Review

Discovery Medicine 2025; 37(198): 1159–1175
https://doi.org/10.24976/Discov.Med.202537198.104

Pathogenesis and Treatment of Idiopathic Membranous Nephropathy

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Published: 20 July 2025

Idiopathic membranous nephropathy (IMN) is among the leading causes of primary glomerular kidney disease and nephrotic syndrome in adults. Meanwhile, it significantly contributes to the incidence of end-stage renal disease. The complex and unique pathogenesis of IMN poses significant challenges to clinical treatments. The growing research evidence suggests a correlation between phospholipase A2 receptor (PLA2R) antibody levels and disease activity in IMN, while thrombospondin type 1 domain containing 7A (THSD7A) also plays a key role in its pathogenesis. However, the reciprocal regulatory relationship between these target antigens and IMN is yet to be explored, thereby preventing the implementation of targeted therapies as the definitive treatment. In recent years, advances in understanding IMN immunopathogenesis have facilitated the development of targeted immunotherapies, particularly B cell-directed agents such as rituximab. These therapies have demonstrated promising clinical efficacy, with significant reductions in proteinuria and delayed disease progression in a subset of patients. However, treatment resistance, relapses, and adverse events remain prevalent, limiting the widespread adoption of these therapies. This review aims to provide a comprehensive overview of the current understanding of IMN, including its pathogenic mechanisms, clinical features, differential diagnosis, and therapeutic strategies rooted in disease biology. Particular emphasis is placed on balancing efficacy with safety to inform the development of more precise and individualized treatment approaches.

Keywords: idiopathic membranous nephropathy; phospholipase A2 receptor; pathogenesis; therapeutic method

Introduction

Membranous nephropathy (MN) is a leading cause of nephrotic syndrome (NS) in the elderly. Histologically, MN is characterized by subepithelial immune complex deposition and thickening of the glomerular basement membrane (GBM) [1]. The global incidence of MN is approximately 1.2 cases per 100,000 individuals per year [2]. MN can be classified into secondary membranous nephropathy (SMN) and idiopathic membranous nephropathy (IMN), with approximately 75% of cases being diagnosed as IMN [3,4]. IMN is an autoimmune glomerular disease primarily targeting GBM and is diagnosed when no secondary causes are identified. Notably, the incidence of IMN has been increasing steadily in China in recent years [5,6]. While about 30–35% of patients experience spontaneous remission after the onset of proteinuria, 30–40% may progress to chronic kidney disease (CKD) or end-stage kidney disease (ESKD) within 5 to 15 years [7–9].

IMN is characterized by the deposition of immune complexes on the capillary walls and the glomerular basement membrane, with pathological "spike" changes and diffuse thickening, which is categorized as an immune-related glomerular disease [10]. The pathogenesis of IMN primarily involves the production of autoantibodies against specific podocyte-associated antigens, which leads to *in situ* immune complex formation, complement activation, and subsequent glomerular injury [11–13]. In recent years, the high-throughput multi-omics technologies have led to the identification of podocyte antigens, such as neutral endopeptidase (NEP), superoxide dismutase 2 (SOD2), M-type phospholipase A2 receptor (PLA2R), and aldose reductase (AR), all of which play crucial roles in the pathogenesis and progression of IMN [14]. Evidence has demonstrated the presence of autoantibodies targeting these antigens in the serum of some IMN patients [15]. However, the exact triggering factors and mechanisms underlying this autoimmune response remain unclear.

Glucocorticoid (GC) combined with cyclophosphamide (CTX) represents the standard treatment regimen for IMN [16]. Current guidelines recommend the adjunct use of rituximab (RTX) or calcineurin inhibitors (CNI) based on different risk stratification in patients [17,18]. For individuals at high risk of renal dysfunction, treatment options may include RTX, a combination of GC and CTX, or CNI and RTX [19]. However, approximately 20–40% of refractory IMN cases exhibit significant resistance to RTX [20]. Emerging biologics such as ofatumumab, ocrelizumab, daratumumab, and eculizumab have shown

potential in treating patients who are refractory to first-line treatments [21–23]. However, critical scientific questions—such as mechanisms of resistance to biologics and the regulation of complement activation—remain unresolved. Overall, despite significant therapeutic advancements, the complex pathogenesis of IMN poses challenges in achieving accurate diagnosis, effective therapeutic targeting, and sustained treatment response.

Given these limitations, there is a pressing need to systematically review recent advances in IMN research. This article focuses on four key areas: (1) the primary immunopathogenic mechanisms underlying IMN; (2) critical molecular markers and their utility in diagnosis and disease monitoring; (3) current therapeutic strategies, along with their benefits and limitations; and (4) future research directions and emerging therapeutic targets. Together, these discussions aim to provide scientific insight and novel perspectives to guide both basic research and clinical management of IMN.

Pathogenesis of IMN

The renal glomerulus constitutes the fundamental structure responsible for filtration within the kidney. It primarily serves to excrete metabolic waste products and excess fluids from the bloodstream, forming the foundational constituents of urine (Table 1) [24]. Podocytes are star-shaped cells with multiple projections [25,26] that play a crucial role in maintaining the filtration barriers. Podocyte-associated proteins, such as nephrin and podocin, are essential for ensuring the filtration function of the glomerulus. Structural abnormalities or damage to these proteins can impair the integrity and stability of the filtration barrier, leading to substantial proteinuria [25,27]. GBM, a 330–460 nm thick semi-transparent membrane, is composed of an inner loose layer, a dense layer, and an outer loose layer [28]. It collaborates with the glomerular endothelial cells and podocyte foot processes to establish the filtration barrier. The GBM also serves as a primary site for the deposition of circulating immune complexes, which can impair the filtration barrier and adversely impact glomerular function, leading to various renal diseases [29]. Current research predominantly indicates that the pathogenesis of IMN is attributed to the binding of circulating autoantibodies to podocyte antigens, resulting in the formation of subepithelial immune complex deposits. These deposits activate the complement system, resulting in the formation of the membrane attack complex, which consequently impairs the structure and function of podocytes, thereby causing significant proteinuria [5].

Phospholipase A2 Receptor (PLA2R)

A comprehensive summary of the known pathogenic antigens implicated in IMN and their clinical relevance is presented in Table 2 (Ref. [30–34]). Among these antigens, PLA2R remains the most extensively characterized and clinically relevant. Identified as the primary antigen in IMN in 2009 [30], PLA2R is a type I transmembrane glycoprotein encoded by the *PLA2R1* gene located on chromosome 2q23-q24. It is primarily expressed on the surface of podocytes and comprises 1463 amino acids, including a transmembrane domain and an extracellular domain. The extracellular domain is highly complex, comprising eight C-type lectin-like domains, a fibronectin 2 domain, and an N-terminal cysteine-rich domain [1]. In healthy kidneys, PLA2R plays an essential role in regulating lipid-mediated signal transduction by binding phospholipase A2 (PLA2). PLA2R can interact with various types of PLA2, including type B PLA2 and type C PLA2 [35]. These PLA2 enzymes are crucial signaling molecules that catalyze the hydrolysis of phospholipids in the cell membrane, generating arachidonic acid and other lipid mediators that promote the release of pro-inflammatory factors, thereby contributing to endogenous shock, inflammatory responses, and immune reactions [36]. Genetic studies have associated single nucleotide polymorphisms (SNPs) in *PLA2R1* and human leukocyte antigen DQ alpha 1 (*HLA-DQA1*) genes as key contributors to the pathogenesis of IMN. Particularly, the *rs35771982* variant has been consistently linked to increased disease susceptibility. This locus may influence immune recognition or modulate antigen expression, thereby promoting abnormal immune responses [37]. These findings provide valuable insights into genetic architecture underpinning IMN and highlight the significance of the host's genetic background in disease development.

In a healthy human body, the expression of PLA2R typically does not elicit an immune response. However, in IMN patients, PLA2R may act as an autoantigen, triggering an autoimmune reaction. Antibodies against PLA2R, produced by B cells, can form immune complexes with PLA2R on the surface of podocytes. These immune complexes then deposit on the basement membrane, resulting in glomerular injury, proteinuria, and renal dysfunction. Beck *et al.* [30] reported that anti-PLA2R antibodies could be detected in the serum of approximately 70% of IMN patients. In contrast, these antibodies were either present at very low titers or absent in the serum of SMN patients or healthy individuals. Zhang *et al.* [38] conducted a meta-analysis involving 1761 IMN patients from 16 clinical studies, correlating anti-PLA2R antibody titers with disease activity and prognosis. The results demonstrated that positive anti-PLA2R antibody status was often associated with lower rates of complete remission (CR) (OR = 0.37, 95% CI = 0.27–0.51, $p < 0.001$) and spontaneous remission (OR = 0.19, 95% CI = 0.08–0.46, $p < 0.001$), and higher antibody titers were linked to worse patient outcomes. Similarly, Xu *et al.* [39] employed single-cell sequencing technology to analyze the transcriptomic data from renal biopsy samples of six patients with anti-PLA2R antibody-positive IMN and two healthy controls. They observed ele-

Table 1. The component cells of glomerulus and their functions.

Cell type	Function	Clinical manifestations	Diseases
Bowman's capsule epithelial cells	Encapsulates and protects the inner cells and structures of the glomerulus, helping to direct the filtrate towards the renal tubular system	Proteinuria	Nephrotic syndrome
		Edema	
		Hypoalbuminema	
Glomerular capillary endothelial cells	Forms the filtration barrier of the glomerulus, allowing small molecules such as water and ions to pass freely, but blocking large molecules like proteins	Proteinuria	Glomerulonephritis
		Hematuria	Nephrotic syndrome
		Edema	
		Hypoalbuminema	
Glomerular basement membrane	Serves as a key selective barrier for solutes in the blood being filtered	Proteinuria	Glomerulosclerosis
		Hematuria	Glomerulonephritis
		Hypoalbuminema	
Mesangial cells	Regulates the glomerular filtration rate, and participates in the repair of glomerular damage	Proteinuria	Nephrotic syndrome Glomerulonephritis
		Hypoalbuminema	
Podocytes	Covers the outer surface of glomerular capillaries, forming a secondary filtration barrier	Proteinuria	Nephrotic syndrome Glomerulonephritis
		Edema	

vated activation of genes associated with inflammation and immune regulation in patients with anti-PLA2R antibody-positive IMN. Notably, the interleukin-17 (IL-17) signaling pathway, tumor necrosis factor (TNF) signaling pathway, nucleotide-binding oligomerization domain (NOD)-like receptor signaling pathway, and mitogen-activated protein kinase (MAPK) signaling pathway were substantially activated. These findings provide crucial insights that can guide the development of therapeutic strategies for patients with anti-PLA2R antibody-positive IMN.

Seitz-Polski *et al.* [40] revealed the heterogeneity of anti-PLA2R1 autoantibodies in MN, identifying at least three critical epitope clusters—cysteine-rich (CysR) domain, fibronectin type II (FNII), and C-type lectin-like domain 1 (CTLD1). Upon examining these epitope clusters in 69 patients with PLA2R-positive MN, they observed that as patients aged, some patients might develop antibodies against additional functional domains, suggesting an epitope-spreading phenomenon. These patients demonstrated a lower response to immunosuppressive therapy and had reduced renal survival rates. Multivariate analysis indicated that epitope spreading of PLA2R and the titers of anti-PLA2R antibodies are risk factors for poor renal prognosis, suggesting that epitope spreading could serve as a significant biomarker for predicting disease outcomes. Furthermore, in the early stages of IMN, circulating anti-PLA2R antibodies may be sequestered by the kidneys, acting as a "sink" by binding to antigens on podocytes and depositing in the GBM, rendering them undetectable in the circulation [41]. As the disease progresses, renal tissues become saturated with anti-PLA2R antibodies, resulting in seropositivity. This phenomenon explains why some patients exhibit seronegative anti-PLA2R antibodies early in the disease and become seropositive at later stages. High levels of anti-PLA2R antibodies are currently believed to indicate a lower likelihood of spontaneous remission in patients, with further increases in antibody levels often signaling a relapse or exacerbation of the disease [42].

Despite the utility of anti-PLA2R antibodies in diagnosing IMN, approximately 10–15% of patients remain seronegative throughout the disease course yet still demonstrate PLA2R antigen positivity on renal biopsy. This discrepancy underscores the limitations of relying solely on serological testing and reinforces the significance of renal biopsy as the diagnostic gold standard. Although renal biopsy is an invasive approach and can potentially impact patient quality of life, it remains indispensable—particularly in seronegative cases or when there is clinical ambiguity [43]. In certain patient populations, such as elderly individuals with frailty, multiple comorbidities, or those who have had failed renal biopsies, anti-PLA2R antibody testing may serve as a valuable non-invasive diagnos-

Table 2. A list of pathogenic antigens causing IMN and their clinical relevance.

Pathogenic antigens	Abbreviation	Positive rate in IMN	Clinical relevance
M-type phospholipase A2 receptor	PLA2R	70–80%	Approximately 70% of patients with IMN exhibit positive anti-PLA2R antibody titers, which are closely correlated with disease activity, outcomes, and remission induction [30].
Thrombospondin type 1 domain containing 7A	THSD7A	3–5%	In 3–5% of PLA2R-negative patients with IMN, anti-THSD7A antibodies have been detected in serum [31].
Neural epidermal growth factor-like 1	NELL1	Rare	In a cohort study involving 126 patients with PLA2R-negative membranous nephropathy, mass spectrometry was initially performed on 35 cases, identifying NELL1 positivity in 6 patients. Subsequent screening of the remaining 91 cases revealed an additional 23 NELL1-positive cases, yielding a total of 29 patients—approximately 23% of the cohort—classified as having NELL1-associated membranous nephropathy [32].
Exostosin 1/2	EXT1/EXT2	Rare	In a cohort of 21 patients with MN who tested negative for anti-PLA2R antibodies, EXT1/EXT2 positivity was detected, and among these, 80.7% were associated with autoimmune diseases [33].
Semaphorin 3B	Sema3B	Rare	Sema3B positive was detected in 3 of 70 MN patients with anti-PLA2R antibody negative [34].

IMN, idiopathic membranous nephropathy; PLA2R, phospholipase A2 receptor; MN, membranous nephropathy; EXT1/EXT2, exostosin 1/2; NELL1, neural epidermal growth factor-like 1; THSD7A, thrombospondin type 1 domain containing 7A.

tic and prognostic tool, helping in both clinical decision-making and therapeutic stratification [44].

Thrombospondin Type 1 Domain Containing 7A (THSD7A)

Thrombospondin type 1 domain containing 7A (*THSD7A*) is a gene that encodes a membrane-associated glycoprotein [45]. This protein is expressed in various human tissues, including the kidneys, heart, lungs, and brain, with a molecular weight of approximately 250 kDa [46]. THSD7A contains multiple thrombospondin-like domains, which are protein domains commonly linked to coagulation and immune processes. THSD7A potentially participates in a range of physiological processes, such as blood coagulation, cell adhesion, and immune responses. Its expression in podocytes, a type of kidney cell, is particularly prominent, as it is closely associated with the structure and function of these cells, especially in the formation and maintenance of foot processes [47]. Dysregulation or aberrant expression of THSD7A can lead to podocyte damage and dysfunction, consequently disrupting glomerular filtration and resulting in significant proteinuria.

In 2014, Tomas *et al.* [31] identified anti-THSD7A antibodies in the serum of 3–5% of all IMN patients, with the positivity rate rising to 8–14% in patients who tested negative for anti-PLA2R1 antibodies. This led to the identification of THSD7A as a novel target antigen implicated in the pathogenesis of IMN. Genetic mutations in THSD7A, along with an autoimmune response mediated by THSD7A-related Immunoglobulin G4 (IgG4) antibodies, are potential crucial pathogenic factors leading to podocyte injury and the onset of nephrotic syndrome associated with IMN [1]. Ren *et al.* [48] conducted a meta-analysis on the titer levels of anti-THSD7A antibodies in the serum of 4121 patients with IMN, using data from 10 clinical studies. The results revealed that the overall positivity rate for anti-THSD7A antibodies among IMN patients was 3% (95% CI: 3%–4%). However, in patients with IMN who were negative for anti-PLA2R antibodies, the positivity rate for anti-THSD7A antibodies increased to 10% (95% CI: 6%–15%). Liu *et al.* [49] observed that anti-THSD7A antibodies exhibited a sensitivity of 4% and a specificity of 99% in the diagnosing IMN. Moreover, for the diagnosing anti-PLA2R antibody-negative IMN, the sensitivity increased to 8%, with a specificity of 100%, achieving an area under the receiver operating characteristic curve (AUC) of 0.99. These observations suggest that anti-THSD7A antibodies possess strong diagnostic efficacy for IMN, particularly in the absence of anti-PLA2R antibodies.

Additionally, mutations in the *THSD7A* gene may alter the structure and function of the THSD7A protein, leading to podocyte dysfunction and a subsequent impairment of glomerular filtration. Intriguingly, THSD7A has also been associated with the occurrence of certain types of malignant tumors, including colorectal cancer, renal cancer, breast cancer, and prostate cancer [50,51]. While the current understanding of the role and pathological significance of THSD7A in IMN is still incomplete, existing studies suggest that THSD7A may serve as a crucial molecular marker in the pathogenesis of IMN and potentially provide a novel

target for its diagnosis and treatment. However, further research is warranted to better utilize anti-THSD7A antibodies for diagnosing and treating IMN, as well as preventing or reversing THSD7A-mediated glomerular injury.

Recent advances in understanding the function and pathogenic mechanisms of THSD7A have positioned anti-THSD7A antibodies as a promising diagnostic tool, particularly in anti-PLA2R-negative IMN cases. These antibodies not only facilitate disease subclassification but also offer the potential to assess disease activity and guide individualized immunotherapy. The development of therapeutic strategies targeting THSD7A-mediated autoimmunity could open new avenues for precision treatment, representing a critical step in translating mechanistic insights into clinical interventions.

Other Novel Pathogenic Antigens

Several clinical studies have shown that the proportion of IMN patients who are negative for both anti-PLA2R and anti-THSD7A antibodies ranges from 28.7% to 73.43% [20,31,52–55]. Thus, it suggests the presence of unidentified or1,1 unconfirmed novel target antigens that may be involved in the pathogenesis of IMN. Recent studies [32,33,56,57] have expanded the landscape of IMN-associated target antigens, identifying reactivity against proteins such as neural epidermal growth factor-like 1 (NELL1), semaphorin 3B (SEMA3B), protocadherin 7 (PCDH7), and exostosin 1/2 (EXT1/EXT2) in specific patient subsets. Additionally, high-temperature requirement A serine protease 1 (HTRA1) has been recognized as a target antigen in approximately 1–2% of IMN cases. Increased levels of circulating anti-HTRA1 antibody have been shown to correlate with disease activity, decreasing as remission is achieved, suggesting their potential as dynamic biomarkers [58].

Al-Rabadi *et al.* [58] further reported that among patients negative for PLA2R, THSD7A, NELL1, and EXT1/EXT2, up to 4.2% tested positive for anti-HTRA1 antibodies. Caza *et al.* [59] used confocal microscopy to observe the co-localization of neural cell adhesion molecule 1 (NCAM1) with IgG1 in renal glomerular immune complexes. Western blot analysis and indirect immunofluorescence assays revealed that 2% of IMN patients and 6.6% of those with membranous lupus nephritis (MLN) tested positive for anti-NCAM1 circulating antibodies. Beyond HTRA1, the expressions of NELL1, SEMA3B, PCDH7, and EXT1/EXT2 in podocytes are notably low. Moreover, the positivity rates of NCAM1 and EXT1/EXT2 are higher in IMN patients with autoimmune diseases like systemic lupus erythematosus (SLE), suggesting a greater relevance of these target antigens to autoimmunity.

Neural Epidermal Growth Factor-like 1 Protein (NELL1)

NELL1 is a 90-kDa secreted protein comprising a signal peptide, an N-terminal platelet-derived growth factor-like domain, a coiled-coil domain, four von Willebrand factor type C domains, and six epidermal growth factor-like repeats [60]. NELL1-associated membranous nephropathy (NELL1-MN) is characterized by substantial clinical and pathological heterogeneity, with etiologies ranging from drug exposure and malignancy to post-transplant immune dysregulation. Notably, the development of NELL1-MN has been closely linked to thiol-containing medications, which may mimic the disulfide bond conformation of the NELL1 protein. This structural mimicry can expose cryptic epitopes and trigger an IgG4-dominant autoimmune response [61,62]. Approximately 15–20% of patients with NELL1-MN are also diagnosed with solid tumors, most commonly colorectal and breast cancer. Pathological analysis has revealed markedly elevated NELL1 expression in tumor tissues compared to adjacent normal tissues, suggesting that tumor antigen escape may contribute to disease pathogenesis [63]. This finding provides new insights into the correlation between tumor immunity and renal autoimmunity.

NELL1 has emerged as a novel target antigen in membranous nephropathy, particularly in patients who are seronegative for both PLA2R and THSD7A. In a cohort of 126 PLA2R-negative MN patients, mass spectrometry identified NELL1 positivity in 6 of the first 35 cases, with an additional 23 positive cases among the remaining 91, yielding an overall prevalence of approximately 23% [32]. Other studies have reported that NELL1 accounts for 5–23% of PLA2R/THSD7A-negative MN cases [64], with a Chinese cohort exhibiting a higher rate of 35%, particularly among female patients [65].

Immunologically, NELL1-MN differs from classical PLA2R-MN, as renal biopsies in NELL1-MN typically show co-deposition of NELL1 and IgG1, whereas PLA2R-MN is characterized by IgG4 dominance [32]. Mechanistic studies suggest that NELL1, an extracellular matrix protein, deposits along the glomerular basement membrane. Its conformation-dependent epitopes are recognized by autoantibodies, resulting in the *in situ* formation of immune complexes that mediate glomerular injury and drive disease progression [32].

Identifying NELL1 as a target antigen expands diagnostic options for PLA2R/THSD7A-negative patients. Given its distinctive immunopathological profile and association with malignancy, NELL1 testing may inform individualized therapeutic strategies and enable early tumor screening, particularly in women and individuals with relevant drug exposure histories.

Semaphorin 3B (SEMA3B)

SEMA3B is a recently identified target antigen implicated in approximately 4–6% of membranous nephropathy cases of previously unknown etiology. It is primarily associated with pediatric-onset disease and displays distinct pathological and immunologic features. In children un-

der two years of age, kidney biopsies often reveal immune complex deposition along glomerular and tubular basement membranes, along with tubuloreticular inclusions in endothelial cells [33]. SEMA3B is an 83-kDa secreted protein that contains a semaphorin domain, a plexin-semaphorin-integrin (PSI) domain, an Ig-like domain, and a basic domain [66]. Its extracellular region is rich in conserved cysteine residues that are essential for its biological activity. Members of the semaphorin 3 protein family and their receptors are expressed in endothelial cells, podocytes, and renal tubular epithelial cells [67,68].

The pathogenesis of SEMA3B-associated MN is thought to involve the release of SEMA3B from podocytes, inducing an autoimmune response. This leads to the *in situ* formation of immune complexes and consequent glomerular injury [34]. Clinically, SEMA3B may serve as a diagnostic biomarker in PLA2R-negative patients. In a study of 70 PLA2R antibody-negative MN patients, three were found to be positive for SEMA3B [34], indicating that while rare, SEMA3B should be considered as a potential antigen even in adult-onset cases.

Regarding therapy, a case report documented a pediatric patient with SEMA3B-MN who did not respond to rituximab but achieved a significant reduction in proteinuria after treatment with obinutuzumab—a dual-targeting anti-CD20/CD19 antibody [69]. This suggests that conventional B cell–depletion strategies may be insufficient, and targeting both CD20 and CD19 may offer a more effective management approach. The discovery of SEMA3B broadens the antigenic spectrum of childhood membranous nephropathy and points to a potentially distinct immunopathological mechanism. Its antigen-specific recognition could aid in early diagnosis and guide the selection of targeted immunotherapies, particularly in children unresponsive to standard treatments.

Exostosin 1/2 (EXT1/EXT2)

Sethi *et al.* [33] identified EXT1 and EXT2 as novel antigens within subepithelial immune deposits in patients with PLA2R-negative MN, suggesting a potential link between EXT1/EXT2 and autoimmune-associated MN. This finding was further validated by Hanset *et al.* [70], who utilized immunofluorescence techniques to detect EXT1/EXT2 positivity in 3 out of 45 PLA2R-negative MN cases from Europe. Notably, two of these patients were female; all three tested positive for antinuclear antibodies, and glomerular C1q deposition was observed in all cases, further supporting the presence of an autoimmune background.

In another study involving 21 patients with PLA2R-negative MN, EXT1/EXT2 positivity was detected in 3 cases, with 80.7% of the cohort having comorbid autoimmune conditions like systemic lupus erythematosus [33]. These findings underscore the clinical relevance of EXT1/EXT2 in MN with unclear antigenic etiology, particularly in identifying underlying autoimmune mechanisms.

EXT1/EXT2-positive MN is primarily found in patients with systemic autoimmunity, including SLE [33,71]. The EXT family comprises five proteins: EXT1, EXT2, EXTL1, EXTL2, and EXTL3. EXT1 (86 kDa) and EXT2 (82 kDa) share structural homology and typically form heterodimers [72]. Mutations in the *EXT1* and *EXT2* genes are associated with autosomal dominant hereditary multiple exostoses [73,74]. Previously, Roberts and Gleadle [75] reported a case of hereditary focal segmental glomerulosclerosis coexisting with multiple exostoses. The identification of EXT1/EXT2 offers a valuable tool for diagnosing autoimmune-associated MN, particularly lupus nephritis with a membranous pattern. As immunologic biomarkers, EXT1/EXT2 aids in accurate and differential diagnosis, and may also guide the intensity of immunosuppressive therapy and monitoring of treatment response.

Complement Activation

As a critical component of the innate immune system, the complement cascade plays a central role in the pathogenesis of IMN, with the membrane attack complex (MAC, C5b-9) being a key effector responsible for podocyte injury and subsequent proteinuria. Complement activation occurs via three classical pathways: the classical, lectin, and alternative pathways [76]. Although IgG4 is the predominant antibody subclass in IMN—and does not activate the classical pathway—studies have shown that IgG1 may predominate in the early stages of the disease, accompanied by C1q deposition, suggesting a transient involvement of the classical pathway in early disease [77,78].

The lectin and alternative pathways are considered the major drivers of complement activation in IMN. IgG4 can bind to mannose-binding lectin (MBL), activating MBL-associated serine proteases, C4, and C2 sequentially, which results in the formation of C3 convertase and, ultimately, the MAC. Elevated MBL levels have been observed in both serum and renal tissue of IMN patients, correlating with proteinuria severity and renal function decline [53,79,80].

The alternative pathway, which does not need immune complexes, is activated when C3b directly binds to target surfaces, stabilized by factors B, D, and properdin. Renal biopsies from IMN patients frequently show deposition of factor B, C3, and C5b-9 in the absence of C1q and C4d, indicating predominant activation via the alternative pathway [81,82]. Furthermore, disruption of the GBM anionic barrier may impair recruitment of factor H, a negative regulator of the alternative pathway, thus exacerbating local complement activation and glomerular injury [83]. C5b-9 not only exerts direct cytotoxic effects on podocytes through membrane attack but also activates a range of downstream signaling pathways that regulate podocyte function, ultimately compromising the integrity of the glomerular filtration barrier [84]. Sublytic C5b-9 has been shown to activate the Transient Receptor Potential Canonical 6 (TRPC6) channel, leading to increased intracellular calcium levels

and aberrant phosphorylation of key cytoskeletal proteins such as nephrin and podocin, which destabilize podocyte architecture [85]. Through the lectin pathway of complement activation, C5b-9 plays a crucial pathogenic role in podocyte injury during idiopathic membranous nephropathy (IMN) [86]. Recent evidence has further revealed that C5b-9 causes structural damage via membrane insertion and activates the Wnt/β-catenin signaling cascade, inducing dysregulated autophagic responses that can disrupt the glomerular filtration barrier [87].

Collectively, these findings highlight the pivotal role of the complement system—particularly lectin- and alternative pathway-mediated formation of C5b-9—in IMN pathogenesis. Targeting complement activation, such as inhibiting C5 cleavage, suppressing MBL pathway activation, or modulating downstream effectors like TRPC6 or the Wnt/β-catenin pathway, could offer novel therapeutic strategies for managing proteinuria and fostering disease remission. Furthermore, the expression levels of MBL and C5b-9 in serum and renal tissue may serve as promising biomarkers for evaluating disease activity and treatment response, thereby supporting precision medicine approaches in IMN management.

Currently, laboratory testing for these unconfirmed target antigens has not been widely adopted in clinical practice, and the significance of these target antigens or their corresponding autoantibodies in assessing disease activity and prognosis in IMN remains unclear. In the future, we anticipate larger sample sizes and more accurate testing methods to offer a better understanding of the clinical utility of these novel biomarkers in diagnosing IMN and predicting its prognosis.

Therapies

As insights into the pathogenesis of IMN continue to increase, treatment strategies have gradually shifted from empirical immunosuppression to mechanism-driven, immunophenotype-based precision interventions. The identification of pathogenic antigens such as PLA2R and THSD7A, along with their corresponding autoantibodies, has enabled the use of antibody titers as key indicators for determining the timing and regimen of immunotherapy. This section summarizes current treatment approaches, focusing on supportive care, immunosuppressive therapy, and emerging targeted therapies.

General Supportive Care

General supportive care is crucial in managing IMN, addressing key facets such as blood pressure management, edema relief, nutritional support, and infection prevention. Given the wide range of symptoms and complications in IMN patients, including proteinuria, hypertension, edema, hyperlipidemia, malnutrition, and thrombosis, a personalized and comprehensive treatment plan is typically necessary to address the specific conditions of each patient [88]. This holistic approach facilitates addressing the diverse needs of the individual effectively. In clinical practice, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are frequently used to manage blood pressure in patients with IMN [89]. These medications can potentially reduce proteinuria by constricting the afferent arteriole, thereby improving the long-term prognosis for patients with kidney disease. Furthermore, managing water and sodium balance is also crucial. To mitigate fluid retention and alleviate edema, restricting sodium intake and judiciously administering diuretics is recommended. Excessive protein intake in IMN patients can exacerbate the disease by elevating proteinuria. Thus, managing protein intake—while ensuring sufficient consumption to avert malnutrition—has significant implications. Hyperlipidemia, a common occurrence in IMN, elevates the risk of thrombosis. Therefore, statins are regularly administered to improve lipid metabolism and reduce the risk of cardiovascular diseases [90].

Additionally, in patients at higher risk of hypercoagulability and thrombosis due to hypoalbuminemia, prophylactic anticoagulation may be considered under physician guidance after ensuring that there are no contraindications to anticoagulation treatment. Lastly, adopting a healthy and proactive lifestyle is an effective form of supportive treatment. This includes avoiding smoking, limiting alcohol intake, engaging in regular physical activity, maintaining a healthy weight, ensuring sufficient sleep, and managing stress.

Immunosuppressive Therapy

Glucocorticoids (GCs)

For many years, GC has been the standard treatment for IMN. This treatment primarily involves using GC, often in conjunction with immunosuppressive agents, with the objective of reducing the host's immune and inflammatory responses against renal tissues, thereby decreasing proteinuria. The basic GC regimen begins with an initial phase of high-dose corticosteroid pulse therapy, typically using methylprednisolone at a dosage of 1 g per day, administered intravenously for three consecutive days. Following this, the patient transitions to oral prednisone, with the dosage adjusted based on the patient's body weight, typically around 1 mg/kg/day, and sustained for a period of 4–6 weeks [18]. Subsequently, the dosage of prednisone is progressively tapered, usually halving the dosage every two weeks until discontinuation. This meticulously designed course aims to attenuate the disease's impacts while minimizing the potential side effects of the pharmacological agents involved. A recent systematic review and network meta-analysis of 28 randomized controlled trials (n = 1830) compared the efficacy and safety profiles of different GC regimens combined with immunosuppressants in IMN [91]. The total remission rate for moderate- to high-dose

GC combined with cyclophosphamide (CTX) was 76.9% (Relative risk (RR) = 2.15, 95% CI: 1.29–3.64), while for low-dose GC combined with calcineurin inhibitors (CNIs), it was slightly higher at 82.6% (RR = 2.16, 95% CI: 1.25–3.95). Although both regimens achieved comparable remission rates, high-dose GC was associated with significantly increased risks of severe adverse events, particularly infections and steroid-induced diabetes, with incidence rates 1.5–2 times higher than those found with alternative regimens.

The therapeutic effects of GC therapy for IMN typically become apparent within 3–6 months of treatment initiation, characterized by a substantial reduction in proteinuria and enhancement in renal function [92,93]. However, GC therapy does not yield positive outcomes among all IMN patients; approximately 30% of patients show no response to the therapy. Moreover, therapy may cause a variety of adverse effects, including infections, hypertension, hyperglycemia, and osteoporosis. Therefore, before initiating GC therapy, a comprehensive assessment of the patient's health status and disease severity is essential. This aids in selecting the appropriate GC and immunosuppressants, determining the correct dosage, and setting the duration of treatment, with the ultimate aim of optimizing symptomatic improvement and prognosis while minimizing side effects. Throughout the treatment course, regular monitoring of proteinuria and renal function is vital for evaluating therapeutic effectiveness and making necessary adjustments. Concurrently, vigilance towards any adverse effects of the GC therapy is crucial; if such effects emerge, the treatment plan should be promptly revised, and appropriate management measures should be implemented. In summary, while hormonal therapy is a crucial element in IMN treatment, it necessitates personalized treatment plans and meticulous therapeutic management to achieve optimal therapeutic outcomes.

Cyclophosphamide (CTX)

According to KDIGO guidelines, the combination of GCs and CTX remains the first-line immunosuppressive regimen for IMN [94]. This regimen has proven effective in inducing remission and preserving renal function. However, its safety profile warrants careful consideration. A prospective study demonstrated that membranous nephropathy patients treated with CTX exhibited a significantly higher incidence of infections within one year (26.58% vs. 15.49%) and a greater frequency of serious adverse events (8.45% vs. 2.86%), including cerebral infarction, stroke, and pneumonia, compared to those receiving rituximab [95]. This has prompted the exploration of alternative or modified regimens aimed at reducing treatment-related toxicity while maintaining therapeutic efficacy. Duan *et al.* [96] compared the traditional GC-CTX regimen with a triple immunosuppressive protocol that included GC, CTX, and mycophenolate mofetil (MMF). While both strategies achieved comparable rates of clinical remission, the triple regimen was associated with fewer adverse events. This combination has been recommended particularly for patients with persistent nephrotic syndrome, where the benefit of alleviating the risk of renal failure may outweigh the risk of mild-to-moderate adverse events.

Internationally, the modified Ponticelli regimen—alternating monthly cycles of GC and CTX—has been widely adopted and has shown therapeutic equivalence to the combination of GC and calcineurin inhibitors in reducing proteinuria and inducing remission [93]. Nevertheless, concerns about the cumulative toxicity of high-dose GC pulses persist. In response to these concerns, Mathrani *et al.* [97] proposed a lower-intensity alternative by replacing intravenous GC pulses with oral GC in combination with CTX. Their results demonstrated similar remission rates but a significant reduction in clinical complications, suggesting superior tolerability of this modified oral protocol. Based on these findings, a gradual tapering schedule of oral prednisone combined with CTX may be more appropriate for patients with stable disease, minimal risk of progression to end-stage kidney disease, or slow disease evolution. Conversely, for patients whose disease worsens—manifested by sustained elevation of autoantibody titers, increased proteinuria, progressive edema, or deteriorating renal function after eight weeks of therapy—the more intensive Ponticelli regimen should be considered.

Despite its efficacy, CTX-based therapy carries a substantial risk of toxicity, including bone marrow suppression, gonadotoxicity, infections, hepatotoxicity, hemorrhagic cystitis, and secondary malignancies [98,99]. To mitigate these risks, a structured monitoring and prevention strategy is essential. This approach should include regular laboratory evaluations (such as blood counts, urinalysis, liver and renal function, and electrolytes), prophylactic hydration, co-administration of Mesna, and infection prevention measures. For female patients, menstrual tracking and serum sex hormone monitoring are recommended to assess reproductive toxicity and guide decisions regarding fertility preservation.

Calcineurin Inhibitors (CNIs)

The anti-PLA2R antibody plays a pivotal role in the pathogenesis of IMN. Therefore, therapeutic strategies targeting the M-type PLA2R, such as calcineurin inhibitors (CKIs), have emerged as promising options for managing IMN. These inhibitors can suppress PLA2R activity, hinder the binding of antibodies, and prevent the formation of immune complexes, thereby ameliorating glomerular inflammation and proteinuria. Recent clinical trials have substantiated the effectiveness and safety of CKIs in the treatment of IMN. He *et al.* [100] conducted a study involving 56 patients diagnosed with IMN, utilizing therapeutic protocols that combined corticosteroids with

either tacrolimus or CTX. The results indicated that the complete remission (CR) rate for patients treated with the corticosteroids-tacrolimus combination was 64.3% (18/28), with a partial remission (PR) rate of 25.0% (7/28). Conversely, the corticosteroids-CTX combination yielded a CR of 28.6% (8/28), with a PR of 35.7% (10/28). Moreover, the corticosteroids-tacrolimus protocol demonstrated superior efficacy in improving serum albumin levels and reducing proteinuria in patients with IMN, suggesting a more favorable long-term prognosis for this patient population. However, the STARMEN trial reported that the corticosteroid combined with CTX was more effective in treating MN than tacrolimus combined with rituximab [101].

Among CNIs, tacrolimus is widely used, but it is associated with nephrotoxicity, which, although reversible, can increase the risk of chronic kidney disease and mortality [102,103]. Other substantial adverse effects include neurotoxicity, hyperglycemia, and increased infection susceptibility. Therefore, therapeutic drug monitoring is essential. During the early phase of treatment, weekly monitoring of tacrolimus or cyclosporine blood concentrations, serum creatinine, and electrolytes is recommended. Dosage adjustments should be made cautiously and individualized to minimize toxicity. The concurrent use of other nephrotoxic agents, such as non-steroidal anti-inflammatory drugs (NSAIDs) or high-dose ACEIs/ARBs, should be avoided.

For patients with IMN who do not respond to traditional immunosuppressive therapies, the use of CNIs provides a novel therapeutic avenue. Despite CNIs potential in treating IMN, additional research is necessary to delineate their optimal application strategies, such as the ideal dosage and treatment duration. Moreover, even though the majority of patients experience relatively mild side effects from CNIs, further investigations are required to ascertain their long-term safety profile. Overall, CNIs represent a new direction in IMN treatment, potentially enhancing the quality of life and prognosis for patients afflicted by this disease.

Biologic Therapies

Rituximab (RTX)

RTX is a monoclonal antibody specifically targeting CD20, a marker on B cells. Since the pathogenesis of IMN may be associated with aberrant B cell activity and the production of auto-reactive antibodies, such as anti-PLA2R antibodies, suppressing B cell activity or reducing the production of auto-reactive antibodies could help reduce IMN symptoms and enhance prognosis [104]. By binding to CD20 on B cells, RTX induces their apoptosis, thereby reducing the production of antibodies and mitigating autoimmune attacks on the glomerular epithelial cells [104,105].

Currently, RTX has shown promising therapeutic efficacy in treating IMN, significantly reducing proteinuria and improving renal function and has been effective in treating certain refractory and recurrent cases. IMN patients treated with RTX had an overall response rate of 66%, with a CR of 27.8%, showing better clinical efficacy compared to standard corticosteroid therapy [106]. The results from the RI-CYCLO trial [107] demonstrated that the RTX monotherapy for MN was comparable to a combined regimen of corticosteroids and CTX, with complete or partial remission rates of 83% for RTX and 82% for the combined treatment regimen over a two-year period. Furthermore, no significant differences have been observed in the incidence of adverse reactions between the two treatment strategies. However, a randomized controlled clinical trial showed that MN patients treated with RTX had a higher clinical response rate, with a faster and more substantial decline in anti-PLA2R antibody titers and a longer duration of remission than those treated with cyclosporine alone [108].

In the management of IMN, serial monitoring of 24-hour proteinuria and serum anti-PLA2R antibody titers provides a practical approach to evaluate therapeutic efficacy and guide treatment adjustments. Ruggenenti *et al*. [109] demonstrated that lower baseline anti-PLA2R antibody levels were associated with a higher likelihood of remission. Six months after RTX therapy, 71.9% of patients achieved seroconversion, and those who became antibody-negative had significantly better remission outcomes than those who remained seropositive. On average, antibody clearance preceded clinical remission by approximately 2.66 months. Conversely, a rebound in antibody titers served as a predictor of relapses, supporting the significance of dynamic serological monitoring in predicting both treatment response and disease recurrence. Dahan *et al*. [20] also observed that serum albumin levels increased before a decline in proteinuria following RTX administration, suggesting that RTX may exert early effects by improving glomerular barrier function or enhancing albumin synthesis. This was especially evident in patients who were anti-PLA2R antibody-negative at baseline, in whom serum albumin could serve as a useful early biomarker of treatment response.

Given the clinical and immunological heterogeneity of IMN, risk stratification and personalized treatment strategies are warranted. Patients with high anti-PLA2R antibody titers (>150 RU/mL) typically present with more severe nephrotic syndrome, including higher levels of proteinuria, hypoalbuminemia, and reduced remission rates. These patients may benefit from more intensive or combination immunosuppressive regimens—such as high-dose or repeated RTX infusions or adjunctive therapies like cyclophosphamide and corticosteroids—to achieve optimal outcomes [110]. Persistent heavy proteinuria also indicates active disease, requiring more aggressive intervention. In patients with declining renal function, RTX should be used cautiously, balancing immunosuppressive efficacy with nephroprotection. Early recovery of serum albumin can serve as a practical surrogate for early treatment response. Future investigations should focus on establishing comprehensive, multidimensional risk stratification models that integrate serological, clinical, and immunopheno-

Table 3. Common drugs used for IMN treatment.

Drug	Dose	Common side effects
Glucocorticoid	Continuous high dose impact: 1 g/d Standard: 1 mg/kg/d, for 4–6 weeks. 10% of the total dose was reduced once every 2 weeks to 20 mg/d. Consequently, the total amount was reduced by 5 mg every 4 weeks, and the treatment was maintained when reduced to 10 mg/d	Obesity, psychiatric symptoms, osteoporosis, hypertension, hyperglycemia
Cyclophosphamide	Usual dosage for adults is 2–2.5 mg/kg/day, for 8–12 weeks	Bone marrow suppression, nausea, hair loss, infertility, infections
Tacrolimus	Starting at a dose of 0.1 mg/kg/d for 6 months and then reduced to 0.05 mg/kg/d in the subsequent 3 months	Kidney damage, neurotoxicity, hyperglycemia, infections
Cyclosporine	Starting at a dose of 3.5 mg/kg/d for 12 months, then gradually reduce the amount	Infections, malignant tumor, neurotoxicity, hepatorenal toxicity, thromboembolic microangiopathy
Mycophenolate mofetil	Usual dosage for adults is 1–1.5 g twice daily	Diarrhea, nausea, vomiting, infections, bone marrow suppression
Rituximab	1 g every 14 days for 6 months until complete or partial remission is achieved	Infections, allergic reactions, B cell depletion

typic parameters to refine therapeutic algorithms, enhance response rates, and minimize relapse risk across diverse IMN subpopulations.

Despite the promising efficacy of RTX, clinicians should remain vigilant about its adverse effects, the most common of which are infusion-related reactions. These reactions—typically occurring during the first infusion—may include non-productive cough, nasal congestion, facial flushing, flu-like symptoms, and rash. These reactions are generally self-limiting and can often be mitigated with premedication using agents such as hydrocortisone [111,112].

Not all patients respond to RTX, and some experience primary treatment failure or relapse after an initial response, indicating the existence of resistance mechanisms [22]. Several factors may contribute to RTX resistance, including the development of anti-drug antibodies, internalization of RTX by B cells, polymorphisms in Fcγ receptors, epitope spreading, and accelerated drug clearance. Additionally, high baseline anti-PLA2R antibody titers, subtherapeutic RTX levels, and the sequestration of B cells within secondary lymphoid tissues have all been associated with suboptimal responses [113]. While RTX represents a major advancement in IMN therapy, further research is needed to delineate patient subgroups most likely to benefit and to optimize dosing strategies. Moreover, long-term studies are required to fully understand its safety profile and immunological impacts.

A comprehensive summary of the commonly used therapeutic agents for IMN, including their dose and common side effects, is presented in Table 3.

Other Potential Biological Agents

For patients who are refractory or intolerant of RTX, several alternative therapeutic options targeting B cells or the complement system are being investigated. Novel anti-CD20 monoclonal antibodies, such as obinutuzumab (a type II antibody with enhanced antibody-dependent cellular cytotoxicity [ADCC]) and ofatumumab (a fully human antibody targeting a distinct CD20 epitope), have demonstrated encouraging efficacy in both treatment-naïve and refractory cases of IMN. In a case series by Sethi *et al.* [114], ten patients with RTX- and cyclophosphamide-resistant membranous nephropathy were treated with obinutuzumab. After 12 months, 90% of patients achieved either complete or partial remission. The only non-responder experienced a 48% reduction in proteinuria from baseline within six months, and none required additional dosing to maintain remission [114]. Podestà *et al.* [22] reported a patient with refractory IMN who had received seven courses of RTX, experiencing multiple relapses and a late-onset serum sickness episode. After a further relapse with renal function deterioration, the patient achieved remission following a 300 mg dose of ofatumumab. When relapse occurred two years later, a 100 mg dose was ineffective, but remission was regained after increasing the dose to 300 mg. Notably, no adverse reactions were observed throughout the ofatumumab treatment course [22].

Agents targeting the B-cell activating factor (BAFF)/B lymphocyte stimulator (BLyS) pathway—such as belimumab—represent another promising class of B cell-modulating therapies. Belimumab is a fully human IgG1-λ monoclonal antibody that inhibits B-cell activating

factors, impairing the survival and differentiation of autoreactive B cells by blocking their receptors [115,116]. While belimumab is approved for systemic lupus erythematosus, where it reduces disease activity and autoantibody levels, its use in IMN is still under investigation. In a prospective, open-label, single-arm study by Barrett *et al.* [117], 14 patients with persistent nephrotic-range proteinuria after 3 months of supportive therapy were treated with belimumab. The intervention led to reductions in both serum anti-PLA2R antibodies and proteinuria. Whether belimumab can be used as monotherapy or in combination regimens for moderate- to high-risk IMN patients is to be determined.

Monoclonal antibodies targeting CD38, such as daratumumab and isatuximab, have also shown promise in managing autoimmune diseases. CD38 is highly expressed on plasma cells and subsets of activated B cells, making it an attractive target for depleting long-lived antibody-producing cells in refractory IMN [118]. Early-phase clinical trials are underway to evaluate their efficacy and safety in this context [119,120].

In summary, overcoming RTX resistance in IMN will require a personalized approach based on immune profiling, antibody dynamics, and resistance mechanisms. Multi-targeted regimens—whether combinatorial or sequential—are likely to play a pivotal role in optimizing outcomes for patients with refractory disease. These emerging biologics offer new therapeutic avenues and highlight the evolving landscape of precision immunotherapy in membranous nephropathy.

Discussion

Recent discoveries have substantially expanded the repertoire of known antigens implicated in IMN, unveiling distinct immunopathological subtypes of the disease. While PLA2R and THSD7A remain the primary target antigens, additional molecules such as NELL1, SEMA3B, and components of EXT1/EXT2 have also been identified. Each antigen is associated with a distinct immunological profile. Antibodies against PLA2R and THSD7A are typical of the IgG4 subclass and generally do not activate the complement cascade. In contrast, anti-NELL1, anti-SEMA3B, and anti-EXT1/EXT2 responses are predominantly IgG1-mediated and are often accompanied by significant complement deposition. These immunological differences translate into clinically relevant phenotypes. For instance, NELL1-associated MN frequently exhibits segmental glomerular deposits and is strongly associated with malignancies—approximately 33% of NELL1-positive cases have concurrent cancer. SEMA3B-associated MN is a unique pediatric subtype, almost exclusively observed in children under two years of age. EXT1/EXT2-associated MN, more prevalent in lupus nephritis, often presents with severe proteinuria despite relatively mild glomerular sclerosis, suggesting a more favorable renal prognosis.

Beyond these qualitative distinctions, antigen-specific antibody profiles offer valuable prognostic and therapeutic insights. High titers of anti-PLA2R antibodies, particularly when epitope spreading extends beyond the cysteine-rich N-terminal domain, are associated with treatment resistance and delayed remission. Conversely, declining antibody levels typically precede and predict immunological remission, often before reductions in proteinuria become evident. Targeted therapies, such as complement inhibitors (e.g., C5 blockers) and modulators of the TRPC6 or Wnt signaling pathways, are being investigated as means to attenuate disease progression. While preliminary findings are promising, randomized clinical trials are required to validate their efficacy.

Despite significant progress in antigen discovery, there are several barriers to routine clinical implementation of these observations. Currently, available serological assays primarily detect PLA2R and THSD7A, leaving a substantial proportion of patients seronegative and reliant on kidney biopsy for diagnosis and immune complex identification. Even when the autoantibody profile is known, monitoring and treatment remain resource-intensive. Immunosuppressive regimens are prolonged and costly—agents such as RTX and CNIs impose significant financial burdens—and patient adherence is often suboptimal. Furthermore, emerging therapies, such as complement inhibitors and antigen-specific biologics, are not yet widely accessible. The lengthy timelines required to assess therapeutic efficacy—often 6 to 12 months for substantial reductions in proteinuria or relapse prevention—further complicate the rapid optimization of treatment strategies. These challenges must be addressed in parallel with scientific advances to ensure that research innovations translate into tangible clinical benefits.

The KDIGO 2021 guidelines recommend treatment strategies guided by immunological profiling and risk stratification [18]. Traditional regimens that combine pulse glucocorticoids and cyclophosphamide can induce durable remissions and delay renal deterioration, but they are associated with significant toxicity. CNIs such as cyclosporine and tacrolimus effectively reduce proteinuria, though relapse rates tend to be high following drug discontinuation. The identification of PLA2R as a dominant autoantigen has led to the emergence of B-cell-targeted therapies as frontline treatment. RTX induces remission in approximately 60–80% of patients, with its efficacy closely linked to declines in anti-PLA2R antibody titers [105]. Clinical management now incorporates dynamic monitoring of antibody titers, IgG subclasses (particularly IgG4), and proteinuria levels to guide therapeutic adjustments. Based on current guideline recommendations and clinical evidence, empiric therapy may be considered for patients presenting with heavy proteinuria and markedly elevated anti-PLA2R antibody levels, even in the absence of renal biopsy confirmation. However, in seronegative or atypical cases or in

patients demonstrating an unusual therapeutic response, renal biopsy remains essential for diagnostic clarification and treatment guidance [18,121,122]. The development of non-invasive, sensitive, and specific diagnostic tools is a priority to improve diagnostic yield and reduce patient burden.

For patients with moderate-risk IMN, RTX is often the first-line treatment, either as monotherapy or in combination with calcineurin inhibitors. In contrast, those at high risk or with markedly elevated anti-PLA2R antibody titers are generally managed with a cyclic regimen of cyclophosphamide and glucocorticoids. For patients who do not respond to RTX or relapse after therapy, novel monoclonal antibodies and combination strategies are emerging as promising alternatives. Second- and third-generation anti-CD20 antibodies, such as obinutuzumab, have shown efficacy in selected refractory cases. Monoclonal antibodies targeting plasma cells (e.g., anti-CD38 daratumumab) and agents modulating B-cell survival factors (e.g., the BAFF inhibitor belimumab) are currently being investigated [123]. Furthermore, complement pathway inhibitors—such as the factor B inhibitor iptacopan—are undergoing clinical trials. Innovative immunotherapies, including CAR-T cells and regulatory T-cell (Treg) therapies, have garnered significant interest in their potential to induce immune tolerance [123]. In clinical practice, treatment choices must balance efficacy with potential adverse effects while also accounting for factors like regimen duration, cost, and patient adherence. Research has highlighted the substantial burden of MN, with annual healthcare costs for high-risk patients reaching several hundred thousand U.S. dollars [124], underscoring the urgent need for optimized, personalized approaches.

Looking ahead, future research in IMN should prioritize elucidating novel antigenic mechanisms and restoring immune tolerance. Investigating emerging autoantigens such as NELL1 and EXT1/EXT2, along with mechanisms like epitope spreading and immune dysregulation, could help develop targeted immunomodulatory strategies, including low-dose interleukin-2 and CAR-Treg therapies. Integrative profiling of antibody titers, subclasses, and epitope specificity may enhance risk stratification and predict treatment responses, laying the foundation for individualized care. Combined or sequential targeting of distinct B-cell subsets and the complement cascade, through therapies like CAR-T cells, anti-CD38 antibodies, BAFF inhibitors, or complement blockers—holds the potential to achieve more durable immunological control. Given high relapse rates and escalating treatment costs, future efforts should also focus on improving therapeutic accessibility and patient adherence. This includes streamlining treatment regimens, developing cost-effective drugs, and strengthening patient management approaches to ultimately enhance both clinical outcomes and quality of life.

Conclusion

This review outlines the intricate relationships between antigenic mechanisms and therapeutic strategies in IMN, offering a conceptual framework to inform both clinical decision-making and research design. Future investigations should aim to establish a translational continuum from mechanistic discoveries to personalized treatment. This includes applying novel antigen and epitope data for patient stratification and therapy response prediction, while leveraging clinical outcomes to refine experimental models and therapeutic targets. A feedback-driven, mechanism-based approach is essential to fully unlocking the potential of precision medicine in IMN and improving patient outcomes.

Availability of Data and Materials

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

Author Contributions

SZ and YL contributed to the conception and design of the study, acquisition of data, or analysis and interpretation of data. SZ contributed to drafting the article. Both authors contributed to important editorial changes in the manuscript. Both authors validated and final approved of the version of the article to be published. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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