AM, Barr PM, Chu CC, Zent CS. Cellular cytotoxicity of next-generation CD20 monoclonal antibodies. Cancer Immunol Res. 2018;6:1150–60, http://doi.org/10.1158/2326-6066.CIR-18-0319
36. Fernández-Juárez G, Rojas-Rivera J, Logt AV, Justino J, Sevillano A, Caravaca-Fontán F, 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, http://doi.org/10.1016/j.kint.2020.10.014
37. Scolari F, Delbarba E, Santoro D, Gesualdo L, Pani A, Dallera N, et al. Rituximab or cyclophosphamide in the treatment of membranous nephropathy: the RI-CYCLO randomized trial. J Am Soc Nephrol. 2021;32:972–82, http://doi.org/10.1681/ASN.2020071091
38. Ruggenenti P, Cravedi P, Chianca A, Perna A, Ruggiero B, Gaspari F, et al. Rituximab in idiopathic membranous nephropathy. J Am Soc Nephrol. 2012;23:1416–25, http://doi.org/10.1681/ASN.2012020181
39. Ruggenenti P, Debiec H, Ruggiero B, Chianca A, Pellé T, Gaspari F, et al. Anti-phospholipase A2 receptor antibody titer predicts post-rituximab outcome of membranous nephropathy. J Am Soc Nephrol. 2015;26:2545–58, http://doi.org/10.1681/ASN.2014070640
40. Fervenza FC, Appel GB, Barbour SJ, Rovin BH, Lafayette RA, Aslam N, et al. Rituximab or cyclosporine in the treatment of membranous nephropathy. N Engl J Med. 2019;381:36–46, http://doi.org/10.1056/NEJMoa1814427
41. Cravedi P, Ruggenenti P, Sghirlanzoni MC, Remuzzi G. Titrating rituximab to circulating B cells to optimize lymphocytolytic therapy in idiopathic membranous nephropathy. Clin J Am Soc Nephrol. 2007;2:932–7, http://doi.org/10.2215/CJN.01180307
42. Guo K, Zhu H, Xu X, Huang L, Li H, Li X. Efficacy and safety of a B-cell-driven rituximab regimen for the treatment of refractory idiopathic membranous nephropathy. BMC Pharmacol Toxicol. 2025;26:131, http://doi.org/10.1186/s40360-025-00954-8
43. Teisseyre M, Destere A, Cremoni M, Zorzi K, Brglez V, Benito S, et al. Artificial intelligence-based personalised rituximab treatment protocol in membranous nephropathy (iRITUX): protocol for a multicentre randomised control trial. BMJ Open. 2025;15:e093920, http://doi.org/10.1136/bmjopen-2024-093920
44. Ahmadian E, Khatibi SMH, Vahed SZ, Ardalan M. Novel treatment options in rituximab-resistant membranous nephropathy patients. Int Immunopharmacol. 2022;107108635, http://doi.org/10.1016/j.intimp.2022.108635
45. Boyer-Suavet S, Andreani M, Lateb M, Savenkoff B, Brglez V, Benzaken S, et al. Neutralizing anti-rituximab antibodies and relapse in membranous nephropathy treated with rituximab. Front Immunol. 2020;10:3069, http://doi.org/10.3389/fimmu.2019.03069
46. Rispens T, Kuijpers TW, Killestein J, van Kempen ZLE, Bloem K. Cross-reactivity of antibodies to rituximab with other therapeutic anti-CD20 antibodies. J Immunol (Baltimore Md: 1950). 2024;212:529–33, http://doi.org/10.4049/jimmunol.2300647
47. Ferreira F, Nunes AT. New treatments in membranous glomerulopathy – from the pitfalls of rituximab to a new era of biological treatments. Port J Nephrol Hypertens. 2020;34:160–4.
48. Fogueri U, Cheungapasitporn W, Bourne D, Fervenza FC, Joy MS. Rituximab exhibits altered pharmacokinetics in patients with membranous nephropathy. Ann Pharmacother. 2019;53:357–63, http://doi.org/10.1177/1060028018803587
49. Ronco P, Beck L, Debiec H, Fervenza FC, Hou FF, Jha V, et al. Membranous nephropathy. Nat Rev Dis Primers. 2021;7:69, http://doi.org/10.1038/s41572-021-00303-z
50. Aleš Rigler A, Jerman A, Orsag A, Kojc N, Kovač D, Škoberne A, et al. Rituximab for the treatment of membranous nephropathy: a single-center experience. Clin Nephrol. 2017;88:27–31, http://doi.org/10.5414/CNP88FX07
51. Klomjit N, Fervenza FC, Zand L. Successful treatment of patients with refractory PLA_2R-associated membranous nephropathy with obinutuzumab: a report of 3 cases. Am J Kidney Dis. 2020;76:883–8, http://doi.org/10.1053/j.ajkd.2020.02.444
52. Mössner E, Brünker P, Moser S, Püntener U, Schmidt C, Herter S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. Blood. 2010;115:4393–402, http://doi.org/10.1182/blood-2009-06-225979
53. Herter S, Herting F, Mundigl O, Waldhauer I, Weinzierl T, Fauti T, et al. Preclinical activity of the type II CD20 antibody GA101 (obinutuzumab) compared with rituximab and ofatumumab in vitro and in xenograft models. Mol Cancer Therap. 2013;12:2031–42, http://doi.org/10.1158/1535-7163.MCT-12-1182
54. Alduaij W, Illidge TM. The future of anti-CD20 monoclonal antibodies: are we making progress? Blood. 2011;117:2993–3001, http://doi.org/10.1182/blood-2010-07-298356
55. Furie RA, Rovin BH, Garg JP, Santiago MB, Aroca-Martínez G, Zuta Santillán AE, et al. Efficacy and safety of obinutuzumab in active lupus nephritis. N Engl J Med. 2025;392:1471–83, http://doi.org/10.1056/NEJMoa2410965
56. 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, http://doi.org/10.1681/ASN.2017040367
57. Su X, Wu B, Tie X, Guo X, Feng R, Qiao X, et al. Obinutuzumab as initial or second-line therapy in patients with primary membranous nephropathy. Kidney Int Rep. 2024;9:2386–98, http://doi.org/10.1016/j.ekir.2024.05.004
58. Hu X, Zhang M, Xu J, Gao C, Yu X, Li X, et al. Comparison of obinutuzumab and rituximab for treating primary membranous nephropathy. Clin J Am Soc Nephrol. 2024;19:1594–602, http://doi.org/10.2215/CJN.0000000000000555

59. Xu M, Wang Y, Wu M, Chen R, Zhao W, Li M, et al. Obinutuzumab versus rituximab for the treatment of refractory primary membranous nephropathy. Nephrol Dial Transplant. 2025;40:978–86, http://doi.org/10.1093/ndt/gfae230
60. Li H, Jin L, Xie X, Sun J, Niu D, Feng J, et al. Additive obinutuzumab achieves high remission rates in rituximab-refractory membranous nephropathy. Am J Nephrol. 2025;1–9, http://doi.org/10.1159/000545995. Advance online publication.
61. Sethi S, Kumar S, Lim K, Jordan SC. Obinutuzumab is effective for the treatment of refractory membranous nephropathy. Kidney Int Rep. 2020;5:1515–8, http://doi.org/10.1016/j.ekir.2020.06.030
62. Hudson R, Rawlings C, Mon SY, Jefferis J, John GT. Treatment resistant M-type phospholipase A2 receptor associated membranous nephropathy responds to obinutuzumab: a report of two cases. BMC Nephrol. 2022;23:134, http://doi.org/10.1186/s12882-022-02761-3
63. Li XQ, Liu Y, Cai ZY, Lv TG, Hao J. Obinutuzumab is effective as an initial treatment for PLA2R-associated primary membranous nephropathy: a retrospective, single-center trial. Drug Des Dev Therapy. 2025;19:5961–72, http://doi.org/10.2147/DDDT.S527661
64. Li L, Wang S, Wei M, Zhang Q, Fang L, Fan X, et al. Observation of the efficacy and safety of obinutuzumab in the treatment of refractory idiopathic membranous nephropathy. Int Urol Nephrol. 2025;57:2603–11, http://doi.org/10.1007/s11255-025-04407-3
65. Casan JML, Wong J, Northcott MJ, Opat S. Anti-CD20 monoclonal antibodies: reviewing a revolution. Hum Vacc Immunother. 2018;14:2820–41, http://doi.org/10.1080/21645515.2018.1508624
66. Hauser SL, Kappos L, Bar-Or A, Wiendl H, Paling D, Williams M, et al. The development of ofatumumab, a fully human anti-CD20 monoclonal antibody for practical use in relapsing multiple sclerosis treatment. Neurol Therapy. 2023;12:1491–515, http://doi.org/10.1007/s40120-023-00518-0
67. Podestà MA, Ruggiero B, Remuzzi G, Ruggenenti P. Ofatumumab for multirelapsing membranous nephropathy complicated by rituximab-induced serum-sickness. BMJ Case Rep. 2020;13:e232896, http://doi.org/10.1136/bcr-2019-232896
68. Chen J, Li DT, Feng X, Zhang BR. Case Report: Subcutaneous ofatumumab for patients with immunosuppressant-dependent or ineffective primary membranous nephropathy. Front Immunol. 2025;161610530, http://doi.org/10.3389/fimmu.2025.1610530
69. Teisseyre M, Allinovi M, Audard V, Cremoni M, Belvederi G, Karamé A, et al. Obinutuzumab and ofatumumab are more effective than rituximab in the treatment of membranous nephropathy patients with anti-rituximab antibodies. Kidney Int Rep. 2024;10:753–61, http://doi.org/10.1016/j.ekir.2024.12.012
70. Hartinger JM, Kratky V, Hruskova Z, Slanar O, Tesar V. Implications of rituximab pharmacokinetic and pharmacodynamic alterations in various immune-mediated glomerulopathies and potential anti-CD20 therapy alternatives. Front Immunol. 2022;131024068, http://doi.org/10.3389/fimmu.2022.1024068
71. Morschhauser F, Marlton P, Vitolo U, Lindén O, Seymour JF, Crump M, et al. Results of a phase I/II study of ocrelizumab, a fully humanized anti-CD20 mAb, in patients with relapsed/refractory follicular lymphoma. Ann Oncol. 2010;21:1870–6, http://doi.org/10.1093/annonc/mdq027
72. Schmidt T, Schulze M, Harendza S, Hoxha E. Successful treatment of PLA_2R1-antibody positive membranous nephropathy with ocrelizumab. J Nephrol. 2021;34:603–6, http://doi.org/10.1007/s40620-020-00874-2
73. Kaegi C, Wuest B, Crowley C, Boyman O. Systematic review of safety and efficacy of second- and third-generation CD20-targeting biologics in treating immune-mediated disorders. Front Immunol. 2022;12788830, http://doi.org/10.3389/fimmu.2021.788830
74. Zong L, Wang S, Zhao K, Lv FY, Qian SK, Yang XD. Efficacy and safety of zuberitamab in the treatment of primary membranous nephropathy: an observational study. Front Immunol. 2026;16:1741564, http://doi.org/10.3389/fimmu.2025.1741564
75. Zand L, Fervenza FC. Anti-CD20 should be the first-line treatment in high-risk membranous nephropathy. Clin Kidney J. 2023;16:1420–5, http://doi.org/10.1093/ckj/sfad075
76. Ruggenenti P, Fervenza FC, Remuzzi G. Treatment of membranous nephropathy: time for a paradigm shift. Nat Rev Nephrol. 2017;13:563–79, http://doi.org/10.1038/nrneph.2017.92
77. Ronco P, Debiec H. Pathophysiological advances in membranous nephropathy: time for a shift in patient's care. Lancet (Lond Engl). 2015;385:1983–92, http://doi.org/10.1016/S0140-6736(15)60731-0
78. Smarz-Widelska I, Chojęta D, Kozioł MM. The role of anti-PLA_2R and anti-THSD7A antibodies in the pathogenesis and diagnostics of primary membranous nephropathy: a review of current knowledge for clinical practice. Int J Environ Res Public Health. 2022;19:5301, http://doi.org/10.3390/ijerph19095301
79. De Vriese AS, Glassock RJ, Nath KA, Sethi S, Fervenza FC. A proposal for a serology-based approach to membranous nephropathy. J Am Soc Nephrol. 2017;28:421–30, http://doi.org/10.1681/ASN.2016070776
80. Barbour SJ, Fervenza FC, Induruwage D, Brenchley PE, Rovin B, Hladunewich MA, et al. Anti-PLA2R antibody levels and clinical risk factors for treatment nonresponse in membranous nephropathy. Clin J Am Soc Nephrol. 2023;18:1283–93, http://doi.org/10.2215/CJN.0000000000000237
81. Pourcine F, Dahan K, Mihout F, Cachanado M, Brocheriou I, Debiec H, et al. Prognostic value of PLA2R autoimmunity detected by measurement of anti-PLA2R antibodies combined with detection of PLA2R antigen in membranous nephropathy: a single-centre study over 14 years. PLOS ONE. 2017;12:e0173201, http://doi.org/10.1371/journal.pone.0173201
82. Wu Y, Jiang H, Hu Y, Dai H, Zhao Q, Zheng Y, et al. B cell dysregulation and depletion therapy in primary membranous nephropathy: prospects and potential challenges. Int Immunopharmacol. 2024;140112769, http://doi.org/10.1016/j.intimp.2024.112769
83. Rosenzwajg M, Languille E, Debiec H, Hygino J, Dahan K, Simon T, et al. B- and T-cell subpopulations in patients with severe idiopathic membranous nephropathy may predict an early response to rituximab. Kidney Int. 2017;92:227–37, http://doi.org/10.1016/j.kint.2017.01.012
84. Liao Y, Hu H, Wan Q, Song H. The role of B lymphocyte subsets in nephrotic syndrome: functions, mechanisms, clinical significance and future perspectives. Front Immunol. 2025;161598197, http://doi.org/10.3389/fimmu.2025.1598197
85. Pozdzik A, Beukinga I, Gu-Trantien C, Willard-Gallo K, Nortier J, Pradier O. Circulating (CD3(−)CD19(+)CD20(−)IgD(−)CD27(high)CD38(high)) plasmablasts: a promising cellular biomarker for immune activity for anti-PLA2R1 related membranous nephropathy? Mediators Inflamm. 2016;20167651024, http://doi.org/10.1155/2016/7651024
86. Dahan K, Debiec H, Plaisier E, Cachanado M, Rousseau A, Wakselman L, et al. Rituximab for severe membranous nephropathy: a 6-month trial with extended follow-up. J Am Soc Nephrol. 2017;28:348–58, http://doi.org/10.1681/ASN.2016040449
87. Barmettler S, Ong MS, Farmer JR, Choi H, Walter J. Association of immunoglobulin levels, infectious risk, and mortality with rituximab and hypogammaglobulinemia. JAMA Netw Open. 2018;1:e184169, http://doi.org/10.1001/jamanetworkopen.2018.4169
88. Favi E, Morabito M. Obinutuzumab in kidney transplantation: past, present, and future. World J Transplant. 2025;15108982, http://doi.org/10.5500/wjt.v15.i4.108982
89. Sridharan K, Gopal B, Wilson S, Pham A, Hutton H. Obinutuzumab in rituximab-resistant and recurrent membranous nephropathy: a case-series. J Nephrol. 2025;38:1809–18, http://doi.org/10.1007/s40620-025-02224-6
90. Peng JJ, Ding JY, Xu Y, Shih HP, Lin YN, Wu TY, et al. Chimeric autoantibody receptor T cells clonally eliminate B cells producing autoantibodies against IFN-γ. Sci Immunol. 2025;10, http://doi.org/10.1126/sciimmunol.adm8186. eadm8186.
91. Lee J, Lundgren DK, Mao X, Manfredo-Vieira S, Nunez-Cruz S, Williams EF, et al. Antigen-specific B cell depletion for precision therapy of mucosal pemphigus vulgaris. J Clin Investig. 2020;130:6317–24, http://doi.org/10.1172/JCI138416
92. Seifert L, Riecken K, Zahner G, Hambach J, Hagenstein J, Dubberke G, et al. An antigen-specific chimeric autoantibody receptor (CAAR) NK cell strategy for the elimination of anti-PLA2R1 and anti-THSD7A antibody-secreting cells. Kidney Int. 2024;105:886–9, http://doi.org/10.1016/j.kint.2024.01.021
93. Altun B, Zhao G, Wang B, Mao X, Manfredo-Vieira S, Willis E, et al. Preclinical evaluation of antigen-specific B-cell depletion for phospholipase A2 receptor membranous nephropathy with chimeric autoantibody receptor T cells. Kidney Int. 2026;109:89–100, http://doi.org/10.1016/j.kint.2025.09.028