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Recent Advances in Membranous Nephropathy

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Membranous nephropathy (MN) is a common cause of the nephrotic syndrome in adults. The pathogenesis of MN, as defined in the experimental rat model of Heymann nephritis, involves antibodies that target antigens on the podocyte foot process and accumulate as immune deposits, activating complement, and leading to sublethal injury of the podocyte, as well as proteinuria. Similar mechanisms are now recognized in human MN, with the recent identification of target antigens. While spontaneous remission occurs in a substantial proportion of individuals with MN, others – especially those with persistent, high-grade proteinuria – require treatment with immunosuppressive agents. This issue of *Nephrology Rounds* reviews recent advances in understanding the pathogenesis and treatment of idiopathic MN.

Background

Idiopathic MN is a glomerulus-specific autoimmune disease and, second only to focal glomerulosclerosis, is a leading primary cause of the nephrotic syndrome in adults. Its name, *membranous* nephropathy, reflects the pathological observation using light microscopy of a thickening in the glomerular basement membrane (GBM) between and around immune deposits that occur beneath the podocyte foot processes. The histological hallmarks of the disease were first described by Jones,¹ and Mellors and Ortega² over 60 years ago. These include “spikes,” stained by methenamine silver, of normal GBM that extend between the immune deposits, a fine granular distribution of immunoglobulin (Ig) G and the complement component C3 in a capillary-loop pattern revealed by immunofluorescence, and the presence of electron-dense subepithelial immune deposits indicated by electron microscopy (EM). Idiopathic MN most commonly occurs in patients between the ages of 30 and 60 years, with men twice as likely to be affected as women. However, MN does occur in children³ as well as the very elderly.⁴ Up to 70% of patients present with the nephrotic syndrome, and the others garner clinical attention due to subnephrotic levels of proteinuria. Microscopic hematuria is observed in up to 50% of cases, although red cell casts are rare. Hypertension and impaired renal function are uncommon at the outset of the disease and are more likely to occur with disease progression.

Primary (idiopathic) vs secondary forms of membranous nephropathy

In developed countries, the majority of MN is primary or “idiopathic,” a term that implies that all known secondary causes have been effectively ruled out. Secondary forms have been attributed to a variety of agents or conditions (Table 1). MN occurring post-hematopoietic stem cell transplantation (HSCT) may be a humoral manifestation of chronic graft-versus-host disease; it is the most common cause of post-HSCT nephrotic syndrome,⁵ and like idiopathic MN, post-HSCT MN disproportionately affects males. MN may recur in up to 42% of renal allografts with slowly progressive proteinuria;⁶ it is also possible for *de novo* MN to occur, perhaps as an alloimmune reaction to minor histocompatibility antigens on the allograft podocytes. Finally, MN may briefly occur early in infancy as a result of fetomaternal alloimmunization.

Idiopathic MN must be distinguished from the various secondary causes, since treating or eliminating those underlying conditions are often sufficient to cause nephrotic syndrome remission. The most frequent secondary form of MN in the United States (US) is membranous lupus nephritis (LN), designated class V LN by the International Society of Nephrology/Renal Pathology Society, and is seen in ~10%-20% of LN cases. The disease may occur in isolation and predate other symptoms or serological abnormalities suggestive of lupus. Thus, even in the absence of positive serological markers such as antinuclear antibodies (ANAs), membranous LN should remain a possibility in any young woman with a biopsy diagnosis of MN.

Features that distinguish idiopathic MN from membranous LN and other secondary forms of MN include the glomerular location of the immune deposits, the predominance of a particular IgG subclass, and other pathological features. Clues to the diagnosis of membranous LN include the



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Table 1: Secondary causes of membranous nephropathy

▶ Autoimmune diseases <ul style="list-style-type: none">• Systemic lupus erythematosus• Other: rheumatoid arthritis, autoimmune thyroid disease, Sjögren syndrome
▶ Infection <ul style="list-style-type: none">• Hepatitis B• Other chronic infections: hepatitis C, syphilis, schistosomiasis, malaria
▶ Alloimmunization <ul style="list-style-type: none">• Fetomaternal alloimmunization• Graft-versus-host disease following hematopoietic stem cell transplantation• <i>De novo</i> membranous nephropathy in the renal allograft
▶ Drugs or toxins <ul style="list-style-type: none">• Parenteral gold salts• Penicillamine• Nonsteroidal anti-inflammatory drugs• Other: mercury, captopril, bucillamine
▶ Malignancy

presence of subendothelial and mesangial deposits, in addition to the predominant subepithelial deposits, and a “full house” pattern of staining for IgG, IgA, IgM, C3, and C1q on immunofluorescence. In idiopathic MN, the predominant IgG subclass found in the glomerular deposits is IgG4, whereas in many secondary forms, IgG1, IgG2, and IgG3 predominate.⁷⁻⁹ Finally, an ultrastructural finding of tubuloreticular structures in the glomerular endothelium suggests lupus, although these structures can also be found in other nonidiopathic forms of MN.¹⁰

Currently, renal biopsy is the exclusive means for diagnosing MN and distinguishing it from other causes of nephrotic syndrome. The results of routine serological studies, including complement levels, are all normal in idiopathic MN. Possibly, antibodies to the human phospholipase A2 receptor (PLA2R) found in many patients with idiopathic MN may allow a serological diagnosis of MN, but this test is only available in the research setting. Secondary causes of MN may be suggested by the presence of ANA, hepatitis B virus (HBV)-antigenemia, or concurrent infection with schistosomiasis or secondary syphilis. Hypocomplementemia may occur in lupus- or HBV-associated MN, but normal complement levels do not rule out these diagnoses. Associations of MN with malignancy have been found in older individuals seemingly more frequent than chance;¹¹ therefore, in older individuals with newly diagnosed MN, tests to exclude malignancy are reasonable.

Pathogenesis

The pathogenesis of idiopathic MN has been determined from decades of study on the experimental rat model of MN known as Heymann nephritis (HN).¹² Rats that are actively or passively immunized against a proximal tubular brush border fraction (Fx1A) will eventually develop nephrotic levels of proteinuria. The glomerular histopathology in these rats is virtually identical to that seen in human MN, with IgG-containing subepithelial deposits and expansion of the GBM. The major target antigen in this tubular brush border fraction has been identified as the transmembrane glycoprotein, megalin, a member of the low-density lipoprotein (LDL)

receptor family. In rats, but not in humans, megalin is additionally present on the podocyte foot processes.¹³ Using *ex vivo* perfusion of isolated rat kidneys with anti-Fx1A antibodies that recognize megalin, it was elegantly demonstrated that the subepithelial deposits form by the binding of antibodies *in situ* to megalin expressed on the basal surface of podocyte foot processes.^{14,15} Once circulating antibodies traverse the GBM and bind their target antigen on the podocyte foot process, small antibody-antigen complexes form via the process of “capping and shedding,”¹⁶ and are deposited into the GBM where they ultimately aggregate to form the larger subepithelial deposits visible by EM. Complement is activated locally by the immune complexes, but because C3a and C5a are generated on the outer aspect of the GBM, there is no recruitment of inflammatory cells. Instead, the complement components C5b through C9 assemble to form the membrane attack complex (MAC), which inserts into the podocyte cell membrane. A number of maladaptive cell-signaling pathways are initiated that induce sublethal injury to the podocyte, leading to cytoskeletal changes, foot process effacement, and proteinuria.¹⁷ Despite the continued generation of C5b-9, the podocyte is not lethally injured, since the MAC is shed from the plasma membrane into the GBM. A thickening of the GBM occurs over time, as immune deposits separate from the basal surface of the podocyte and become incorporated into the expanded GBM; these “intramembranous” deposits are due to the new extracellular matrix deposited by injured podocytes.

Since megalin is not expressed in the human glomerulus, some have suggested that an alternative podocyte membrane protein serves as the target antigen in human idiopathic MN. The existence of this antigen was first indicated by the discovery that neutral endopeptidase (NEP), expressed on podocytes, is the target in an antenatal alloimmune form of MN.¹⁸ The transplacental passage of anti-NEP antibodies (from a mother genetically deficient in NEP who experienced fetomaternal alloimmunization during a prior pregnancy) caused MN with subepithelial deposits (anti-NEP and NEP) in the developing fetus. The nephrotic syndrome was present at birth, but resolved several months later after physiological clearance of the maternal antibodies from the infant’s circulation. Several other cases of alloimmune antenatal MN induced by anti-NEP have been described;¹⁹ however, NEP was not initially considered as the target antigen in most adult cases of idiopathic MN. More recent but unpublished research by these same authors has suggested that many adults with idiopathic MN may also have low levels of antibodies that recognize NEP. The significance of this finding remains uncertain.

Recently, our laboratory identified the M-type PLA2R as a major target antigen in MN.²⁰ Using several geographically diverse patient cohorts with biopsy-proven diagnoses of idiopathic MN, >70% of patients were uniformly found to have circulating antibodies reactive to PLA2R. In contrast, such antibodies are absent in patients with secondary forms of MN, other glomerular diseases, and normal controls. Intriguingly, all anti-PLA2R-positive patients exhibited reactivity only with the nonreduced protein, suggesting the presence of ≥1 reduction-sensitive epitopes in the molecule. Consistent with the known subclass distribution of IgG within the immune deposits of idiopathic MN, the predominant circulating anti-PLA2R subclass is IgG4, a marker of a type 2 T helper cell (Th2) response. Interestingly, IgG4 is an immunoglobulin

that may be functionally bivalent and only weakly activates the classical complement pathway.²¹ IgG4 colocalizes with PLA2R within immune deposits in idiopathic (but not secondary) MN biopsy specimens. Furthermore, PLA2R-reactive IgG can be specifically eluted from these biopsies. A role for anti-PLA2R antibodies in disease is suggested by observations that the presence of such antibodies is closely associated with clinical disease activity, disappearing with spontaneous or treatment-induced remission, and recurring with relapse of disease. However, final proof of pathogenicity awaits the development of a suitable animal model. PLA2R, a member of the mannose receptor family,^{22,23} is a transmembrane glycoprotein expressed on human podocytes. Although recent studies in fibroblasts reveal a possible role in regulating cell senescence,²⁴ both the exact function of PLA2R and whether the role will hold true in the podocyte remains unknown.

The immune response in idiopathic MN is Th2-predominant with no glomerular inflammation. Although proliferative forms of LN are Th1-predominant, a Th2 response may also account for the membranous form of LN. Supportive observations are found in a mouse model of LN where genetic disruption of the interleukin (IL)-27 signaling pathway, integral for mounting a Th1 response in mice, causes a shift toward the Th2 response and converts the otherwise diffuse proliferative pattern of glomerular injury to a predominantly membranous pattern.^{25,26} The role of the Th2-selective IgG4 isotype in MN is not entirely clear because this subclass has been considered unable to activate the classical complement pathway.²¹ A role for IgG subclasses other than IgG4 in the pathogenesis of MN is supported by observations that children with NEP-deficient mothers who only had IgG4 anti-NEP did not develop disease, while those from mothers with IgG1 and IgG4 were born with the nephrotic syndrome.¹⁹ A variable presence of additional circulating anti-PLA2R subclasses is found in patients with idiopathic MN,²⁰ which may explain the presence of complement in the glomerular deposits.

In primary, secondary, and antenatal alloimmune MN, complete clinical remission can occur with a reduction in proteinuria from nephrotic to completely normal levels. This is accompanied by the gradual disappearance of subepithelial and intramembranous deposits, reorganization of the podocyte foot processes, and re-establishment of slit diaphragms. Repeat biopsies performed in several patients following complete remission after treatment with rituximab found a virtual disappearance of immunofluorescence staining for IgG4 (but not total IgG), a trend towards decreased C3 staining, as well as a complete or partial disappearance of subepithelial deposits.²⁷ The structural changes that underlie a partial remission are less well known. The transplantation of kidneys from rats with experimental HN into naïve rats revealed that, although a significant amelioration of proteinuria occurred in the absence of circulating antimegalin antibodies, the immune deposits required time to clear and the animals were left with permanent residual proteinuria.²⁸

The mechanisms for the formation of subepithelial deposits in secondary MN are not well understood, and may involve planted antigens or low-avidity circulating immune complexes rather than native podocyte antigens. The presence of deoxyribonucleic acid (DNA)/histone complexes and the HBV e-antigen have been variably demonstrated in subepithelial deposits; it has been assumed that circulating immune complexes, which may be cationic, eventually deposit on the

outer aspect of the GBM, perhaps after dissociation and re-association. Several isolated reports have detected various tumor antigens in these deposits, although it is unclear that such complexes represent the initiators of disease or are only passively trapped in existing deposits. The molecular differences underlying the immune complexes deposit location in membranous versus mesangial or proliferative forms of LN are not currently known. Similarly, the mechanisms whereby therapeutic drugs or chronic infections lead to secondary MN have not yet been established.

Natural history and prognosis of idiopathic MN

Predicting the clinical course of a patient with MN at disease presentation is impossible given the variable and fluctuating disease course. A widely appreciated yet oversimplified view is that one-third of all patients will spontaneously remit without treatment, another third will remain proteinuric with preserved renal function, and the final third will progress to end-stage kidney disease (ESKD). Young females and those with subnephrotic levels of proteinuria are most likely to experience spontaneous remission, justifying several months of observation prior to any initiation of treatment in the absence of problematic clinical features. Baseline demographic differences in natural-history studies lead to a blurred prognostic picture. A widely quoted study by Schieppati et al²⁹ reported the incidence of spontaneous remission in 100 untreated patients with idiopathic MN: more than one-third *never* had nephrotic-range proteinuria, and complete or partial remission was achieved in 65% with an estimated 5-year renal survival of 88%. Other studies are not as optimistic; many studies were performed in the era before angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) were routinely used for the treatment of nephrotic patients. Excluding the non-nephrotic patients (who have an excellent chance of full renal survival from the outset), a systematic review of published natural-history studies yielded an estimate that ~50% of untreated nephrotic patients would experience a loss of renal function over a 10-year period.³⁰ These same authors advised caution in interpreting trials with short follow-up, noting that development of ESKD in idiopathic MN takes at least 5 years, and a decline in renal function may not be apparent for 2.5 years. The median times to partial and complete remission are 11-23 months and 16-40 months, respectively, whereas the median time to complete remission in treated patients is 18-22 months. Studies drawing conclusions about remission rates or renal survival without the benefit of 5-10 years of follow-up data must be reconsidered given this information.

Ideally, only patients unlikely to spontaneously remit and those at risk for significant renal deterioration should be treated. Several risk factors for MN progression have been proposed: older age at onset, male sex, nephrotic-range proteinuria (especially >8 g), and increased serum creatinine at presentation. As with most renal diseases, progression correlates with the amount of tubulointerstitial disease on renal biopsy, and a tubulointerstitial disease score has been included as a prognostic variable in several studies. Although the rate of renal decline may not differ in comparison with MN patients having preserved renal function, patients with a higher serum creatinine or increased interstitial disease at presentation will reach ESKD in a shorter time; therefore, it is advisable to

consider early treatment in these patients. Asians with MN appear to have a more favorable long-term prognosis than their non-Asian counterparts.³¹ Achieving complete remission predicts an excellent long-term renal prognosis and those patients have nearly universal renal survival at 10 years, whereas the number falls to 90% with partial remission, and 45% with no remission.³²

Cattran and colleagues³³ proposed a prognostic model dividing patients with MN into low-, moderate-, and high-risk groups based on their degree of proteinuria and clinical course over 6 months of observation. Those with normal renal function and lower amounts of proteinuria (<4 g daily) over 6 months constitute a group at low risk for developing progressive renal insufficiency from the disease. Intermediate levels of proteinuria (4–8 g daily) with stable renal function over 6 months define a group at moderate risk. The highest-risk patients are those with >8 g of daily proteinuria for 6 months, and/or reduced renal function at outset or deterioration of renal function over 6 months. The risk of further renal deterioration in this group is at least 75%.

Treatment of idiopathic MN

Treatment goals in MN are to prevent loss of renal function and to ameliorate the complications of the nephrotic syndrome (eg, hyperlipidemia, volume overload, hypertension, and thrombophilia). Debates continue on how to achieve these goals, and the literature concerning the treatment of MN is far from conclusive. The relatively low incidence of MN hampers recruitment into clinical trials, and the variable natural history of the disease adds further treatment decision complications. In addition, substantial risks for treatment are associated with established immunosuppressive agents and newer, potentially less toxic agents (eg, mycophenolate or rituximab) have been introduced for the treatment of MN without the benefit of long-term clinical trials. A meta-analysis³⁴ compiling data on 1025 patients with MN from 18 randomized clinical trials concluded that immunosuppressive treatment had no benefits in patient or renal survival; however, a thoughtful reanalysis of the existing data³⁰ and the publication of another clinical trial with long-term follow-up data³⁵ have convinced most nephrologists that treatment is warranted. Several excellent articles reviewing existing and novel treatment options in idiopathic MN have recently been published.^{36,37}

Given the relatively high rate of spontaneous remission in MN, newly diagnosed patients with nephrotic syndrome and normal renal function should initially receive conservative therapy with an ACE inhibitor or ARB, diuretics, salt restriction, and statins. No convincing data exist to support inhibition of the renin-angiotensin system for long-term benefits in MN;^{30,32} however, this treatment is the current standard of care for most nephrotic conditions. If a patient remains proteinuric with normal renal function, such conservative treatment can be continued, but those patients who remain frankly nephrotic after 6 months or who initially present with (or develop) renal dysfunction should be treated with an immunosuppressive agent.

Some data suggest benefits with treatment even in advanced renal disease. MN patients with heavy baseline proteinuria and progressive renal dysfunction, who were randomized to cyclosporine, had decreased proteinuria and slower progression of renal disease at 1 year, compared with those receiving supportive therapy alone.³⁸ Based on this ability to successfully treat MN despite worsening renal function and given the potential toxicity of treatment, one group recommended a restrictive policy of treatment; they provided data indicating that delaying treatment until there is evidence of renal disease progression does not alter long-term outcomes.³⁹

Alkylating agents

Corticosteroids as monotherapy are not indicated for MN; instead, typical immunosuppressive regimens for idiopathic MN combine corticosteroids with alkylating agents for 6–12 months. Treatment with cyclophosphamide or chlorambucil in conjunction with corticosteroids is supported by randomized controlled trials (RCTs); cumulative data suggest that 30%–40% of those treated will achieve complete remission, with 30%–50% attaining partial remission and only 10% developing progressive renal disease.⁴⁰ Relapse occurs in approximately 25%–30% within 5 years of discontinuing the alkylating agent, but often responds to a repeat course of immunosuppressive therapy. A remission rate of 88% (vs 47% for control patients) and a 10-year dialysis-free survival of 92% (vs 60%) was provided by a regimen of 6 alternating months of corticosteroids and chlorambucil.⁴⁰ A subsequent study by the same group indicates that the substitution of cyclophosphamide for chlorambucil may decrease the incidence of side effects while yielding equivalent efficacy.⁴¹

Recently, Jha and colleagues³⁵ provided confirmatory evidence from a 10-year follow-up of an Indian population with idiopathic MN. This open-label RCT compared a 6-month course using alternating months of steroids and oral cyclophosphamide with supportive therapy. There were 34 remissions (15 complete) in the 51 treated patients followed for the full 10 years, versus 16 remissions (5 complete) in the 46 patients in the supportive-therapy group. Ten-year dialysis-free survival was higher in the treatment arm (89% vs 65%).

The calcineurin inhibitors (CNIs): cyclosporine and tacrolimus

Cyclosporine is an alternative, clinically validated immunosuppressive agent used in the treatment of MN.⁴² In 51 patients with steroid-resistant MN, treatment with cyclosporine plus steroids for 6 months with tapering over 4 weeks resulted in a 75% complete or partial remission rate, versus only 22% in the placebo (steroids alone) group.⁴³ Typically, many patients in cyclosporine-based treatment regimens are partial remissions, and many relapse after discontinuing treatment. Another similarly-sized trial compared 12 months of cyclosporine and corticosteroids to cyclosporine alone.⁴⁴ Although both groups achieved ~80% remission rate at 12 months, the relapse rate was lower in the group receiving adjunctive corticosteroids from the beginning. Longer courses of cyclosporine (1–2 years) with a slow taper may be

necessary to avoid a high rate of relapse. Other investigators demonstrated that treatment with tacrolimus in heavily nephrotic patients resulted in higher remission rates compared with conservative treatment alone; however, nearly half of these patients had a nephrotic relapse within several months of tapering tacrolimus.⁴⁵

Alternative agents

Due to the often severe adverse or nephrotoxic effects associated with cyclophosphamide and cyclosporine, several newer and potentially less toxic agents are under evaluation for the treatment of MN. Several small studies indicate the potential efficacy of rituximab, mycophenolate, or synthetic adrenocorticotrophic hormone (ACTH) in MN; unfortunately, none are large RCTs nor do they provide long-term follow-up data. **Rituximab:** A plausible rationale for the use of rituximab, a monoclonal anti-CD20 antibody that depletes B cells, is provided by the suggested pathophysiological basis for MN of autoantibodies targeting a putative glomerular antigen. Although rituximab appears to induce remission with an initial efficacy comparable to alkylating agents and corticosteroids, long-term data on dialysis-free survival have not been reported. In an open-label trial of rituximab with a group of 15 high-risk idiopathic MN patients, there were 2 complete and 6 partial remissions at final follow-up.⁴⁶ Others reported the effects of treatment with 4 weekly doses of rituximab on 50 consecutive patients with persistent nephrotic levels of proteinuria despite 6 months of conservative therapy.²⁷ Ten patients achieved a full remission after treatment; however, they were more likely female and with lower baseline serum creatinine values, which is a population of high spontaneous remission. Recently, Segarra et al⁴⁷ demonstrated that rituximab was of benefit in 13 Spanish patients with idiopathic MN and CNI dependence, allowing successful weaning of the nephrotoxic CNI. A systematic review of the published literature describing the use of rituximab in MN highlights that, while promising, the existing literature consists of too few patients, heterogeneous populations, and insufficient follow-up to recommend the use of rituximab outside the research setting.⁴⁸

Mycophenolate: Mycophenolate is another agent used in small, short-term trials for MN treatment with varying results. Initial studies^{49,50} demonstrated that mycophenolate could reduce proteinuria in patients with MN who had been resistant to other conventional therapies. In contrast, a recent RCT detected no effect of mycophenolate monotherapy in patients with normal renal function and nephrotic levels of proteinuria, as compared with conservative antiproteinuric therapy.⁵¹ The addition of corticosteroids to mycophenolate achieved a 1-year cumulative remission rate of 66% in a group of MN patients with moderate renal dysfunction, but was inferior to alkylating agents and steroids in a historically treated control group and demonstrated a relapse rate of nearly 40%.⁵² However, a small RCT revealed similar effects from 6 months of mycophenolate and steroids compared with chlorambucil and steroids at 15 months of follow-up.⁵³ Given these small studies with insufficient

long-term follow-up, mycophenolate is not a first-line agent for the treatment of MN, but may be considered with adjunctive corticosteroids, if standard therapies are not effective or cannot be tolerated.

Adrenocorticotrophic hormone (ACTH): Another intriguing agent that may show promise in MN is ACTH. In an open-label study, Berg and colleagues⁵⁴ treated 14 patients subcutaneously with a synthetic form of ACTH over an 8-week period, and achieved short-term results similar to the more established treatments mentioned above. Since exogenous corticosteroids alone lack therapeutic effect in MN, it is currently unknown whether ACTH has salutary effects in addition to stimulating endogenous corticosteroid production. Another small trial⁵⁵ randomized 32 idiopathic MN patients with preserved renal function and no prior therapy to 1 year of ACTH or 6 months of therapy with alkylating agents and steroids. At 1 year, 87% in the ACTH group had achieved complete or partial remission, versus 93% in the standard-therapy group. Although not significant, there were twice as many complete remissions in the ACTH group; however, this formulation of synthetic ACTH is not available in the US and there are no long-term follow-up studies documenting the efficacy of this agent.

Future possibilities

If anti-PLA2R or other MN-specific autoantibodies prove to be tightly associated with immunological disease activity in idiopathic MN, a serologic immunoassay developed on the basis of these data would have several potential applications. First would be the use of anti-PLA2R as an initial assay for the diagnosis of idiopathic MN without reliance on kidney biopsy. Serial assays for the presence and titer of anti-PLA2R prior to therapeutic intervention in clinical trials could help reduce the uncertainty that currently exists as to whether rapid responders represent a true therapeutic effect or a spontaneous remission. Anti-PLA2R could also be followed during treatment to assess the efficacy of immunosuppressive therapy and to determine the length of treatment. It could also be useful in situations of partial remission, when residual proteinuria may be caused either by ongoing but attenuated immune activity or by structural glomerular changes in the absence of immune activity.

Conclusions

MN is a common cause of the nephrotic syndrome in adults of all races and ethnicities. Its molecular pathogenesis is becoming increasingly well understood, and the identification of PLA2R as a major target antigen may allow better diagnosis, improved monitoring of disease activity, and sensible decisions about the necessity and duration for treatment. Treatment should be provided to those at high risk of progression to ESKD, including patients with persistent severe proteinuria or a documented loss of renal function. Alkylating agents and cyclosporine are the only clinically validated treatments with sufficient follow-up data; however, as experience with the newer agents tacrolimus, rituximab, mycophenolate, and ACTH expands, these too may become treatments of choice for idiopathic MN.

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