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REVIEW

Obinutuzumab in membranous nephropathy: a potential game-changer in treatment

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Abstract

Membranous nephropathy (MN) is a kidney disease characterized by thickening of the glomerular basement membrane due to immune complex deposition, often leading to nephrotic syndrome and potentially progressing to end-stage renal disease. Traditional treatments, including corticosteroids and immunosuppressive agents, have significant side-effects and variable efficacy. Recently, obinutuzumab, a fully humanized monoclonal antibody targeting CD20, has emerged as a promising therapeutic option for MN. Herein, we review the pathophysiology of MN, the mechanism of action of obinutuzumab, clinical data supporting its use and highlight its potential as a game changer in MN treatment.

Keywords: autoimmune kidney disease, B cell depletion, immunotherapy, membranous nephropathy, obinutuzumab, proteinuria.

Citation

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Introduction

Membranous nephropathy (MN) is an autoimmune disease characterized by the deposition of immunoglobulin G (IgG) and complement in the glomerular basement membrane and consequent kidney damage. MN is a common cause of nephrotic syndrome in adults, leading to significant morbidity and mortality if kidney failure develops without remission of proteinuria.[1,2] In recent years, the therapeutic landscape for MN has evolved considerably. Whilst rituximab has been a cornerstone in treatment, emerging evidence suggests that obinutuzumab, a type II anti-CD20 monoclonal antibody (mAb), may offer significant benefits. This review discusses the available evidence supporting obinutuzumab in MN, highlighting its potential as a game changer in this context.

The primary epitope in idiopathic MN is M-type phospholipase A2 receptor (PLA2R) along with exostosin 1; however, in recent years, several new antigens have been identified and probably others will emerge.[3] T cell dysfunction and abnormal peripheral B cells play critical roles in the pathogenesis of MN.[4] Conventional treatment is based on immunosuppressive agents to mitigate the harmful effects of glucocorticoid therapy.[5] However, these treatments have significant risks. Therefore, exploring targeted biological therapies like obinutuzumab, a full humanized mAb targeting CD20, has become crucial.[6]

Methods

Review criteria

A systematic literature search of original studies in humans was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using PubMed, Scopus and Web of Science databases (last accessed on August 2024) without restrictions on the year of publication. The search terms were "((Obinutuzumab [title/abstract]) and (membranous nephropathy [title/abstract]))". The inclusion criteria were (i) peer-reviewed publications reporting original data; (ii) English or Italian language; and (iii) access to the main data through full text or through abstract. We excluded (i) all works written in a language other than English or Italian and (ii) repeated works by the same authors.

Two independent reviewers (C.S. and D.G.) selected the studies for inclusion in this systematic review. According to the Delfi method, the titles of the studies were first screened for relevance. In case of doubt, conflict, or discussion between the two independent reviewers, the article was retained. Second, publications with titles or abstracts appearing to meet these inclusion criteria were selected for detailed review. In cases of doubt on the inclusion of an article, a decision was achieved by consensus. The reference lists of the analysed studies were also searched. These studies were subjected to the same selection procedures. A narrative review of the collected data is reported in the discussion. Because of the high heterogeneity of the studies, a meta-analysis was not performed.

Review

The results of this review emphasize the promising efficacy and safety profile of obinutuzumab in treating MN. A growing body of literature, including case reports, case series and retrospective studies, strongly supports the safety and efficacy of obinutuzumab in MN.

The PRISMA flow diagram (Figure 1) summarizes the number of studies included for analysis based on the search criteria of this systematic review. Using the search terms, a total of 13 studies were identified. One study was excluded after reading the full text; 25 studies from other sources were added. These additional studies were identified by reviewing the reference lists of relevant articles included in the systematic review as well as manual searches in related literature. The studies were included based on their relevance to the topic and the availability of the full text following the same selection criteria applied during the initial systematic review.

Review

Background of MN

MN is a major cause of nephrotic syndrome in adults characterized by the thickening of the glomerular basement membranes and sub-epithelial immune complexes.[1,2] MN can be idiopathic or secondary to conditions such as malignancies, autoimmune diseases or certain medications. Conventional treatments include angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers to reduce proteinuria and immunomodulatory approaches, including corticosteroids and immunosuppressants (such as cyclophosphamide and calcineurin inhibitors), all of which are associated with long-term toxicity.[4,5] The primary MN mechanism involves immune complex formation, predominantly IgG4, which is deposited along the glomerular basement membrane and activates complement, leading to the formation of the membrane attack complex (C5b-9). This leads to podocyte injury and proteinuria, resulting in progressive renal damage over time.[1,7] B cells produce autoantibodies forming immune complexes that activate the complement system, leading to podocyte injury. Targeting B cells to reduce autoantibody production is a logical therapeutic approach.[7–9]

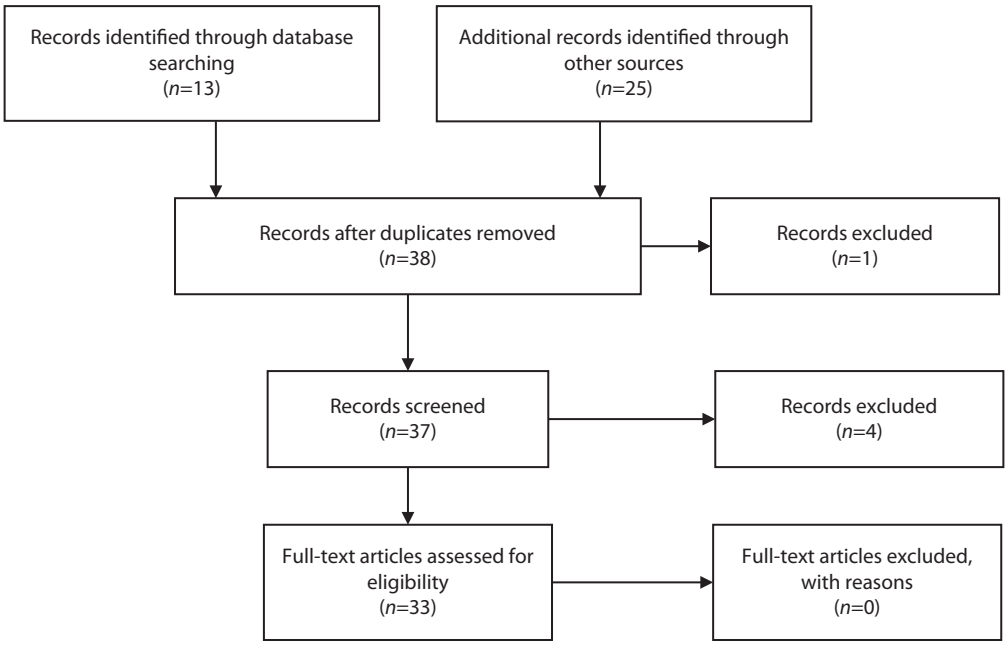
Rituximab, a type I anti-CD20 mAb, has been a pivotal development in the treatment of primary MN, demonstrating efficacy in clinical trials and offering a favourable safety profile compared to traditional immunosuppressive therapies, with overall remission rates of 80.2%, and 25.9% of patients achieving complete remission and 54.3% partial remission after 12 months of treatment.[10] Rituximab's mechanism of action primarily relies on complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC). The efficiency of these mechanisms may vary depending on each patient's immune cell composition and functionality.[4] For example, some patients with MN with refractory disease may have immune profiles that are less responsive to the CDC and ADCC pathways of rituximab, potentially leading to less effective B cell depletion and, consequently, a sub-optimal therapeutic response.

Although rituximab is a cornerstone in the treatment of MN, it is not without limitations. Approximately 20% of patients fail to achieve remission, and relapse rates can reach 40–50% in certain patient populations treated with conventional immunosuppressive regimens. These clinical limitations underscore the need for alternative therapeutic options to address gaps in efficacy and durability of response. A major drawback of rituximab is the variability in patient outcomes. Whilst many achieve remission, approximately 20–40% of patients exhibit sub-optimal responses or experience relapses following initial improvement. This variability may stem from individual differences in rituximab pharmacokinetics or its limited ability to fully deplete CD20-positive B cells in certain cases. Incomplete B cell depletion can lead to persistent immune complex deposition, ongoing proteinuria and disease progression.[1–3,5,6]

Additionally, whilst rituximab generally has a manageable safety profile, risks of infections and systemic adverse effects persist, particularly in immunocompromised patients or those with comorbidities.[7,8]. The need to balance efficacy with patient safety further limits the utility of rituximab in some MN cases, where the goal is to achieve remission without substantial immunosuppressive toxicity.

The duration of remission achieved with rituximab is also a concern. Studies such as Membranous Nephropathy

Figure 1. PRISMA flow diagram.[11]



Trial of Rituximab (MENTOR) and Rituximab or cyclophosphamide (RI-CYCLO) indicate that, whilst rituximab can sustain remission, this may not always be long-lasting, and certain patients may require repeated or adjunct therapies to maintain disease control.[12,13] The variability in long-term outcomes has highlighted a clinical need for more potent, targeted mAbs that can deliver sustained remission with fewer relapses.

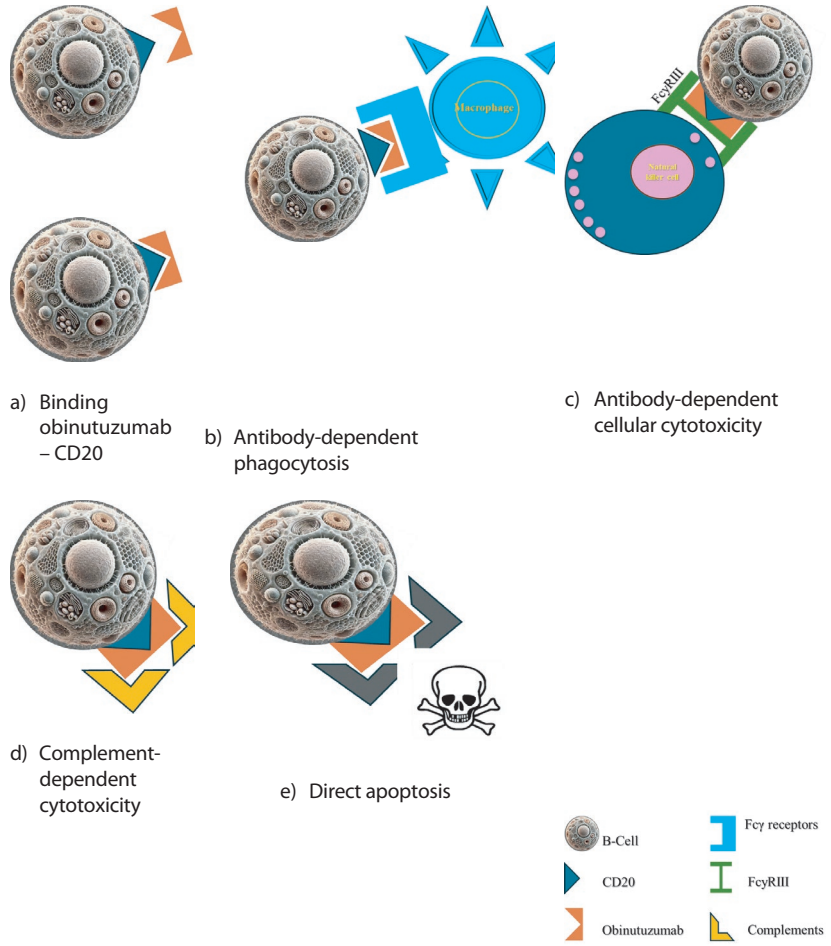
In light of these limitations, alternative molecules have been explored, amongst which obinutuzumab stands out as a promising alternative. Obinutuzumab, a type II glycoengineered anti-CD20 mAb, shows several structural modifications designed to enhance its efficacy in B cell depletion.[14] Its glycoengineered structure provides stronger affinity for FcγRIII receptors on immune effector cells, amplifying ADCC. Moreover, obinutuzumab can induce direct cell death, which can lead to a more profound and lasting B cell depletion compared to rituximab.[15] This improvement in B cell cytotoxicity could potentially overcome the response variability seen with rituximab, offering a more consistent therapeutic effect across diverse patient populations.

The unique structure and mode of action of obinutuzumab suggest that it may reduce the need for repeated dosing and the associated risk of immunosuppression-related side-effects, particularly infections and malignancies.[16,17] As evidence continues to accumulate, obinutuzumab could present a more robust and sustainable approach to MN treatment, particularly for patients who have not achieved adequate results with rituximab.

Obinutuzumab is structurally highly glycosylated. The glycoengineering process involved in its development, specifically the removal of fucose residues from the Fc region oligosaccharides of IgG, aims to enhance obinutuzumab therapeutic activity by increasing its binding affinity to the FcγRIII receptor on immune effector cells. Type I mAbs, such as rituximab, primarily rely on CDC and ADCC to achieve B cell depletion. In contrast, type II mAbs, like obinutuzumab, exhibit a distinct mechanism of action characterized by reduced CDC activity and increased direct cell death induction via lysosome-mediated pathways.

Obinutuzumab features a distinct elbow-hinge amino acid sequence, differing from type I mAbs. Combined with its unique epitope specificity, this leads to structural changes in the CD20–mAb complex on B cells, which is thought to underlie its type II biological activity. Notably, both its type II characteristics and ability to induce cell death can be modulated by alterations in this elbow-hinge region. As a result, there is improvement in CDC, ADCC and antibody-dependent phagocytosis with the glycosylated part of obinutuzumab structural design, compared to rituximab. Interactions with FcγRIIb, especially with natural killer cells, have been excluded and are labelled by two additional changes in the hinge domain and C2 region, which are indispensable for its enhanced effect[14,15,18] (Figure 2).

Figure 2. Mechanism of action of Obinutuzumab.



Obinutuzumab recognizes CD20 and has a modified elbow-hinge amino acid sequence (substitution of leucine by valine) compared to type 1 agents, resulting in spatial alterations to the CD20-mAb assembly complex on B cells (Panel a). De-fucosylation of the Fc region enhances its binding affinity to the FcγRIII receptor, leading to increased direct cell death induction and enhanced antibody-dependent phagocytosis (b) and antibody-dependent cellular cytotoxicity (c). Moreover, after binding CD20, obinutuzumab can activate complement-dependent cytotoxicity (d) and provide direct cellular apoptosis (e).

Clinical studies and efficacy

As detailed in Table 1, recent advancements in the treatment and understanding of MN have been well-documented through various research studies. There have been promising developments in the treatment of primary MN in clinical trials over the past years. Historically, the primary approach has involved the use of steroids combined with alkylating agents, a regimen known as the modified Ponticelli regimen, or the use of calcineurin inhibitors.[1] However, recent advancements in understanding the pathophysiology of MN, particularly the identification of auto-antibodies against PLA2R, have paved the way for novel therapeutic approaches.

One of the most significant changes is the use of mAbs targeting CD20 on B-lymphocytes, specifically rituximab and obinutuzumab. The MENTOR randomized controlled trial in 2019 demonstrated that rituximab was non-inferior to cyclosporine in achieving complete or partial remission of proteinuria and was superior in maintaining remission over a 24-month period.[19] This finding marked a crucial step forward, providing evidence for rituximab as a viable alternative to traditional therapies.[19] Additionally, the RI-CYCLO pilot study, presented at the American Society of Nephrology national congress in 2020, suggested comparable efficacy between rituximab and cyclophosphamide in inducing remission of proteinuria.[12]

Table 1. Clinical studies on membranous nephropathy.

Author	Drug dosage	Follow-up times	Previous treatment history	Safety concerns
Waldman et al. (Unpublished)[20]	Rituximab: 375 mg/m², cyclosporine: 3 mg/kg/day	12 months	Previous immunosuppressive treatments	Infection risk, hepatic side-effects
Zhang et al. (Unpublished)[29]	Obinutuzumab: 1 g every 3 weeks	24 months	Rituximab, failure with cyclosporine	Infusion reactions, moderate neutropenia
Mario Negri Institute (Unpublished)[34]	Obinutuzumab: 1 g every 3 weeks	18 months	Failed with rituximab, corticosteroids and other immunosuppressants	Mild infections, manageable infusion reactions
Hoffmann-La Roche (Unpublished)[31]	Obinutuzumab: 1,000 mg every 3 weeks	36 months	Rituximab and tacrolimus	Monitoring for malignancies, infusion reaction management
University of Queensland (Unpublished)[32]	Obinutuzumab: 1 g every 4 weeks	24 months	Tacrolimus, cyclosporine	Neutropenia, long-term infection risk
Su et al. (2024)[28]	Obinutuzumab: 1 g every 3 weeks	12 months	No previous immunosuppressive treatment	Infusion reactions, no severe events
Zhang et al. (2024)[23]	Obinutuzumab: 1 g, single dose	6 months	Ineffective with rituximab	Mild reactions, no severe adverse events
Hao et al. (2024)[8]	Obinutuzumab: 1 g every 3 weeks	12 months	No prior treatment	Infusion reactions, no severe events
Conversano et al. (2024)[9]	Obinutuzumab: 1 g, single dose	6 months	Ineffective with rituximab	Mild reactions, no severe adverse events
Caravaca-Fontán et al. (2023)[18]	Obinutuzumab: 1 g every 3 weeks	18 months	Rituximab and corticosteroids	Moderate infections, temporary neutropenia
Naik et al. (2023)[7]	1 g every 4 weeks	24 months	Cyclosporine, prednisone	Infection and infusion reaction risk
Deng et al. (2023)[15]	Obinutuzumab: 1 g every 3 weeks	12 months	Cyclosporine and tacrolimus	Monitoring for infectious and safety events
Davies et al. (2022)[14]	1000 mg every 3 weeks	18 months	Rituximab and corticosteroids	Infusion-related events, infection risk
Kaegi et al. (2022)[16]	1 g every 4 weeks	12 months	Cyclosporine, tacrolimus, rituximab	Infection risk and neutropenia
Hartinger et al. (2022)[22]	Rituximab: 375 mg/m²	6 months	Ineffective with rituximab	Mild reactions, infection risk
Hudson et al. (2022)[17]	Obinutuzumab: 1 g, single dose	12 months	Ineffective with rituximab	Mild reactions
Ginthör et al. (2021)[27]	Obinutuzumab: 1 g every 3 weeks	12 months	Ineffective with rituximab, steroids	Mild neutropenia, infection risk
Scolari et al. (2021)[12]	Rituximab: 375 mg/m²	24 months	Rituximab and tacrolimus	Infection monitoring, infusion reactions
Sethi et al. (2020)[25]	Obinutuzumab: 1 g every 3 weeks	18 months	Ineffective with rituximab	Neutropenia and infection risk
Klomjit et al. (2020)[24]	Obinutuzumab: 1 g, single dose	12 months	Ineffective with rituximab	Infusion reactions, moderate infection risk

(*Continued*)

Table 1. (Continued)

Author	Drug dosage	Follow-up times	Previous treatment history	Safety concerns
Salvadori et al. (2020)[19]	Rituximab: 375 mg/m², cyclosporine: 3 mg/kg/day	12 months	Rituximab and steroids	Infection risk, hepatic toxicity
Fernández-Juárez et al. (2021)[13]	Rituximab: 375 mg/m², tacrolimus: 5 mg/kg/day	24 months	Rituximab and steroids	Renal toxicity risk
Nasser et al. (2020)[21]	Rituximab: 375 mg/m², cyclosporine: 3 mg/kg/day	18 months	Ineffective with Ponticelli regimen	Infection risk, hepatic toxicity
Fervenza et al. (2019)[2]	Rituximab: 375 mg/m², cyclosporine: 3 mg/kg/day	24 months	Rituximab and cyclosporine	Mild infections, infusion reactions
Cosio et al. (2017)[26]	Rituximab: 375 mg/m²	6 months	None indicated	Mild risk of infusion reactions
Cattran et al (2017)[4]	Rituximab: 375 mg/m²	12 months	Corticosteroids	Infection and infusion reactions
Beck LH et al. (2014)[5]	Rituximab: 375 mg/m²	18 months	Cyclosporine, previous failed treatments	Infection and adverse immune response risks
Ponticelli et al. (2014)[1]	Obinutuzumab: 1 g every 4 weeks	24 months	Prednisone, calcineurin inhibitors	Immunosuppression-related infections

Contrastingly, the STARMEN trial yielded less favourable results for the combination of rituximab and tacrolimus when compared to the modified Ponticelli regimen.[13] Despite this, the exploration of rituximab's role continues, as evidenced by the ongoing clinical trial NCT00977977, which aims to evaluate the safety and efficacy of combining rituximab with cyclosporine in patients with MN.[20,21] The variability in patient response to rituximab, with up to 40% not responding to treatment, has driven interest towards obinutuzumab as a potential alternative, particularly for refractory cases. Table 2 presents principal studies about historical treatment of MN.

Obinutuzumab has shown promising efficacy in achieving proteinuria remission in small case series. However, direct comparisons with cyclophosphamide and corticosteroids are not available and more rigorous trials are needed to confirm its superiority.

Its targeted mechanism enables effective B cell depletion with a lower risk of systemic immunosuppression, reducing adverse effects such as infections and malignancies.[16,22,23] Moreover, obinutuzumab safety profile in patients with MN is favourable. Common adverse effects include mild and manageable infusion-related reactions, which can be easily prevented or mitigated with premedication, including steroids, antipyretics and antihistamines. Long-term safety data are still being collected but early results suggest a lower incidence of severe infections and malignancies compared to conventional immunosuppressive regimens.[18,24]

Obinutuzumab has shown promise in small-scale studies and exhibits excellent B-cell cytotoxic profiles in treating B cell malignancies, though larger trials are necessary to confirm its efficacy in MN.[24,25] Below is a detailed listing of the clinical studies involving obinutuzumab, organized for clarity.

Completed studies: evidence on obinutuzumab

A recent retrospective study conducted at the Second Hospital of Shanxi Medical University evaluated the efficacy and safety of obinutuzumab in 59 patients with primary MN. This study cohort included patients who received obinutuzumab either as an initial therapy or as a second-line therapy following prior immunosuppressive treatments. The study demonstrated that 90% of patients in the initial therapy group and 82.1% in the second-line therapy group achieved either complete or partial remission of proteinuria. Moreover, the study observed significant reductions in anti-PLA2R antibody levels, with 89.6% of patients with PLA2R-related MN showing marked improvements. Importantly, obinutuzumab was well tolerated, with no serious adverse events reported, and the most

Table 2. Historical treatment in membranous nephropathy.

Trial/study	Treatment regimen	Outcome	Key findings
Ponticelli regimen, 2014[1]	Steroids + alkylating agents	Remission of proteinuria	Cornerstone of membranous nephropathy treatment for decades
STARMEN Trial, 2021[13]	Rituximab + tacrolimus	Less favourable compared to Ponticelli	Alternative approaches to traditional therapy
MENTOR Trial, 2019[2]	Rituximab *versus* cyclosporine	Rituximab superior in maintaining remission	Established rituximab as a viable option
RI-CYCLO Study, 2021[12]	Rituximab *versus* cyclophosphamide	Comparable efficacy	Rituximab considered a safer alternative

common side-effects were mild infusion-related reactions and neutropenia.[26,27] These findings suggest that obinutuzumab could be a highly effective and safe treatment option, even when used as an initial therapy. The promising results observed in patients resistant to rituximab further indicate that obinutuzumab may serve as a valuable therapeutic alternative in challenging cases.[28]

Additional evidence comes from case reports and small case series. Hudson et al. reported two cases of M-type PLA2R-associated MN resistant to standard therapies, including rituximab, successfully treated with obinutuzumab; both patients achieved significant proteinuria reduction and demonstrated clinical remission without severe adverse events.[17] Similarly, Conversano et al. described a paediatric case of semaphorin 3b-associated MN, refractory to rituximab, that responded well to obinutuzumab; the child achieved remission with no significant side-effects, showcasing the drug's potential even in unique paediatric presentations.[9]

Klomjit et al. presented a series of three patients with PLA2R-associated MN unresponsive to conventional treatments.[24] These patients showed an average reduction in proteinuria of 60% within 12 weeks after initiating obinutuzumab therapy. This small cohort also highlighted the manageable safety profile of the drug, with adverse effects limited to mild infusion-related reactions.

Hao et al. conducted an observational case series on patients with untreated primary MN managed with obinutuzumab; the study demonstrated promising outcomes, with significant improvements in proteinuria and minimal adverse events.[8]

Ongoing studies: future perspectives

A Chinese still unpublished observational trial (NCT05845762) reports 30 patients receiving obinutuzumab as second-line therapy in idiopathic MN who have failed glucocorticoid therapy combined with cyclophosphamide or other immunosuppressive agents or rituximab or have recurrent relapses.[29] An ongoing trial (NCT05050214), estimated to be completed in 2025, is evaluating obinutuzumab efficacy and safety in 20 patients with rituximab-resistance, rituximab-dependence or rituximab-intolerance in the context of primary MN.[30] Another ongoing trial (NCT04629248) started enrolment in 2021 and is scheduled to be completed in 2027, and aims to compare obinutuzumab *versus* tacrolimus, exploring its potential as a first-line therapeutic option in naive patients.[31] A new international multi-centre, prospective, randomized, open-label, parallel-group trial (NCT06120673), scheduled to start enrolment this year, will randomize patients to receive either corticosteroid and cyclophosphamide (standard Ponticelli protocol) or obinutuzumab.[32]

These ongoing studies represent a significant shift in the treatment landscape for MN, potentially providing alternatives to the Ponticelli regimen, which has been the cornerstone of first-line therapy for over three decades. The development of these new therapies is particularly important given the toxicity and administration challenges associated with alkylating agents, highlighting the need for more manageable and effective treatment options.

Table 3 provides an overview of these ongoing studies, detailing their objectives and expected outcomes.

Indications, efficacy, administration and risk assessment of obinutuzumab in MN

Refractory MN is defined as the failure to achieve partial or complete remission of proteinuria despite adequate treatment with standard first-line therapies such as corticosteroids, calcineurin inhibitors or rituximab. This condition is often associated with persistent nephrotic syndrome, elevated anti-PLA2R antibody levels

Table 3. Ongoing studies with obinutuzumab in membranous nephropathy.

Trial ID	Condition	Study design	Key objective	Estimated completion
NCT04629248	Membranous nephropathy	Randomized, open label	Compare obinutuzumab *versus* tacrolimus	2027
NCT05050214	Primary membranous nephropathy: in patients with rituximab-resistant or rituximab-dependent nephrotic syndrome and in patients intolerant to rituximab	Open label	Efficacy of obinutuzumab in rituximab-resistant disease	2025
NCT05845762	Idiopathic membranous nephropathy	Observational	Obinutuzumab as second-line therapy	Unpublished
NCT06120673	Membranous nephropathy	Randomized, parallel group	Obinutuzumab *versus* Ponticelli protocol	2028

or progressive renal impairment. Recent evidence suggests that obinutuzumab may be particularly beneficial for patients with rituximab resistance or dependence, frequent relapses, or aggressive disease phenotypes characterized by high baseline PLA2R titres. Its indications extend to second-line therapy for patients unresponsive to rituximab or intolerant due to adverse reactions, and ongoing trials are investigating its potential as a first-line treatment in naive MN patients. The drug's glycoengineered structure, designed for enhanced B cell depletion, supports a more complete and durable therapeutic response compared to rituximab, potentially reducing relapse rates. However, careful risk assessment remains essential, with a focus on monitoring for infections, managing infusion-related reactions with premedication, and ensuring long-term safety through surveillance for immunosuppression-related complications. Preliminary data indicate a favourable relationship between obinutuzumab dosing and efficacy, with regimens of 1 g every 3 weeks demonstrating significant proteinuria remission and reductions in anti-PLA2R antibodies. Whilst comparative studies are still ongoing, early findings suggest that obinutuzumab may offer advantages over rituximab in achieving sustained remission and minimizing relapses, positioning it as a promising alternative for refractory or relapsing MN cases.

Obinutuzumab is administered following a specific protocol, with an initial cycle that includes three doses within the first 28 days: a split dose (100 mg administered initially and 900 mg subsequently on the following day), followed by two full doses of 1,000 mg on days 8 and 15. Subsequent cycles, repeated every 28 days for up to six cycles, involve a single 1,000 mg dose on day 1.[33,34] The infusion protocol requires a gradual increase in infusion rate, starting at 50 mL/h and progressively increasing to a maximum of 200 mL/h, with continuous monitoring of blood pressure, heart rate and oxygen saturation. Premedication is essential to reducing the risk of infusion-related reactions and includes chlorphenamine (10 mg), hydrocortisone (200 mg), paracetamol (1,000 mg) and ranitidine (100 mg).[3] The most common adverse reactions include neutropenia, moderate infections and infusion-related reactions such as fever, chills, nausea and headache, which are generally well managed with premedication. More severe events, though rare, include serious infections and a potential increased risk of malignancies.[6] These characteristics underscore the importance of close monitoring during and after treatment to ensure an optimal balance between therapeutic efficacy and safety.

Another protocol, the MAJESTY protocol, involves a total dose of 4,000 mg of obinutuzumab administered over 6.5 months, with four infusions at weeks 0, 2, 24 and 26. This regimen emphasizes a gradual infusion rate and comprehensive premedication to minimize infusion-related reactions, ensuring both safety and efficacy in B cell depletion.[31]

A detailed summary of the dosing and premedication protocols is presented in Table 4.

Future directions

Whilst the current evidence base for obinutuzumab in MN is promising, ongoing trials will be crucial to determine its future role in clinical practice. As more data become available, obinutuzumab may establish itself as a cornerstone therapy in the management of MN, offering hope for improved treatment outcomes and reduced treatment-related toxicity. Despite its therapeutic potential, the existing evidence and research on the use of obinutuzumab

Table 4. Summary of obinutuzumab administration protocol and premedication steps.

Protocol 1 (from the ORION Study)[30]

Total dose: 3000 mg; duration: 1 month

Time	Dose	Dilution	Infusion rate
Day 1	100 mg	NaCl 0.9% 100 mL	25 mg/h for 4 hours
Day 2	900 mg	NaCl 0.9% 250 mL	Start at 50 mg/h and increase by 50 mg/h every 30 minutes to a maximum rate of 400 mg/h
Day 15	1000 mg	NaCl 0.9% 250 mL	Start at 100 mg/h and increase by 100 mg/h every 30 minutes to a maximum rate of 400 mg/h
Day 29	1000 mg	NaCl 0.9% 250 mL	Start at 100 mg/h and increase by 100 mg/h every 30 minutes to a maximum rate of 400 mg/h

Premedication

30–60 minutes prior to the obinutuzumab infusion:

1. Methylprednisolone: 80 mg IV
2. Acetaminophen or paracetamol: 650–1000 mg PO or IV
3. Diphenhydramine 50 mg (or equivalent dose of a similar agent) PO or IV

Cautions: Continuous monitoring of blood pressure, heart rate and oxygen saturation

Protocol 2 (from MAJESTY and REMIT Studies)[31,32]

Total dose: 4000 mg; duration: 6.5 months

Time	Dose	Dilution	Infusion rate
Week 0	1000 mg	NaCl 0.9% 250 mL	Start at 50 mg/h and escalate in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h
Week 2	1000 mg	NaCl 0.9% 250 mL	Start at 50 mg/h and escalate in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h
Week 24	1000 mg	NaCl 0.9% 250 mL	Start at 50 mg/h and escalate in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h
Week 26	1000 mg	NaCl 0.9% 250 mL	Start at 50 mg/h and escalate in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h

Premedication

30–60 minutes prior to the obinutuzumab infusion:

1. Methylprednisolone: 80 mg IV
2. Acetaminophen or paracetamol: 650–1000 mg PO or IV
3. Diphenhydramine 50 mg (or equivalent dose of a similar agent) PO or IV

Cautions: Continuous monitoring of blood pressure, heart rate and oxygen saturation

in MN face several challenges. First, the rarity of the disease poses an obstacle to collecting adequate cohorts for clinical trials in MN; thus, many physicians would have limited experience in diagnosing, evaluating and managing the disease. Moreover, due to the relatively small number of kidney biopsies performed at each centre, it often takes a long time to collect sufficient and representative data for retrospective experiences.

Further research is needed to establish obinutuzumab long-term efficacy and safety in MN. Ongoing studies are exploring its use in combination with other therapies and in different disease stages. Additionally, biomarkers predicting response to obinutuzumab could help personalize treatment and improve outcomes as indicators of biological processes, states or conditions, and can be used to predict how well a patient will respond to a specific treatment. In the context of obinutuzumab therapy for MN, potential biomarkers could include (i) anti-PLA2R antibody levels: serum anti-PLA2R antibodies might provide a valuable staging tool for predicting remission duration, facilitating ongoing consent and protocol tailoring for many

patients treated early in the course. Monitoring these levels before and during treatment with obinutuzumab could provide insights into the likelihood of a positive therapeutic response. Patients with higher baseline levels of these antibodies may show a more pronounced decline after treatment, indicating a favourable response.[24] (ii) B cell subsets and activity: the composition and activity of B cell subsets can influence the efficacy of obinutuzumab. Assessment of these parameters before treatment may help predict which patients are more likely to benefit from B cell depletion. For instance, patients with a higher proportion of CD20-positive B cells may respond better to obinutuzumab.[17,22,35]

Obinutuzumab represents a significant advancement in MN treatment. Its targeted mechanism provides effective B cell depletion with a favourable safety profile, addressing many of the limitations of traditional immunosuppressive therapies. As clinical evidence continues to accumulate, obinutuzumab has the potential to become a cornerstone in MN management, improving patient outcomes and quality of life.

Conclusion

The recent advancements in understanding and treating MN through novel therapies, such as rituximab and obinutuzumab, herald a new era of treatment possibilities. The outcomes of the ongoing trials will be crucial in determining the future standard of care for this condition and provide hope for improved patient outcomes and reduced treatment-related toxicity. Incorporating obinutuzumab into the treatment paradigm for MN addresses critical gaps in managing refractory cases, identifying patients most likely to benefit, and optimizing efficacy whilst minimizing risks. Ongoing studies are essential to clarify its role in the therapeutic hierarchy and establish standardized protocols for its use.

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