

# Membranous nephropathy: an update

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## ABSTRACT

Great advances have been made in the pathophysiologic and therapeutic areas of membranous nephropathy in the last years. The description of autoantibodies directed against phospholipase A2 receptor in the glomerulus has confirmed the autoimmune nature of the disease and has changed our diagnostic, classification, and treatment strategies. Rituximab has emerged as a great tool in the therapeutic armamentarium of membranous nephropathy, but a one-size-fits-all approach is far from being the rule. Nowadays, an individualized therapeutic scheme based on clinical and serologic data appears to be the most appropriate method to manage patients with membranous nephropathy. We present a review of the most important aspects published in the literature regarding membranous nephropathy, with an emphasis on the most novel topics with the intention of updating clinicians involved in the management of this disease.

**Keywords:** glomerulonephritis, nephrotic syndrome, membranous nephropathy, phospholipase A2 receptor (PLA2R), autoimmune diseases.

## INTRODUCTION

Membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in adults.<sup>1,2</sup> It is a glomerular pattern of injury characterized by thickening of the glomerular basement membrane (GBM) because of deposition of subepithelial immune complexes.<sup>3</sup> About 20% of the cases have a recognizable etiology (secondary MN), but in the majority of patients the pathogenesis remains incompletely defined (idiopathic membranous nephropathy).<sup>4</sup> The identification in 2009<sup>5</sup> of autoantibodies directed against the M-type phospholipase A2 receptor (PLA2R) located in the podocytes significantly changed the way we understand this entity. Most cases of membranous nephropathy (70-85%)<sup>5,6</sup> present antibodies against PLA2R, while 3-5%<sup>7</sup> present antibodies against thrombospondin type 1 domain containing 7A (THSD7A), and approximately 10% have negative serology (unknown pathophysiology).<sup>6</sup> Thus, the term “idiopathic membranous nephropathy” has been gradually abandoned for the more appropriate term *primary membranous nephropathy* (PMN). Several treatment schemes for PMN have been proposed by different groups around the world, including chlorambucil plus steroids,<sup>8,9</sup> cyclophosphamide plus steroids,<sup>10,11</sup> calcineurin inhibitors,<sup>12</sup> and rituximab.<sup>13,14</sup> Prognosis of PMN is variable since ~30% of the patients reach spontaneous remission (SR), a third are stable, and a third have persistent nephrotic syndrome and progressive deterioration of renal function.<sup>15,16</sup>

## EPIDEMIOLOGY

The incidence of MN is estimated at about 5-10 cases per million per year. In adults, MN represents between 20-40% of cases of nephrotic syndrome.<sup>1,2,6</sup> It has a 2:1 male predominance with a mean age of 50-60 years.<sup>6</sup> It is infrequent in the pediatric population and is most common in Caucasians followed by Asians, blacks and Hispanics.<sup>2,6</sup>

## PATHOGENESIS

### Primary membranous nephropathy

The search for the antigen or antigens responsible for the cases of the so-called idiopathic membranous nephropathy was unsuccessful for many years. Ronco *et al*<sup>17</sup> were the first group to demonstrate the decisive participation of a podocyte antigen (neutral endopeptidase) in an infantile case of MN, although the cases of pediatric MN secondary to anti-neutral endopeptidase antibodies are very rare. More recently, Beck *et al*<sup>5</sup> shown that the M-type phospholipase A2 receptor is a target antigen in primary membranous nephropathy in 70-85% of cases. Many other groups have confirmed this finding.<sup>2,3,6</sup> Although PLA2R binds PLA2 under normal circumstances, its exact physiological role is unclear. Moreover, the trigger for antibody production is currently unknown.<sup>18</sup> The antibodies formed against PLA2R (mainly IgG4) cross the glomerular capillaries and bind to the protein along the subepithelial side of the capillary wall forming the typical subepithelial deposits that are seen in MN.<sup>5</sup> In another subset of patients (3-5%), other receptor located on the podocyte membrane (THSD7A) has been identified as a target autoantigen in MN.<sup>7</sup> In some cases, the development of autoantibodies against THSD7A has been linked to malignant tumors.<sup>19,20</sup> As in the case of PLA2R, it is not clear why antibodies develop. The remaining cases of PMN with negative serology (~10-30%) are probably caused by autoantibodies against as yet unidentified specific antigens. Besides the previously mentioned neutral endopeptidase, a possible pathogenic role of aldose reductase and manganese superoxide dismutase as podocyte antigens has been suggested.<sup>21</sup> Moreover, immunization against bovine serum albumin has been proposed as a potential cause of MN in young children.<sup>22</sup>

The identification of anti-PLA2R has been an enormous breakthrough in the differential diagnosis of MN, as the positivity of anti-PLA2R is strongly indicative of a primary character. However, it should

be noted that although rarely, patients with secondary MN may also have antibodies against PLA2R.<sup>23</sup>

The complement system also plays an important pathogenic role in MN. Ronco *et al*<sup>17</sup> observed that the neutral endopeptidase system is related to the activation of complement within immune deposits and the generation of membrane-attack complex (C5b-9). Once the antibodies are deposited in the capillary wall, the complement terminal factors alter the podocyte structure causing the onset of massive proteinuria.<sup>24</sup>

Finally, some studies have reported a genetic basis associated with certain HLA alleles and genes encoding PLA2R that predispose to membranous nephropathy.<sup>25,26</sup> These genetic variants could become useful biomarkers in the future to stratify the risk of developing the disease.

### ■ Secondary membranous nephropathy

Membranous nephropathy is a prototype of kidney disease caused by immune complexes. The most common causes of secondary MN include infections, cancer, autoimmune diseases, and drugs (Table 1). Implicated antigens are deposited between glomerular basement membrane and podocytes, and subsequently, be bound by circulating antibodies.<sup>3,22</sup> Other explanation is that antigens may form circulating immune complexes that are subsequently trapped in glomerular capillaries or may dissociate and reform in the subepithelial space.<sup>3,27</sup> The identification and treatment of the underlying cause leads in many cases to the resolution of the nephrotic syndrome.

Membranous nephropathy is the most frequent paraneoplastic glomerulopathy associated with solid tumors,<sup>28</sup> but it is not always a linear relationship. Besides, in some cases, the association may be casual (two diseases at the same time) rather than causal. It has been reported that approximately 10% (up to 25% after age 60 years) of adult patients with MN had a malignancy at the time of renal biopsy

**Table 1**

Main causes of secondary membranous nephropathy.<sup>6,28,33</sup> HIV: human immunodeficiency virus, ANCA: anti-neutrophil cytoplasmic autoantibody, NSAIDs: non-steroidal anti-inflammatory drugs, TNFα: tumor necrosis factor alpha.

Groups	
<b>Cancer</b>	Lung and bronchus, gastric, renal, prostatic, breast, colorectal, plasma cell dyscrasias, non-Hodgkin lymphoma, chronic lymphocytic leukemia mesothelioma, melanoma
<b>Infections</b>	Hepatitis B, hepatitis C, HIV, syphilis, schistosomiasis, malaria, filariasis, hydatid disease, leprosy
<b>Autoimmune diseases</b>	Systemic lupus erythematosus, Hashimoto's disease, Graves' disease, diabetes, rheumatoid arthritis, Sjogren syndrome, dermatomyositis, mixed connective tissue disease, ankylosing spondylitis, primary biliary cirrhosis, bullous pemphigoid, retroperitoneal fibrosis, Guillain-Barré syndrome, graft-versus-host disease, bone marrow and stem cell transplantation, anti-GBM disease, IgA nephropathy, ANCA-associated vasculitis, renal transplantation, IgG4 disease
<b>Drugs/toxins</b>	NSAIDs, penicillamine, gold, captopril, buccillamine agents, probenecid, anti-TNFα, mercury, lithium, formaldehyde, hydrocarbons

or within a year thereafter.<sup>3,29</sup> Solid tumors more frequently related to MN include lung and bronchus, gastric, renal, prostatic, breast, and colorectal.<sup>28</sup>

### ■ CLINICAL MANIFESTATIONS

In about 80% of cases, membranous nephropathy presents with a full nephrotic syndrome (proteinuria >3.5g/24h, hypoalbuminemia, and dyslipidemia).<sup>30-32</sup> As most patients present with the typical edema of nephrotic syndrome, early diagnosis is almost the rule. In the remaining cases (20-30%), subnephrotic proteinuria may be the only sign of disease and therefore diagnosis can be significantly delayed due to the absence of symptoms. Proteinuria in MN is nonselective. Although microhematuria is relatively frequent (30% to 40%),<sup>33</sup> macroscopic hematuria is rare and suggests a different glomerular pathologic process, renal vein thrombosis or urologic neoplasms. Other clinical manifestations and complications are those of a nephrotic syndrome (edema, hyperlipidemia, and hypercoagulable state). Edema is usually less severe than in minimal change disease or primary focal segmental glomerulosclerosis,<sup>6</sup> although there is great variability. Occasionally, renal vein thrombosis or pulmonary thromboembolism could be the initial clinical scenarios. The majority of cases (~90%) present normal renal function at presentation.<sup>33</sup> Only 10-20% have hypertension at the time of diagnosis but up to 50% of cases present hypertension during the course of the disease,<sup>6</sup> usually as a consequence of the development of renal insufficiency. In PMN, complement levels are normal and serologic markers (antinuclear antibodies, ANCA) are negative.

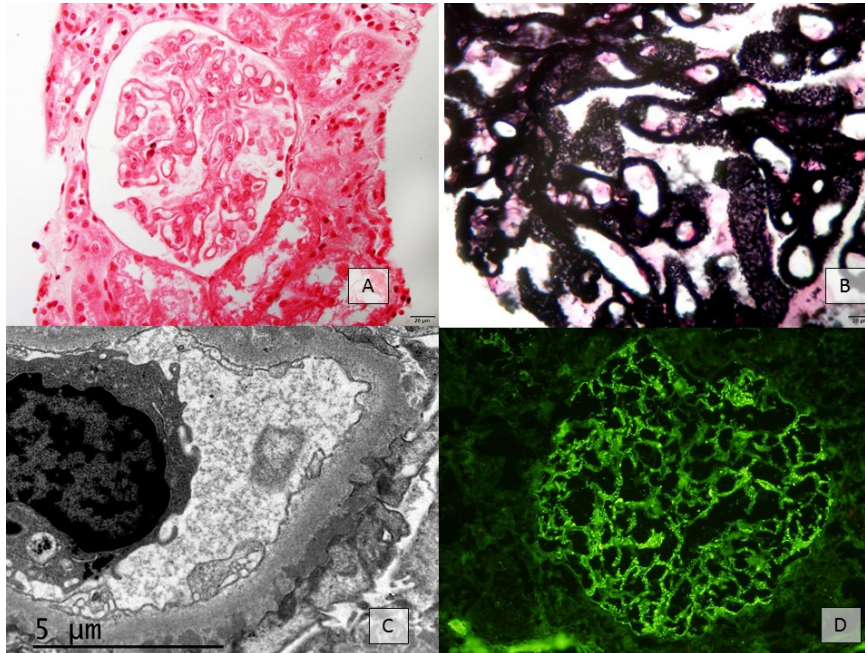
In cases with massive proteinuria and severe hypoalbuminemia, a progressive deterioration of renal function can be observed in the first months of clinical course. Moreover, as in any other cause of nephrotic syndrome, reversible episodes of acute kidney injury may be triggered as a consequence of excessive diuretic treatment or the use of renin-angiotensin-aldosterone system inhibitors. In the most severe cases of MN, the presence of renal glycosuria and other manifestations of tubular injury can be found,<sup>34</sup> probably related to direct tubular toxicity of massive proteinuria.

### ■ Pathology

Membranous nephropathy is characterized by a uniform and diffuse thickening of the glomerular basement membrane without associated cellular proliferation. The prominent GBM is a consequence of subepithelial immune complexes of IgG and complement along the outer surface of the capillary wall.<sup>16,33</sup> By light microscopy, small deposits are visualized in the basement membrane as pinpoint lucencies on silver methenamine stain (Figure 1). Also, matrix reaction to the immune deposits results in subepithelial speculated extensions known as “spikes”.<sup>6,16,33</sup> There are four pathologic stages of MN. In stage I, the only lesion on light microscopy consists of diffuse thickening of the GBM. Visualization of “spikes” and thickening of the GMB on light microscopy are the characteristics of stage II. Diffuse and extensive podocyte effacement and prominent subepithelial deposits on electron microscopy are observed in stage III. Finally, diffuse thickening of the GMB and deposits along the whole thickness of the GBM are seen in

**Figure 1**

Pathology in membranous nephropathy. (A) Thickened glomerular capillary loops with a rigid appearance (hematoxylin & eosin 40x). (B) Glomerular basement membranes with pinpoint lucencies and “spikes” (silver-methenamine 100x). (C) Electron micrograph showing subepithelial homogeneous electron-dense deposits and podocyte foot process effacement in the adjacent areas. (D) Immunofluorescence microscopy showing finely granular staining for IgG in the subepithelial side of the glomerular basement membrane (IgG 40x).



stage IV. It is important to point out that pathologic lesions and stages of MN have a poor correlation with prognosis and treatment response (with the exception of tubulointerstitial fibrosis).<sup>30,31</sup>

Immunofluorescence shows granular subepithelial deposits of IgG along the GBM.<sup>35</sup> In about 50% of cases C3 is also positive.<sup>33</sup> In cases of primary membranous nephropathy the predominant immunoglobulin is IgG4. If preponderant IgG1 or IgG3 is observed, a secondary cause should be suspected. Positivity for IgM, IgA, or C1q, should also prompt a careful search for secondary MN.<sup>2</sup> Another finding in favor of primary membranous nephropathy is the presence of PLA2R or THSD7A colocalized with IgG4.<sup>3,6</sup> It is important to remember that some patients may have negative serum anti-PLA2R with positive anti-PLA2R in renal tissue (seroconversion may occur during follow-up when the rate of production exceeds the buffering capacity of the kidney).<sup>3</sup>

In electron microscopy, the characteristic finding is the presence of homogeneous electron-dense deposits distributed along the subepithelial surface of glomeruli. If mesangial and subendothelial deposits are found, a secondary cause should be considered. The presence of cellular proliferation in glomeruli and endothelial tubuloreticular inclusions should raise the suspicion of membranous lupus nephritis.<sup>1</sup>

Some authors have proposed that a biopsy is not essential to make the diagnosis of PMN as antibodies against PLA2R are not detected in other renal diseases. However, renal biopsy remains the gold

standard unless the patient has a specific contraindication for the procedure. In our opinion, renal biopsy can be obviated in patients with normal renal function and positive anti-PLA2R.

## ■ OUTCOME

Approximately half of the patients with non-nephrotic proteinuria have a favorable prognosis, with stable renal function and without hypertension.<sup>30,31</sup> This subgroup of patients will have a high rate of spontaneous remission. However, up to 60% of these cases may develop a full nephrotic syndrome within 2 years of presentation.<sup>2</sup>

Among patients with nephrotic syndrome, three different types of clinical evolution can be identified: spontaneous remission (30-45%),<sup>36,37</sup> persistent nephrotic syndrome with preserved renal function (20-30%), and persistent nephrotic syndrome with progressive deterioration of renal function (~30%).<sup>15,16</sup> Spontaneous remission is defined as the disappearance of the nephrotic syndrome with preservation of normal renal function, in the absence of any type of immunosuppressive treatment. Partial remission is defined as urinary protein excretion <3.5g/24h and a 50% or greater reduction from peak values, accompanied by an improvement or normalization of serum albumin and a stable renal function.<sup>38</sup> Complete remission is defined as a urinary protein excretion <0.3g/24h, accompanied by a normal serum albumin and a normal renal function.<sup>38</sup>

Spontaneous remission is a well-known characteristic of idiopathic membranous nephropathy. Patients with subnephrotic proteinuria and normal renal function, as well as women and patients with low levels of anti-PLA2R, have a higher chance of presenting SR. In a study by Polanco *et al*<sup>15</sup> in more than 300 patients with PMN that were treated with conservative therapy, SR occurred in 32% of the cases at 14.7±11.4 months after diagnosis. The decline of proteinuria was progressive rather than abrupt. An interesting finding was that although SR was more frequently observed in patients with lower levels of baseline proteinuria, up to 22% of patients with proteinuria >12g/24h also presented spontaneous remission. A high percentage of patients who developed SR received treatment with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor antagonists (ARBs). Other factors that significantly predicted SR were baseline renal function and proteinuria, and the reduction of baseline proteinuria by more than 50% during the first year. The long-term prognosis of patients with complete or partial spontaneous remission was excellent, with very few relapses (6%) and a 100% renal survival. Pathophysiology of spontaneous remission is unknown to this day.

About 20-30% of cases present an aggressive clinical course with massive proteinuria and progressive deterioration of renal function during the first or second year from diagnosis.<sup>39,40</sup> It is important to differentiate these cases from patients with acute kidney injury secondary to reversible factors, such as the excessive use of diuretics, hypotension or volume depletion. Although some cases with an initial aggressive disease can present SR followed by stabilization or improvement of renal function, the vast majority has a poor prognosis in the absence of immunosuppressive treatment.<sup>39-41</sup>

The remaining patients (~30%)<sup>15,16</sup> can present with persistent nephrotic syndrome without developing SR or deterioration of renal function. Although this scenario may persist for years, renal prognosis is poor if remission is not achieved. Moreover, persistent nephrotic syndrome increases the risk of atherosclerosis and thromboembolic events as a consequence of dysregulated lipid metabolism and dyslipidemia.<sup>42</sup>

## ■ PROGNOSTIC MARKERS

Patients with membranous nephropathy should be followed closely during the first 6 months since diagnosis, with careful monitoring (monthly or bimonthly) of renal function, proteinuria, and anti-PLA2R titers. Changes in these parameters will help the clinician to identify those patients more likely to develop spontaneous remission and those in whom prompt initiation of immunosuppression may be warranted.

The evolution of proteinuria and renal function during the first 6 months has been formulated mathematically by the Toronto Registry of Glomerulonephritis with the well-known Toronto Risk Score.<sup>43</sup> This model has been validated in several countries with an accuracy of prediction of 85-90% to predict an unfavorable clinical course. According to this model, patients are stratified into the following categories: 1) low risk of progression (normal renal function, proteinuria <4g/24h), 2) moderate risk of progression (normal renal function, proteinuria 4-8g/24h), and 3) high risk of progression (proteinuria >8g/24h regardless of renal function).

Some studies have shown that a high urinary excretion of IgG and some low-molecular weight proteins such as  $\alpha$ -1 microglobulin and  $\beta$ 2-microglobulin are excellent markers to predict the development of renal insufficiency, with a sensitivity and a specificity of 88% and 91%, respectively.<sup>44,45</sup> The potential advantage of these urinary markers is that monitoring would not be necessary since the initial measurement yields important predictive information.

In patients with PMN and positive anti-PLA2R, the major advance in terms of prognostic markers is undoubtedly the monitoring of anti-PLA2R titers. High titers of anti-PLA2R at presentation suggest spontaneous remission will be unlikely, especially if increasing levels are observed over time.<sup>18,46</sup> On the other hand, disappearance of anti-PLA2R levels (immunologic remission), either spontaneous or induced by immunosuppressive therapy, precedes a clinical remission by a period of several months (up to 18 months in some cases).<sup>47-50</sup> Antibody levels are also useful in the follow-up of patients who achieve remission as the reappearance of anti-PLA2R levels precede clinical relapse (by ~3 months).<sup>46,50</sup> Likewise, those patients who still present detectable anti-PLA2R levels after immunosuppressive treatment are more likely to experience a clinical relapse.<sup>51</sup> Moreover, persistence or reappearance of anti-PLA2R levels after kidney transplantation can also predict recurrence of the disease.<sup>52-54</sup> In patients with *de novo* MN after a renal transplant, anti-PLA2R are invariably negative.<sup>55,56</sup>

At the present time, several PLA2R epitopes have been described (cysteine-rich domain [CysR], fibronectin type II domain, and eight distinct C-type lectin domains [CTLD1-8]).<sup>57</sup> A recent study has proposed that epitope spreading at baseline is an indicator of poor prognosis and its presence should be considered in the decision for early therapeutic intervention.<sup>58</sup>

## ■ TREATMENT

The great advances made in the pathophysiologic field of PMN, accompanied by few but very relevant controlled clinical trials, have improved the therapeutic approach of these patients in recent years. It is now widely accepted that the type of treatment should be adapted or personalized to each patient, according to the clinical scenario (renal function, proteinuria) and the levels of anti-PLA2R (Figure 2). Although the optimal goal is to reach complete remission, the induction of partial remission is associated with a significantly superior renal survival compared to non-remission, and thus, it can be considered a satisfactory objective.

### ■ Conservative strategy

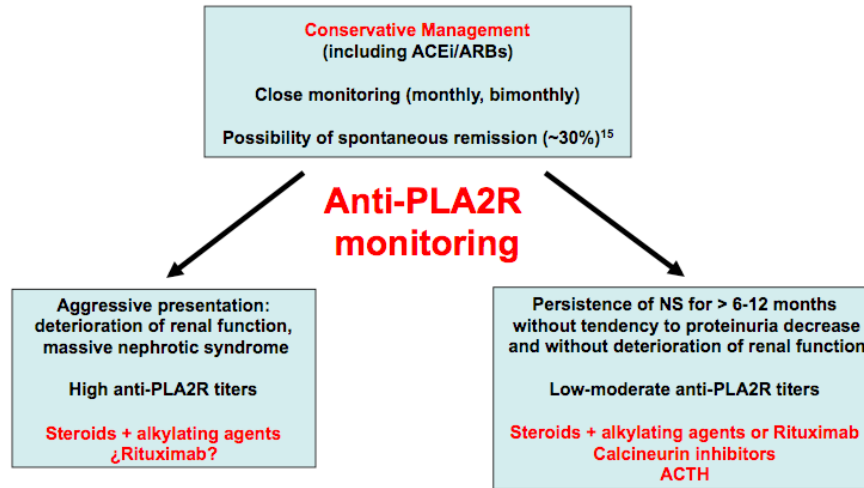
Scientific guidelines<sup>38</sup> recommend starting immunosuppressive treatment only in those patients who maintain nephrotic proteinuria after an observation period of at least 6 months as long as proteinuria does not have a clear tendency to decrease during such period.

In all patients with MN, optimal supportive care should be initiated at the time of diagnosis with the main goal of reducing proteinuria. Treatment should include ACEI/ARBs, statins for dyslipidemia,



**Figure 2**

Proposed therapeutic strategy in membranous nephropathy.



NS – nephrotic syndrome.

hypoproteic diet, salt restriction, and diuretics as needed.<sup>2,6,33,59</sup> Prophylactic anticoagulation should be considered if hypoalbuminemia is severe (<2.5g/dl) and other risk factors for thrombosis are present.<sup>60,61</sup> Patients with progressive deterioration of renal function and those with severe, disabling, or life-threatening symptoms related to the nephrotic syndrome should be excluded from this observation period.<sup>38</sup> In that cases, immunosuppressive treatment should be started unless there are specific contraindications. Increasing anti-PLA2R titers over time should also guide towards initiation of immunosuppression.<sup>3</sup> Immunosuppressive therapy in patients with persistently low glomerular filtration rate (<30 ml/min per 1.73m<sup>2</sup>) or advanced interstitial fibrosis and tubular atrophy at biopsy is not recommended.<sup>4,38</sup>

Treatment with ACEI decreases glomerular hypertension and improves glomerular barrier size selectivity.<sup>59,62</sup> This results in reduction of proteinuria and improvement of hypoalbuminemia. Also, as previously mentioned, ACEI have been associated with the development of spontaneous remission.<sup>15</sup> Nonetheless, its use should be cautious in patients without hypertension or with a compromised effective circulating volume.

### ■ Immunosuppressive treatment

**Steroids and alkylating agents.** Several randomized clinical trials have conclusively demonstrated the effectiveness of treatment with steroids and alkylating agents (cyclophosphamide and chlorambucil) when compared to conservative management.<sup>8-11,63</sup> Cyclophosphamide is preferred over chlorambucil because of its better safety profile. However, cyclophosphamide can also cause severe adverse effects such as infections, cancer, and infertility. The modified Ponticelli regimen consist of 6 months of alternating pulse steroids and cyclophosphamide, achieving complete or partial remission in approximately 70-80% of the cases at 2-3 years.<sup>9,11,63</sup> Some authors have

administered steroids and alkylating agents concomitantly rather than alternating,<sup>64</sup> with no studies comparing which regimen is superior. Prospective studies have shown that monotherapy with steroids is

**Table 2**

Summary of immunosuppressive treatment schemes for primary membranous nephropathy.

Pharmacologic agent(s)	Dose scheme
<b>Alkylating agents<sup>8-11,38</sup></b>	
<b>Italian Ponticelli protocol</b>	Months 1, 3, 5: 1 g/d IV MPDN x 3 d, followed by oral PDN 0.5 mg/kg/d x 27 d Months 2, 4, 6: oral CHL 0.2 mg/kg/d x 30 d
<b>Modified Ponticelli</b>	Months 1, 3, 5: 1 g/d IV MPDN x 3 d, followed by oral PDN 0.5 mg/kg/d x 27 d Months 2, 4, 6: oral CYC 2–2.5 mg/kg/d x 30 d
<b>Dutch protocol</b>	Months 1, 3, 5: 1 g/d IV MPDN x 3 d, followed by oral PDN 0.5–1 mg/kg/d x 6 months (then taper) plus oral CYC 1.5–2 mg/kg/d x 12 months
<b>Calcineurin inhibitors<sup>12,38,66,67</sup></b>	
<b>Tacrolimus</b>	0.05–0.075 mg/kg/d x 12 months (through levels 5–7ng/mL), then taper over 6 months +/- low dose PDN
<b>Cyclosporine</b>	3.5–5.0 mg/kg/d (through levels 120–200 ng/mL) x 12 months, then taper over 6 months +/- low dose PDN
<b>B cell-targeted<sup>13,14,59,69</sup></b>	
<b>Rituximab</b>	375mg/m <sup>2</sup> IV every week x 4 weeks 1g IV x 2 (days 1 and 15) 375mg/m <sup>2</sup> IV single dose and follow B-cell counts
<b>ACTH<sup>6,78,79</sup></b>	
<b>Tetracosactrin</b>	1 mg IM twice weekly x 6–12 months
<b>Corticotropin</b>	80 U IM twice weekly x 6–12 months

IV – intravenous; IM – intramuscular; MPDN – methylprednisolone; PDN – prednisone; CHL – chlorambucil; CYC – cyclophosphamide.

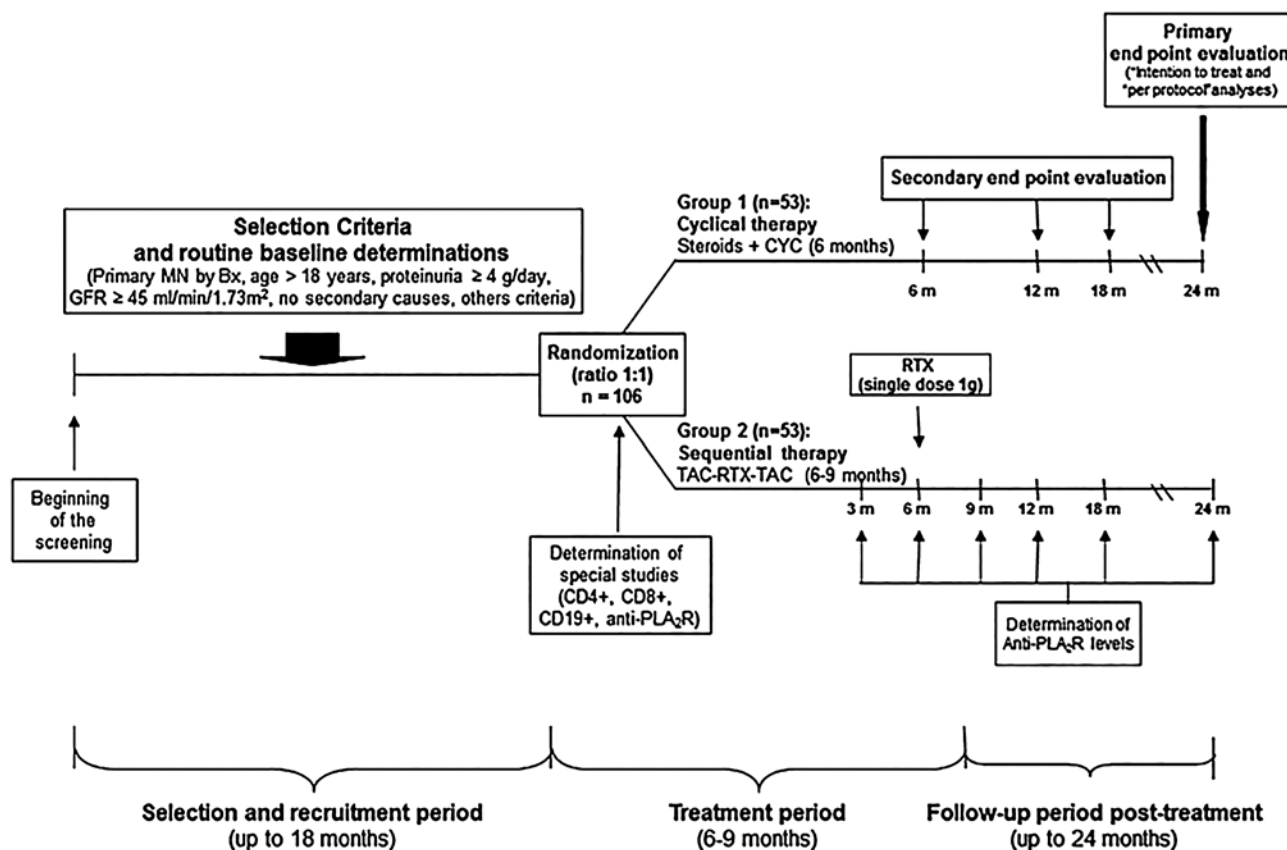
not effective.<sup>65</sup> KDIGO guidelines recommend the modified Ponticelli regimen as the preferred initial immunosuppressive therapy in patients resistant to a conservative strategy.<sup>38</sup>

**Calcineurin inhibitors [CNIs].** Randomized prospective trials have also demonstrated the effectiveness of cyclosporine and tacrolimus in the treatment of MN.<sup>12,66,67</sup> In addition to its immunosuppressive effect, CNIs exert a direct antiproteinuric effect on the structure of the podocyte through its interaction with synaptopodin.<sup>68</sup> Complete or partial remission has been observed in 70-85% of cases after 6-12 months of therapy.<sup>12,66,67</sup> In fact, the short-term efficacy of CNIs might be better than cyclophosphamide plus prednisone.<sup>67</sup> Despite the high efficacy of CNIs in the management of MN, a relapse rate of ~40-50% has been reported after treatment discontinuation.<sup>12,66</sup> On the other hand, the potential nephrotoxic effect of CNIs in the long term should be considered. Suggested initial doses of cyclosporine and tacrolimus are 3.5-5mg/kg/d and 0.05-0.075mg/kg/d, respectively.<sup>12,67</sup> Subsequent doses of CNIs should be adjusted to blood through levels (Table 2). The association of steroids in the case of tacrolimus is not mandatory.<sup>12</sup> Recommended duration of treatment with CNIs is 12-18 months and withdrawal should be gradual.

**Rituximab.** B-cell depletion is certainly the most promising therapy for membranous nephropathy. Rituximab has proven to be an effective agent in several recent studies, with the advantage of a superior safety profile compared to steroids and immunosuppressants.<sup>13,14,69</sup> Complete or partial remission has been observed in 60-65% of cases (up to 88% at 24 months),<sup>70</sup> with a median time to remission of ~7 months.<sup>13,14</sup> Lower anti-PLA2R antibody titer at baseline and immunologic remission (disappearance of anti-PLA2R levels) at 6 months are strong predictors of clinical remission.<sup>71</sup> No clear correlation has been observed between B-cell counts and response or relapse rates.<sup>6</sup> The optimal dose (375mg/m<sup>2</sup> x 4 or 1g x 2) and the need of re-treatment remain incompletely defined,<sup>4</sup> but lower doses (375mg/m<sup>2</sup> x 1) have proven to be poorly effective.<sup>72</sup> MENTOR is a randomized controlled trial in which rituximab was compared to cyclosporine in patients with PMN.<sup>73</sup> STARMEN is a randomized clinical trial that compared the efficacy of sequential tacrolimus-rituximab therapy to a modified Ponticelli protocol (Figure 3).<sup>74</sup> This trial also evaluated the role of anti-PLA2R and other antibodies as markers of response to treatment and long-term prognosis. Results from the MENTOR and STARMEN trials are eagerly expected to better understand which patients benefit the most from rituximab therapy.

**Figure 3**

Schematic overview of the STARMEN trial.



CYC – cyclophosphamide; TAC – tacrolimus; RTX – rituximab.<sup>74</sup>

**Mycophenolate Mofetil (MMF).** The effectiveness of MMF in the treatment of membranous nephropathy has not been clearly demonstrated. In one randomized clinical trial,<sup>75</sup> no differences were found in remission rates between MMF monotherapy and a conservative strategy. In another study,<sup>51</sup> only 44% of the patients were in remission after 23 months of MMF plus prednisone treatment. However, better results with combined MMF + prednisone therapy have been reported in Asian patients in two randomized trials,<sup>76,77</sup> with a remission rate similar to that observed with other immunosuppressants. More studies are needed to establish if MMF is useful in the treatment of MN.

**Adrenocorticotrophic hormone (ACTH).** Subcutaneous or intramuscular administration of ACTH has shown considerable efficacy in patients with MN and nephrotic syndrome in retrospective case series<sup>78</sup> and in one prospective pilot study.<sup>79</sup> Remission rates up to 80% at 6 months have been reported,<sup>6,79</sup> although one open label cohort study found that ACTH was less effective than cyclophosphamide in high risk patients.<sup>80</sup> It should be noted that ACTH is very expensive and many of the available data of its efficacy and safety comes from small clinical trials (some of them observational). Therefore, the possible role of ACTH in the treatment of MN remains to be established.

**New Therapies.** Promising or alternative therapies include ofatumumab (third generation anti-CD20 monoclonal antibody),<sup>59</sup> belimumab (monoclonal antibody that targets the soluble form of B lymphocyte stimulator [BLyS]),<sup>81</sup> and bortezomib (proteasome inhibitor).<sup>82</sup> One prospective randomized clinical trial (unpublished) failed to demonstrate the efficacy of eculizumab in MN, although possibly as a result of underdosing.<sup>59,83</sup>

## MEMBRANOUS NEPHROPATHY AND KIDNEY TRANSPLANTATION

The real incidence of recurrence after kidney transplantation (KT) is difficult to assess but it has been estimated to be around 30–44%.<sup>59,84,85</sup> Many patients are diagnosed incidentally during protocol biopsies while others present progressive proteinuria or even full nephrotic syndrome.<sup>86</sup> Spontaneous remission is uncommon. In patients with PMN, the appearance of subepithelial deposits has been observed within days after KT.<sup>6,50,53</sup> Nevertheless, clinical manifestations usually present between the second and third year after transplantation, or even later in some cases.<sup>86</sup> Although some studies had reported that allograft survival in patients with recurrent MN is similar to those patients transplanted with other renal diseases,<sup>87</sup> others had suggested a worse outcome.<sup>50,53,88</sup> The presence of anti-PLA2R antibodies at the time of KT is a risk factor for recurrent disease, especially if positivity persists during follow-up.<sup>53,89</sup>

*De novo* MN presents in approximately 2% of transplanted patients.<sup>90</sup> Histologic pattern is practically indistinguishable from recurrent MN. It has been associated with new-onset hepatitis C virus infection, Alport syndrome, ureteral obstruction, renal infarction, recurrent IgA nephropathy, and graft rejection.<sup>88,91</sup> Despite this, the pathogenic mechanisms involved in *de novo* MN are still speculative. While PMN is strongly associated with the presence of anti-PLA2R

antibodies, patients with *de novo* MN have typically negative serology<sup>55</sup> and staining on biopsy is almost always negative.<sup>92</sup> As in recurrent MN, whether *de novo* MN affects the outcome of kidney allografts is still controversial.<sup>93</sup>

Treatment with antiproteinuric agents should be initiated in all cases. The use of diuretics, statins, and anticoagulants is indicated on individual basis. Rituximab has been successfully used in cases of MN recurrence with complete and partial remission rates in up to 80% of cases.<sup>94,95</sup> Similarly to treatment in native kidneys, the appropriate dose regime of rituximab has not been established. Prophylactic rituximab administration before KT has been attempted in some cases and may have been effective in preventing recurrence. Nonetheless, evidence in this sense is scarce.<sup>6,59</sup>

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