New Advances in the Treatment of Primary Membranous Nephropathy Postprint

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Abstract

Primary membranous nephropathy (PMN) is a kidney-specific autoimmune disease and one of the most common causes of nephrotic syndrome in adults. Its incidence has been increasing year by year, and effective treatment can significantly improve patient prognosis. With in-depth research into the pathogenesis of membranous nephropathy and the discovery of new specific antibodies, the treatment of PMN has made great progress in recent years. An increasing number of drugs and regimens are being attempted for the treatment of PMN, enhancing therapeutic efficacy for patients. This article reviews previous classic treatment regimens, focuses on analyzing the efficacy of rituximab in PMN and the reasons for resistance, and discusses other novel treatment strategies.

Full Text

Preamble

New Advances in the Treatment of Primary Membranous Nephropathy

Primary Membranous Nephropathy (PMN) is a common pathological type of nephrotic syndrome in adults and remains one of the leading causes of end-stage renal disease (ESRD). Characterized by the formation of subepithelial immune complexes and diffuse thickening of the glomerular basement membrane, its clinical course is highly variable. Approximately one-third of patients achieve spontaneous remission, while another third progress to ESRD despite standard care. In recent years, the discovery of the phospholipase A2 receptor (PLA2R) and thrombospondin type-1 domain-containing 7A (THSD7A) as major autoantigens has revolutionized the diagnosis, risk stratification, and therapeutic monitoring of PMN.

1. Traditional Immunosuppressive Therapies

For patients at high risk of disease progression, traditional immunosuppressive regimens remain the cornerstone of treatment. The "Modified Ponticelli Regimen," which alternates corticosteroids with alkylating agents (such as cyclophosphamide), has long been considered the gold standard for inducing remission. However, its clinical application is often limited by significant systemic toxicities, including bone marrow suppression, infections, and gonadal toxicity.

Calcineurin inhibitors (CNIs), such as cyclosporine and tacrolimus, serve as effective alternatives, particularly for patients who wish to avoid the side effects of alkylating agents. While CNIs are highly effective at inducing rapid remission of proteinuria, they are associated with high relapse rates upon discontinuation and potential nephrotoxicity. Consequently, long-term maintenance at low doses is often required to sustain clinical response.

2. Targeted B-cell Depletion Therapy

The paradigm of PMN treatment has shifted significantly toward B-cell-targeted therapies, with Rituximab (RTX) emerging as a first-line treatment option. As a monoclonal antibody against the CD20 antigen on B cells, Rituximab effectively reduces the production of pathogenic autoantibodies.

Clinical trials, such as MENTOR and GEMRITUX, have demonstrated that Rituximab is non-inferior to CNIs in inducing long-term remission and superior in maintaining it. Furthermore, the quantification of anti-PLA2R antibody titers has proven to be a reliable biomarker for predicting treatment response to Rituximab. For patients who are refractory to Rituximab, newer generation anti-CD20 antibodies (such as Ocrelizumab and Ofatumumab) or plasma cell-targeted therapies (such as daratumumab) are being explored.

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Zhang Yongzhe and Guo Zixia, from the Department of Nephrology at Liaoning Electric Power Central Hospital in Shenyang, Liaoning Province, discuss other novel treatment protocols.

New Advances in the Treatment of Primary Membranous Nephropathy

Membranous nephropathy (MN) is a group of diseases characterized pathologically by the subepithelial deposition of immune complexes on the glomerular basement membrane (GBM), accompanied by diffuse thickening of the basement membrane. Based on its etiology, MN can be classified into primary membranous nephropathy (PMN) and secondary membranous nephropathy (SMN).

SMN is often caused by infections, malignant tumors, drugs, or autoimmune diseases, accounting for 20% to 25% of MN cases. In contrast, PMN refers to MN without a definitive causative factor and accounts for 75% to 80% of cases. PMN is a common clinical primary glomerular disease and is the most frequent pathological type of primary nephrotic syndrome in middle-aged and elderly patients.

In recent years, the incidence of MN has risen significantly, accounting for 24.9% of primary glomerular diseases in adults, with some regions reporting even higher proportions. Current research considers PMN to be a kidney-specific autoimmune disease. It involves the production of autoantibodies against podocyte target antigens, which deposit subepithelially in the glomeruli to form immune complexes. This process leads to complement activation, podocyte injury, and destruction of the GBM, ultimately resulting in the development of MN. The discovery of the podocyte-specific antigen M-type phospholipase A2 receptor 1 (PLA2R) in 2009 has been most closely linked to PMN.

Effective treatment can significantly improve patient prognosis. With in-depth research into the pathogenesis of membranous nephropathy and the discovery of new specific antibodies, the treatment of PMN has made great progress in recent years. An increasing number of drugs and protocols are being explored to treat PMN, improving therapeutic efficacy for patients. This article reviews classic treatment regimens, focuses on analyzing the efficacy of rituximab in PMN and the reasons for resistance, and discusses other novel treatment strategies.

Keywords: Membranous nephropathy; M-type phospholipase A2 receptor; Rituximab; Immunosuppressants

Abstract

Primary membranous nephropathy (PMN) is a kidney-specific autoimmune disease, which is one of the most common causes of nephrotic syndrome in adults, and its incidence is increasing year by year, and effective treatment can significantly improve the prognosis of patients. With the in-depth study of the pathogenesis of membranous nephropathy and the discovery of new specific antibodies, the treatment of PMN has made great progress in recent years, and more and more drugs and protocols have been attempted to be used in the treatment of PMN, which has improved the efficacy of patient treatment. This paper reviews the classic treatment options, focuses on the efficacy of rituximab on PMN and the reasons for resistance, and also discusses other novel treatment strategies.

Key words: Membranous nephropathy; M-type phospholipase A2 receptor 1; Rituximab; Immunosuppressant

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Closely related antigens have been identified in recent years due to advancements in techniques combining glomerular laser microdissection with liquid chromatography-tandem mass spectrometry (LC-MS/MS). A variety of membranous nephropathy (MN)-associated antigens have been discovered, including thrombospondin type-1 domain-containing 7A (THSD7A), exostosin 1/exostosin 2 (EXT1/EXT2), neural epidermal growth factor-like 1 (NELL-1), semaphorin 3B (SEMA3B), neural cell adhesion molecule 1 (NCAM1), protocadherin 7 (PCDH7), protocadherin FAT1, and high-temperature requirement A1 (HTRA1). To some extent, these novel antigens have filled the diagnostic gap for phospholipase A2 receptor (PLA2R)-negative MN. However, the clinical value of these antigens regarding the diagnosis, treatment, and prognosis of MN still requires further research for validation and comprehensive evaluation.

The prognosis of MN varies significantly among individuals. Approximately one-third of patients experience spontaneous remission of the disease; however, another third of patients respond poorly to treatment and eventually progress to end-stage renal disease (ESRD). Effective treatment can significantly reduce the risk of progression to ESRD. Research has demonstrated that the renal survival rate for patients achieving partial remission is 70%, while the renal survival rate for those achieving complete remission reaches 100%.

Improving the effectiveness of treatment is currently a critical focus of clinical concern. With an increasing understanding of the pathogenesis of primary membranous nephropathy (PMN), therapeutic strategies for PMN have advanced considerably over the past decade. Therefore, this review focuses on discussing the recent progress in the treatment of PMN.

1 Stratified Individualized Treatment

Previous treatment protocols for membranous nephropathy (MN) did not emphasize individualized therapeutic models. According to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, patients who continued to exhibit nephrotic syndrome after six months of supportive care were recommended to receive immunosuppressive therapy, including cytotoxic drugs and calcineurin inhibitors (CNIs). In recent years, as our understanding of the risk factors for progression and prognosis of MN has deepened, the 2021 KDIGO guidelines updated the treatment protocols for MN to emphasize an individualized approach.

First, patients with primary membranous nephropathy (PMN) are categorized into four groups based on clinical and laboratory indicators—including quantitative urinary protein, glomerular filtration rate (eGFR), serum anti-PLA2R antibody titers, serum albumin levels, and urinary IgG excretion. These categories represent low, moderate, high, and very high risk of disease progression . Individualized treatment strategies are then proposed based on these risk lev-

els. For example, supportive care is recommended for low-risk patients, while immunosuppressive therapy is discouraged. For moderate-risk patients, supportive care alone or in combination with immunosuppressive therapy—such as rituximab (RTX) or CNIs with or without glucocorticosteroids (GC)—is recommended. High-risk patients are advised to undergo immunosuppressive regimens including RTX, cyclophosphamide (CTX) combined with GC, or a combination of CNI and RTX. Very high-risk patients should be considered for CTX combined with GC. This stratified treatment model allows for better identification of patients likely to undergo spontaneous remission, thereby avoiding unnecessary immunosuppression, effectively balancing efficacy and safety, and further improving patient outcomes.

Normal eGFR, urinary protein < 3.5 g/d, and serum albumin > 30 g/L; or normal eGFR with urinary protein < 3.5 g/d and a reduction in proteinuria of $> 50\%$ after 6 months of ACEI/ARB treatment.

Normal eGFR, urinary protein > 3.5 g/d, with a reduction in proteinuria of $< 50\%$ after 6 months of ACEI/ARB treatment, provided that other indicators do not meet the criteria for high risk.

2 High Risk: Proteinuria > 8 g/d persistent for 6 months

The criteria include a normal eGFR and urinary protein levels > 3.5 g/d, where urinary protein has decreased by $< 50\%$ within 6 months of receiving ACEI/ARB treatment, and at least one of the following conditions is met: (1) serum albumin < 25 g/L; (2) PLA2Rab > 50 RU/ml; (3) urinary α_1-microglobulin > 40 μg/min; (4) urinary IgG > 1 μg/min; (5) urinary β_2-microglobulin > 250 mg/d; or (6) a selective proteinuria index > 0.20.

An eGFR < 60 ml/min/1.73m^2 indicates life-threatening nephrotic syndrome or rapid progression of renal dysfunction. Note: eGFR = estimated glomerular filtration rate; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; PLA2Rab = anti-PLA2R antibody.

2 Non-immunosuppressive Therapy for PMN

Non-immunosuppressive therapy for primary membranous nephropathy (PMN), also known as supportive care, serves as the foundation of treatment for all PMN patients. According to the 2021 KDIGO guidelines, all patients with PMN require supportive therapy. This includes a low-salt diet, blood pressure control, lipid management with statins, and the management of cardiovascular risk factors. Furthermore, the guidelines emphasize the use of renin-angiotensin system inhibitors (RASi) to control both blood pressure and proteinuria.

In recent years, the roles of sodium-glucose cotransporter-2 inhibitors (SGLT2i) and the non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone in supportive therapy have also gained significant attention.

Extensive previous research has confirmed that RASi can effectively reduce proteinuria, delay the progression of kidney disease, and lower the risk of progressing to end-stage renal disease (ESRD). Consequently, RASi therapy is the cornerstone of treatment for proteinuric nephropathies and is recommended by various domestic and international guidelines [**?**]. However, the evidence regarding the benefits of RASi in the specific context of nephrotic syndrome remains a subject of debate.

A small prospective study by Praga et al. demonstrated that the use of angiotensin-converting enzyme inhibitors (ACEI) did not lead to a reduction in proteinuria levels in patients with urinary protein > 5 g/d and concomitant hypoalbuminemia. Another multicenter retrospective study suggested that while RASi use in PMN patients could significantly increase the spontaneous remission rate (79.8% vs. 60.7%, $P = 0.009$), this benefit was limited to patients with baseline urinary protein quantification < 8 g/d. These findings indirectly suggest that high-risk PMN patients with massive proteinuria often require immunosuppressive therapy in addition to standard supportive care.

Recent studies have confirmed that SGLT2i can effectively delay the progression of chronic kidney disease (CKD) and reduce cardiovascular risk in patients. The first randomized controlled trial (RCT) conducted in CKD patients with or without type 2 diabetes demonstrated that dapagliflozin significantly reduced the risk of the primary endpoint (including a $\geq 50\%$ decline in eGFR, progression to ESRD, or renal/cardiovascular death) by 39% (HR 0.70, 95% CI 0.59–0.82, $P < 0.001$). It also reduced the risk of the kidney-specific composite endpoint (including a $\geq 50\%$ decline in eGFR, progression to ESRD, or renal death) by 44% (HR 0.56, 95% CI 0.45–0.68, $P < 0.001$).

The EMPA-KIDNEY study, an RCT evaluating empagliflozin for the treatment of CKD, similarly showed that in CKD patients with or without type 2 diabetes, empagliflozin significantly reduced the risk of the primary composite endpoint (including progression to ESRD, a sustained decline in eGFR of at least 40% from baseline, renal death, or cardiovascular death) by 28% compared to placebo (HR 0.72, 95% CI 0.64–0.82, $P < 0.001$). Meta-analyses of RCT data have further confirmed the role of SGLT2i in slowing CKD progression. Consequently, multiple guidelines and expert consensuses recommend SGLT2i for the treatment of CKD patients [**?**, **?**]. Although there are currently no specific studies focused solely on PMN, SGLT2i is already being considered in clinical practice as a supportive therapeutic option for PMN, which is a common form of non-diabetic CKD.

Existing research indicates that in addition to the renal collecting ducts, mineralocorticoid receptors (MR) are expressed in cardiomyocytes, vascular endothelial cells, vascular smooth muscle cells, podocytes, and mesangial cells. It is currently believed that long-term chronic overactivation of the MR stimulates a series of inflammatory responses, the expression of pro-fibrotic factors, and oxidative stress, leading to cardiorenal tissue damage. Intervention with MRAs has been shown to reduce oxidative stress and inflammatory markers in animal

models while significantly alleviating fibrosis, providing a theoretical basis for the clinical use of MRAs. Finerenone is a non-steroidal MRA with high receptor selectivity and stronger binding affinity, thereby providing more potent anti-inflammatory, anti-fibrotic, and cardiorenal protective effects.

The FIDELITY study, a pre-specified pooled analysis of the entire cohort from two Phase III clinical trials of finerenone in patients with CKD and type 2 diabetes (FIGARO-DKD and FIDELIO-DKD), showed that over a median follow-up of 3 years, the finerenone group had a 23% lower risk of the renal composite endpoint (HR 0.77, 95% CI 0.67–0.88, $P = 0.0002$) and a 14% lower risk of the cardiovascular composite endpoint (HR 0.86, 95% CI 0.78–0.95, $P = 0.0018$) compared to the placebo group. Based on this evidence, current domestic and international guidelines recommend finerenone for patients with type 2 diabetes and CKD.

MR overactivation also occurs in non-diabetic CKD patients. Small-scale retrospective studies have suggested that three months of finerenone treatment can effectively reduce proteinuria in non-diabetic CKD patients, demonstrating favorable efficacy and safety. Furthermore, the FIND-CKD study is an ongoing multicenter, randomized, double-blind, placebo-controlled Phase III clinical trial designed to evaluate the efficacy and safety of adding finerenone to standard therapy in non-diabetic CKD. Therefore, the cardiorenal protective effects of finerenone in non-diabetic kidney disease are currently receiving significant attention, and it is expected to become one of the supportive treatment modalities for MN in the future.

3 Immunosuppressive Therapy

For patients at moderate-to-high risk of disease progression, immunosuppressive therapy is required in addition to supportive care to further improve remission rates and patient prognosis. Current first-line treatment regimens include glucocorticoids (GC) combined with cyclophosphamide (CTX), calcineurin inhibitors (CNIs) [including cyclosporine A (CsA) and tacrolimus] with or without GC, and rituximab (RTX).

The combination of CTX and GC is the most classic treatment regimen. A study comparing this regimen with supportive care for the treatment of membranous nephropathy (MN) demonstrated that CTX combined with GC significantly improved remission rates (74% vs. 34%) and effectively reduced the 10-year risk of progression to end-stage renal disease (ESRD). Consequently, CTX therapy is currently the only treatment proven to reduce the risk of ESRD. Despite its definitive therapeutic efficacy, the higher incidence of adverse events during treatment has limited the widespread clinical application of this regimen. In the 2021 KDIGO guidelines, this protocol is recommended only for patients at high or very high risk. For moderate-to-high-risk patients with primary membranous nephropathy (PMN), CNIs (including CsA and tacrolimus) ± GC represent an alternative therapeutic approach. Previous studies have indicated that 70%–

75% of PMN patients achieve effective remission of nephrotic syndrome following CNI-based therapy, showing efficacy comparable to CTX regimens but with a better safety profile. Compared to CNI monotherapy, combination with GC can further enhance therapeutic efficacy. Although CNI-based treatments offer definitive efficacy and safety—providing early relief of clinical symptoms—this regimen is associated with a high risk of relapse after discontinuation. Therefore, the 2021 KDIGO guidelines suggest that if tacrolimus or CsA treatment is ineffective after 4 months, it should be discontinued; if effective, maintenance therapy is recommended for 12 months before considering a dose reduction to mitigate the risk of relapse.

3.3 RTX

Over the past decade, significant progress has been made in understanding the pathogenesis of membranous nephropathy (MN). Following the discovery that autoantibodies targeting specific phospholipase A2 receptor (PLA2R) antigens on glomerular podocytes—along with other specific antibodies—can be detected in the majority of patients with primary membranous nephropathy (PMN), the role of B lymphocytes in the production of these autoantibodies has garnered extensive clinical attention. These findings provide a strong theoretical foundation for the use of rituximab (RTX) in the treatment of PMN.

Rituximab (RTX) is a chimeric human-murine monoclonal antibody that targets the CD20 molecule on the surface of B lymphocytes. As a first-generation anti-CD20 monoclonal antibody, it eliminates pre-B and mature B lymphocytes through antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and direct cell death mechanisms, thereby effectively inhibiting antibody production. A series of clinical studies have fully demonstrated the efficacy and safety of RTX in treating PMN. Consequently, RTX has now become a first-line treatment regimen for patients with PMN who are at moderate to high risk of progression.

3.3.1 Efficacy of RTX Treatment

According to the 2021 KDIGO guidelines, initial treatment for moderate-to-high risk PMN should include RTX. An observational study suggested that Rituximab (RTX) can effectively reduce anti-PLA2R antibody titers and proteinuria while maintaining a favorable safety profile, indicating that patients may consider RTX as a viable treatment option. GEMRITUX was the first randomized controlled trial (RCT) to evaluate the efficacy and safety of RTX in the treatment of Primary Membranous Nephropathy (PMN) compared to non-immunotherapy alone. The study included 75 patients with PMN and demonstrated that, compared to the control group receiving only non-immunotherapy, six months of RTX treatment led to increased serum albumin levels and decreased anti-PLA2R antibody titers. Although there was no significant difference in the overall response rate (including partial and complete remission) at 6 months (35% vs. 21%), the overall response rate in the RTX group was sig-

nificantly higher than that of the control group at 17 months (65% vs. 35%), confirming the efficacy of RTX in PMN treatment.

A series of clinical studies have also been conducted to compare the efficacy and safety of RTX with other immunotherapy regimens. The MENTOR study, a multicenter RCT involving 130 PMN patients presenting with nephrotic syndrome, compared the efficacy of RTX with Cyclosporine A (CsA), with the primary endpoint being the remission rate at 24 months. The results indicated that the overall remission rate in the RTX group was significantly higher than in the CsA group at 24 months (60% vs. 20%). Furthermore, the RTX group exhibited a faster and more sustained immunological response and better preservation of renal function. While the overall incidence of adverse events was comparable between the two groups, serious adverse events were more frequent in the CsA group (31% vs. 17%). RI-CYCLO, another RCT, compared the efficacy and safety of RTX with a regimen of Cyclophosphamide (CTX) plus Glucocorticoids (GC). The results showed that the overall and complete remission rates, as well as the incidence of adverse reactions, were comparable between the two groups throughout the follow-up period.

Although many clinical studies have evaluated RTX monotherapy in PMN patients, some research has explored combining RTX with other immunosuppressants to further improve outcomes in high-risk patients. A prospective study reported that a combination of low-dose RTX, CTX, and GC achieved a higher clinical remission rate and a shorter median time to remission compared to conventional-dose RTX or CsA plus GC. Another study similarly confirmed that the triple combination of RTX, CTX, and GC yielded higher remission rates and shorter median remission times than the other two groups, while maintaining a good safety profile. For high-risk PMN patients, the combination of RTX and CsA also demonstrated excellent efficacy; results showed that among 13 patients, the overall remission rate reached 85% after 24 months of treatment, with 54% achieving complete remission. The mean urinary protein excretion decreased from (10.8 ± 2.8) g/d to (0.5 ± 0.9) g/d. These findings suggest that combining RTX with other immunosuppressive agents can further enhance therapeutic efficacy in high-risk patients.

Beyond its role in the initial treatment of PMN, RTX maintains therapeutic efficacy in refractory cases, including patients with frequent relapses or those resistant to other immunotherapy regimens. A prospective study from China involving 36 PMN patients who failed to respond to previous immunosuppressive therapy found that the overall response rate reached 42% after RTX treatment. Similar results were obtained in a study from Italy. Furthermore, for patients with refractory PMN, the combination of RTX and low-dose Tacrolimus can further improve clinical remission rates. Consequently, the application of RTX in refractory PMN patients who are resistant to other immunosuppressive treatments or who have experienced relapse is recommended by the 2021 KDIGO guidelines.

3.3.2 Resistance to RTX Treatment

Although Rituximab (RTX) has become a first-line treatment for medium- to high-risk primary membranous nephropathy (PMN), approximately 20% to 40% of patients still exhibit resistance to RTX during the course of treatment. Identifying the causes of RTX resistance is critical for the rational selection and application of therapeutic agents and remains a subject of significant academic interest. Current understanding suggests that, in addition to chronic renal changes, RTX resistance may be associated with the following factors:

(1) Insufficient RTX dosage: In PMN patients with nephrotic syndrome, RTX excretion in the urine is significantly increased, leading to biological activity that is markedly lower than that observed in patients with non-nephrotic autoimmune diseases. Studies have indicated that in 56% of PMN patients presenting with nephrotic syndrome who received RTX treatment (1 g per dose, administered twice at a 2-week interval), the drug was undetectable in the blood three months post-treatment. This phenomenon is particularly pronounced in patients with baseline serum albumin levels below 22.5 g/L, who also show a significantly reduced probability of achieving clinical and immunological remission. Beyond urinary loss, the endocytosis of RTX by targeted B lymphocytes further reduces its biological activity. Consequently, the optimal dosage and administration interval for RTX in patients with nephrotic syndrome have yet to be definitively established.

One study compared the efficacy of different RTX dosages for the treatment of PMN. Patients from the NICE cohort received high-dose RTX (1 g per dose, twice, at a 2-week interval), while patients from the GEMRITUX cohort received low-dose RTX (375 mg/m^2 per dose, twice, at a 1-week interval). The results demonstrated that the high-dose regimen was more effective at depleting B lymphocytes and resulted in higher clinical remission rates. Furthermore, a recent study compared the therapeutic efficacy of four different RTX administration protocols reported in clinical literature, including the two-dose regimen (1 g per dose, twice, at a 2-week interval), the four-dose regimen (375 mg/m^2 administered once weekly for four consecutive weeks), and regimens with additional RTX doses administered based on whether B-lymphocyte repopulation occurs. Low-dose regimens (e.g., 375 mg/m^2 per week $\times$2, 500 mg per week $\times$2, or 100 mg per month) have also been explored. Research suggests that the standard 2-dose or 4-dose regimens are associated with higher remission rates, faster onset of action, and superior B-lymphocyte depletion. For patients with severe nephrotic syndrome, selecting full-dose RTX may reduce the risk of treatment resistance. However, a recent study using pharmacokinetic/pharmacodynamic (PK/PD) modeling suggested that a novel regimen (100 mg per month for 6 consecutive months) achieved B-cell depletion capacity and duration comparable to standard regimens, while significantly reducing the cumulative dose and safety risks. Therefore, monitoring serum RTX concentrations during treatment or utilizing PK/PD models to guide optimized drug use remains a focus for future

research. One study indicated that low serum RTX concentrations at 3 months are an independent risk factor for treatment failure at 6 and 12 months.

(2) Production of anti-RTX antibodies: RTX is a chimeric human-mouse anti-CD20 monoclonal antibody that can stimulate the body to produce anti-RTX antibodies. Studies have shown that 23%–43% of patients receiving RTX treatment develop anti-RTX antibodies during follow-up. The presence of these antibodies leads to more rapid B-lymphocyte repopulation and a higher risk of relapse. Consequently, for patients who exhibit treatment resistance upon RTX re-administration, attention should be paid to the detection of anti-RTX antibodies.

(3) Long-lived plasma cells producing anti-PLA2R antibodies: Mature B-lymphocytes in the periphery are stimulated by foreign antigens, leading to activation, proliferation, and further transformation into plasma cells. Plasma cells include short-lived and long-lived varieties; the latter reside in the bone marrow and inflamed tissues. These long-lived plasma cells can continuously secrete autoantibodies independently of antigen stimulation or B and T-lymphocyte involvement, contributing to pathogenesis, treatment resistance, or disease recurrence. Because long-lived plasma cells do not express the CD20 antigen on their surface, they cannot be effectively cleared by RTX, which may be one of the reasons for RTX treatment resistance.

(4) PLA2R1 epitope spreading: Epitope spreading refers to the immune response targeting epitopes other than the initial dominant epitope of an antigen, which do not show cross-reactivity with the dominant epitope. PLA2R1 contains several epitopes: a cysteine-rich domain (CysR), which is the dominant epitope, a fibronectin type II domain (FNII), and eight C-type lectin-like domains (CTLD1–CTLD8). One study found that in 67% of patients with PLA2R-associated membranous nephropathy, anti-PLA2R antibodies recognized several different epitopes in addition to the dominant one, indicating the occurrence of epitope spreading. Epitope spreading is an independent risk factor for poor renal prognosis and is correlated with treatment failure. Patients with epitope spreading may require higher doses of RTX; however, some studies have reached different conclusions. Therefore, the correlation between epitope spreading and RTX treatment resistance requires further investigation.

3.4 Other Novel Therapeutic Regimens

Current research has confirmed that treatments based on CTX ± GC, RTX, and CNIs can effectively induce remission in PMN. However, approximately 30% of patients remain non-responsive to these regimens, leading to an increased risk of progressive kidney disease. Additionally, some patients experience treatment intolerance or disease recurrence. Therefore, there is a clinical need to seek more effective drugs with different or complementary mechanisms of action. This will

facilitate the establishment of individualized treatment strategies and improve long-term patient outcomes.

3.4.1 Biological Agents Targeting B Lymphocytes

3.4.1.1 Application of Other Anti-CD20 Monoclonal Antibodies Obinutuzumab is a humanized Type II anti-CD20 monoclonal antibody. Through glycoengineering, it significantly enhances direct cell death, antibody-dependent cellular phagocytosis (ADCP), and antibody-dependent cellular cytotoxicity (ADCC), enabling more effective clearance of B lymphocytes. Based on these characteristics, obinutuzumab has been explored for the treatment of patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis who are refractory to rituximab (RTX) or have a history of RTX allergy, demonstrating favorable safety and efficacy. As a new generation of anti-CD20 targeted antibody, it has also become a therapeutic option for primary membranous nephropathy (PMN). Over the past year, several studies have observed the efficacy of obinutuzumab in PMN. Su et al. analyzed the therapeutic outcomes of 59 PMN patients treated with obinutuzumab, of whom 20 received it as initial therapy and 39 had previously received at least one immunosuppressant (second-line therapy); the results showed that 84.7% of patients achieved complete or partial remission. Hu et al. compared the efficacy of obinutuzumab and RTX in PMN patients, demonstrating that obinutuzumab-treated patients had higher remission rates at 12 months and higher immunological remission rates at 6 months compared to the RTX group, with similar safety profiles between the two groups. Xu et al. compared the efficacy of RTX and obinutuzumab in patients with refractory PMN (resistant to previous treatment or relapsed), suggesting that patients treated with obinutuzumab achieved higher clinical remission rates. These studies indicate that obinutuzumab has definitive therapeutic efficacy as both initial and second-line treatment for PMN. Furthermore, case reports suggest that obinutuzumab remains effective even in patients resistant to RTX. For instance, one clinical case report observed three patients with refractory PMN who failed RTX treatment but achieved clinical and immunological remission after switching to obinutuzumab. Currently, two clinical trials (NCT04629248, NCT05050214) are underway, which will provide further evidence for the future application of obinutuzumab in PMN.

Ofatumumab and RTX are both Type I anti-CD20 monoclonal antibodies; however, compared to RTX, ofatumumab exhibits stronger complement-dependent cytotoxicity (CDC). A recent case series demonstrated that seven PMN patients intolerant to RTX all achieved partial or complete remission after receiving ofatumumab. Among ten RTX-refractory PMN patients, three achieved partial or complete remission, suggesting that ofatumumab is a viable, effective, and safe alternative treatment for PMN.

3.4.1.2 Therapies Interfering with B Lymphocyte Activity B cell-activating factor (BAFF) and a proliferation-inducing ligand (APRIL) are both B cell-stimulating factors. They function by binding to three receptors on the surface of B cells: the BAFF receptor (BAFF-R), transmembrane activator and CAML interactor (TACI), and B cell maturation antigen (BCMA). These factors are critical for maintaining B cells and humoral immunity. BAFF plays an essential role in supporting B cell survival and proliferation, regulating class-switch recombination, and selecting autoreactive B cells, while APRIL primarily regulates B cell function and survival and promotes their differentiation into plasma cells. One study found that low serum levels of BAFF and APRIL in anti-PLA2R antibody-positive PMN patients predicted better clinical outcomes. This suggests that, in addition to direct B lymphocyte depletion via anti-CD20 monoclonal antibodies, blocking BAFF and APRIL cytokines to inhibit the production of autoreactive B lymphocytes may also serve as an alternative therapeutic strategy for PMN. Belimumab is a monoclonal antibody targeting BAFF. A study involving 14 anti-PLA2R antibody-positive PMN patients treated with belimumab showed that proteinuria and anti-PLA2R antibody levels decreased by 86% and 97%, respectively. The remission rate at 104 weeks was 64%, with an excellent safety profile. An ongoing randomized controlled trial (RCT, NCT03949855) is currently evaluating whether combining belimumab with anti-CD20 monoclonal antibody therapy yields superior clinical outcomes.

Telitacicept is a monoclonal antibody capable of simultaneously targeting BAFF and APRIL, thereby reducing B lymphocyte survival and their transformation into plasma cells. It also reduces the survival of long-lived plasma cells by inhibiting the binding of APRIL to these cells. A small number of clinical case reports have indicated that refractory PMN patients achieved significant clinical remission after receiving telitacicept, with a relatively long duration of maintained remission. This suggests it may be suitable as a second-line therapy for refractory PMN patients; however, its safety and efficacy still require further validation through large-scale clinical trials. Current research suggests that RTX treatment may promote an increase in systemic BAFF levels, which in turn stimulates the activation of residual B cells and B cell recovery. Considering the different mechanisms of action for inhibiting B lymphocytes, the combined use of RTX with belimumab or telitacicept might achieve faster and more effective therapeutic results, though further studies are needed to confirm this.

3.4.2 Clearance of Autoreactive B Lymphocytes and Induction of Immune Tolerance

Growing evidence suggests the presence of abnormal B lymphocyte subsets and functions in membranous nephropathy (MN). B lymphocytes play distinct roles across the various stages of disease onset, progression, and recurrence. Initially, B lymphocytes facilitate autoantigen presentation, activate effector T cells, and initiate cellular immunity. Subsequently, the breakdown of immune

tolerance leads to the emergence of autoreactive B lymphocytes, which serve as the primary source of MN-related autoantibodies. Furthermore, critical B lymphocyte subsets—including regulatory B cells (Bregs), memory B cells, and plasma cells—contribute to the immune dysregulation involved in disease relapse and treatment resistance. Consequently, strategies focused on the clearance of autoreactive B lymphocytes and the induction of immune tolerance in primary membranous nephropathy (PMN) have gained significant attention.

Chimeric antigen receptor T cells (CAR-T cells) and chimeric autoantibody receptor T cells (CAAR-T cells) are considered promising therapeutic strategies for eliminating pathogenic autoreactive B lymphocytes in antibody-mediated autoimmune diseases. In murine lupus models, CAR-T cells targeting CD19 have demonstrated the ability to continuously deplete $CD19^{+}$ B cells, thereby eliminating autoantibody production, reducing clinical disease manifestations, and extending lifespan.

Another potential therapeutic avenue is the induction of immune tolerance. Patients with PMN often exhibit a deficiency in regulatory T cells (Tregs); thus, the development of CAR-Tregs may represent a promising therapeutic approach to suppress autoimmune responses. Previous studies have explored the application of CAR-Tregs in conditions such as ulcerative colitis. For patients with PMN, particularly those who are refractory to conventional treatments, these emerging biotechnologies may offer new clinical options, though further clinical validation remains essential for the future.

3.4.3 Therapy Targeting Plasma Cells

It has been confirmed in mouse models that disease activity can be effectively inhibited. As previously mentioned, long-lived plasma cells lack CD20 expression on their surface, rendering them resistant to anti-CD20 antibodies. Consequently, these cells can continue to produce autoantibodies even when circulating B lymphocytes are depleted, contributing to treatment resistance and disease relapse. Therefore, therapeutic strategies targeting plasma cells may offer new alternatives.

3.4.3.1 Proteasome Inhibitors Bortezomib, a proteasome inhibitor, can effectively eliminate plasma cells. Several clinical case reports have demonstrated that bortezomib effectively promotes clinical and immunological remission in patients with refractory PMN [**?**, **?**].

3.4.3.2 CD38 Biologics CD38 is expressed on plasmablasts as well as both short-lived and long-lived plasma cells; thus, CD38 biologics can effectively deplete these cell populations. Daratumumab is approved for the treatment of multiple myeloma and light-chain amyloidosis, but its role in the treatment of MN has not been explicitly defined. A recent case report suggested that the use of daratumumab in patients with PMN who were resistant to both CTX and RTX could effectively reduce anti-PLA2R antibody levels and proteinuria.

However, the duration of efficacy was relatively short, which may be related to the induction of B-lymphocyte hyperresponsiveness. Recently, a therapeutic targeting CD38 has shown promise.

The fully human monoclonal antibody felzartamab has released results from its Phase 1b/2a study (NCT04145440) conducted in high-risk patients with primary membranous nephropathy (PMN) who are positive for anti-PLA2R antibodies. The findings indicate that felzartamab induces a rapid partial or complete immunological response in this patient population. By the end of the study, 34.6% of patients achieved partial remission of proteinuria, and 76.9% of patients showed improvement in serum albumin levels.

3.4.4 Complement Inhibitors

Current research has confirmed that activation of the complement system promotes podocyte and tubulointerstitial injury, playing a significant role in the progression of Membranous Nephropathy (MN). Consequently, blocking complement activation and the formation of the C5b-9 membrane attack complex has emerged as a highly anticipated therapeutic strategy. However, eculizumab —a monoclonal antibody that specifically binds to C5 and inhibits its cleavage —failed to demonstrate efficacy in treating primary membranous nephropathy (PMN) in one clinical study. Currently, research is underway for other agents targeting the complement pathway, including MASP2 antagonists, C3 and factor C3b antagonists, and C3aR antagonists.

Mechanistically, anti-complement therapy primarily functions by blocking the renal damage induced by complement activation. Therefore, there is growing interest in whether these agents can serve as synergistic components of other immunosuppressive regimens. This dual approach aims to achieve superior renal protection through two pathways: first, by using anti-complement therapy to rapidly inhibit intrarenal complement activity and mitigate acute injury; and second, by combining this with other immunosuppressants, such as anti-CD20 monoclonal antibodies, to deplete B lymphocytes at the source and reduce the production of pathogenic circulating antibodies. The efficacy of such combination therapy regimens requires further evaluation through future clinical trials.

3.4.5 Extracorporeal Treatment Strategies

In a study involving 10 patients with primary membranous nephropathy (PMN) who were refractory to conventional therapy, researchers evaluated the efficacy of combined treatment using plasmapheresis and rituximab (RTX). The results demonstrated a response rate of 90%. Conversely, a multicenter clinical study in the UK (the PRISM study) assessed the therapeutic efficacy of immunoadsorption in 12 patients with anti-PLA2R antibody-positive membranous nephropathy. Each patient underwent five sessions of immunoadsorption to selectively remove IgG_1, IgG_2, and IgG_4. During the subsequent 12-month follow-up, it was observed that although anti-PLA2R titers decreased immediately following

the immunoadsorption sessions, the clinical outcomes were not significant. Furthermore, anti-PLA2R titers rebounded in some patients during the follow-up period, and only one patient achieved partial remission. While the mechanisms of plasmapheresis and immunoadsorption suggest they may exert therapeutic effects by clearing autoantibodies, the overall efficacy of these extracorporeal treatment strategies remains unclear. Large-scale studies are required to further evaluate their clinical utility.

4 Conclusion

In summary, Membranous Nephropathy (MN) is currently a common clinical pathological type with an incidence rate that is increasing annually. In recent years, the discovery of podocyte-specific antigens has provided a comprehensive understanding of the pathogenesis of MN, leading to the increasing application of various immunosuppressants in its treatment. Currently, Rituximab (RTX) is widely used for the treatment of Primary Membranous Nephropathy (PMN); however, a small subset of patients remains resistant to RTX, the specific mechanisms of which require further investigation and confirmation.

Beyond RTX, other anti-CD20 monoclonal antibodies and extracorporeal treatment regimens have been applied to the treatment of MN, leading to significant progress in its diagnosis and management. Nevertheless, many pathogenic mechanisms remain unclear. As research into the mechanisms of MN continues to deepen and new targets are discovered, more therapeutic drugs targeting different pathways will be developed. These advancements aim to achieve individualized treatment plans characterized by superior efficacy and higher safety profiles.

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