Am J Transl Res 2026;18(6):4777-4790
www.ajtr.org /ISSN:1943-8141/AJTR0171918

Original Article

Clinical effect of obinutuzumab in the treatment of idiopathic membranous nephropathy

Shaoxiong Ning[1], Qian Zhang[1], Zhixing Shang[2], Hongting Liu[1]

[1]Department of Nephrology, Yuncheng Central Hospital, Yuncheng 044000, Shanxi, China; [2]Department of Cardiology, Yuncheng Central Hospital, Yuncheng 044000, Shanxi, China

Received February 6, 2026; Accepted May 6, 2026; Epub June 15, 2026; Published June 30, 2026

Abstract: Objectives: This study aimed to evaluate the clinical efficacy and safety of obinutuzumab (OBZ) in patients with Idiopathic membranous nephropathy (IMN), comparing outcomes between treatment-naïve and previously treated individuals. Methods: This was a single-center, retrospective cohort study involving 163 adult IMN patients who received at least one cycle of OBZ between January 2020 and December 2023. Participants were stratified into an Initial Therapy group (first-line OBZ, n=51) and a Non-Initial Therapy group (prior immunosuppressive treatment failure, n=112). Key data assessed at baseline, 1, 3, 6, and 12 months included: 24-hour urinary protein excretion (UPE), serum albumin, estimated glomerular filtration rate (eGFR), serum anti-phospholipase A2 receptor antibody (anti-PLA2R) titer, peripheral B-cell counts, and treatment-related adverse events. Results: Among 163 enrolled patients, clinical remission rates at 3 months were significantly higher in the Initial Therapy group (54.90% vs. 37.50%, P=0.037), though rates converged by 12 months (90.20% vs. 82.14%, P=0.186). The Initial Therapy group showed greater reductions in UPE (e.g., 1.42 vs. 2.47 g/24 h at 12 months, P<0.001) and greater increases in serum albumin (41.23 vs. 37.84 g/L at 12 months, P<0.001). Anti-PLA2R titers declined more rapidly in the Initial Therapy group (8.27 vs. 24.86 RU/mL at 12 months, P<0.001). Safety profiles were similar between groups. Conclusion: OBZ is an effective and well-tolerated treatment for IMN, with an earlier initiation associated with faster clinical and serological response.

Keywords: Obinutuzumab, idiopathic membranous nephropathy, B-cell depletion therapy, anti-PLA2R antibody, clinical remission

Introduction

Idiopathic membranous nephropathy (IMN) represents the most common pathologic cause of nephrotic syndrome in non-diabetic adults, constituting a significant burden of primary glomerular disease worldwide [1]. Its global incidence is estimated at 1 to 2 cases per 100,000 person-years, with a notably higher and increasing prevalence observed in Asian populations, particularly in China where it now accounts for a substantial proportion of glomerular diseases [2]. This immune-mediated disorder is fundamentally characterized by the deposition of antigen-antibody complexes along the subepithelial side of the glomerular basement membrane, leading to complement activation, podocyte injury, and consequent proteinuria [1]. The identification of specific podocyte antigens, primarily the M-type phospholipase A2 receptor (PLA2R) and thrombospondin type-1 domain-containing 7A (THSD7A), has revolutionized the understanding of IMN as an organ-specific autoimmune condition, providing crucial diagnostic and prognostic biomarkers [3, 4].

The pathogenesis of IMN is intrinsically linked to B-cell dysregulation, as these lymphocytes are responsible for generating the pathogenic autoantibodies, predominantly of the IgG4 subclass, that target antigens like PLA2R [3, 4]. The clinical course of IMN is highly variable; while approximately one-third of patients may experience spontaneous remission, another third risk progressive renal decline towards end-stage renal disease (ESRD) over a decade if left untreated. This shows the necessity for effective therapeutic intervention [4, 5]. Current management strategies, as per guidelines, involve supportive care for all patients and immunosuppressive therapy for those at high risk of progression [4]. Traditional immunosup-

https://doi.org/10.62347/HHHF9971

pressive regimens, including corticosteroids combined with alkylating agents or calcineurin inhibitors, though effective in many cases, are often limited by suboptimal efficacy, significant toxicity profiles, and high relapse rates [6].

The central role of B cells in IMN pathophysiology logically positions B-cell depletion as a targeted therapeutic strategy. The anti-CD20 monoclonal antibody rituximab has emerged as a cornerstone in this approach, demonstrating efficacy and securing a recommendation in contemporary treatment guidelines [7]. However, clinical experience reveals substantial limitations: rituximab fails to induce remission in a considerable proportion of patients (up to 40%), and its mechanism may be inadequate due to incomplete depletion of autoreactive B-cell clones or its inability to target antibody-producing plasma cells that do not express CD20 [8]. Furthermore, variable pharmacokinetics and potential immunogenicity can compromise its effectiveness, highlighting a clear unmet need for more potent and reliable B-cell-targeted therapies in IMN [9].

Obinutuzumab is a novel, humanized, glycoengineered type II anti-CD20 monoclonal antibody designed to overcome the limitations of earlier agents like rituximab [10]. Its distinct mechanism of action includes enhanced antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis (ADCP), as well as a superior capacity to induce direct, non-apoptotic B-cell death, while exhibiting reduced complement-dependent cytotoxicity [11-13]. Preclinical models have consistently shown obinutuzumab to be more effective than rituximab in depleting B cells and controlling disease [13]. This enhanced biologic activity has translated into clinical success in B-cell malignancies and shows promising signals in autoimmune conditions like lupus nephritis, providing a strong rationale for its investigation in IMN [14]. Therefore, evaluating the clinical effect of obinutuzumab, both in treatment-naïve patients and in those refractory to prior therapies, is a critical step towards improving the outcome of this challenging glomerulopathy.

Materials and methods

Research design and study participants

This was a single-center, retrospective, observational cohort study conducted at the Department of Nephrology, Yuncheng Central Hospital, China. The primary objective was to evaluate the clinical efficacy and safety of obinutuzumab in the treatment of adult patients with IMN. The study retrospectively enrolled a total of 163 patients who received at least one cycle of obinutuzumab between January 2020 and December 2023. All included patients were aged 18 years or older and had a confirmed diagnosis of IMN, established either by renal biopsy demonstrating characteristic findings of membranous nephropathy or by a persistently positive serum anti-phospholipase A2 receptor (anti-PLA2R) antibody titer (>20 RU/mL) in the appropriate clinical context, in accordance with current diagnostic guidelines. Secondary causes of membranous nephropathy, such as systemic lupus erythematosus, viral infections (hepatitis B/C, HIV), solid tumors, or exposure to specific drugs or toxins, were rigorously excluded through comprehensive clinical, serological, and radiologic evaluations at the time of initial diagnosis and prior to obinutuzumab initiation.

Patients were categorized into two distinct groups based on their treatment history at the time of initiating obinutuzumab. The “Initial Therapy Group” comprised patients who received obinutuzumab as the first-line immunosuppressive regimen for IMN, having not been previously treated with corticosteroids, alkylating agents, calcineurin inhibitors, or other B-cell depleting agents like rituximab for their nephropathy. The “Non-Initial Therapy Group” included patients who received obinutuzumab after failing to achieve an adequate clinical response (defined as persistent nephrotic-range proteinuria or failure to attain partial/complete remission) or experiencing intolerance to at least one prior line of standard immunosuppressive therapy, which could include corticosteroids, cyclophosphamide, calcineurin inhibitors, or rituximab. The minimum follow-up period after the first obinutuzumab infusion was set at 6 months for inclusion in the final analysis to allow for meaningful assessment of treatment response. Key exclusion criteria were: 1) a known history of severe hypersensitivity to obinutuzumab or any of its excipients; 2) presence of severe, uncontrolled concurrent medical conditions including advanced heart failure (NYHA Class III/IV), decompensated liver cirrhosis, or end-stage renal disease (ESRD) requiring renal replacement therapy

prior to obinutuzumab initiation; 3) active severe infection requiring intravenous antimicrobial therapy at the time of treatment initiation; 4) pregnancy or breastfeeding; and 5) documented evidence of significant non-adherence to clinical follow-up, resulting in incomplete essential data for analysis. As this was a retrospective study, the requirement for written informed consent for data analysis was waived by the Institutional Review Board. However, all patients had provided general informed consent for treatment at the time of hospital admission.

Treatment grouping and therapeutic protocol

The 163 patients with IMN was stratified into two distinct groups based on their prior treatment history at the time of initiating obinutuzumab. This stratification resulted in 51 patients receiving obinutuzumab as the Initial Therapy, meaning it was their first-line immunosuppressive agent for IMN, with no prior exposure to corticosteroids, alkylating agents, calcineurin inhibitors, or rituximab for this condition. The remaining 112 patients constituted the Non-Initial Therapy group. These patients were switched to obinutuzumab after demonstrating an inadequate response (defined as persistent nephrotic-range proteinuria or failure to achieve at least partial remission) or intolerance to at least one prior conventional immunosuppressive regimen, which included therapies such as corticosteroids combined with cyclophosphamide, calcineurin inhibitors (tacrolimus or cyclosporine), or the anti-CD20 monoclonal antibody rituximab [15].

All patients received obinutuzumab treatment during a planned hospitalization to ensure close monitoring. The administered therapeutic protocol was consistent across both groups. Each infusion consisted of a fixed dose of 1000 mg of Obinutuzumab (Roche Diagnostics GmbH, Germany, Approval No. SJ20210018). The standard cycle involved two infusions: the first dose was followed by a second 1000 mg dose administered two weeks later. For intravenous administration, the 1000 mg dose was reconstituted and diluted in 500 mL of 0.9% normal saline solution. To mitigate the risk of infusion-related reactions, a standardized premedication regimen was administered approximately 30-60 minutes prior to each obinutuzumab infusion. This regimen included intravenous dexamethasone (20 mg; Chensin Pharmaceutical Co., Ltd., China, Approval No. H37021969), oral ibuprofen suspension (10 ml; Wuhan Renfu Pharmaceutical Co., Ltd., China, Approval No. H10980021), and intramuscular diphenhydramine (40 mg; Guangzhou Baiyunshan Mingxing Pharmaceutical Co., Ltd., China, Approval No. H44022387). The infusion itself was initiated cautiously at a rate of 10 mL per hour. Starting 30 minutes after the infusion commencement and in the absence of adverse reactions, the infusion rate was gradually increased by 30 mL per hour every 30 minutes, up to a maximum permissible rate of 150 mL per hour, as tolerated by the patient. Vital signs were monitored closely throughout the infusion period and for at least one hour post-completion. Concomitant supportive medications, including angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers for antiproteinuric effect, were optimized according to standard clinical practice.

Data collection and outcome assessment

Clinical and laboratory data were systematically extracted from the electronic medical record (EMR) system of Yuncheng Central Hospital. Data collection spanned from baseline (prior to the first obinutuzumab infusion) through follow-up visits at 1 months, 3 months, 6 months, and 12 months post-treatment. The primary efficacy outcome was the rate of clinical remission (complete remission [CR] + partial remission [PR]) at 3, 6, and 12 months. Secondary outcomes included changes in 24-hour urinary protein excretion (UPE), serum albumin, estimated glomerular filtration rate (eGFR), serum anti-phospholipase A2 receptor (anti-PLA2R) antibody titer, peripheral B-cell counts, and the incidence of treatment-related adverse events.

Assessment of clinical and biochemical parameters: Routine clinical and biochemical data were measured using standard laboratory techniques. Twenty-four-hour urine collections were performed for the quantification of total urinary protein (UPE). Serum albumin, creatinine, and immunoglobulin (IgG, IgA, IgM) levels were analyzed using a Beckman Coulter AU5800 automatic biochemical analyzer (Beckman Coulter, USA) with the manufacturer's original reagents. Serum creatinine was used to calculate the estimated glomerular filtration rate (eGFR) by

the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [16].

Measurement of serum anti-PLA2R antibody titer: The serum anti-PLA2R antibody titers were detected using commercial ELISA kits (Beckman Coulter, USA; cat. no. ab211573) in strict accordance with the manufacturer's instructions. The assay's reported measurement range is 2-1500 RU/mL. Samples exceeding the upper limit were re-analyzed after appropriate dilution. According to the kit's specifications and established diagnostic criteria, a titer ≥20 RU/mL was considered positive. The intra-assay and inter-assay coefficients of variation for this kit, as per the manufacturer, are <8% and <10%, respectively, ensuring the reliability of the measurements. Immunological remission was designated if anti-PLA2R antibody titer was less than 20 RU/mL. Complete immunological remission was defined as: anti-PLA2R antibody titer less than 2 RU/mL [17, 18].

Evaluation of lymphocyte subsets and B-cell depletion: Peripheral blood lymphocyte subsets were quantified by flow cytometry to monitor the pharmacodynamic effect of obinutuzumab, with a primary focus on B-cell depletion. Blood samples collected in EDTA tubes were analyzed using a BD FACSCanto II flow cytometer (Becton, Dickinson and Company, USA). For the assessment of B cells, samples were stained with a fluorescently conjugated anti-human CD19 monoclonal antibody (BD Biosciences, USA; catalog no. 340951). The absolute count of CD19+ B cells (cells/μL) was determined. B-cell depletion was defined as a CD19+ B-cell count <5 cells/μL, and this binary outcome is reported as the proportion of patients achieving depletion at each time point. Baseline counts of T cells (CD3+) and natural killer (NK) cells (CD16+/CD56+) were also measured at study entry using a standardized multicolor panel (BD Multitest 6-color TBNK reagent, BD Biosciences, USA; catalog no. 644611) for comprehensive patient characterization.

Definition of treatment response and safety monitoring: Clinical response was categorized according to established criteria. Complete remission (CR) was defined as UPE <0.3 g/24 h with serum albumin ≥35 g/L and stable renal function (eGFR decline <25% from baseline). Partial remission (PR) was defined as UPE <3.5 g/24 h with a ≥50% reduction from baseline, accompanied by improved or normal serum albumin and stable renal function [19]. Patients not meeting these criteria were classified as non-responders. Relapse was defined as recurrence of proteinuria ≥3.5 g/24 h after achieving CR or PR. Safety was assessed by actively recording all adverse events during infusion and throughout the follow-up period, including infusion-related reactions, infections, hematologic toxicity, and other clinically significant events, graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [20].

Ethical considerations

This retrospective study adhered to the Declaration of Helsinki. Due to the retrospective nature of the study and the use of anonymized data extracted from electronic medical records, the requirement for written informed consent for data analysis was waived by the Institutional Review Board (IRB) of Yuncheng Central Hospital. The study protocol and the consent waiver were reviewed and approved by the IRB of Yuncheng Central Hospital prior to data collection. Data from electronic medical records were anonymized and de-identified before analysis.

Statistical analyses

All statistical analyses were performed using R language (version 4.2.1). Continuous variables were tested for normality using the Shapiro-Wilk test. Data conforming to a normal distribution are presented as mean ± standard deviation (SD), while non-normally distributed data are summarized as median with interquartile range (IQR). Categorical variables are expressed as frequencies and percentages (n, %).

For baseline comparisons between the Initial Therapy and Non-Initial Therapy groups, continuous variables were compared using the independent Student's t-test (for normally distributed data) or the Mann-Whitney U test (for non-normal data). Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. To evaluate the treatment effect within each group, paired comparisons of key data from baseline to fol-

Table 1. Baseline demographic, clinical, and immunological characteristics of patients with idiopathic membranous nephropathy treated with obinutuzumab, stratified by treatment group

Characteristic	Obinutuzumab as Initial Treatment (n=51)	Non-Initial Treatment (n=112)	t/χ^2	*P* value
Demographics				
Age (years)	48.73 ± 12.26	52.14 ± 11.89	1.681	0.095
Male/Female, n (%)	34 (66.67)/17 (33.33)	74 (66.07)/38 (33.93)	0.006	0.941
Diabetes Mellitus, n (%)	6 (11.76)	18 (16.07)	0.518	0.472
Hypertension, n (%)	28 (54.90)	70 (62.50)	0.844	0.358
Disease Status at Diagnosis				
Disease Duration before OBZ (months)	3.82 ± 1.74	28.36 ± 14.21	17.987	<0.001
Positivity of anti-PLA2R antibody, n (%)	47 (92.16)	98 (87.50)	0.774	0.379
B cell counts (cells/μL)	312.47 ± 68.32	289.14 ± 71.53	1.958	0.052
T cell counts (cells/μL)	1542.36 ± 279.47	1487.29 ± 288.63	1.141	0.256
NK cell counts (cells/μL)	328.14 ± 71.29	317.86 ± 69.47	0.869	0.386
Previous Therapy, n (%)				
Rituximab	\	84 (75.00)		
Corticosteroids + Cyclophosphamide	\	31 (27.68)		
Calcineurin Inhibitors	\	64 (57.14)		
Mycophenolate Mofetil	\	18 (16.07)		
Tripterygium Wilfordii	\	12 (10.71)		
Number of Previous Therapy Lines, n (%)				
1 line	\	48 (42.86)		
≥2 lines	\	64 (57.14)		

OBZ, obinutuzumab; PLA2R, phospholipase A2 receptor; NK, natural killer.

low-up time points were conducted using the paired t-test (for normal differences) or the Wilcoxon signed-rank test (for non-normal differences).

The primary analysis focused on comparing the clinical remission rates (CR+PR) between the two groups at 3, 6 and 12 months using the Chi-square test. Time-to-event analyses were employed for time to first remission and relapse-free survival. To identify factors associated with achieving clinical remission, univariate and subsequent multivariate Cox proportional hazards regression models were constructed. Variables with a *P*-value <0.1 by univariate Cox regression analysis (for time to clinical remission) or of known clinical relevance were considered for inclusion in the multivariate model. Note that this criterion applied to the univariate Cox regression results, not to baseline between-group comparisons. Results from regression analyses are reported as hazard ratios (HR) with 95% confidence intervals (CI). A two-tailed *P*-value of less than 0.05 was considered significant for all tests.

Results

Baseline characteristics of the study population

A total of 163 patients with idiopathic membranous nephropathy (IMN) were included and stratified into two groups based on prior treatment exposure. The Obinutuzumab as Initial Treatment group comprised 51 patients, while the Non-Initial Treatment group included 112 patients. As shown in **Table 1**, both groups were comparable in terms of age, gender, prevalence of diabetes and hypertension, baseline positivity for anti-PLA2R antibody, and baseline lymphocyte subsets (all *P*>0.05). However, disease duration before obinutuzumab initiation was significantly shorter in the Initial Treatment group (3.82 ± 1.74 months) compared to the Non-Initial Treatment group (28.36 ± 14.21 months; *P*<0.001). In the Non-Initial Treatment group, 75% had previously received rituximab, 57.14% had been treated with calcineurin inhibitors, and 57.14% had received ≥2 lines of prior immunosuppressive therapy.

Table 2. Obinutuzumab treatment protocol and concomitant medications in initial versus Non-initial therapy groups

Item	Obinutuzumab as Initial Treatment (n=51)	Non-Initial Treatment (n=112)	χ^2	*P* value
Obinutuzumab Dosing				
Induction Dose (1 g × 2), n (%)	51 (100)	112 (100)		\
Patients Receiving Additional Maintenance Dose, n (%)	8 (15.69)	26 (23.21)	1.203	0.273
Total OBZ Dose during Follow-up (g)	2.24 ± 0.47	2.47 ± 0.52	2.617	0.010
Concomitant Medications during OBZ therapy, n (%)				
ACEI/ARB	48 (94.12)	106 (94.64)	0.000	1.000
SGLT2 Inhibitor	12 (23.53)	34 (30.36)	0.806	0.369
Oral Corticosteroids (low-dose, transient)	9 (17.65)	31 (27.68)	1.904	0.168

OBZ, obinutuzumab; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; SGLT2, sodium-glucose co-transporter-2.

Treatment protocol and concomitant medications

All patients received the standard induction regimen of obinutuzumab (1000 mg × 2 doses). As presented in **Table 2**, the total cumulative dose of obinutuzumab during follow-up was slightly lower in the Initial Treatment group (2.24 ± 0.47 g) compared to the Non-Initial Treatment group (2.47 ± 0.52 g; *P*=0.010). Concomitant use of ACEI/ARB was nearly universal in both groups (94.12% vs. 94.64%, *P*=1.000), while the proportion of patients receiving SGLT2 inhibitors or transient low-dose oral corticosteroids did not differ significantly between groups (all *P*>0.05).

Clinical and immunological remission rates

The primary analysis comparing clinical remission rates at fixed time points revealed significant differences at 3 months between patients receiving Obinutuzumab as initial treatment and those for whom it was not the initial treatment (54.90% vs. 37.50%, χ^2=4.331, *P*=0.037) (**Figure 1**). However, no significant differences were noted in clinical remission rates at 6 months (80.39% vs. 69.64%, χ^2=2.055, *P*=0.152) or at 12 months (90.20% vs. 82.14%, χ^2=1.75, *P*=0.186) between the two groups. Similarly, there were no significant differences observed in immunological remission rates at any of the time points: 3 months (62.75% vs. 51.79%, χ^2=1.702, *P*=0.192), 6 months (86.27% vs. 75.89%, χ^2=2.288, *P*=0.130), and 12 months (94.12% vs. 87.50%, χ^2=1.643, *P*=0.200). These results suggest that while Obinutuzumab as an initial treatment may confer a significant advantage in achieving clinical remission early on, this benefit does not persist significantly over longer periods.

Renal function and biochemical parameter changes

The longitudinal analysis of key renal and biochemical data following Obinutuzumab treatment revealed several significant trends. For 24-hour urinary protein, there was a significant reduction in both groups over time, with greater reductions observed in patients receiving Obinutuzumab as initial treatment compared to non-initial treatment at one month (6.12 ± 1.87 g/24 h vs. 6.89 ± 2.14 g/24 h, t=2.221, *P*=0.028), three months (3.47 ± 1.24 g/24 h vs. 4.68 ± 1.73 g/24 h, t=5.058, *P*<0.001), six months (2.13 ± 0.89 g/24 h vs. 3.24 ± 1.32 g/24 h, t=6.288, *P*<0.001), and twelve months (1.42 ± 0.67 g/24 h vs. 2.47 ± 1.18 g/24 h, t=7.183, *P*<0.001) (**Figure 2A**). Serum albumin levels showed a significant increase in both groups over time, but the increase was significantly higher in the initial treatment group compared to the non-initial treatment group at three months (35.67 ± 4.21 g/L vs. 32.84 ± 4.73 g/L, t=3.666, *P*<0.001), six months (38.92 ± 3.74 g/L vs. 35.16 ± 4.28 g/L, t=5.405, *P*<0.001), and twelve months (41.23 ± 3.26 g/L vs. 37.84 ± 4.12 g/L, t=5.190, *P*<0.001) (**Figure 2B**). No significant differences were found between groups for serum creatinine levels across all time points (all *P*>0.05, **Figure 2C**). However, estimated glomerular filtration rate (eGFR) showed a trend

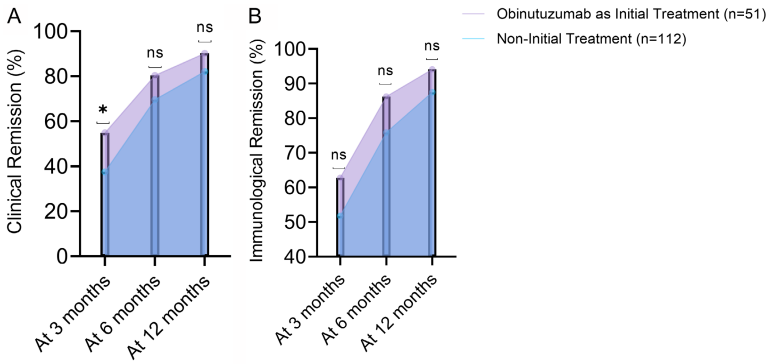

Figure 1. Clinical and immunological remission rates following obinutuzumab treatment at 3, 6, and 12 months. A. Clinical remission, n (%); B. Immunological remission, n (%). Inter-group comparisons are shown. At 3 months, χ^2=4.331, *P=0.037; at 6 and 12 months, differences were not significant (ns).

towards improvement, reaching significance at six months (83.12 ± 14.68 mL/min/1.73 m^2 vs. 77.64 ± 15.92 mL/min/1.73 m^2, t=2.086, P=0.039) and twelve months (84.73 ± 13.87 mL/min/1.73 m^2 vs. 78.97 ± 15.48 mL/min/1.73 m^2, t=2.275, P=0.024) in favor of the initial treatment group (**Figure 2D**). Overall, these findings suggest that Obinutuzumab administered as an initial treatment may lead to more pronounced improvements in renal function, as indicated by decreased urinary protein excretion and increased serum albumin levels.

Immunological serum dynamics and B-cell depletion

Serum anti-PLA2R antibody titers decreased markedly from baseline in both groups, but the decline was consistently and significantly greater in the Initial Treatment group at all post-treatment time points (at 1 month: 102.36 ± 31.47 vs. 124.67 ± 38.52 RU/mL, P<0.001; at 3 months: 47.28 ± 18.73 vs. 78.92 ± 26.14 RU/mL, P<0.001; at 6 months: 18.64 ± 8.42 vs. 42.37 ± 16.28 RU/mL, P<0.001; at 12 months: 8.27 ± 4.13 vs. 24.86 ± 11.47 RU/mL, P<0.001) (**Figure 3A**). Serum IgG levels decreased comparably in both groups over time, with no significant inter-group differences observed at baseline (6.84 ± 1.72 vs. 6.47 ± 1.86 g/L, P=0.227) or at any follow-up visit (all P>0.05) (**Figure 3B**). Similarly, serum IgA levels showed no significant differences between the groups at any assessed time point (all P>0.05) (**Figure 3D**). In contrast, while serum IgM levels were comparable between groups at baseline and up to 6 months (all P>0.05), they were significantly lower in the Initial Treatment group at 12 months (0.46 ± 0.16 vs. 0.53 ± 0.21 g/L, P=0.020) (**Figure 3C**). B-cell depletion was highly effective and similar between groups shortly after treatment initiation, with 98.04% of Initial and 96.43% of Non-Initial therapy patients achieving depletion (CD19+ <5 cells/μL) at 1 month (P= 0.950) (**Figure 3E**). Depletion rates remained high and not significantly different at 3 months (94.12% vs. 91.07%, P=0.723) and 6 months (82.35% vs. 75.89%, P=0.357). By 12 months, B-cell counts had recovered to a similar extent in both cohorts, with 54.90% and 55.36% of patients remaining depleted, respectively (P=0.957) (**Figure 3E**).

Safety profile and adverse events

The overall incidence of any adverse event was similar between the Initial Treatment (37.25%) and Non-Initial Treatment groups (42.86%; P=0.500) (**Table 3**). Infusion-related reactions occurred in 17.65% and 12.50% of patients, respectively (P=0.381). Infections were reported in 15.69% and 23.21% of patients (P=0.273), predominantly upper respiratory tract infections. Hematologic toxicity, primarily grade 1-2 leukopenia, was observed in 5.88% and 9.82% of patients (P=0.596). The incidence of serious adverse events was low (1.96% vs. 5.36%; P=0.565).

Predictors of time to clinical remission: cox regression analysis

Univariate Cox regression analysis was performed to identify predictors of time to clinical remission. In this analysis, baseline B-cell count (as a continuous variable) was not a significant predictor (P=0.142), which differs from the between-group baseline comparison because the two analyses address different research questions. Univariate Cox analysis identified baseline 24-hour UPE (HR 0.857, P< 0.001), serum albumin (HR 1.083, P=0.001), eGFR (HR 1.014, P=0.016), anti-PLA2R titer

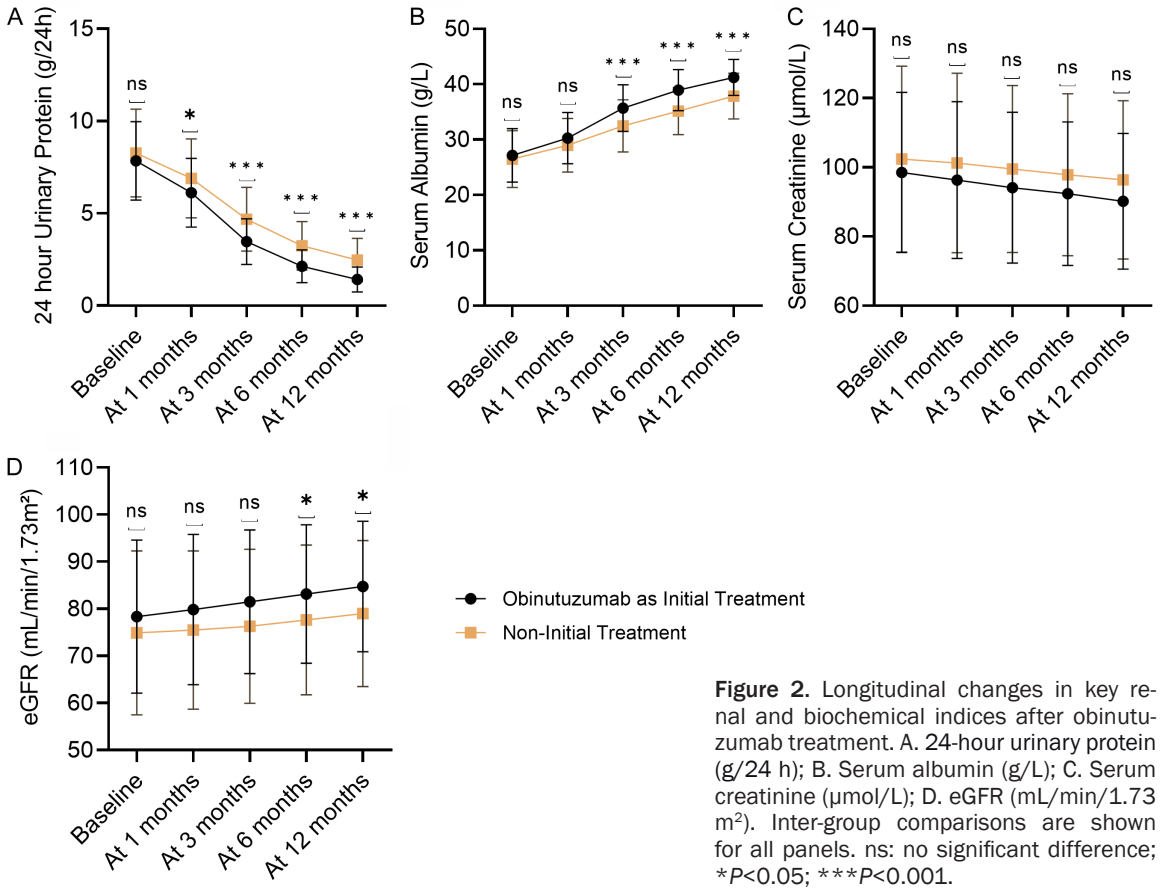

Figure 2. Longitudinal changes in key renal and biochemical indices after obinutuzumab treatment. A. 24-hour urinary protein (g/24 h); B. Serum albumin (g/L); C. Serum creatinine (μmol/L); D. eGFR (mL/min/1.73 m^2). Inter-group comparisons are shown for all panels. ns: no significant difference; **P*<0.05; ****P*<0.001.

(HR 0.972 per 10 RU/mL, *P*=0.002), and treatment group (Initial vs. Non-Initial, HR 1.763, *P*=0.001) as significant predictors of clinical remission (**Table 4**). Variables with a univariate Cox regression *P*-value ≥0.1 (e.g., baseline B-cell count, *P*=0.142) were not entered into the multivariate model, consistent with the pre-specified criterion (*P*<0.1 for inclusion) described in the Statistical Analyses section. The baseline B-cell count comparison between groups is a different analysis and does not affect the multivariate Cox inclusion criterion. In the multivariate model, higher baseline 24-hour UPE (HR 0.872, *P*=0.001) and higher anti-PLA2R titer (HR 0.978 per 10 RU/mL, *P*=0.018) remained independent negative predictors, while higher baseline serum albumin (HR 1.062, *P*=0.023) and receiving obinutuzumab as initial therapy (HR 1.682, *P*=0.003) were independent positive predictors of achieving remission.

Discussion

This single-center retrospective study evaluated the clinical effect of obinutuzumab in adults with idiopathic membranous nephropathy, with a specific focus on comparing outcomes between patients receiving it as first-line immunosuppression and those with prior treatment exposure. The findings provide insights into the role of this glycoengineered anti-CD20 monoclonal antibody in the management of IMN.

Our study demonstrated that patients receiving obinutuzumab as initial therapy achieved a significantly higher clinical remission rate at 3 months compared to the non-initial therapy group, corroborated by multivariate Cox analysis identifying initial therapy as an independent positive predictor of remission. This indicates that treatment initiation with obinutuzumab is associated with a faster achievement of clinical response. The early advantage likely reflects a less entrenched immunological disturbance and less cumulative glomerular damage in treatment-naïve patients, allowing a targeted agent like obinutuzumab to act more rapidly [21, 22]. Consistent with this hypothesis, Townsend et al. [23] reported in the GALLIUM study that obinutuzumab-based immunochemotherapy resulted in faster and deeper B-cell

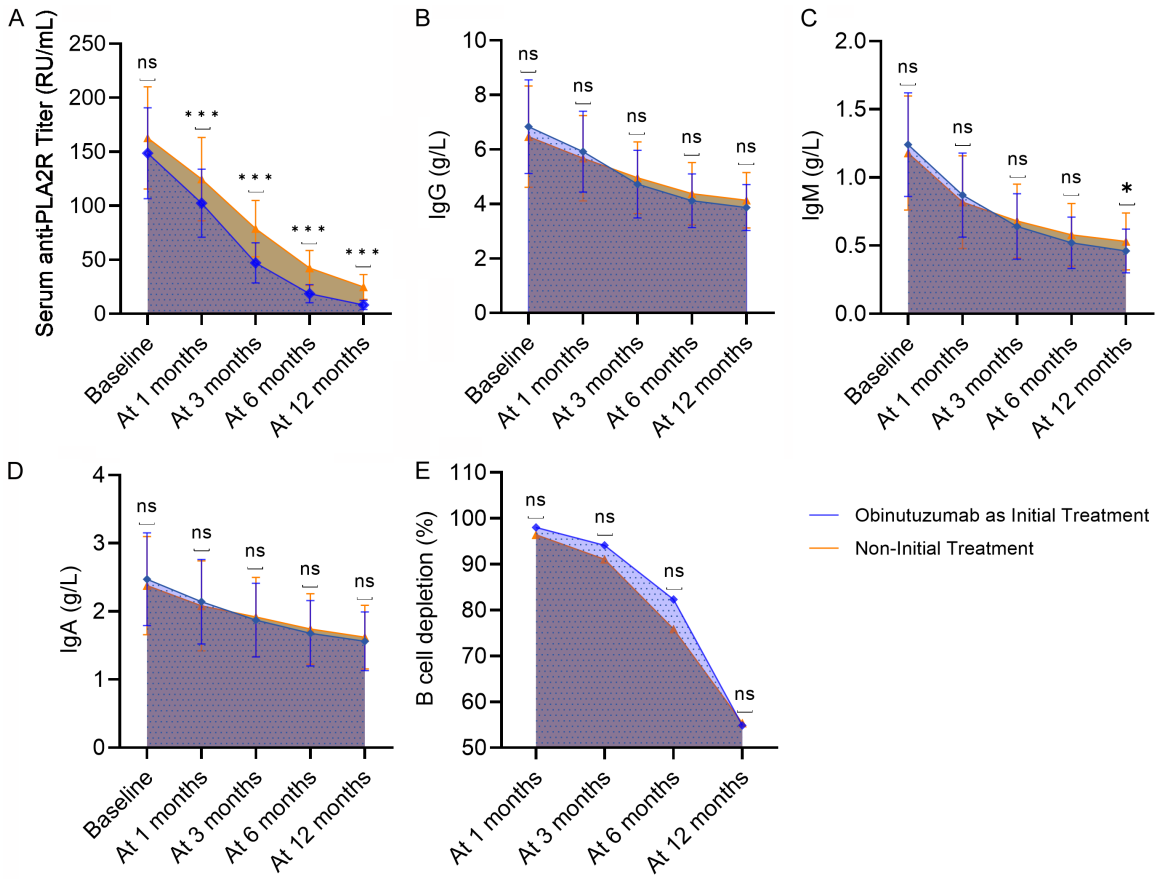

Figure 3. Dynamics of immunological indices and B-cell depletion following obinutuzumab therapy. A. Serum anti-PLA2R titer (RU/mL); B. IgG (g/L); C. IgM (g/L); D. IgA (g/L); E. B cell depletion, n (%). Inter-group comparisons are shown for all panels. ns: no significant difference; *P<0.05; ***P<0.001.

depletion compared to rituximab in patients with previously untreated indolent non-Hodgkin's lymphoma, supporting the notion that obinutuzumab may offer superior early efficacy when used as first-line therapy. Similarly, in the context of autoimmune diseases, obinutuzumab has been shown to induce more potent depletion of peripheral and tissue B cells than rituximab in patients with lupus nephritis, which may contribute to more rapid serological and clinical responses [14]. These observations align with our findings and suggest that the glycoengineered structure of obinutuzumab enhances antibody-dependent cellular cytotoxicity and direct B-cell killing, potentially leading to accelerated reduction in pathogenic anti-PLA2R antibody-producing clones.

Notably, this remission rate advantage was not sustained long-term, as rates converged by 12 months. This convergence aligns with the fundamental efficacy of B-cell depletion, which can ultimately induce remission even in refractory disease [23, 24], and explains why the survival curves do not show prolonged separation. Therefore, the key benefit of initial obinutuzumab therapy appears to be the acceleration of clinical and serological response, rather than a higher ultimate remission rate. Regarding the obinutuzumab dosing, the slightly higher total cumulative dose in the Non-Initial Therapy group is attributable to the higher, though not statistically significant, proportion of patients in that group who received additional maintenance doses. This clinical practice aligns with the group's refractory nature [21]. Importantly, despite receiving a modestly higher total dose, the Non-Initial Therapy group did not achieve superior remission rates, especially at the early 3-month time point. This suggests that the accelerated response seen in the Initial Therapy group is driven more by the treatment sequence and disease state at initiation than by minor variations in total drug exposure. The comparable long-term efficacy between groups, despite the dose difference, further under-

Table 3. Safety profile and adverse events associated with obinutuzumab treatment in idiopathic membranous nephropathy

Adverse Event	Obinutuzumab as Initial Treatment (n=51)	Non-Initial Treatment (n=112)	χ^2	*P* value
Any Adverse Event, n (%)	19 (37.25)	48 (42.86)	0.454	0.500
Infusion-Related Reactions, n (%)	9 (17.65)	14 (12.50)	0.766	0.381
Chills/Fever	6	9		
Dyspnea/Palpitations	2	3		
Nausea/Vomiting	1	2		
Infections, n (%)	8 (15.69)	26 (23.21)	1.203	0.273
Upper Respiratory Tract Infection	5	12		
Urinary Tract Infection	1	5		
Herpes Zoster	1	4		
Pneumonia (requiring hospitalization)	1	5		
Hematological Toxicity, n (%)	3 (5.88)	11 (9.82)	0.282	0.596
Leukopenia (Grade 1-2)	3	9		
Neutropenia (Grade 1-2)	0	2		
Other Non-infectious AEs, n (%)	2 (3.92)	7 (6.25)	0.055	0.815
Abnormal Liver Function	1	3		
Tinnitus	1	2		
Amenorrhea	0	2		
Serious Adverse Events, n (%)	1 (1.96)	6 (5.36)	0.331	0.565

AE, adverse event.

Table 4. Univariate and multivariate Cox regression analysis of predictors for clinical remission in obinutuzumab-treated patients

Variable	Univariate Cox analysis			Multivariate Cox analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (per 1-year increase)	0.981	0.963-1.000	0.053	0.984	0.965-1.004	0.118
Gender (Male vs. Female)	1.124	0.832-1.517	0.446	\	\	\
Baseline 24 h UPE (per 1 g/24 h increase)	0.857	0.792-0.926	<0.001	0.872	0.804-0.945	0.001
Baseline Serum Albumin (per 1 g/L increase)	1.083	1.032-1.137	0.001	1.062	1.008-1.118	0.023
Baseline eGFR (per 1 mL/min/1.73 m^2 increase)	1.014	1.003-1.026	0.016	1.008	0.996-1.020	0.196
Baseline anti-PLA2R Titer (per 10 RU/mL increase)	0.972	0.956-0.989	0.002	0.978	0.961-0.996	0.018
Baseline B-cell Count (per 10 cells/μL increase)	0.994	0.986-1.002	0.142	\	\	\
Treatment Group (Initial vs. Non-Initial)	1.763	1.263-2.461	0.001	1.682	1.194-2.371	0.003
Concomitant SGLT2 Inhibitor Use (Yes vs. No)	1.214	0.894-1.649	0.214	\	\	\

HR, hazard ratio; CI, confidence interval; UPE, urinary protein excretion; eGFR, estimated glomerular filtration rate; anti-PLA2R, anti-phospholipase A2 receptor; SGLT2, sodium-glucose co-transporter-2.

scores the potent efficacy of the standard induction regimen in both settings.

Consistent with the remission data, the improvement in key renal indices was more pronounced in the initial therapy group. The reduction in proteinuria and the concomitant rise in serum albumin were both of a greater magnitude at all post-treatment intervals in patients receiving obinutuzumab upfront. Furthermore, a trend towards better preservation of estimated glomerular filtration rate was observed in this group at the later stages of follow-up. These findings underscore that early, targeted B-cell intervention may not only lead to faster proteinuria reduction but also to more robust renal functional preservation [25, 26]. The superior decline in proteinuria likely reflects more effective mitigation of the underlying autoimmune attack on podocytes. The en-

hanced direct cell death and antibody-dependent cellular cytotoxicity/phagocytosis mechanisms of obinutuzumab, compared to earlier anti-CD20 antibodies, may be particularly effective in neutralizing the autoimmune response before irreversible structural changes occur [27, 28]. This aligns with the fundamental goal in IMN management: to promptly suppress autoantibody production and halt ongoing glomerular injury [29, 30].

The immunological data offer a potential mechanism for the observed clinical differences. While B-cell depletion was effectively achieved and maintained similarly in both groups, the decline in serum anti-PLA2R antibody titers was more rapid and profound in the initial therapy cohort. This dissociation between peripheral B-cell depletion kinetics and antibody titer reduction is noteworthy. It implies that the superior clinical and serological response in treatment-naïve patients may not stem from a difference in the depth of circulating B-cell clearance but possibly from a greater effect on autoreactive B-cell clones [31, 32], or on short-lived plasma cells [33, 34]. However, without direct immunophenotyping data (e.g., memory B cells, plasmablasts, or antigen-specific B-cell clones), this remains speculative. The observed dissociation between B-cell depletion kinetics and anti-PLA2R decline highlights an important area for future investigation, including longitudinal profiling of B-cell subsets and measurement of peripheral autoantibody-secreting cells. The significantly lower serum IgM level observed in the Initial Therapy group at 12 months may suggest a more profound or sustained modulation of the humoral immune repertoire, affecting specific B-cell subsets responsible for IgM production [35, 36]. While this did not translate into a higher infection risk in our safety analysis, it underscores a biological difference in immune reconstitution that merits further investigation.

The safety profile of obinutuzumab in this IMN cohort was manageable and consistent with its known effects [27], with no major differences between the two treatment groups. The incidence of infusion-related reactions and infections was not increased in the initial therapy group, which is reassuring for its potential use earlier in the treatment algorithm. The similar rates of adverse events suggest that the treatment sequence does not materially alter the drug's tolerability in this population [37].

Multivariate analysis identified that receiving obinutuzumab as initial therapy was an independent positive predictor of achieving clinical remission, alongside higher baseline serum albumin. Conversely, higher baseline proteinuria and anti-PLA2R antibody titer were negative predictors. This reinforces the clinical intuition that patients with a high disease burden pose a greater therapeutic challenge. More importantly, it provides quantitative support for the strategy of employing potent B-cell depletion as first-line therapy in high-risk IMN, as it appears to offer a higher likelihood of success compared to reserving it for refractory cases. This adds a new dimension to the evolving treatment paradigm, which has traditionally escalated therapy based on response.

The clinical implications of these findings are substantial. This study suggests that obinutuzumab is an effective therapeutic option for IMN, both as an initial and a subsequent line of therapy. The data provide a rationale for considering obinutuzumab as a first-line biologic agent, particularly for patients presenting with characteristics predictive of a poor outcome, such as heavy proteinuria and high anti-PLA2R titers. Its use in this setting may lead to quicker remission, more complete biochemical recovery, and potentially better long-term renal survival. For patients who have failed conventional therapies including rituximab, obinutuzumab represents a valuable rescue option, capable of inducing remission in a considerable proportion, thereby filling an important unmet need. The comparable long-term remission rates between groups ultimately support its efficacy across the disease spectrum.

This study has several limitations. Its retrospective, single-center, and non-randomized design introduce potential for selection and information bias. The comparison groups differed inherently in disease duration and prior treatment exposure, which are confounding factors that cannot be fully adjusted for statistically. The follow-up duration of 12 months is relatively short for a chronic disease like IMN, limiting conclusions regarding long-term durability of response, relapse rates, and renal survival. The lack of a direct comparative control group (e.g., patients treated with rituximab) pre-

cludes definitive conclusions about the relative superiority of obinutuzumab. In addition, the study population was exclusively Chinese, and the findings may not be generalizable to other ethnicities without further validation. Fifth, due to the retrospective nature, detailed parameters of prior therapies in the Non-Initial Therapy group - such as the specific duration of each immunosuppressive regimen, the exact interval between discontinuing prior therapy (especially rituximab) and initiating obinutuzumab, and the precise dosing and titration of concomitant ACEI/ARB medications - were not consistently available in the medical records. Although all patients in the Non-Initial Therapy group had documented inadequate response or intolerance to prior therapy, the absence of these granular data limits our ability to fully exclude any potential delayed or carry-over effects from previous treatments or to finely attribute the proteinuria reduction. Sixth, this study was designed as a clinical efficacy and safety analysis. Therefore, it did not include exploratory deep immunophenotyping of B-cell subsets (e.g., memory B cells, plasmablasts), measurement of complement pathway components (e.g., C3, C4), or assessment of specific podocyte injury biomarkers (e.g., urinary podocin). While we observed effective peripheral CD19+ B-cell depletion and a correlated decline in anti-PLA2R titers, the differential impact of obinutuzumab on specific pathogenic B-cell clones and its effects on downstream complement activation and direct podocyte protection remain to be elucidated. Prospective studies incorporating these biomarkers are warranted to fully delineate the mechanism of action of obinutuzumab in IMN.

Future prospective, randomized controlled trials directly comparing obinutuzumab with rituximab as first-line therapy in IMN are warranted to establish its relative efficacy and safety. Studies with longer follow-up are needed to assess the durability of remission and the impact on hard endpoints like end-stage renal disease. Further research should also explore biomarkers that can predict response to obinutuzumab and investigate its potential in combination with other novel agents targeting different arms of the immune response in IMN.

In conclusion, this study demonstrated that obinutuzumab is an effective and well-tolerated treatment option for both treatment-naïve and refractory idiopathic membranous nephropathy. Initiation of obinutuzumab as first-line immunosuppressive therapy is associated with a more rapid induction of clinical and serological remission, alongside greater improvements in proteinuria and serum albumin, compared to its use after other treatment failures. These findings support the consideration of obinutuzumab as an initial biologic therapy for high-risk patients and underscore its value as a rescue option. Prospective randomized trials are warranted to confirm these observations and define its long-term role in the IMN treatment landscape.

Disclosure of conflict of interest

None.

Address correspondence to: Hongting Liu, Department of Nephrology, Yuncheng Central Hospital, No. 3690 Hedong East Street, Salt Lake District, Yuncheng 044000, Shanxi, China. E-mail: hongting902@163.com

References

[1] Yang L, Wang G, Ye N, Xu X, Cheng W, Sun L, Dong H, Kong L, Zhao X, Geng Y and Cheng H. Clinicopathological and prognostic characteristics of idiopathic membranous nephropathy with dual antigen positivity. Front Immunol 2023; 14: 1297107.

[2] Jiang R, Li L, Yan Y, Li H, Yu R, Huang Y and Wang L. Renal arteriolosclerosis impact on clinicopathological features and outcomes of idiopathic membranous nephropathy: a retrospective cohort analysis. Front Med (Lausanne) 2025; 12: 1594990.

[3] Xu Z, Chen L, Xiang H, Zhang C and Xiong J. Advances in pathogenesis of idiopathic membranous nephropathy. Kidney Dis (Basel) 2020; 6: 330-345.

[4] Couser WG. Primary membranous nephropathy. Clin J Am Soc Nephrol 2017; 12: 983-997.

[5] Zhang BO, Cheng M, Yang M, Han S, Zhang YH, Shi HG, Zhu L and Zhao XZ. Analysis of the prognostic risk factors of idiopathic membranous nephropathy using a new surrogate endpoint. Biomed Rep 2016; 4: 147-152.

[6] Chen S, Huang Y and Qu Z. Telitacicept monotherapy for refractory idiopathic membranous nephropathy: a case report and literature review. Front Med (Lausanne) 2025; 12: 1571616.

[7] Del Vecchio L, Allinovi M, Rocco P and Brando B. Rituximab therapy for adults with nephrotic syndromes: standard schedules or B cell-targeted therapy? J Clin Med 2021; 10: 5847.

[8] Chung EYM, Wang YM, Keung K, Hu M, McCarthy H, Wong G, Kairaitis L, Bose B, Harris DCH and Alexander SI. Membranous nephropathy: clearer pathology and mechanisms identify potential strategies for treatment. Front Immunol 2022; 13: 1036249.
[9] Jin Y, Xie Y, Fu H, Liu F and Mao J. Anti-B cell strategy in nephrotic syndrome: beyond rituximab. Biomedicines 2025; 13: 2063.
[10] Brown JR, Porter DL and O'Brien SM. Novel treatments for chronic lymphocytic leukemia and moving forward. Am Soc Clin Oncol Educ Book 2014; e317-325.
[11] Nguyen V, Cheung A, Hendricks R, Peng K and Chung S. An antibody-dependent cellular cytotoxicity assay for detecting ocrelizumab neutralizing antibody. AAPS J 2023; 25: 97.
[12] Akkad N, Feng L, Westin JR, Hagemeister FB, Lee HJ, Fayad L, Ahmed S, Nair R, Rodriguez MA, Strati P, Chihara D, Flowers CR, Claret L, Ibanez K, Wang M, Fowler NH, Henderson J, Davis RE, Neelapu SS, Green M and Nastoupil LJ. A phase 2 study of obinutuzumab combined with lenalidomide in previously untreated high tumor burden follicular lymphoma. Blood Adv 2025; 9: 4396-4404.
[13] Looney CM, Schroeder A, Tavares E, Garg J, Schindler T, Vincenti F, Redfield RR, Jordan SC, Busque S, Woodle ES, Khan J, Eastham J, Micallef S, Austin CD and Morimoto A. Obinutuzumab effectively depletes key B-cell subsets in blood and tissue in end-stage renal disease patients. Transplant Direct 2023; 9: e1436.
[14] Robinson WH, Fiorentino D, Chung L, Moreland LW, Deodhar M, Harler MB, Saulsbery C and Kunder R. Cutting-edge approaches to B-cell depletion in autoimmune diseases. Front Immunol 2024; 15: 1454747.
[15] Ahsan MU, Tabassum A, Naseem K and Zahid IB. Obinutuzumab: a new frontier in the treatment of refractory idiopathic membranous nephropathy. Int Urol Nephrol 2025; 57: 3075-3076.
[16] Garofolo M, Vitale M, Penno G, Solini A, Orsi E, Grancini V, Bonora E, Fondelli C, Trevisan R, Vedovato M, Nicolucci A and Pugliese G; Renal Insufficiency And Cardiovascular Events (RIACE) Study Group. Prognostic impact of switching to the 2021 chronic kidney disease epidemiology collaboration creatinine-based equation in Caucasian patients with type 2 diabetes: the Renal Insufficiency and Cardiovascular events (RIACE) Italian Multicenter Study. Cardiovasc Diabetol 2024; 23: 377.
[17] Chapter 7: Idiopathic membranous nephropathy. Kidney Int Suppl (2011) 2012; 2: 186-197.
[18] Deng L, Huang Q, Wang J, Luo K, Liu J, Yan W, Jiang F and Xu G. Efficacy and safety of different immunosuppressive therapies in patients with membranous nephropathy and high PLA2R antibody titer. Front Pharmacol 2021; 12: 786334.
[19] Qin HZ, Liu L, Liang SS, Shi JS, Zheng CX, Hou Q, Lu YH and Le WB. Evaluating tacrolimus treatment in idiopathic membranous nephropathy in a cohort of 408 patients. BMC Nephrol 2017; 18: 2.
[20] Shah S. Common terminology criteria for adverse events. National Cancer Institute: USA 2022; 784: 331.
[21] Arnold J, Dass S, Twigg S, Jones CH, Rhodes B, Hewins P, Chakravorty M, Courtney P, Ehrenstein M, Md Yusof MY and Vital EM. Efficacy and safety of obinutuzumab in systemic lupus erythematosus patients with secondary non-response to rituximab. Rheumatology (Oxford) 2022; 61: 4905-4909.
[22] Liu J and Guan F. B cell phenotype, activity, and function in idiopathic nephrotic syndrome. Pediatr Res 2023; 93: 1828-1836.
[23] Townsend W, Hiddemann W, Buske C, Cartron G, Cunningham D, Dyer MJS, Gribben JG, Phillips EH, Dreyling M, Seymour JF, Grigg A, Trotman J, Lin TY, Hong XN, Kingbiel D, Nielsen TG, Knapp A, Herold M and Marcus R. Obinutuzumab versus rituximab immunochemotherapy in previously untreated iNHL: final results from the GALLIUM study. Hemasphere 2023; 7: e919.
[24] Wang C, Dong Y, Men P, Zhang R, Xiao Y, Bu Y, Qin Y, Zhang X, Dou Q, Yang Y, Gao H and Zhang Y. Efficacy, safety and cost-effectiveness of obinutuzumab in patients with follicular lymphoma: a rapid review. Front Pharmacol 2024; 15: 1426772.
[25] Li XQ, Liu Y, Cai ZY, Lv TG and Hao J. Obinutuzumab is effective as an initial treatment for PLA2R-associated primary membranous nephropathy: a retrospective, single-center trial. Drug Des Devel Ther 2025; 19: 5961-5972.
[26] Marques F, Reis J, Godinho I, Pereira M, Fernandes P, Jorge S, Lopes JA and Gameiro J. Impact of early proteinuria reduction in glomerular disease and decline of kidney function: a retrospective cohort. J Clin Med 2022; 11: 5968.
[27] Lin Y, Han Q, Chen L, Wang Y, Ren P, Liu G, Lan L, Lei X, Chen J and Han F. Obinutuzumab in refractory membranous nephropathy: a case series. Kidney Med 2024; 6: 100853.
[28] Basu B, Angeletti A, Islam B and Ghiggeri GM. New and old anti-CD20 monoclonal antibodies for nephrotic syndrome. Where we are? Front Immunol 2022; 13: 805697.
[29] Trujillo H, Caravaca-Fontán F and Praga M. Ten tips on immunosuppression in primary membranous nephropathy. Clin Kidney J 2024; 17: sfae129.

[30] Dantas M, Silva LBB, Pontes BTM, Dos Reis MA, de Lima PSN and Moysés Neto M. Membranous nephropathy. J Bras Nefrol 2023; 45: 229-243.
[31] Reed JH. Transforming mutations in the development of pathogenic B cell clones and autoantibodies. Immunol Rev 2022; 307: 101-115.
[32] Corneth OBJ, Neys SFH and Hendriks RW. Aberrant B cell signaling in autoimmune diseases. Cells 2022; 11: 3391.
[33] Merino-Vico A, Frazzei G, van Hamburg JP and Tas SW. Targeting B cells and plasma cells in autoimmune diseases: from established treatments to novel therapeutic approaches. Eur J Immunol 2023; 53: e2149675.
[34] Doglio M, Alexander T, Del Papa N, Snowden JA and Greco R; Autoimmune Diseases Working Party (ADWP) of the European Society for Blood and Marrow Transplantation (EBMT). New insights in systemic lupus erythematosus: from regulatory T cells to CAR-T-cell strategies. J Allergy Clin Immunol 2022; 150: 1289-1301.
[35] Alexopoulos H, Biba A and Dalakas MC. Anti-B-cell therapies in autoimmune neurological diseases: rationale and efficacy trials. Neurotherapeutics 2016; 13: 20-33.
[36] Sarrigeorgiou I, Tsinti G, Kalala F, Germenis A, Speletas M and Lymberi P. Levels of natural antibodies before and after immunoglobulin replacement treatment affect the clinical phenotype in common variable immunodeficiency. J Clin Immunol 2024; 45: 13.
[37] Sakamoto R, Mukai J, Kotake Y, Takehara R, Nishimura M, Yamada K, Okuda H and Wada Y. Modified premedication of infusion reaction with obinutuzumab therapy. Gan To Kagaku Ryoho 2023; 50: 1073-1076.