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REVIEW ARTICLE

Membranous nephropathy: A review on the pathogenesis, diagnosis, and treatment

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In adults, membranous nephropathy (MN) is a major cause of nephrotic syndrome. However, the etiology of approximately 75% of MN cases is idiopathic. Secondary causes of MN are autoimmune diseases, infection, drugs, and malignancy. The pathogenesis of MN involves formation of immune complex in subepithelial sites, but the definite mechanism is still unknown. There are three hypotheses about the formation of immune complex, including preformed immune complex, *in situ* immune-complex formation, and autoantibody against podocyte membrane antigen. The formation of immune complex initiates complement activation, which subsequently leads to glomerular damage. Recently, the antiphospholipase A_2 receptor antibody was found to be associated with idiopathic MN. This finding may be useful in the diagnosis and prognosis of MN. The current treatment includes best supportive care, which consists of the use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, lipid-lowering agents, and optimal control of blood pressure. Immunosuppressive agents should be used for patients who suffer from refractory proteinuria or complications associated with nephrotic syndrome. Existing evidence supports the use of a combination of steroid and alkylating agents. This article reviews the epidemiology, pathogenesis, diagnosis, and the treatment of MN.

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Introduction

Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults.[1] Patients with MN usually present with severe proteinuria, edema, hypoalbuminemia, and hyperlipidemia. MN is a glomerulopathy with characteristic histopathological features of subepithelial immune-complex deposit and subsequent thickening of glomerular basement membrane. The etiology of approximately 75% of MN cases is idiopathic. During the past decade, several studies have led to the identification of possible pathogenesis. Although spontaneous remission occurs in approximately one third of MN patients, 30—40% of the patients progress toward end-stage renal disease within 5—15 years. All patients with MN should receive excellent supportive care. Immunosuppressive agents are central to the treatment of MN. Risk and benefit for prescription should be individualized, and patient-dependent factors, such as age and comorbidities, should be considered. The purpose of this review is to highlight these considerable progresses and discuss their implications in clinical practice.

Epidemiology

The incidence of primary MN is 10 per million populations per year.[2—4] The peak incidence of MN is in the fourth to fifth decade of life.[5] A pooled analysis of studies of patients with idiopathic MN found a 2:1 predominance of men.[6]

Approximately 75% of the MN cases occur as an idiopathic (primary) disease.[7] The remainder, as secondary MN, is associated with autoimmune diseases (e.g., systemic lupus erythematosus), infection (e.g., hepatitis B or hepatitis C), drugs (e.g., penicillamine, gold), and malignancies (e.g., colon or lung cancer).

In patients older than the age of 60 years, MN is associated with malignancy in 20—30% of cases. In a cohort study in France, the incidence of cancer was significantly higher in these patients than in the general population (standardized incidence ratio = 9.8 for men and 12.3 for women). The most common malignancies were lung cancer and prostate cancer. The frequency of malignancy increased with age.[1] In another large cohort study in Norway, the incidence of cancer was significantly higher in patients with MN than in the age- and sex-adjusted general population (standardized incidence ratio, 2.25). The median time from diagnosis of MN to cancer was 60 months. Patients with MN who developed cancer were older (65 years vs. 52 years, $p < 0.001$).[8] Although spontaneous remission of the nephrotic syndrome occurs in approximately one third of patients, 30—40% of the patients progress toward end-stage renal disease within 5—15 years.[1]

Pathogenesis

The formation of immune complex in subepithelial sites is central to MN. However, the mechanisms of deposit formation remain elusive. Three major putative mechanisms are proposed so far.

The first hypothesis stresses the passive entrapment of preformed immune complexes (Fig. 1A). Most protein might be forced across the glomerular capillary wall due to higher intraglomerular pressure and negatively charged capillary wall. Lupus nephritis is an excellent example of immune-complexes-related human kidney disease. Preformed immune complexes, containing antibodies to double-stranded DNA, histone, ribonucleoproteins, and others, are found in patients with systemic lupus erythematosus.[9] In addition, levels of circulating immune complexes were found to correlate with disease activity.[10] Anti-DNA and DNA immune complexes were detected in glomerular elutes from lupus patients.[11] Therefore, it was proposed that immune-complex deposits in the glomeruli of lupus patients reflect entrapment of preformed immune complexes.

The second hypothesis is that the pathogenic circulating antigens are localized, or planted, in the subepithelial sites, and these antibodies subsequently form *in situ* immune-complex deposits with antibodies (Fig. 1B). The hepatitis B virus (HBV) was found to be strongly associated with glomerulonephritis, especially MN. With regard to pathologic findings in patients with HBV-related glomerulonephritis, HBeAg is found to be distributed along the glomerular capillary wall. Clusters of viral-like particles were detected within immune deposits. It is proposed that the HBV antigen might serve as the circulating antigens, which are localized in the glomerulus. Further interaction with antibodies forms immune-complex deposits in HBV-related glomerulonephritis patients.[12—14] In addition, hepatitis C virus antigens,[15—17] *Helicobacter pylori* antigens,[18,19] tumor antigens,[20—24] and thyroid antigens[25—28] were found in immune deposits in patients with secondary MN.

In a small group of children with MN, cationic bovine serum albumin (BSA) acts, through binding to the anionic glomerular capillary wall, as an externally planted antigen. Antibodies then bind to the planted antigen to form the immune complex [immunoglobulin (Ig)G4 and IgG1]. Cow's milk is the major source of BSA, which is processed by the intestine and modified by intestinal microbiota. In comparison with normal individuals, the immature intestinal wall of these patients may be more permeable to cationic BSA and allow for the entry of BSA antigen into circulation. Elimination of BSA from the diet might be beneficial in BSA-related MN. The titer of circulating BSA and anti-BSA antibodies strongly correlates with the clinical condition and decreases substantially during remission.[29] It is noteworthy that the *in situ* mechanism also contributes to pathogenesis of lupus nephritis. DNA, nucleosomes, histone, and other antigens can bind to glomeruli, and serve as planted antigen.[30]

The third mechanism focuses on the effect of autoantibodies that bind to podocyte membrane antigens, thereby causing subepithelial deposition of immune complex (Fig. 1C). The Heymann nephritis model has been extensively studied as a model of MN. It was first described in 1959 and played a vital role in the identification of a culprit antigen.[31] In 1978, Couser et al[32] reported the formation of subepithelial immune complex following the direct perfusion of bloodless kidneys with the pathogenic IgG antibody. This study established a novel mechanism, *in situ* immune-complex formation, in the development of MN.

Several possible culprit antigens were identified in experiments. Kerjaschki and Farquhar in the early 1980s

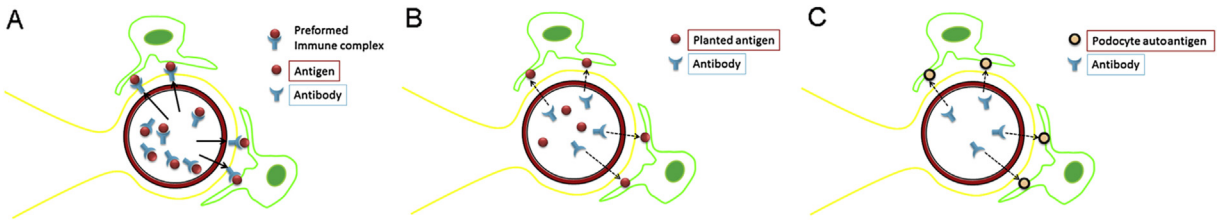

Figure 1 Three possible immunological mechanisms of membranous nephropathy. (A) Preformed immune complex. The preformed immune complexes are entrapped in subepithelial space. (B) Planted antigens. The circulating pathogenic antigens are localized, or planted, in the subepithelial sites, which subsequently form *in situ* immune-complex deposits with antibodies. (C) Podocyte autoantigen. Autoantibodies bind to podocyte membrane antigens and lead to subepithelial deposition of immune complex.

identified the podocyte antigen, megalin, in rats.[33] Megalin is a 600-kDa single transmembrane receptor protein that belongs to the low-density lipoprotein receptor family. Megalin is responsible for the normal tubular reabsorption, and is also expressed in human podocytes.[34] Epitope-specific responses are involved in the pathogenesis. In a previous study in an animal model, a fragment of megalin can induce autoantibodies against podocyte, therefore initiate podocyte injury leading to glomerular damage and proteinuria.[35] However, thus far, antimegalin antibodies were not isolated from a patient with MN.

The neutral endopeptidase was identified in a rare subset of patients with alloimmune neonatal MN.[36] A neutral endopeptidase-deficient mother may develop an antibody against neutral endopeptidase during conception and transmit the antibody during next pregnancy to subsequent fetus. Alloimmunization was due to the truncation of exon 7 of the *MME* gene, which encodes neutral endopeptidase.[37] Screening of the families with the disease is crucial to subsequent pregnancies.

In 2009, Beck et al[38] identified a novel podocyte antigen, which is mainly an M-type transmembrane phospholipase A_2 receptor (PLA_2R). Using serum from patients with MN, the experiment successfully demonstrated a specific antibody targeting PLA_2R. PLA_2R and IgG4 are colocalized within subepithelial deposits. The sensitivity of the anti-PLA_2R test for MN is approximately 70%; the specificity is nearly 100%. The anti-PLA_2R antibodies are promising biomarkers to discriminate between primary and secondary MN.[38–41] Patients with other causes of the nephrotic syndrome or healthy individuals have no detectable anti-PLA_2R antibody. A very low prevalence of the anti-PLA_2R antibody was observed in secondary forms of MN associated with infectious diseases, drug intoxication, graft-versus-host disease, or malignancy. There was also a strong correlation of anti-PLA_2R antibodies with disease activities.[42,43] A possible autoimmune disease nature of the currently classified idiopathic MN is also elucidated. Other culprit antigens were also identified in experiments, including α-enolase,[44] aldose reductase, and superoxide dismutase 2.[45,46]

Despite these progresses, the autoimmune basis of MN is not fully understood. The recent genomewide association studies using single-nucleotide polymorphism (SNP) technology identified two significant alleles. Two genomic loci associated with primary MN were identified. Chromosome 2q24 contains the gene encoding M-type PLA_2R (*PLA_2R1*; SNP rs4664308), previously shown to be the target of an autoimmune response. Furthermore, chromosome 6p21 contains the gene encoding human leukocyte antigen (HLA) complex class II HLA-DQ alpha chain 1 (*HLA-DQA1*; SNP rs2187668), which was found to have a strong correlation with MN as well. The association with *HLA-DQA1* is significant in all three populations from the French, Dutch, and British groups. The odds ratio for idiopathic MN with homozygosity for both risk alleles is 78.5. Interactions between a trigger (genetic variants of immune-system proteins), a bullet (PLA_2R autoantibodies), and a target (glomerular antigen) is proposed. However, the causality remains unknown.[47]

In a Spanish cohort, the *HLA-DQA1* and *PLA_2R1* polymorphisms were reported to predict idiopathic MN response to immunosuppressant and disease progression.[48] In a Chinese cohort, among individuals who carried risk alleles for both genes, 73% had anti-PLA_2R antibodies and 75% expressed PLA_2R in glomeruli. Individuals carrying risk alleles are predisposed to the generation of circulating anti-PLA_2R autoantibodies, which may contribute to the development of idiopathic MN.[49] Polymorphism in other non-HLA alleles, such as tumor necrosis factor (TNF) alpha alleles G308A, TNFA2, and TNFd2, are associated with the development of MN.[50,51] In a Taiwanese population, polymorphism in *NPHS1*, *PAI1*, *IL-6*, *STAT4*, and *TLR9* genes is associated with susceptibility to the development and progression of MN.[52–57]

The complement system plays a major role in the pathogenesis of podocyte injury and proteinuria. Subepithelial immune deposits initiate the complement system activation leading to activation of C3 component, conversion of C5, and subsequent formation of the C5b-9 complex in podocyte membranes.[58–63] The attack on C5b-9 complex leads to intracellular production of reactive oxygen species[64–66] and proteases,[67] endoplasmic reticulum stress, and cytoskeletal changes.[68–70] These reaction-induced cell apoptosis,[71] detachment of the cells from glomerular basement membrane,[72] degradation of glomerular basement membrane, and dislocation of slit diaphragm protein result in proteinuria and renal failure.

Early studies in Heymann nephritis showed the presence of C3 and C5b-9 that colocalized with the immune deposits. In a small-sized study, C3 deposits were first detected in half of the patients with primary MN.[73] Currently, C3c deposition (a short-lived breakdown product of C3) is found in almost all cases of MN.[74] Besides, the level of C3d, a stable breakdown product of C3, is increased in approximately 70% of patients

with MN.[75] A recent study suggested basement membrane deposition of C4d in 100% of MN.[76]

The opinion about which specific complement pathway dominates in MN is still inconclusive. IgG4 is the predominantly deposited Ig in MN.[73] This finding argues against a predominant role for the classical pathway of complement activation, because IgG4 does not activate the classical pathway. C1q is generated during activation of the classical pathway but some studies do not report deposition of C1q in primary MN.[77] The presence of C4 in most cases of primary MN[76,78] challenges the role for the alternative pathway, which does not generate C4. The mannan-binding lectin (MBL) pathway may be involved in MN.[74] Based on these Ig-related findings, a hypothesis that MBL directly binds to hypogalactosylated IgG molecules and thereby activates the lectin complement pathway has been proposed.[79] This finding may explain the presence of glomerular C4 in primary MN. Segawa et al[74] suggested that both the alternative and lectin pathways were involved in the complement activation in patients with global MN. Different complement pathways may cooperate. Previous studies suggested that IgG1 is the major subclass in early stage deposits, whereas IgG4 is predominant in later stages.[80] Thus, it is proposed that IgG1 may initially activate the classic pathway in the early stage with activation of the lectin or alternative pathways in later stages. However, further studies are needed to clarify the interplay of different complement systems.

Diagnosis of MN

The diagnosis of MN can only be made by renal biopsy. Pathologic sine qua non of MN is the presence of subepithelial immune-complex deposit, which was best demonstrated by electron microscopy (Fig. 2).[81] Churg and Ehrenreich[82] have described four ultrastructural stages of MN: Stage I is characterized by the presence of scattered or more regularly distributed small immune-complex-type electron-dense deposits in the subepithelial zone. Stage II is characterized by projections of basement membrane material around the subepithelial deposits. In Stage III, the new basement membrane material surrounds the deposits. Stage IV is characterized by the loss of electron density of the deposits, which often results in irregular electron-lucent zones within an irregularly thickened basement membrane (Fig. 3). The characteristic immunofluorescence picture is diffuse global granular capillary wall staining for immunoglobulin and complement.[81] IgG is the most frequent and usually the most intense. C3 staining is also frequently presented.[83] Under light microscopy, the characteristic histological abnormality of MN is diffuse global capillary wall thickening in the absence of significant glomerular hypercellularity (Fig. 4).[83]

To diagnose idiopathic MN, secondary MN should be excluded first. It is worth mentioning that secondary MN is more common in children (75%) than adults (25%). Autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, etc.), infections (hepatitis B and hepatitis C), malignancies (lung cancer, prostate cancer, and hematological malignancies), and medications were reported to be the cause of secondary MN.[84]

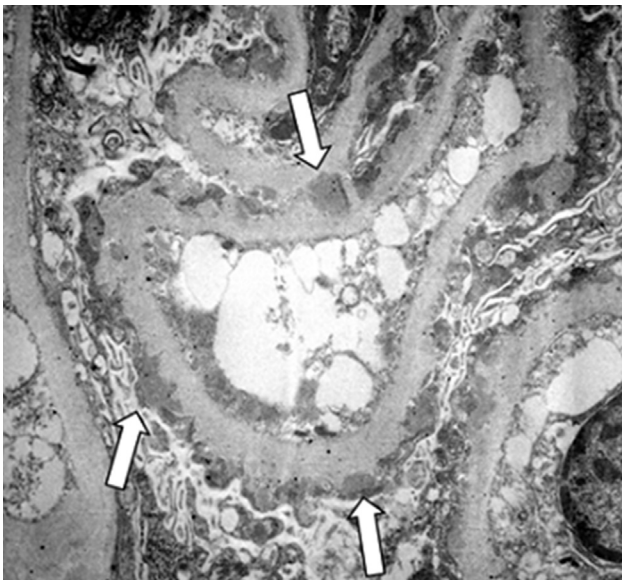

Figure 2 Membranous nephropathy seen under an electron microscope. An electron microscopy image shows electron-dense deposits in the subepithelial space (arrows). Courtesy Wei-Chou Lin, MD, National Taiwan University Hospital, Taipei, Taiwan.

The identification of circulating autoantibodies against the M-type PLA_2R (anti-PLA_2R) has been a major discovery as mentioned earlier. Anti-PLA_2R antibodies were found in 70% of patients with idiopathic MN, and were minimal in secondary etiologies.[38] However, more studies are needed to understand whether the anti-PLA_2R antibody is usually present in general populations with idiopathic MN. Besides, the accuracy of the test to identify idiopathic MN awaits well-designed prospective studies.[41]

The distinction between primary and secondary MN can be suggested by IgG subclasses. IgG4-rich deposits, sometimes including IgG1, especially for very early disease, characterize primary MN.[73,80] By contrast, IgG1, IgG2, and IgG3 were mostly found in secondary MN.[85,86] In addition, the presence of a full-house pattern, IgG, IgM, IgA, C3, and C1q, is very specific for secondary MN.[87]

Clinical features and natural history of MN

Proteinuria is the typical presentation of MN, and nephrotic syndrome occurs in 70—80% of patients.[88,89] Most patients have normal or slightly decreased renal function upon diagnosis. If progressive renal insufficiency develops, it is usually relatively indolent. An abrupt change in renal function indicates the necessity for prompt investigation of a superimposed condition, such as a crescentic glomerulonephritis, bilateral renal vein thrombosis, and drug toxicity.[83]

A multicenter study from the Spanish Group for the Study of Glomerular Disease (GLOSEN) examined the course of nephrotic idiopathic membranous nephropathy patients (n = 328): angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) treatment was started in 219 patients (66.7%). A total of 104 patients

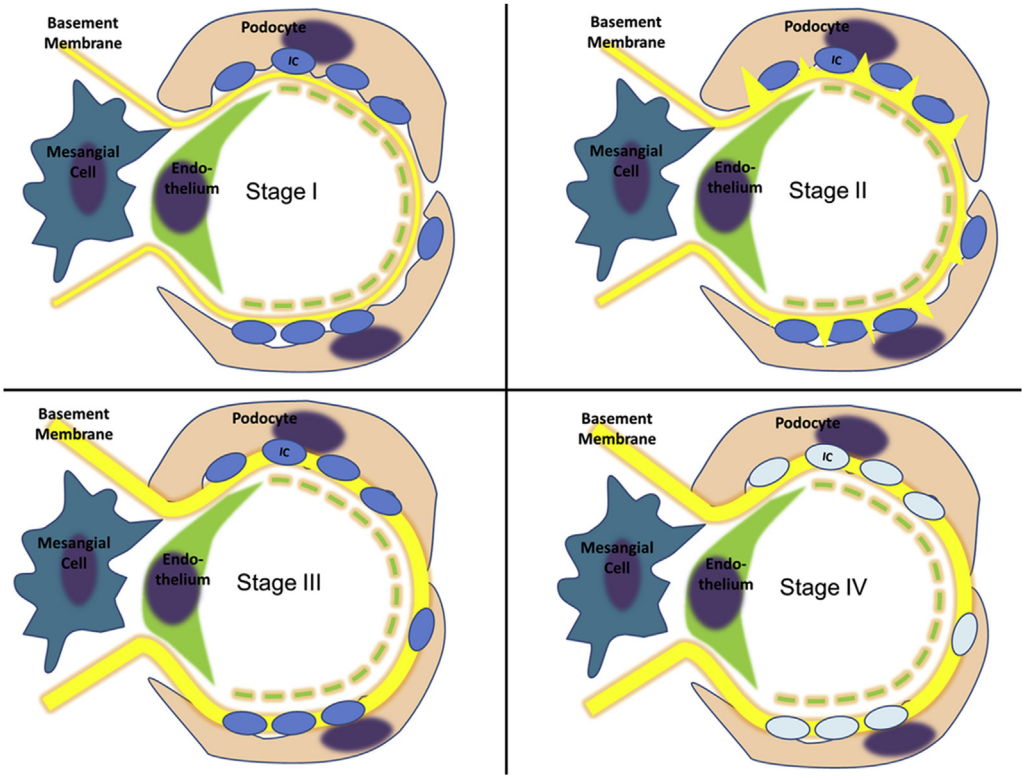

Figure 3 Four pathological stages of membranous nephropathy. Stage I is characterized by the presence of immune-complex-type electron-dense deposits in the subepithelial zone between the basement membrane and the podocyte. Stage II is characterized by projections of basement membrane material around the subepithelial deposits. In Stage III, the new basement membrane material surrounds the deposits. Stage IV is characterized by the loss of electron density of the deposits, which results in irregular electron-lucent zones. IC = immune complex.

(31.7%) developed spontaneous remission. Fifty percent of patients with spontaneous remission developed complete remission, and the time to achieve partial and complete remission was 14.7 months and 38.5 months, respectively.

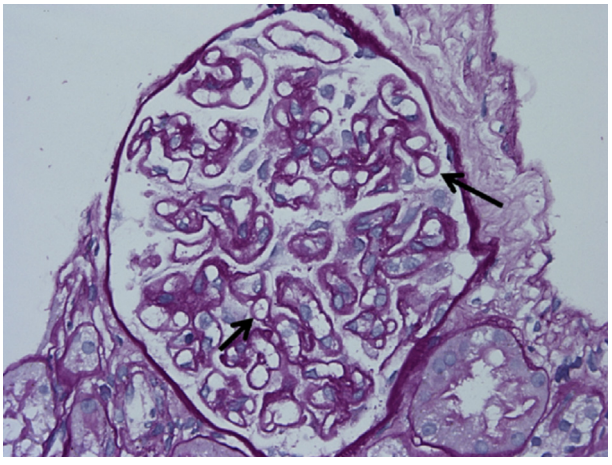

Figure 4 Membranous nephropathy under a light microscope (periodic acid—Schiff stain). A light microscopy image reveals diffuse thickening of glomerular basement membrane (arrows). Courtesy of Wei-Chou Lin, MD, National Taiwan University Hospital, Taipei, Taiwan.

Spontaneous remission was associated with excellent long-term outcome; by contrast, failure to achieve spontaneous remission was associated with increased risk of dialysis (18.7%) and death (10.7%).[90] In the GLOSEN study, baseline serum creatinine level, the amount of baseline proteinuria, treatment with ACEIs/ARBs, and a spontaneous proteinuria decrease > 50% of the baseline value during the 1st year of follow-up emerged as significant independent predictor factors for spontaneous remission.[90] The natural history and the rate of spontaneous remission in Asian countries still await large-scale studies. Besides, high levels of anti-PLA_2R were associated with a striking increase in the risk of progression.[91]

Prediction of prognosis

Traditionally, the Toronto Risk Score is the most commonly used tool to predict the prognosis in idiopathic MN. The risk score is calculated based on time-average proteinuria (highest sustained 6-month period of proteinuria), creatinine clearance (CCr) at diagnosis, and the slope of CCr over 6 months.[92] The Toronto Risk Score could identify patients at risk of progression with 85—90% accuracy.[92] However, prolonged observation is necessary for calculation of Toronto Risk Score, and treatment may be delayed. As a result, several markers were used to predict the prognosis of idiopathic MN.

Urinary excretion of β2-microglobulin or α1-microglobulin was used to predict the prognosis of MN.[93,94] The sensitivity and specificity of urinary excretion of β2-microglobulin in predicting renal failure were 88% and 91%, respectively, at the cutoff point of 0.5 μg/min. The sensitivity and specificity of urinary α1-microglobulin were 84% and 94%, respectively, in the same study, with the threshold level at 40 μg/min.[93] When comparing the prognostic accuracies of Toronto Risk Score with those of urinary excretion of β2-microglobulin or α1-microglobulin, no significant difference was noted.[95]

A prospective multicenter study revealed that the anti-PLA_2R antibody possessed prognostic values. The patients who achieved remission of proteinuria after 12 months had lower anti-PLA_2R antibody at the time of study inclusion, and the anti-PLA_2R antibody level is an independent risk predictor for remission of proteinuria.[96]

Treatment of idiopathic MN

All patients with MN should receive excellent supportive care, including treatment with ACEI/ARB, lipid-lowering agents, and adequate control of blood pressure.[83,97] According to the newest "Kidney Disease: Improving Global Outcomes" Guideline, treatment with immunosuppressive agents should be started only in patients with nephrotic syndrome when (1) urinary protein excretion persistently exceeds 4 g/d and remains at $>$ 50% of the baseline value during an observation period of at least 6 months; (2) severe, disabling, or life-threatening symptoms related to the nephrotic syndrome is present; (3) the creatinine level increases by $\geq$ 30% within 6—12 months from the time of diagnosis. For patients with serum creatinine level $>$ 3.5 mg/dL [or estimated glomerular filtration rate (eGFR) $<$ 30 mL/min] and reduced kidney size ($<$ 8 cm in length on ultrasound), or concomitant severe or potentially life-threatening infections, immunosuppressive therapy is not suggested.[84]

Immunosuppressive agents: Steroid

The efficacy of corticosteroid monotherapy is still being debated. Three randomized control trials in Western countries have shown that oral steroid monotherapy is not superior to symptomatic therapy alone in idiopathic MN.[84] However, in a Japanese study, steroid monotherapy (oral prednisolone 40—60 mg/d, then tapered over $\geq$ 4 weeks) was associated with significantly better renal survival when compared with supportive therapy.[98] In our experience, steroid use (prednisolone 0.5—1 mg/kg/d) also achieved remission within 1 year in approximately 60—70% of patients.

Immunosuppressive agents: Alkylating agents with steroid

Ponticelli et al[99—101] used a 6-month regimen consisting of daily oral chlorambucil (0.2 mg/kg) or cyclophosphamide (2—2.5 mg/kg), alternating monthly with corticosteroids (1 g/d intravenous methylprednisolone for 3 days, and followed by oral prednisolone 0.4—0.5 mg/kg/d), known as the "Ponticelli protocol", to treat the patients with idiopathic MN. For patients with nephrotic-range proteinuria and normal/near normal renal function, alternating monthly cycles of corticosteroids and an alkylating agent were found to be more effective than supportive therapy to achieve remissions of proteinuria and renal function preservation. Despite the favorable results with alkylating agents, physicians are reluctant to prescribe them due to their short-term and potential long-term adverse effects, including myelosuppression, infection, hemorrhagic cystitis, infertility, and increased risk of malignancy.[97] Therefore, the risk and benefit for prescription should be individualized.[84] In a recent study analyzing the treatment policy of idiopathic MN, immunosuppressive therapies were prescribed only if deterioration of renal function, persistent hypoalbuminemia, or complications of the nephrotic syndrome such as infection and thrombosis occurred.[102] This strategy prevented the use of potentially harmful immunosuppressive drugs in half of the patients, but long-term outcomes were still favorable.

Immunosuppressive agents: Calcineurin inhibitors

Calcineurin inhibitors (CNIs) are an effective alternative for induction, with a remission rate of 80%. Cyclosporine (3.5 mg/kg/d, levels of 125—200 mcg/L for 6—12 months, then tapered to the lowest possible maintenance dose) and tacrolimus (0.05 mg/kg/d, levels of 7—9 mcg/L for 6—12 months, then tapered) were used in clinical trials.[103—106] CNIs show favorable responses in patients who have been unresponsive to other immunosuppressants, including alkylating agents.[103,104,107,108] The antiproteinuric effect of CNIs is typically evident early. However, if even a trivial decrease in proteinuria was not noted by 3 months, it is unlikely that a significant response will occur later.[97] Besides, relapse is a well-recognized problem, occurring in 13—50% of patients within 1 year of drug withdrawal.[106]

Immunosuppressive agents in patients with deteriorating renal function

Alternating cycles of prednisolone and chlorambucil treatment may be beneficial for patients with idiopathic MN and deteriorating renal function. A randomized controlled trial showed that 6 months of alternating cycles of prednisolone and chlorambucil had the best outcome, and there were no differences between the cyclosporine and supportive treatment groups.[109] Despite a seemingly better renal outcome, hematological or metabolic adverse events were more common in the prednisolone and chlorambucil groups.[109]

Other immunosuppressive agents and novel agents

Among the newly explored therapeutic agents for idiopathic MN, rituximab has emerged as the most likely candidate, although it is yet to be tested in randomized controlled trials and there is a lack of longitudinal data.[97] Different regimens have been tried for idiopathic MN; regardless of the regimen administered, proteinuria tends to decline slowly and remissions may occur up to 2 years after treatment.[110]

Mycophenolate mofetil was also evaluated as initial therapy in idiopathic MN.[111–113] Although a regimen of mycophenolate mofetil plus steroid might have a comparable efficacy to cyclical alkylating agents and steroid, high frequency of relapses with mycophenolate mofetil substantially reduces interest in its application.[84,111]

Adrenocorticotropic hormone (ACTH) was used to treat the patients with idiopathic MN.[114] The actual mechanism by which ACTH exerts its antiproteinuric effects is currently unknown.[97] Possible mechanisms are steroid-related anti-inflammatory actions and direct interactions between melanocortin receptors and ACTH, which lead to immunomodulation and anti-inflammatory effects.[114] In this study, among the patients who received ACTH (40 U or 80 U twice per week), 10% achieved complete remission and 50% patients achieved partial remission by 1 year. A cumulative dose of at least 80 IU twice weekly for 3–6 months was necessary for response, and the drug was well tolerated.[114]

Pentoxifylline, a phosphodiesterase inhibitor, may be used in treatment of MN because it has anti-inflammatory and protective effects and can decrease proteinuria in patients with chronic kidney disease.[115–117] In a small-scale study, add-on pentoxifylline decreased urinary protein excretion in nondiabetic MN patients.[118] Leflunomide is an inhibitor of dihydroorotate dehydrogenase, which is the key enzyme in pyrimidine synthesis. It has antiproliferative and anti-inflammatory effects, and is used to treat patients with rheumatoid arthritis.[119] In a retrospective study including 32 patients, combination treatment with leflunomide and steroid achieved a favorable result with 31.3% complete remission and 40.6% partial remission. The median time to remission was 8 months; younger age was associated with increased remission rate. Leflunomide was well tolerated by the majority of the patients. However, a 21.3% relapse of nephrotic syndrome was noted after cessation of leflunomide.[120]

Herbal medicine *Astragalus membranaceus* was associated with remission of proteinuria in patients with idiopathic MN.[121,122] Recently, an open-label, randomized controlled trial had demonstrated the efficacy of traditional Chinese medicine (Shenqi particle) for patients with idiopathic MN.[123] Shenqi particle consists of 13 herbs, including *A. membranaceus*. When comparing Shenqi particle treatment with traditional immunosuppressive therapy using cyclophosphamide and prednisone, the remission rate was found to be similar between groups (73% vs. 78%). The patients who received Shenqi particle had greater improvement of eGFR at 48 weeks.

Conclusion

MN is a major cause of nephrotic syndrome in adults. The pathogenesis of MN involves the formation of subepithelial immune complex, and current evidence points out that the anti-PLA_2R antibody is strongly associated with primary MN, and proteinuria is caused by complement-mediated process. Currently, diagnosis of MN still depends on pathology, but the discovery of anti-PLA_2R may provide a useful tool for diagnosis and prediction of outcome of MN. The patients with spontaneous remission have excellent outcomes. Immunosuppressive agents should be administered to patients with persistent proteinuria, deteriorating renal function, or severe complications. Various studies suggest that the combination of steroid and alkylating agents is the most effective evidence-based therapy. However, the clinical features and treatment response vary among different races, and there is a need to conduct more trials to validate the efficacy of newer agents.

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