REVIEW

Primary membranous nephropathy: an endless story

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Abstract

Primary membranous nephropathy (PMN) is an autoimmune disease caused by the attack of autoantibodies against podocyte antigens leading to the in situ production of immune complexes. However, the etiology is unknown and the pathogenesis is still far from being completely elucidated. MN is prevalently idiopathic or primary, but in about 20–30% of cases it is secondary to chronic infections, systemic diseases, exposure to drugs, or malignancy. The differentiation between primary and secondary MN may be difficult, particularly when MN precedes signs and symptoms of the original disease, as in some cases of cancer or systemic lupus erythematosus. The natural course of PMN is variable, but in the long term 40–60% of patients with nephrotic syndrome progress to end-stage renal disease (ESRD) or die from thrombotic or cardiovascular events. PMN is a treatable disease. Patients with asymptomatic proteinuria should receive supportive care. Immunosuppressive treatments should be given to patients with nephrotic syndrome or risk of progression. The most frequently adopted treatments rely on cyclical therapy alternating steroids with a cytotoxic agent every other month, i.e., rituximab at different doses, or calcineurin inhibitors plus low-dose steroids. A good rate of response may be obtained but relapses can occur. Randomized controlled trials, with adequate size, long-term follow-up, and fair definition of endpoints are needed to identify treatment with the best therapeutic index.

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Graphical abstract

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PMN is an autoimmune disease caused by autoantibodies against podocyte antigens (more frequently phospholipase A2 receptor) leading to the *in situ* production of immune complexes.

The etiology is unknown and pathogenesis is still far from being fully established.

The natural course of PMN is variable with spontaneous remission or progression to end-stage renal disease (ESRD) or death in the long-term.

Treatments more frequently used are cyclical therapy alternating steroids and a cytotoxic drug every other month, rituximab at various doses or a calcineurin inhibitor with or without low-dose steroids. A good rate of response (more often partial responses) may be obtained but relapses are frequent. These drugs should be limited to patients with nephrotic syndrome or risk to progression.
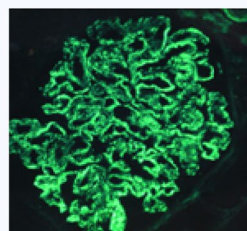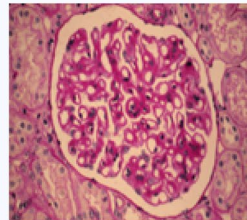
Keywords Membranous nephropathy · Nephrotic syndrome · Cyclical regimen · Rituximab · Calcineurin inhibitors

Introduction

The term membranous nephropathy (MN) was proposed years ago to define a glomerular disease clinically characterized by proteinuria, usually in nephrotic range, and histologically by an apparent thickening of the glomerular basement membrane (GBM) [1]. Further studies with electron microscopy and immunofluorescence showed that this apparent thickening of the GBM was actually due to subepithelial deposits of immune complexes in which the antibodies were mainly represented by immunoglobulin G4 (IgG4), at least in the so-called primary form. After the discovery of many antigens (see below) the etiology remains unknown only in few cases and the disease is called primary, but in 20–30% of cases MN is called secondary, being associated with other diseases, exposure to drugs, or infections. Progress in elucidating the pathophysiology of MN has been made in the last years but some doubts still remain. The course of primary MN (PMN) is variable and it may be difficult to predict the long-term natural outcome. Different treatments may favor remission of proteinuria and stabilization of kidney function, but which therapy might offer the best efficacy and safety is still uncertain. In this manuscript we will discuss the main, unsolved topics in idiopathic MN.

Is it possible to differentiate primary from secondary MN?

Secondary MN may be associated with chronic infections (particularly hepatitis B or C), autoimmune diseases (particularly lupus nephropathy), exposure to drugs or toxic agents (such as nonsteroidal antiinflammatory drugs or mercury compounds) or other conditions (including kidney or bone marrow transplantation, etc.) [2] (Table 1). The clinical history may lead to a correct diagnosis, but in several cases it can be difficult to recognize the original disease or the responsible drug. In these instances, kidney biopsy may help. At light microscopy, it is possible to observe endocapillary proliferation and cellular infiltration in some types of secondary MN, including those associated with lupus or cancer, while these findings are usually absent in PMN. At immunofluorescence, IgG4 are predominant in PMN, while IgG 1–3 deposits are frequent in secondary MN [3, 4]. IgA, IgM and C1q deposits are rare in PMN and frequent in secondary forms, particularly in lupus nephritis. Staining with phospholipase A2 receptor (PLA2R) is frequently positive in PMN [5, 6] but it can also be seen in sarcoidosis, hepatitis B and C or cancer [7–10]. On electron microscopy, subepithelial

Table 1 MN may be associated with chronic infections, autoimmune diseases, malignancy, exposure to drugs or toxic agents, or may be seen in different conditions

INFECTIONS
Hepatitis B-C
Enterococcal endocarditis
Filariasis
Hydatid disease
Leprosy
Quartan malaria
Schistosomiasis
Streptococcal infections
Syphilis

AUTOIMMUNE DISORDERS
SLE
Dermatomyositis
Mixed connect.tissue dis
Sarcoidosis

Rheumatoid arthritis
Systemic sclerosis
Alkylosing spondylitis

DRUGS OR TOXIC AGENTS
NSAID
Captopril
Gold
Hydrocarbons
Trimetadione

Lithium
Mercury compounds
Penicillamine
Probenecid
Sulindac
Thiola

MALIGNANCY
Carcinomas
Hodgkin's disease
Melanoma
Mesothelioma
Non-Hodgkin's lymphoma
Pheochromocytoma
Retroperitoneal sarcoma
Leukemia

MISCELLANEOUS CONDITIONS
Diabetes
Bone marrow transplant
Crohn's disease
Dermatitis herpetiformis
Guillan-Barrè syndrome
Multiple sclerosis
Myastenia gravis
Myelodysplasia
IgG4 disease

Primary biliary cirrhosis
Renal tranplantation
Sarcoidosis
Temporal arteritis
Thyroid dsease
Sickle cell disease
Sjogren's syndrome
Systemic mastocytosis
Periaortic fibrosis

electron-dense deposits are typical of PMN, while subendothelial mesangial, and subepithelial deposits can be seen in some forms of secondary MN. Tubuloreticular inclusions can be found in patients with lupus [11].

A main problem is represented by the fact that in some patients with cancer, sarcoidosis, or lupus the signs and symptoms of MN may precede those of the original disease by weeks or even years. Cancer may occur in 10% of patients with untreated MN either at the time of kidney biopsy or one year later [12]. A misdiagnosis of cancer is a true nightmare. Thus, invasive and noninvasive procedures to detect a possible underlying cancer may be suggested, especially in patients older than 50 years, heavy smokers or in those with negative anti-PLA2R antibodies [13, 14]. However, this approach is not shared by all investigators who feel that the cost of investigating cancer and other possible causes of secondary MN would become excessive.

Etiopathogenesis of primary MN

The etiology of PMN is unknown by definition. The disease might be triggered by viral infection or exposure to toxic agents, including hydrocarbons, but the search for the agent(s) responsible for the disease remains difficult.

A great deal of progress has been made in understanding the patophysiology of idiopathic MN. Experimental models showed that in Heymann nephritis the disease is caused by an in situ deposit of immune complexes resulting from the reaction of a circulating antibody against an antigen planted in the subepithelial position. In 2002, Debiec et al. [15] showed that MN in the newborn of a neutral endoproteinase (NEP)–deficient mother was mediated by maternal anti-NEP antibodies which formed immune complexes with NEP on the podocyte membranes of the infant. This was the first demonstration that antibodies against a podocyte antigen can induce MN in humans by mechanisms similar to those proposed for Heymann nephritis [16].

A few years later, Beck et al. [17] showed that 70% of adults with PMN exhibited circulating IgG4 antibodies against the M-type PLA2R expressed on the podocyte surface. Other reports confirmed the presence of anti-PLA2R antibodies in 65–80% of patients with MN. However, PLA2R is not the only antigen in MN. In 2–10% of patients with MN, circulating antibodies are directed against thrombospondin 1 domain containing 7 A expressed on the podocyte surface [18–20]. These antibodies are pathogenic [21, 22] and can be found not only in PMN, but also in MN associated with cancer [6, 10, 23]. Novel antigens of primary and secondary MN have recently been detected by mass spectrometry or immunochemistry: exostosin 1 and 2 in type V lupus nephritis, NELL-1, semaphorin 3B, protocadherin-7, serinprotease AHTRA1, contactin1 [24–26].

Research on the epitope of PLA2R demonstrated that the main epitope is located in an outer cysteine-rich (CysR)

domain [27]. Two inner epitopes have also been found, respectively in the C-type lectin domains 1 and 7:CTLD1, and CTLD7 [28, 29]. While the disease progresses, the target epitope may change from outer CysR to the inner CTDL1 to CTDL7. This epitope *spreading* can be associated with a poor prognosis [30]. Patients showing antibodies against the inner epitopes tend to be elderly and resistant to therapy [31].

In the last years, genetic studies have proliferated [32–36]. A recent genome-wide association study (GWAS) for primary MN in 3782 cases and 9038 controls of East Asian and European ancestries reported that the disease was associated with three classical HLA alleles: DRB1*1501 in East Asians (OR = 3.81), DQA1*0501 in Europeans (OR = 2.88), and DRB1*0301 in both ethnicities (OR = 3.50). GWAS loci explained 32% of MN risk in East Asians and 25% in Europeans, and re-classified 20–37% of the cases that were antibody-negative by the serum anti-PLA2R ELISA diagnostic test. Two previously unreported loci, NFKB1 and IRF4 were also discovered [37].

One may postulate that viral infection or other exogenous factor(s) might induce a conformational change of the epitopes in some proteins of the podocytes (more frequenty PLA2R) in genetically predisposed individuals. The abnormal epitope may be recognized by toll-like receptors as a damage-associated molecular pattern (DAMP), with activation of proinflammatory molecules and cells of the innate immunity. In the inflammatory microenvironment dendritic cells recognize the DAMP as an antigen, become mature and migrate to lymph nodes where they present the antigen to the T cells, thereby activating the adaptive immunity. Activated T cells proliferate and differentiate into effector Th1 and Th17 or T reg. The collaboration between T and B cells activates B cells to produce plasmablasts and antibodies (IgG4) directed against the podocyte antigen, with in situ formation of immmune complexes and activation of complement. The late complement components C5b-C9 induce the production of reactive oxygen species, cytokines, extracellular matrix, and proteolysis of synaptopodin and nephrin These changes result in disruption of actin cytoskeleton, podocyte effacement and proteinuria. C5b-C9 may also induce podocyte hypertrophy and proliferation leading to glomerular sclerosis [38]. One may ask why complement is activated, since IgG4 cannot activate complement [39]. However, it has been demonstrated that glycosylated IgG4 can activate the lectin pathway and induce podocyte injury in a podocyte culture model [40].

In summary, the current research demonstrated that PMN is an autoimmune disease in which the antigen is located in the podocytes and is reached by circulating antibodies with in situ formation of immune complexes that activate complement. However doubts remain. What is the etiology of idiopathic MN? What causes the loss of tolerance to PLA2R and other endogenous molecules? Can polymorphism of PLA2R (or other molecules) create a conformational change of epitopes, representing a target for autoantibodies? How many genetic factors regulate antigens in MN?

Prediction of the natural course of MN

Many studies have tried to identify parameters that could predict the long-term outcome of the disease. Only a few histologic and clinical risk factors for progression are used in clinical practice. Old studies could not find any correlation between the stage of glomerular lesions in the initial biopsy and the long-term results [41, 42]. The presence of segmental glomerular sclerosis can be associated with high risk of renal failure [43]. Instead, the presence of severe interstitial fibrosis and tubular atrophy is associated with a poor outcome [44]. High intensity C3 deposition can also predict renal function deterioration [45].

Increased serum creatinine levels at presentation presage the later development of end stage renal disease (ESRD), unless renal insufficiency is functional and reversible, as in the cases of hypovolemia, excessive dosage of diuretics, or drug-associated acute interstitial nephritis. Based on retrospective analysis of three international centers, Cattran et al. reported that patients with normal serum creatinine and proteinuria remaining < 4 g/day over 6 months have a low risk of progression; those with normal or near normal serum creatinine and proteinuria ranging between 4 and 8 g/day over 6 months have a 55% probability of being in ESRD at 10 years; patients with abnormal or deteriorating serum creatinine and proteinuria > 8 g per day over 6 months have a 66–80% probability of ESRD within 10 years [46]. After the discovery of anti-PLA2R antibodies, DeVries et al. suggested considering these antibodies as predictors of progression [47]. Other investigators confirmed that high baseline or increasing anti-PLA2R antibody levels predict poor outcome [48–50]. Accordingly, the most recent KDIGO recommendations decided to incorporate PLA2R antibody > 50 RU/ml among the criteria that indicate a high risk of progression: i.e.—estimated glomerular filtration rate (eGFR) < 60 ml/min /1.73 m² and/or proteinuria < 8 g/day for at least 6 months—or normal eGFR, proteinuria > 3.5 g/day without a > 50% decrease after 6 months of renin-angiotensin system inhibitors and at least serum albumin < 2.5 g/l and/or PLA2R antibodies > 50 RU/ml [51]. Patients who obtained complete remission, either spontaneously or after treatment, have excellent chances of stable kidney function in the long-term. A fair outcome was also observed with partial remission, although not as good as for complete response [52, 53].

The current opinion is that about 1/3 of patients with PMN may enter spontaneous remission, 1/3 show persistent

Table 2 Complete and partial remissions with cyclical therapy (corticosteroids alternated with cyclophosphamide) in randomized controlled trials

Author	Patients	Complete remission	Partial remission	Follow-up (months)
Ponticelli [60]	43	16 (37%)	24 (56%)	42
Jha [61]	47	15 (32%)	19 (40%)	120
Scolari [62]	37	16 (42%)	15 (40%)	24
Ramachandran [63]	35	20 (57%)	10 (29%)	60
Fernandez-Juarez [64]	43	26 (60%)	10 (23%)	24
Total	205	93 (45%)	78 (38%)	54

The arithmetic average is 54

proteinuria and 1/3 progress to ESRD [54]. However, if one considers the outcome of PMN at 10 years after clinical onset it appears that at least half of them died or required regular renal replacement therapy [55]. Thus the rule of thirds may be replaced by the rule of halves and MN cannot be considered a benign disease not requiring immunosuppressive therapy but rather a main cause of ESRD, at least in patients with persistent nephrotic syndrome or very high levels of PLA2R antibodies.

What treatment for PMN?

The most recent KDIGO guidelines recommend that all patients with PMN and proteinuria should receive optimal supportive care [51]. Immunosuppressive therapy should be limited to patients at risk for disease progression or with serious complications of nephrotic syndrome. The initial treatment may consist of rituximab or cyclophosphamide and corticosteroids, or tacrolimus-based therapy for ≥ 6 months, depending on the estimate of risk. Longitudinal monitoring of anti-PLA2R antibody levels after starting therapy may be useful for evaluating treatment response in patients with MN, and can be used to guide adjustments to therapy.

In 1984, a randomized controlled trial demonstrated that a 6-month treatment based on alternating corticosteroids with chlorambucil every other month significantly increased the probability of nephrotic syndrome remission and protected kidney function [56] These results were confirmed by two other trials with the same therapeutic regimen [57, 58]. An overall estimate of these studies reported that 9% of participants complained of serious adverse events, the most frequent being infections and gastric intolerance [59]. To evaluate whether cyclophosphamide could be better tolerated than chlorambucil, a multicenter randomized trial compared the efficacy and safety of 6-month regimens alternating corticosteroids with either of the two drugs in PMN. Participants who received cyclophosphamide (2 mg/kg/day) obtained a numerically higher number of remissions than those assigned to chlorambucil (0.2 mg/kg/day) and

Table 3 Complete and partial remission with Rituximab in patients with IMN (observational studies)

Author	Patients	Complete remission	Partial remission
Fervenza [69]	20	4	12
Beck [70]	25	5	13
Michel [71]	23	6	13
Souqiyyeh [72]	25	10	7
Ruggenenti [50]	132	43	48
Roccatello [73]	17	14	1
Moroni [74]	34	5	10
Wang [75]	36	2	13
Bagchi [76]	13	4	15
Seitz-Polski [77]	28	9	15
Total	353	102 (28.8%)	147 (41.6%)

lower number of side effects [60]. A few years later, a multicenter Indian trial compared 6-month cyclical therapy with cyclophospamide alternated with steroids vs symptomatic treatment. The mean follow-up was 11 years. Altogether, 72% of treated patents entered complete or partial remission vs 35% of controls. At 10 years, 89% of treated patients and 65% of controls were alive without dialysis, the differences being highly significant. Hypertension, hypercholesterolemia and edema were significantly less frequent in the treated arm. Serious infections occurred in 15% of treated participants vs 24% of controls. No cases of malignancy were reported [61]. Recently, three randomized, controlled trials compared cyclical therapy with other treatments. An Italian multicenter trial involving 74 patients with PMN reported a better trend to remission at one year with steroid-cyclosphosphamide therapy compared to intravenous rituximab 1 g at days 1 and 15. At two years the probability of total and complete remission was the same in the two groups (82% and 43% in cyclical therapy vs 83% and 42% in rituximab). Serious adverse events occurred in 19% of patients in the rituximab arm and in 14% in the cyclical-regimen [62]. An Indian collaborative trial reported the superior efficacy

of cyclical therapy vs tacrolimus combined with corticosteroids. At the end of a 6-year follow-up period, 62% and 28% of participants maintained relapse-free remission in the cyclical therapy and tacrolimus-glucocorticoid groups, respectively. There was no significant difference in the proportion of patients who had a 40% decline in eGFR, death, or ESRD. None of the patients treated with the cyclical regimen reported malignancy [63]. A Spanish multicenter trial enrolled patients with PMN to receive six-month cyclical treatment with corticosteroids and cyclophosphamide or tacrolimus (full-dose for six months and tapering for another three months) and rituximab (one gram at month six). The cumulative rate of remission was 84% for participants assigned to the steroid-cyclophosphamide vs 58% for those assigned to the tacrolimus-rituximab group. Complete remission at 24 months occurred in 26 participants (60%) in the cyclical therapy and in 11 participants (26%) in the tacrolimus-rituximab group. Relapse occurred in one patient in the corticosteroid-cyclophosphamide group, and in three patients in the tacrolimus-rituximab group. Serious adverse events were similar in both groups. However, only one dose of rituximab was given in the tacrolimus group [64]. Taken together, the results of the available controlled trials with combined corticosteroid-cyclophosphamide therapy would appear to show that after an arithmetic average of 54 months, 45% of treated participants obtained complete remission and another 38% achieved partial remission (Table 2).

Some measures should be taken to prevent serious complications. Methylprednisolone pulse administration is usually safe but exceptionally, seizures or anaphylactic reactions may occur when steroids are infused too rapidly into a central vein. Cardiac arrhythmias are rare events that may be favored by hypokalemia. Transient hyperglycemia is frequent. During cyclophosphamide therapy, white blood cells should be measured every 7–10 days, and the dosage should be adjusted in case of leukopenia. This can minimize the risk of infections. To prevent malignancy, the total doses should be less than 360 mg/kg or 2 mg/kg/day for 6 months [65]. Thus, it is unsafe to repeat the standard cyclical regimen (3 months of cyclophosphamide 2 mg/kg/day for each 6-months cycle, resulting in a cumulative dose of 180 mg/kg for ech cycle) more than twice. Therefore, the cumulative dose of cyclophosphamide for each cycle is 180 mg/kg. The risk of gonadal toxicity is mainly related to the use of high dosages. It has been suggested not to exceed a cumulative dose of 250 mg/kg in children and adolescents [66]. If higher doses are needed, semen cryopreservation is recommended in males, while the use of leuprolide acetate can reduce the risk of ovarian damage in females [67].

Rituximab is a monoclonal antibody with a high affinity for the CD20 antigen. It was first used by Remuzzi et al. in eight cases of PMN [68]. The drug was administered intravenously at a dose of 375 mg/m^2 every week for four doses. After 20 weeks mean proteinuria significantly decreased from 8.6 to 3.6 g/day. Since then, a number of observational studies have been carried out. A review of those studies showed that rituximab was given at low or high doses and the follow-ups were different [50, 69–77]. The cumulative results showed that of 353 enrolled patients, 102 (28.8%) entered complete remission, and another 147 (41.6%) had partial remission (Table 3). A first multicenter controlled trial randomized 75 patients with PMN to renin-angiotensin system inhibitors (RASi) plus rituximab—375 mg/m^2 intravenously on days 1 and 8- or RASi alone. At 6 months, 13 (35%) patients given RASi and rituximab and 8 (21%) controls achieved complete or partial remission. In a post-hoc analysis after a mean period of 23 months the remission rate rose to 24/37 patients (65%) in the rituximab group vs 13/38 (34%) in controls. Complete remission rates were respectively, 19% vs 2.6%. The use of rituximab had no impact on safety [78]. Another multicenter trial assigned 130 patients with PMN to receive intravenous rituximab 1 g × 2 repeated after 6 months or cyclosporine 3.5 mg/kg/day for 12 months. At one year the cumulative incidence of complete plus partial remission did not differ between the two groups (60% vs 52%). At 24 months the number of remissions remained stable in the rituximab arm (60%, of which 35% were complete remissions), while it fell to 20% in the cyclosporine group [79]. As mentioned above, two other randomized controlled trials reported, respectively, the superiority of steroid-cyclosphosphamide therapy compared to tacrolimus and a single dose of rituximab [64] or the equivalence between a cyclical therapy with steroids and cyclophosphamide and rituximab [62]. In these trials the side effects of rituximab were mainly related to reactions to the first dose. Of note, the mean follow-up was similar in all these studies, i.e., 23–24 months. Strangely, rituximab-treated participants in these trials showed important differences in the rate of cumulative and complete remissions, ranging between 60 and 83%, and between 19 and 42%, respectively.

Some questions remain unanswered with rituximab. Does the efficacy depend on the different doses of rituximab? Should the doses be based on their effects on circulating B cells? Should rituximab be used as monotherapy or together with other immunosuppressive agents to reinforce the efficacy?

Calcineurin inhibitors (CNIs)

Both cyclosporine and tacrolimus have been largely used in PMN. A number of observational studies demonstrated the efficacy of CNIs in reducing proteinuria and in inducing remission in patients with normal renal function. However, in many

patients proteinuria relapsed after discontinuation of CNIs, and the MENTOR trial showed that cyclosporine obtained fewer remissions than rituximab [79]. Similar results have been reported with tacrolimus. Good rates of response have been followed by relapses of proteinuria after discontinuation of the drug. A prospective randomized trial assessed the role of monotherapy with tacrolimus in PMN. Twenty-five patients were randomized to receive tacrolimus (0.05 mg/kg/day) over 12 months with a 6-months taper, whereas 23 patients were assigned to the control group. The probability of remission at 18 months was 94% in the treatment group vs 35% in the control group. The decrease in proteinuria was significantly greater in the treatment group. Nephrotic syndrome reappeared in almost half of the patients who were in remission by the 18th month after tacrolimus discontinuation [80]. A long-term Indian trial and the STARMEN trial concluded that tacrolimus plus steroids or low-dose rituximab achieved fewer responses than cyclical therapy with cyclophosphamide [63, 64]. A pilot study reported that combined treatment with cyclosporine and rituximab can reduce the risk of relapse. In 13 patients with PMN and elevated proteinuria, induction therapy with rituximab plus cyclosporine was given for 6 months, followed by a second cycle of rituximab and tapering of cyclosporine over an 18 months maintenance phase. Complete or partial remission was attained in 92% of participants and 54% were in complete remission at 12 months [81]. The ability of CNIs to modify the risk of ESRD in the long-term remains unproven. There are no data on the use of voclosporin in PMN. Preliminary studies with this new CNI in lupus nephritis reported that voclosporin could reduce proteinuria and maintain stable kidney function [82].

In summary, CNIs may maintain a role in the management of PMN in patients who do not respond or result intolerant to rituximab or cyclical therapy. Given the high relapse rate, long-term therapy is necessary. To reduce the risk of nephrotoxicity, serum creatinine and blood pressure should be frequently monitored, the lowest possible dosage of CNIs should be used for maintenance, and repeat renal biopsy should be performed in those undergoing long-term therapy.

Further treatments

The adrenocorticotropic hormone (ACTH) is composed of 39 amino acids. The first 13 amino acids may form a melanocortin peptide that, after binding to its receptor, can exert anti-inflammatory and immunomodulating effects. Both synthetic and natural ACTH have been used in PMN. Berg et al. [83] administered intramuscular synthetic ACTH, 1 mg twice a week for one year, to 5 patients with PMN and mean proteinuria fell from 7.87 to 0.09 g/day in 3 of them. In the other two participants

proteinuria dropped from 13.2 to 0.51 g per day. In Italy, a small multicenter study on 32 participants with PMN and nephrotic syndrome compared cyclical therapy for 6 months and synthetic ACTH 1 mg twice a week for one year. At the end of a mean follow-up of 22 months 12 of the 16 participants assigned to cyclical therapy and 14 of the 16 assigned to ACTH responded with complete or partial remission [84]. In an observational study, 20 patients received a subcutaneous dose of 40 or 80 IU twice weekly of H.P. Acthar(®) Gel. The drug was well tolerated and a decrease in proteinuria > 50% was observed in 2/3 of the patients. Anti-PLA2R antibodies cleared in some, but not all patients [85]. A retrospective study compared a cohort of patients given synthetic ACTH for 12 months with a historical group of patients treated with cyclophosphamide and steroids for 6–12 months. ACTH was less effective in inducing remission and was associated with many adverse events [86]. A systematic review reported that in 149 pts with MN treated with synthetic or natural ACTH complete or partial remission occurred in 69% at 12 months, and in 95% at 24 months. The drug was well tolerated. However, all papers but one were retrospective and many of them were Abstracts [87]. Further studies are needed before recommending the use of ACTH as a first approach in patients with PMN.

Mycophenolate salts are prodrugs that release active mycophenolic acid. This inhibits the de novo pathway of guanosine nucleotide synthesis of T and B cells. A retrospective study compared the effects of mycophenolate mofetil (MMF) plus corticosteroids vs a historical group treated with cyclophosphamide plus corticosteroids. Both treatments lasted one year. After 23 months of follow-up, complete (12% vs 22%) and partial (53% vs 62%) remissions did not significantly differ between the two groups but relapses (57% vs 15%) were significantly more frequent in patients receiving MMF [88]. A randomized controlled trial assigned 36 participants with PMN to receive symptomatic therapy or MMF at a dose of 2 g per day over 12 months. At the end of the study no difference between the two arms was found in mean proteinuria, or partial and complete remissions. Serious adverse effects were observed in 20% of participants receiving MMF [89]. In a Korean trial 39 participants with PMN were treated with MMF plus corticosteroids or cyclosporine plus corticosteroids. At 48 weeks, 76.1% of the MMF group and 66.7% of the cyclosporine group had achieved remission. There was no difference in eGFR between the two groups [90]. There are insufficient data to sustain the role of MMF as a single agent in the management of PMN.

Belimumab is a monoclonal antibody that inhibits the BLyS protein which is necessary for B cell stimulation. In a prospective, open-label, study, 14 participants with

PMN and persistent nephrotic-range proteinuria received up to 2 years of belimumab monotherapy (10 mg/kg, every 4 weeks). Proteinuria decreased from 724 to 130 mg/mmol after 24 months. Participants with abnormal albumin and/or cholesterol at baseline reached normal or near normal levels by the last follow-up. Adverse events were consistent with those expected in this population [91].

Ofatumumab is a human anti-CD20 monoclonal antibody that proved to be effective in patients with PMN complicated by rituximab-induced serum sickness [92]. Ofatumumab associated with double-filtration plasmapheresis to obtain antibody depletion has been proposed as a novel therapeutic option in patients with severe PMN [93].

Obinutuzumab is a type II anti-CD20 monoclonal antibody approved for use in chronic lymphocytic leukemia. In a study, obinutuzumab was administered to ten patients with MN resistant to previous treatments including rituximab. Four patients entered complete remission and five had partial remission. The drug was well tolerated [94]. In another study, three patients with PMN resistant to rituximab were given obinutuzumab. All patients obtained complete immunologic response and two of them had partial remission [95].

Bortezomib, a proteasome inhibitor, has been successfully used in anecdotal cases of PMN [96–98].

In a prospective study, 43 patients with PMN received hydroxychloroquine and RASi and 83 patients received RASi alone. At 6 months, both the clinical remission rate and percentage change in proteinuria were significantly higher in the hydroxychloroquine group [99].

What to do in patients with kidney insufficiency?

Most observational and randomized studies have been carried out in patients with normal or subnormal kidney function. Only a few studies reported the results of different treatments in patients with severe renal insufficiency.

In the UK, a multicenter, randomized trial was conducted in patients with PMN and a serum creatinine concentration of less than 3.4 mg/dL and at least a 20% decline in estimated creatinine clearance. The 106 participants were randomly assigned to receive no further treatment, 6 months of cyclical therapy with prednisolone and chlorambucil, or 12 months of cyclosporine at a dose of 5 mg/kg/days. The risk of a further 20% decline in kidney function was significantly lower in the prednisolone and chlorambucil group (58%) than in the cyclosporine (81%) or the supportive care groups (87%). Side effects were more frequent and two cases of malignancy occurred in the steroid-chlorambucil group

[100]. A main drawback of this trial was that the doses of chlorambucil and cyclosporine had to be adapted to the reduction of kidney function in order to prevent side effects. In addition, clinical control of participants was poor since no measures were taken in patients who did not tolerate the prescribed treatment [101].

In a retrospective study, 13 patients with PMN and mean eGFR of 16 ml/min received 2 weekly infusions of 375 mg/m^2 of rituximab or 2 rituximab infusions of 1 g/day 2 weeks apart. Ten treatment courses led to an increase in eGFR and remission of nephrotic syndrome after a median follow-up of 40.8 months in nine patients, while in the other four patients treatments were unsuccessful, and patients needed regular hemodialysis within 1 year [102].

In an Indian study, 64 patients with PMN and an eGFR < 60 ml/min were treated with rituximab or cyclical therapy with corticosteroids and cyclophosphamide. Participants were followed up for a mean period of 24 months. At the end of the study 30 (47%) patients were in remission and 8 had progressed to ESRD. Rituximab and cyclical therapy were equally effective, but rituximab had fewer adverse events [103].

Conclusions

In the last decades enormous advancements have been made in our knowledge of the physiopathology, long-term outcome, and management of PMN. Many clinicians, pathologists and scientists from different countries have participated in this progress. Yet, the etiopathogenesis of PMN has not been completely elucidated; the genetic influence on disease susceptibility is poorly defined, and the available treatments are far from optimal as a number of patients still progress to ESRD or suffer from the complications of severe nephrotic syndrome. Thus, after almost 80 years of exciting studies the story of PMN is not over. Let us hope that continuing research in this field will fill the gaps that still limit a complete understanding of this disease.

Declarations

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