Obinutuzumab as a Promising Treatment for Membranous Nephropathy

Membranous nephropathy (MN), the predominant cause of nephrotic syndrome (NS) in adults without diabetes, is an autoimmune disorder characterized by antibodies directed against podocyte antigens, most commonly the M-type Phospholipase A2 receptor (PLA2R). As a result, B cell-targeting therapies, such as rituximab, have become the treatments of choice for MN.[1] Despite a well-defined pathophysiological basis, 40% of cases exhibit resistance to rituximab therapy. Several mechanisms may account for rituximab resistance, including reduced bioavailability due to urinary loss, development of antibodies against rituximab, and chronic kidney biopsy findings. Current research focuses on overcoming these challenges with innovative therapies, such as novel B cell-targeted treatments, complement inhibitors, proteasome inhibitors, and anti-CD38 therapies.

Obinutuzumab is a next-generation anti-CD20 antibody designed to address various mechanisms associated with rituximab resistance and enhance therapeutic efficacy. The precursor antibody for obinutuzumab was chosen for its "type II" properties, which enable it to induce homotypic adhesion and a distinctive direct cell death (DCD) mechanism.[2] Type II antibodies are engineered to overexpress glycosylation enzymes, resulting in a non-fucosylated Fc region that may enhance the effector function of the antibodies. Unlike rituximab, which relocates CD20 to lipid rafts and induces minimal DCD while activating complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC), obinutuzumab does not trigger CDC. It binds differently to the CD20 molecule, leading to more substantial DCD through caspase-independent mechanisms. The afucosylated Fc region of obinutuzumab enhances ADCC and antibody-dependent phagocytosis (ADP) more effectively than rituximab. Consequently, obinutuzumab offers improved ADCC and ADP, contributing to its superior therapeutic potential.

The superiority of obinutuzumab over rituximab was first reported in patients with non-Hodgkin lymphomas, and in 2013, it was recognized as a breakthrough therapy. In the CLL11 clinical trial involving patients with chronic lymphocytic leukaemia (CLL) and other co-existing conditions, obinutuzumab demonstrated a 51% reduction in the risk of disease progression and a lower mortality rate compared to rituximab.[3]

The superior efficacy of obinutuzumab in CLL paved the way for its use in difficult-to-treat MN. In seminal reports by Klomjit *et al.*, three patients with PLA2R-associated MN who had not achieved immunologic or clinical remission with rituximab were successfully treated with obinutuzumab.[4] Treatment with obinutuzumab resulted in immunologic remission in all three patients, with two achieving partial remission (PR). These findings indicate that obinutuzumab could be a promising treatment strategy for PLA2R-associated MN cases resistant to rituximab. Subsequently, numerous case series have documented the efficacy of obinutuzumab in treating refractory or relapsing MN.

In this issue of the Journal, Jha *et al.* presented a retrospective case series on the successful treatment of PLA2R-related MN using Obinutuzumab in patients with relapsing or refractory MN.[5] Before receiving obinutuzumab, three patients had undergone rituximab and tacrolimus-based therapy, while another three had been treated with rituximab, cyclical cyclophosphamide, and corticosteroids (CYC/CS), and tacrolimus.[5] Despite these conventional treatments, these patients continued to exhibit overt nephrotic syndrome. Obinutuzumab was administered as two 1-gram injections, given 14 days apart. These patients had minimal chronicity on kidney biopsy, with the interval between the initial renal biopsy and drug administration ranging from 2 to 6 years. Five out of six cases achieved immunologic remission and normalization of serum albumin levels, with stable kidney function. One patient, who also had diabetes mellitus but no diabetic nephropathy on biopsy, showed no response to obinutuzumab. This patient had not received cyclical CYC/CS. Follow-up CD19 levels were below 5 cells/µl in all cases, although pre-obinutuzumab CD19 levels were unavailable. The series by Jha *et al.* is the largest case series from India demonstrating the efficacy and safety of obinutuzumab in difficult-to-treat MN.[5] The authors rightly acknowledge the study's limitations, including a small sample size, lack of a comparator, and the potential legacy effect of previous immunosuppressive therapy.

Another advantage of obinutuzumab over rituximab is its rapidity of response. Rituximab is often criticized for the delay in achieving remission. In the study by Sethi *et al.,* most patients achieved remission within 6 months.[6] Moreover, patients who achieved remission at 12 months maintained it without requiring additional doses of obinutuzumab. In contrast, a significant proportion of patients treated with rituximab require additional doses to induce remission or address relapse. This may be due to a more profound and prolonged depletion of B-lymphocytes with obinutuzumab. In another study by Lin *et al.*, the median time to first remission was 2.7 months.[7]

Another important aspect is the utility of obinutuzumab in patients with severe chronic kidney disease (CKD) (stage 4/5). Most published reports to date involve patients with normal kidney function. However, in the case series by Naik *et al.,* favorable responses to obinutuzumab were reported in two patients with MN despite advanced chronicity and severe kidney dysfunction.[8] Depletion of anti-PLA2R by Obinutuzumab, which is resistant to other

immunosuppressive medications, likely leads to improved kidney function and remission of proteinuria.

Emerging evidence suggests the role of obinutuzumab in treatment-naive cases as well. In a recent series by Su *et al.,* 20 out of 59 patients received obinutuzumab as initial therapy.[9] During a median follow-up of 9.4 months, 50 patients (84.7%) achieved complete or partial remission. The likelihood of remission was significantly higher when obinutuzumab was used as initial therapy compared to second-line therapy. These findings highlight the potential of obinutuzumab as an initial treatment for MN.

At least three studies are evaluating the efficacy of Obinutuzumab in treating membranous nephropathy (MN), including two randomized controlled trials and one non-controlled study. The MAJESTY trial (NCT04629248), which compares the efficacy and safety of obinutuzumab versus tacrolimus in MN patients, is actively recruiting participants. However, the trial appears to be behind schedule, with primary data collection initially expected to be completed by April 2025. The ORION study (NCT05050214) focuses on the efficacy, safety, and tolerability of obinutuzumab in patients with rituximab-resistant or rituximab-dependent MN. This study began in 2022 and aims to complete primary data collection by April 2025. Finally, the REMIT Trial (NCT06120673) is the first investigator-initiated transcontinental study aims to compare obinutuzumab with the established standard of care, CYC/CS, although patient enrollment has not yet started. Notably, this study will include Indian centres. These trials will provide comprehensive evidence on the efficacy of obinutuzumab in MN compared to current standard treatments.

While most evidence relates to PLA2R-related MN, a case report showed a significant reduction in circulating anti-SEMA3B antibodies following obinutuzumab infusion.[10]

Obinutuzumab is generally well-tolerated, with fewer side effects. To date, there have been no reports of anaphylactic shock, sepsis, malignancy, or death in patients with MN. Obinutuzumab is well-tolerated in patients who previously experienced infusion-related anaphylaxis with rituximab, probably due to obinutuzumab being a humanized monoclonal antibody with a lower risk of immunogenicity.[6] Studies have reported leukopenia after the first dose, which resolved within 2 months in three patients but could persist for up to 18 months.[9] Although some series have reported minor infections,[7] such as upper respiratory and urinary tract infections, the index series did not report any hematological or infectious complications following treatment with obinutuzumab therapy. Since most reports are retrospective, minor complications that may not have required immediate attention could have been underreported.

Overall, current evidence, including the present Indian series, suggests that obinutuzumab is a promising therapeutic option for patients with difficult-to-treat PLA2R-related MN. Its rapid and sustained response, combined with a favorable safety profile, underscores its potential both as an initial and second-line treatment.

Conflicts of interest

There are no conflicts of interest.

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