Chapter

Membranous Nephropathy

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Abstract

Membranous nephropathy (MN) is a glomerular disease that is the leading cause of nephrotic syndrome in non-diabetic Caucasian adults. MN is most often primary (idiopathic) and the remaining is secondary to systemic disease or exposure to infection or drugs. The majority of patients with MN have circulating antibodies to the podocyte antigens phospholipase A_2 receptor (PLA2R) (70%) and thrombospondin type-1 domain-containing 7A (THSD7A) (3–5%). Immunologic remission (depletion of PLA2R antibodies) often precedes and may predict clinical remission. Untreated, about one-third of patients undergo spontaneous remission, one-third have persistent proteinuria but maintain kidney function and the remaining one-third will develop end stage kidney failure. All patients with idiopathic MN should be treated with conservative care from the time of diagnosis to minimise proteinuria. Immunosuppressive therapy is traditionally reserved for patients who have persistent nephrotic-range proteinuria despite conservative care. Immunosuppressive agents for primary MN include combination of corticosteroids/alkylating agent or calcineurin inhibitors and rituximab. This chapter will review the epidemiology, diagnosis and treatment of MN, particularly focusing on idiopathic MN.

Keywords: membranous nephropathy, PLA2R antibody, cytotoxic agents, calcineurin inhibitor, rituximab

1. Introduction

Idiopathic membranous nephropathy (MN) remains the leading cause of nephrotic syndrome in Caucasian adults and one of the most common primary glomerular diseases to progress to end-stage kidney disease (ESKD) [1, 2]. Secondary MN is associated with autoimmune diseases (e.g., systemic lupus erythematosus), infections (e.g., hepatitis B and C), medications (e.g., nonsteroidal anti-inflammatory drugs, D-penicillamine, gold), and neoplasias [3]. As idiopathic and secondary forms have similar clinical presentations, the designation of idiopathic is made only after ruling out secondary causes by a careful history, physical examination, and laboratory evaluation. This chapter will primarily focus on idiopathic MN.

2. Epidemiology

MN accounts for 20–30% of cases of nephrotic syndrome in Caucasian adults [4, 5]. Although the disease affects patients of all ages, all ethnicities and both sexes, it is more common in white men [4, 6]. MN has a peak incidence during

the fourth and fifth decades of life, and is relatively uncommon in patients aged under 20 years [4, 6]. The incidence of ESKD is about 35% at 10 years [7].

3. Pathogenesis

In the past decade, the understanding of the pathogenesis of idiopathic MN has significantly improved. In 2009, phospholipase A_2 receptor (PLA2R) was identified as the major antigen responsible for autoantibody binding in idiopathic MN [8]. PLA2R is a transmembrane receptor that is highly expressed in glomerular podocytes and anti-PLA2R (typically of IgG4 subtype) was initially identified in 70% of patients with idiopathic MN [8]. Subsequent studies from various cohorts have shown that PLA2R antibodies are positive in 50–80% of patients with idiopathic MN [4, 6, 9–12]. PLA2R antibodies are uncommon in patients with MN associated with malignancies [13, 14]. PLA2R antibody has been reported in hepatitis-B associated membranous nephropathy [15] and also in hepatitis-C associated membranous nephropathy [14]. In genetic studies, there was association with HLA-DQA1 risk alleles [16, 17] and PLA2R1 alleles [16]. Furthermore, the presence of HLA DQA1*05:01 and DQB1*02:01 alleles are associated with higher PLA2R antibody levels [18].

PLA2R is a 180-kDa membrane receptor with a large extracellular region comprising 10 distinct globular domains, including a cysteine-rich domain, a fibronectin type II domain, and eight distinct C-type lectin domains (CTLD1–8) [19]. Each domain is separated by a small linker sequence of <10 amino acids. CysR is the immunodominant epitope for PLA2R [20]. Epitope spreading refers to the development of immune responses to endogenous epitopes secondary to the release of self-antigens during a chronic autoimmune or inflammatory response. In MN, epitope-spreading starts with the cysteine-rich domain then extends to CTLD1, CTLD7 or other nearby regions. This results in an augmented immune response through heightened antibody diversity. In a study of 69 patients with MN from five French centres, Seitz-Polski et al. demonstrated that higher anti-PLA2R antibody titres and serum reactivity to CTLD1 and/or CTLD7 in addition to the cysteine-rich domain were associated with a higher rate of kidney failure [21].

A second IgG4 auto-antibody against thrombospondin type-1 domain-containing 7A (THSD7A) was identified in a smaller number of patients with MN. THSD7A, like PLA2R, is also a protein highly expressed in podocytes and was identified in European and North American patients with anti-PLA2R-negative idiopathic MN but not in healthy controls or patients with other glomerular diseases [22]. It occurred in 2–5% of all patients with idiopathic membranous nephropathy, which corresponded to 8–14% of patients who were seronegative for anti-PLA_2R antibodies. A recent meta-analysis of 10 studies involving 4121 patients showed that the prevalence of THSD7A was low at 3% (95% CI 2–4%) of all patients with idiopathic MN, which corresponded to 10% (95% CI 6–15%) of anti-PLA2R antibody negative patients [23]. However, this meta-analysis was limited by a limited number of studies and small sample size. This meta-analysis also showed that cancer may be more common in patients with THSD7A antibodies and the incidence varied from 6 to 25%. Further studies to elucidate the role of THSD7A as a marker of prognosis and response to therapy are required.

Antibodies against both PLA2R and THSD7A can coexist but only in 1% of cases [24].

4. Pathology

Despite the availability of anti-PLA2R antibody, kidney biopsy remains the standard of care in diagnosing MN. In early MN, glomeruli may appear normal by

light microscopy. However, with time, the glomerular basement membrane thickens and there is formation of subepithelial "spikes" of basement membrane on the outer surface of the capillary wall. These "spikes" are more apparent with silver methenamine staining (**Figure 1**). Immunofluorescence microscopy reveals diffuse, uniform, finely granular deposits of IgG4 along the outer surfaces of capillary walls (**Figure 2**). Complement components, including C3, C4d and C5b-9, are also

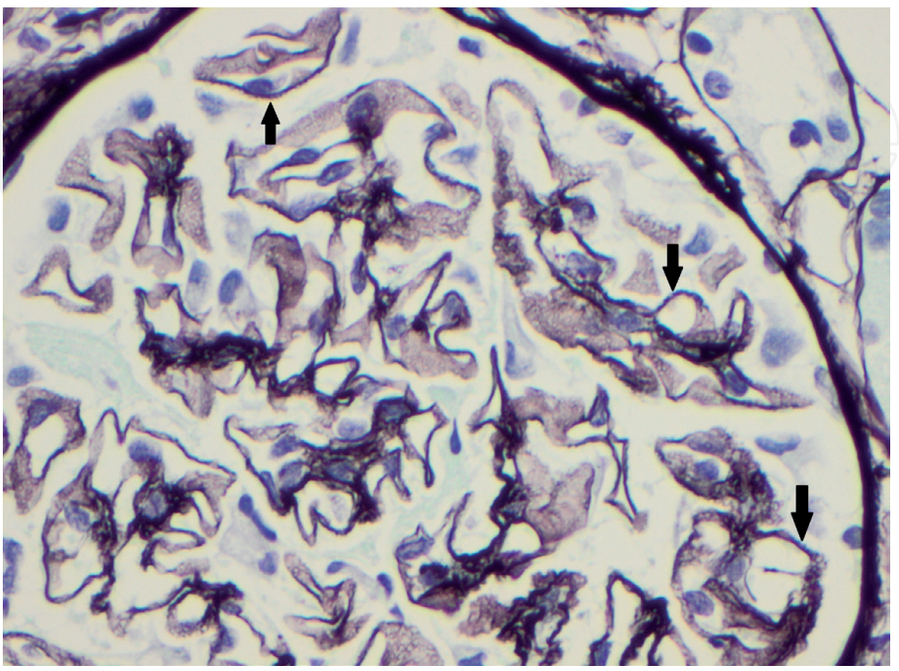

Figure 1.
Glomerulus showing thickening of glomerular basement membrane and subepithelial "spikes" (see arrowhead) in MN (silver-methamine stain).

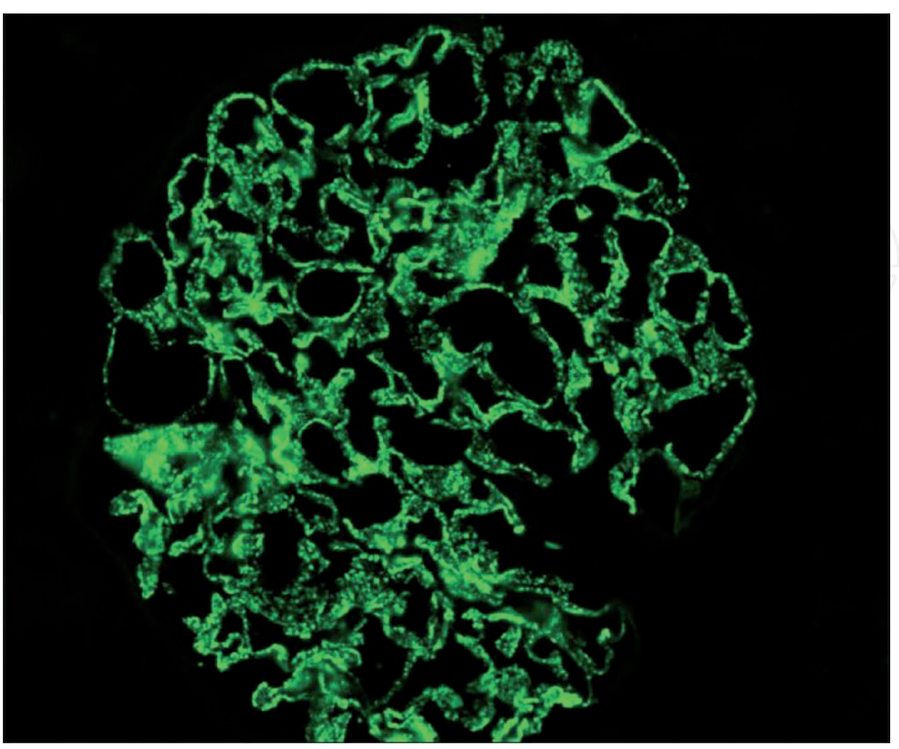

Figure 2.
Immunofluorescence showing diffuse fine granular distribution pattern of immunoglobulin G (IgG) along the glomerular basement membrane.

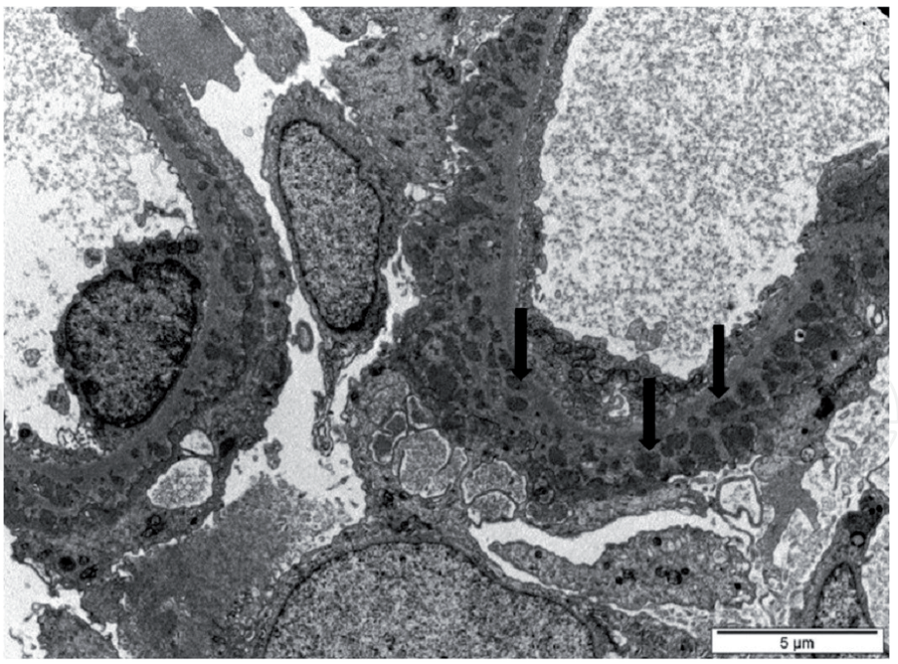

Figure 3.
Electron microscopy showing diffuse subepithelial electron dense deposits (see arrowheads) in MN.

commonly present, but not C1q. The antigens, PLA2R and THSD7A, co-localise with IgG4 in most patients with idiopathic MN.

Electron microscopy shows diffuse subepithelial electron-dense deposits and also glomerular basement membrane thickening (**Figure 3**). The deposits are gradually incorporated within new glomerular basement membrane and become more electron-lucent as they are resorbed before eventually disappearing in patients following the development of complete remission (CR).

5. Clinical manifestations

At presentation, 60–70% of patients will have nephrotic syndrome [25, 26]. The remaining one-third is presented with sub nephrotic-range proteinuria (<3.5 g/day) [27]. Microscopic hematuria also occurs in approximately one-third of patients; however, macroscopic hematuria is unusual and should prompt consideration of alternative diagnoses [28]. Hypertension and moderate-to-severe kidney failure occur in a minority of patients and tend to occur more commonly in older individuals [29]. Dyslipidaemia is common and venous thromboembolism has been reported to occur in approximately 7% [30].

6. Natural history

MN is a chronic disease, with spontaneous remission and relapses. There is great variability in the rate of disease progression, and the natural course is difficult to assess [31–33]. Spontaneous remissions are said to occur in up to 30% of cases. The proportion of patients going into spontaneous remission is much lower when patients have higher grades of proteinuria or high anti-PLA2R antibody titre (>85 RU/mL) at presentation [34]. The remaining two-thirds of patients who do not undergo spontaneous remission either have persistent proteinuria with stable kidney function long-term or will progress to kidney failure. Even patients who do not progress but remain nephrotic are at an increased risk for life-threatening

thromboembolic and cardiovascular events [30, 35, 36]. A rapid decline in kidney function should raise the possibility of a superimposed condition, such as interstitial nephritis, renal vein thrombosis or acute tubular necrosis due to sepsis in an immunocompromised patient.

7. Predicting factors

Many individual factors, such as advanced age, male sex, degree of kidney impairment on presentation, degree of chronicity in the kidney biopsy (e.g., degree of interstitial fibrosis, tubular atrophy, vascular damage and glomerulosclerosis), degree of proteinuria and anti-PLA2R antibody titre have all been reported to be predictors of prognosis and/or response to immunosuppressive therapy in patients with MN [34, 37]. Pei et al. observed a 47% higher risk of kidney disease progression in patients with proteinuria exceeding 4 g/24 hour for longer than 18 months and a 66% higher risk in patients with proteinuria exceeding 8 g/24 hour for more than 6 months [38]. Similarly, PLA_2R antibodies appear to correlate with disease activity, response to therapy and also prognosis [18, 34, 39, 40]. In particular, higher antibody levels are linked to a higher risk of declining kidney function, suggesting that these affected individuals may benefit from earlier initiation of immunosuppression [18]. Conversely, favourable outcomes have been shown in patients who are negative for anti-PLA_2R antibodies.

8. Response measurements

The best-accepted responses are improved kidney survival and CR of proteinuria. CR is defined as a urine protein excretion of <0.3 g/24 hour accompanied by a normal serum albumin concentration and normal serum creatinine [41]. Partial remission (PR) has been also recognised as a positive outcome and is defined as urine protein excretion of <3.5 g/24 hour or reduced by at least 50% from peak values accompanied by an improvement or normalisation of the serum albumin concentration and stable serum creatinine [41]. Approximately 30% of MN cases will relapse subsequent to a CR [42]. The great majority who do, however, will relapse to sub-nephrotic-range proteinuria and will have stable long-term function [42]. A review of 350 nephrotic patients with MN found that the 10-year kidney survival was 100% in the CR group, 90% in the PR group, and 45% in the no-remission group [43]. Respective rates of glomerular filtration rate decline were −0.12 ± 0.40, −0.17 ± 0.50 and −0.86 ± 1.08 mL/minute/month, such that the attainment of CR or PR independently predicted a much more favourable kidney function prognosis [43]. In patients who are anti-PLA2R antibody positive, reduction in circulating antibody titre precedes clinical remission, and furthermore, persistence of antibody despite treatment is associated with clinical resistance [44]. Future definitions of remission of this disease may well incorporate elements of both clinical and serological remission.

9. Treatment

Based on the predictive factors described above, patients can be rationally assigned to either conservative (non-immunosuppressive) therapy or immunosuppressive therapy.

10. Conservative therapy

Conservative therapy includes controlling oedema, dietary protein intake, blood pressure, and hyperlipidaemia. MN patients develop significant oedema and to control the oedema, loop diuretic is the mainstay of treatment along with low-salt diet. High salt diet intake, apart from worsening the oedema, can also significantly impair the beneficial effects of renin-angiotensin blockade, which are one of the key components of conservative therapy. A normal dietary protein intake (0.75–1.0 g/kg/day) is usually recommended. A recent meta-analysis including 44,989 participants showed more intensive blood pressure-lowering (mean blood pressure levels of 133/76 mm Hg, compared with 140/81 mm Hg in the less intensive treatment group) achieved a relative risk reduction of albuminuria by 10% [45]. Anti-proteinuric agents, such as angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), should be used as first-line antihypertensive agents [46, 47]. In patients with lower levels of proteinuria (<4 g/24 hour), treatment with an ACEi or an ARB may be sufficient to reduce proteinuria to sub-nephrotic levels thereby appreciably mitigating kidney and cardiovascular risks. However, in patients with higher degrees of proteinuria, the use of these medications alone is unlikely to result in a substantial reduction in proteinuria or preservation of kidney function [48].

Statins should be prescribed to control hypercholesterolaemia and attenuate the heightened cardiovascular risk observed in patients with MN [49].

Patients with severe nephrotic syndrome are at increased risk of thromboembolic complications. Lionaki et al. reported that clinically apparent venous thromboembolism occurred in 7% of patients with MN and the risk was higher if the serum albumin was below 2.8 g/dL [30]. In a retrospective review of MN patients with nephrotic range proteinuria, use of prophylactic anticoagulation has been shown to be associated with a reduction in fatal thromboembolic episodes and benefits of anticoagulation outweigh the risk of bleeding [50]. In general, MN patients who are severely nephrotic (proteinuria >10 g/24 hour and serum albumin of <2.5 g/dL) should be considered for anticoagulation [30].

11. Immunosuppressive therapy

Several treatment strategies using immunosuppressive therapy have been shown to be successful in reducing proteinuria in MN [51]. Based on their risk factor profiles, patients are grouped into low, medium and high-risk categories.

12. Treatment of low-risk patients

Patients in the low-risk group are categorised by a <5% risk of kidney disease progression over 5 years of observation. Patients in this group would have normal kidney function and proteinuria of ≤4 g/24 hours over a 6-month observation period. Evidence to support this approach comes from published validation studies [43, 52]. Such patients therefore do well with a conservative treatment approach, as outlined above [53].

13. Treatment of medium-risk patients

Patients in this group have preserved renal function and daily urinary protein excretion rates of 4–8 g/24 hours which continue unabated following a 6 month

period of conservative therapy. These patients warrant immunosuppressive therapy with one or more of the following options:

13.1 Corticosteroid monotherapy

An early collaborative randomized study of 72 adult patients with idiopathic nephrotic syndrome demonstrated that a 2–3 month course of high-dose alternate-day prednisone when compared to placebo resulted in a significant reduction in progression to kidney failure but there was no effect on the degree of proteinuria. Ten of the 38 placebo-treated and one of the 34 prednisone-treated patient were in renal failure (creatinine more than 5 mg/dL [440 μmol/L]) or dead ($p < 0.02$) [54]. A subsequent prospective randomised study comparing a 6-month course of alternate day prednisone (45 mg/m^2) or no specific treatment in 158 patients with idiopathic MN showed no significant benefit of corticosteroid treatment alone in either induction of remission or preservation of kidney function over a mean follow-up period of 48 months [55]. Hence, corticosteroid monotherapy have been shown to be ineffective inducing remission in patients with MN.

13.2 Cytotoxic agents combined with corticosteroids

A number of randomised trials have suggested that alternating monthly regimen of steroids and cytotoxic agents is more likely to induce CR of nephrotic syndrome, and halt disease progression compared to no therapy or corticosteroids alone. The first study by Ponticelli's group compared the effects of corticosteroids alternating monthly with chlorambucil to conservative treatment in 67 adult patients with MN [56]. The regimen was given over a 6-month period. It consists of 1 g of intravenous methylprednisolone (MTP)/day for first 3 days of months 1, 3 and 5 followed by 27 days of oral methylprednisolone 0.5 mg/kg/day for the remainder of the month. In the alternating months (months 2, 4 and 6), chlorambucil 0.2 mg/kg/day is used instead of corticosteroids. Compared with controls, patients in the intervention group experienced higher rates of CR or PR (72 vs. 30%, $p = 0.001$) and significantly better preserved kidney function at 1 year ($p = 0.011$) and 2 years ($p < 0.0001$). After 10 years of follow-up, patients treated with combination therapy had a 92% probability of kidney survival compared with 60% in the control group ($p = 0.004$), and the probability of achieving a CR or PR was 83% in the treatment group, and only 38% in the controls ($p = 0.000$) [57]. A second study by the same group, compared the original chlorambucil regimen (45 patients) as described above to MTP pulses plus steroid alone for 6 months (47 patients) [58]. Compared to the steroids alone regimen, treatment with the chlorambucil regimen resulted in higher proportions of patients without nephrotic syndrome at 3 years (66 vs. 40%, $p = 0.011$), although the result was no longer statistically significant by 4 years (62 vs. 42%, $p = 0.102$) chlorambucil-treated patients also had longer mean ratios of months in remission (0.52 vs. 0.31, $p = 0.008$) [58]. In a third study from the same investigators, patients were enrolled in a 6-month study comparing corticosteroids (1 gm of intravenous MTP day for first 3 days of months 1, 3 and 5 followed by 27 days of oral methylprednisolone 0.5 mg/kg/day for the remainder of the month) alternating monthly with either chlorambucil (0.2 mg/kg/day) or oral cyclophosphamide (2.5 mg/kg/day) in months 2, 4 and 6 [59]. No significant differences were observed between the two groups with respect to remission rate (CR or PR) at 1 year (82 vs. 93%, respectively, $p = 0.116$), subsequent relapse rate (31 vs. 25%, or changes in proteinuria or reciprocal serum creatinine over time.

In an open-label, parallel-arm, randomised controlled trial, Jha and colleagues compared the effects of alternating monthly prednisolone and cyclophosphamide

for 6 months versus conservative treatment (salt restriction, blood pressure control and diuretic therapy) on remission, kidney disease progression and quality of life in adult patients with MN and nephrotic syndrome [60]. Compared with controls, those who received cyclophosphamide and steroids were more likely to achieve remission (72 vs. 35%, $p < 0.001$) and have better kidney survival, defined as not experiencing doubling of serum creatinine, dialysis or death (79 vs. 44%, $p = 0.0006$) [60]. They also had higher mean quality of life scores at 10 years, as measured by a visual analogue scale (7.31 ± 0.76 vs. 6.61 ± 1.08, $p < 0.01$). Infectious complications were similar between the groups.

Adverse effects associated with these agents, particularly infertility and malignancy, are the major drawbacks of cytotoxics combined with corticosteroids. The risk of malignancy is not increased for patients treated with cumulative cyclophosphamide doses of up to 36 g but increases significantly thereafter [61].

13.3 Cyclosporine

Early uncontrolled studies of cyclosporine (CSA) suggested an initial benefit but a high relapse rate [62, 63]. In the first single-blind randomised controlled study, 51 patients with steroid-resistant MN were treated with low-dose prednisone (0.15 mg/kg/day up to a maximum dose of 15 mg and reduced after 26 weeks by thirds at 4-week intervals) plus CsA (3.5 mg/kg/day in two divided doses and aiming for a trough level between 125 and 225 μg/L) and compared to patients treated with placebo plus prednisone (similar dose to treatment arm) [64]. At the end of 26 weeks of treatment, 75% of patients (21 of 28) in the CsA group versus only 22% of patients (5 of 23) in the controls had achieved a CR or PR ($P < 0.001$). Relapses occurred in about 40% of patients within 1 year of discontinuation of CsA treatment. In an observational study of 36 adults with idiopathic MN and steroid-dependent or -resistant nephrotic syndrome treated with CsA (5.54 ± 0.81 mg/kg/day), the German Cyclosporine in Nephrotic Syndrome Study Group reported that prolonging CsA treatment (>1 year) resulted in a higher (34% CR at 1 year) and more sustained rate of remission [65]. Prolonged low-dose CsA (~1.5 mg/kg/day) could be considered for long-term maintenance of patients who achieve CR or PR, especially in patients at high risk of relapse [66]. However, this needs to be weighed against the risk of renal scarring from long-term exposure to CsA.

13.4 Tacrolimus

Tacrolimus is also a reasonable consideration for the treatment of MN. In an open-label, randomised controlled trial of tacrolimus versus conservative therapy in 48 patients with MN, normal kidney function and nephrotic syndrome from 13 Spanish centres, Praga et al. demonstrated that tacrolimus monotherapy resulted in a higher probability of remission (CR or PR) at 12 months (76 vs. 22%, $p < 0.001$) with shorter mean time to remission (61. vs. 11.3 months, $p = 0.003$) [67]. In patients with CR or PR at 18 months who subsequently had their tacrolimus withdrawn, 47% of patients experienced a relapse of nephrotic syndrome within a mean period of 4.2 months.

14. Treatment of high-risk patients

This group of patients is characterised by worsening kidney failure, extremely high anti-PLA2R antibodies or persistent high proteinuria (≥8 g/day).

14.1 Corticosteroids

A prospective double-blind randomised controlled trial by the UK Medical Research assessed the medium-term effect of an 8-week course of high-dose prednisolone (100–150 mg on alternate day) in a high risk MN population [68]. A total of 103 patients with preserved kidney function (average creatinine clearance 88 ± 30 mL/minute) were randomised to the treatment group (n = 52) or to the control group (n = 51). At 36 months, there was no significant difference regarding the degree of proteinuria or loss of kidney function between the control and the treatment group.

14.2 Cytotoxic agents combined with corticosteroids

Another randomised controlled trial by the same group assessed whether immunosuppression preserved kidney function in patients with idiopathic MN and declining kidney function [69]. The study randomised patients to either combination of prednisolone and chlorambucil (intravenous methyl prednisolone 1 g per day for 3 consecutive days then oral prednisolone 0·5 mg/kg per day for 28 days during months 1, 3, and 5. During months 2, 4, and 6, patients received oral chlorambucil at a starting dose of 0·15 mg/kg per day) (n = 33) or CsA (12 months of CsA received a starting dose of 5 mg/kg per day, aiming for trough level of 100–200 μg/L) (n = 37) or supportive therapy alone (n = 38). The primary endpoint was a further 20% decline in Cockcroft-Gault estimated creatinine clearance and occurred less frequently in the prednisolone and chlorambucil group than in either the cyclosporin or supportive therapy groups (58 vs. 81 vs. 84%, respectively, p = 0.003). Serious adverse events were also most common in the prednisolone and chlorambucil group (52 vs. 46 vs. 29%, respectively).

14.3 Cyclosporine

So far, there has been only one controlled trial with CsA in patients with high-grade proteinuria and progressive kidney failure. In this study, patients with high risk features were randomly assigned to either CsA (3.5 mg/kg/day taken in two divided doses, and aiming for trough level between 110 and 170 μg/L) treatment (nine patients) or placebo (eight patients) for 12 months) [70]. The average creatinine clearance of these patients was 51 mL/minute/1.73 m^2 and they had an average daily urine protein excretion of 11.5 g/day. After 12 months, there was a significant improvement in renal function as measured by the change in slopes, being greater in the CsA versus placebo patients [70 vs. 7% improvement, mean difference 1.5 (95% CI 0.2–3.1)]. Proteinuria in the CsA group was reduced by an average of 4.5 g/day, where in the placebo group there was an increase of 0.7 g/day by month 3 (p = 0.02).

14.4 Mycophenolate mofetil

In a pilot study, Miller et al. treated 16 medium or high risk MN patients with 1.5–2 g/day of mycophenolate mofetil for a mean period of 8 months [71]. There were no significant changes in mean serum creatinine or albumin levels over the course of the study. Similar results were reported in a retrospective analysis of 17 patients with MN [72], in which treatment with mycophenolate mofetil for 12 months combined with steroids resulted in a 61% reduction of proteinuria. Kidney function improved in three of six patients with kidney failure.

Branten et al. reported 32 patients with MN and kidney insufficiency treated with mycophenolate mofetil (1 g twice a day) plus steroids (IV MTP 1 g for 3 consecutive days at the beginning of months 1, 3, and 5 and oral prednisone, 0.5 mg/kg every other day, for 6 months with subsequent tapering for 12 months) and compared the results with those obtained for 32 patients from a historic control group treated for the same period of time with oral cyclophosphamide (1.5 mg/kg/day) and steroids (similar steroid schedule to above) [73]. Overall, 21 mycophenolate-treated patients developed PR of proteinuria, six patients experienced at least 50% reduction in proteinuria, and five patients experienced no response. No significant differences were observed between the intervention and control groups at 12 months with respect to the occurrence of CR or PR (66 vs. 72%, respectively, $p = 0.30$) or adverse drug reactions (75 vs. 69%, $p = 0.60$), although relapse occurred more frequently in those who received mycophenolate mofetil (38 vs. 13%, $p < 0.01$).

14.5 Rituximab

In a pilot study of eight MN patients treated with four weekly courses of rituximab (375 mg/m^2), two achieved CR and three achieved PR by 12 months [74, 75]. Mean 24-hour urinary protein excretion rates fell by 66% from 8.6 to 3.0 g ($p < 0.005$). Kidney function remained stable in all patients. Adverse effects were reported as mild and included chills, fever and an anxiety reaction.

In another prospective open-label pilot trial, 15 patients with idiopathic MN and proteinuria of >4 g/24 hour despite conservative therapy for >3 months received two doses of rituximab (1 g) 2 weeks apart [76]. At 6 months, another two fortnightly doses of rituximab were administered to patients with measured 24-hour urinary protein excretion rates exceeding 3 g and total CD19$^+$ B-cell counts exceeding 15 cells/μL. Mean proteinuria levels decreased by 54% from 13.0 g/24 hour at baseline to 6.0 g/24 hour at 12 months. At 12 months, two patients achieved CR, six achieved PR, five did not respond and two progressed to ESKD. Rituximab was well-tolerated and was effective in reducing proteinuria in patients with idiopathic MN.

The Evaluate Rituximab Treatment for Idiopathic Membranous Nephropathy (GEMRITUX) study was a French multicentre, randomised, controlled trial which evaluated the efficacy of rituximab in inducing remission in medium- to high-risk patients with idiopathic membranous nephropathy [77]. Thirty-seven patients received both rituximab (375 mg/m^2 on days 1 and 8) and conservative therapy and 38 patients received conservative therapy alone. There was no significant difference in remission rates at 6 months (35.1% in rituximab group compared to 21.1% in conservative group, $p = 0.21$). However, with extended follow up (median 17.0 months), remission rates were significantly higher in the rituximab group (64.9 vs. 34.2%, $p < 0.01$).

The Membranous Nephropathy Trial Of Rituximab (MENTOR) study (NCT01180036) was a multicentre, randomised controlled trial comparing the efficacy and safety of rituximab to CsA in medium to high-risk patients with idiopathic MN [78]. Patients with proteinuria ≥5 g/24 hour following a minimum period of 3 months of conservative non-immunosuppressive therapy were randomised to receive IV rituximab 1000 mg (day 1 and 15, then repeated at 6 months) or oral CsA (3.5 mg/kg/day for 12 months). Patients who received CsA had a higher rate of treatment failure at 24 months compared with those who received rituximab (79.4 vs. 37.5%), and CR or PR occurred in 62.5% of the rituximab cohort compared with 20.6% of those who received CsA (odds ratio 6.0, 95% CI 2.7–13.2, $P < 0.0001$).

Numerous prospective uncontrolled studies have been performed evaluating the efficacy of rituximab in idiopathic MN and are summarised in **Table 1** [75, 77–87].

14.6 Eculizumab

Eculizumab is a humanised anti-C5 monoclonal antibody designed to prevent the cleavage of C5 into its proinflammatory by-products. In a randomised placebo-controlled trial in 200 patients with MN, eculizumab, although well-tolerated, failed to show any significant reduction of proteinuria. There were concerns that the dosing schedules were inadequate as inhibition of complement was not uniformly demonstrated. Patients in the eculizumab arm were treated every 2 weeks with two different intravenous dose regimens over a total of 16 weeks [88]. Neither of the active drug regimens of eculizumab showed any significant effect on proteinuria or kidney function compared to placebo. More encouraging results were seen in a continuation of the original study, in which eculizumab was used for up to 1 year, with a significant reduction in proteinuria in some patients (including two patients who went into CR). More long-term studies need to be performed with anti-C5 monoclonal antibody to determine its role in the treatment of MN.

14.7 Adrenocorticotropic hormone

In a study by Berg and colleagues, synthetic adrenocorticotropic hormone (ACTH) administered 1 mg twice per week for 1 year decreased proteinuria in patients with idiopathic MN [89, 90]. Ponticelli et al. conducted a randomised pilot study comparing methylprednisolone plus a cytotoxic agent versus synthetic ACTH in 32 patients with idiopathic MN [91]. In this study, 16 patients were randomly assigned to receive three cycles of MTP (IV MTP 1 g, administered for 3 consecutive days, and then 0.4 mg/kg body weight per day for 27 days, administered orally) and each cycle was followed by 1 month of treatment with either chlorambucil (0.2 mg/kg/day orally) or cyclophosphamide (2.5 mg/kg/day orally), and 16 were assigned to receive ACTH 1 mg intramuscular injections administered initially one injection every other week to two injections per week for a total treatment period of 1 year. No significant differences were observed in remission rates between the ACTH and control groups (87 vs. 93%, respectively), Medication discontinuation rates due to lack of efficacy or adverse drug reactions were 12.5% in both groups. A pilot study by Hladunewich et al. administered 20 idiopathic MN patients with either 40 or 80 IU twice-weekly dose of Acthar® gel and found a significant improvement in proteinuria at 12 months in the entire cohort [92]. There was >50% decrease in proteinuria in 65% of patients and no significant adverse effects were documented. Improvement in serum anti-PLA_2R antibodies was not noted in all patients. Measured anti-PLA2R antibodies became undetectable in three out of 15 patients and appreciably declined in another four patients.

A suggested, risk-based treatment algorithm is displayed in **Figure 4**. It is intended as a guide only and should additionally take into account individual patient circumstances and preferences. Patients who do not respond well or relapse after a first course of immunosuppression therapy may benefit from a second course of immunosuppression.

Patients with severe kidney insufficiency (serum creatinine of ≥3.5 mg/dL or 309 μmol/L) are less likely to benefit from immunosuppression therapy and more likely to experience treatment-related harm, such that consideration should be given to conservative therapy only and plans made for transplantation in the future [41].

Author/year	Level of evidence	Risk group	N	Treatment regimens	Median follow-up (months)	Outcomes/comments
Dahan/2017 [77]	RCT	Medium-high	75	RTX 375 mg/m^2 on day 1 and 8 + NIAT vs. NIAT alone	17	At 6 months, 13 of 37 (35.1%) treated with RTX + NIAT achieved remission vs. 8 of 38 (21.1%) controls (p = 0.21). Significantly higher rates of PLA_2R antibody depletion at 3 and 6 months in RTX + NIAT group.
Fiorentino/2016 [79]	Prospective uncontrolled	Medium-high	38	RTX 375 mg/m^2 monthly × 6	15	29 of 38 (76.3%) achieved remission –15 (39.5%) CR and 14 (36.8%) PR. Proteinuria significantly reduced. Kidney function stable. No significant adverse events.
Bagchi/2018 [80]	Retrospective uncontrolled	High	21	RTX 500 mg × 2 doses 7–10 days apart ± 3rd dose after 4–6 weeks if CD19 not depleted	13	13 of 21 (61.9%) achieved remission –4 (19.05) CR and 9 (42.9%) PR. One patient relapsed after achieving PR. Kidney survival was significantly better in responders (p –0.0037).
Moroni [81]	Prospective uncontrolled	Medium-high	34	RTX 375 mg/m^2 × 1 dose (n = 18) or ×2 2 weeks apart (n = 16)	23.9 (mean)	At 12 months, 5 (14.7%) CR, 10 (29.4%) PR and 19 (55.8%) no response. Outcome similar for one vs. two doses.
Waldman/2016 [82]	Prospective	High	13	CsA 3 mg/kg/day for 6 months then tapered by 50 mg/day every 3 weeks plus RTX 1000 mg day 1 and 15, then after 6 months when CD19+ B cell count ≥5 cells/μL.	41 (mean)	By 6 months 85% achieved remission (CR + PR). By 12 months, 54% achieved CR. 2 relapsed by 24 months. Treatment well tolerated.
Ruggenenti/2015 [83]	Prospective	High	132	RTX 375 mg/m^2 weekly ×4	30.8	84 of 132 (63.6%) achieved remission (CR + PR), 43 (32.6%) achieved CR. Anti-PLA_2R antibody depletion preceded remission.
Ruggenenti/2003 [75]	Prospective	Medium	8	RTX 375 mg/m^2 weekly ×4	Not specified	Significant reduction in proteinuria. Kidney function stabilised. two achieved CR and three achieved PR.

Author/year	Level of evidence	Risk group	N	Treatment regimens	Median follow-up (months)	Outcomes/comments
Ruggenenti/2012 [84]	Prospective	High	100	RTX 375 mg/m^2 weekly ×4	29 (median)	At end of follow up, 65% achieved CR or PR. Median time to remission 7.1 months. Kidney function improved in those who achieved CR.
Fervenza/2010 [85]	Prospective	Medium	20	RTX 375 mg/m^2 weekly ×4, repeated at 6 months	Not specified	Proteinuria reduced from 11.9 g/24 hours to 4.2 and 2.0 g/24 hours at 12 and 24 months, respectively. At 24 months, 4 of 18 achieved CR, 12 of 18 achieved PR and 1 relapsed. Remission rates higher than fortnightly dosing.
Fervenza/2008 [86]	Prospective	High	14	RTX 1000 mg on day 1 and 15, repeated at 6 months if proteinuria >3 g/24 hours and CD9 + B cell >15 cells/μL	12	At 6 months, four achieved PR. At 12 months, two achieved CR and 6 PR.
Fervenza/2015 [78] Results from abstract	RCT	High	130	RTX 1000 mg on day 1 and 15, repeated at 6 months vs. CsA 3.5–5 mg/kg/day for 6 months	24	At 24 months, CR or PR in RTX arm was 62.5 vs. 20.6% in the CsA arm Treatment failure higher in CsA group compared to RTX group (79.4 vs. 37.5%).
Rojas-Rivera/2015 [87]	RCT	High		MTP 1 g IV day 1–3 then MTP PO 0.5 mg/kg/day for day 4–30 on months 1, 3 and 5 and cyclophosphamide PO 2.0 mg/kg/day for 30 days on months 2, 4 and 6 vs. tacrolimus 0.05 mg/kg/day for 6 months, then tapered to withdrawal by 9 months + RTX 1 g at day 180.		Results awaited

Abbreviations are: RCT, randomised controlled trial; RTX, rituximab; NIAT, non-immunosuppressive antiproteinuric therapy; CsA, cyclosporine; CR, CR; PR, partial remission; MTP, methylprednisolone; PO, per oral.

Table 1.
Rituximab treatment of idiopathic MN.

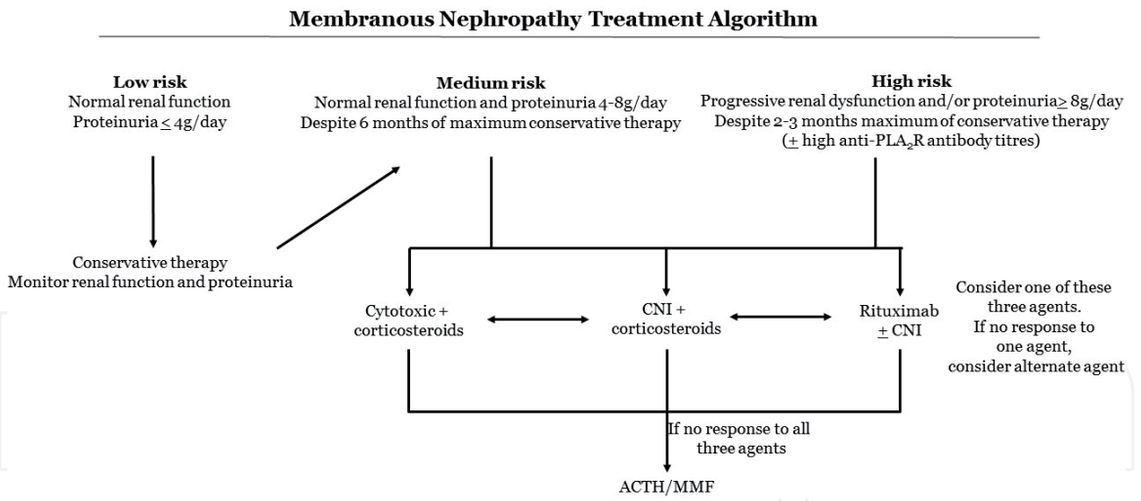

Figure 4.
*Treatment algorithm for idiopathic MN. Based on the renal function and degree of proteinuria at presentation, patients with MN can be classified in to low, medium and high risk category for progression. Patients in the low risk category should be managed with conservative therapy alone but during follow up if they transform in to medium or high risk category then they should be considered for immunosuppressive therapy. Patients in the medium risk category should be treated with conservative therapy for at least 6 months and despite that if they still have more than 4 g/day of proteinuria then they should be considered for immunosuppressive therapy. Patients in the high risk category shouldn't wait for 6 months before starting immunosuppressive therapy. Patients in the medium or high risk category could be treated with either cytotoxics plus corticosteroids or CNI plus corticosteroids or rituximab with or without CNI. If there is no response to one agent, consider alternate agent. If the patient is refractory to all three agents, then they could be treated either with MMF or ACTH. *Conservative treatment involves the use of ACEi ± ARB blocker to maintain BP < 125/75 mmHg, lipid control with HMG-CoA reductase inhibitor, dietary protein restriction (0.6–0.8 g/kg ideal body weight/day), dietary NaCl intake (goal is 2–3 g Na) to optimise antiproteinuric effects of ACEi and ARBs, smoking cessation, and attempt to reduce obesity, if present. Abbreviations are: anti-PLA2R, phospholipase A_2 receptor antibody; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CNI, calcineurin inhibitor; ACTH, adrenocorticotrophic hormone; MMF, mycophenolate mofetil.*

15. Conclusion

In conclusion, controlling proteinuria (either CR or PR) in MN is clearly associated with a slower rate of kidney disease progression. Newer biomarkers, such anti-PLA2R antibody and THSD7A, are showing some promising role in differentiating between primary versus secondary MN, predicting prognosis and response to therapy. There are no standard or universal first-line specific therapeutic options for idiopathic MN. Supportive or conservative care, including dietary salt restriction, anti-proteinuric therapy with ACEi or ARB, optimisation of blood pressure and serum cholesterol, and management of cardiovascular and thromboembolic risks, should be given in all cases. Immunosuppressive therapy, such as cytotoxic agents and steroids, calcineurin inhibitors and steroids, rituximab (with or without calcineurin inhibitors), and ACTH, should be considered in patients at medium or high risk of kidney disease progression, cardiovascular disease or thromboembolic complications, as evidenced by heavy proteinuria (>4 g/day) and/or deteriorating kidney function.

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Conflict of interest

Authors declare no conflict of interest.

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