PRIMARY MEMBRANOUS NEPHROPATHY AND ITS TREATMENT: PAST, PRESENT AND FUTURE

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ABSTRACT

Primary membranous nephropathy (PMN) is the most common cause of primary nephrotic syndrome. In the last few years scientific interest mainly focused on the search for new more effective and safer therapeutic strategies and on the guide to their use based on markers of clinical outcomes and disease activity such as the antibodies to the podocyte-expressed phospholipase A2 receptor (PLA2R). The results of the latest trials with the newest pharmacologic approaches open promising horizons in the treatment of membranous glomerulonephritis. This brief review, following the road paved by the previous treatment options, overviews the new advances in the pharmacologic treatment of MN, which represent the near future of its therapy.

Key words*: Membranous nephropathy, phospholipase A2 receptor, Rituximab, calcineurin inhibitors.*

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Membranous nephropathy: definition and epidemiology

Membranous nephropathy (MN) is the most common cause of primary nephrotic syndrome in older white adults. 1 Primary MN has an incidence of 12 cases per million of people per year in adults, 2 while the Italian Registry of Renal Biopsies few years ago 3 extimated an incidence of 4.9 cases per million of people per year. Epidemiological data from the Triveneto (Veneto, Friuli Venezia Giulia and Trentino Alto Adige regions of North-East of Italy) Register of Renal Biopsy reported that MN is the second most common primary glomerulonephritis with an incidence of 1,01 new cases/years/105 population[4].

MN may occur at any age and in all ethnic groups but is rare in children and is most common in whites followed by Asians, Blacks and Hispanics. Men have twice higher prevalence than women and MN has its peak of incidence during the fourth and fifth decades of life[1,2].

Primary MN (PMN) is an organ-specific autoimmune disease. It accounts for about 75%-80% of patients with MN and occurs in the absence of any identifiable initiating event (idiopathic MN). Secondary MN is associated with several conditions, such as autoimmune diseases (class V lupus nephritis, autoimmune thyroid disease, IgG4-related systemic disease), infections (HCV, HBV, HIV), malignancy (solid tumors-lung, colon and kidney are the most common primary sites, non-Hodgkin's lymphoma, chronic lymphocytic leukemia) and drugs (NSAIDs)[1].

PMN is mediated by IgG4 antibodies to the podocyte-expressed M-type phospholipase A2 receptor (anti-PLA2R) (85%) and thrombospondin type 1 domain containing 7A (THSD7A) (3%-5%), another podocyte membrane antigen with similar properties to PLA2R. About 10% of patients with PMN are negative for both antibodies and dual expression of antibodies to both PLA2R and THSD7A has been reported, althouth this is rare. PLA2R and THSD7A antibodies are present in the circulation and also deposited in glomeruli[2].

Clinical Characteristics

About 80% of patients with PMN present with the nephrotic syndrome, the remaining 20%-30% present with subnephrotic proteinuria (<3.5 g/24 h). Renal function is usually normal at presentation, with only <10% of patients presenting with renal impairment[1,2]. The clinical consequences include complications of nephrotic syndrome, such as thromboembolic events, that are related to the degree of hypoalbuminemia, and an increased risk of infection due to urinary loss of Igs. About one third of patients undergo spontaneous remission, one third progress to ESRD over 10 years and the remainder develop nonprogressive CKD[2].

Histopathologic characteristics

When a renal biopsy cannot be performed, a positive sierologic test for anti-PLA2R or anti-THSD7A makes the diagnosis of MN very likely, although a negative test does not exclude PMN. Few patients, in fact, may have positive glomerular staining for PLA2R or THSD7A despite negative serology. In addition, patients positive for anti-PLA2R or anti-THSD7A antibodies may have secondary MN (cancer-related)[2].

Renal biopsy remains the gold standard for the diagnosis of MN. At light microscopy, glomeruli appear normal in the earliest stages of MN. Later, glomerular basement membrane (GBM) becomes thick and subepithelial spikes of basement membrane on the outer surface of the capillary wall may be detected on silver methenamine staining. Immunofluorescence microscopy in anti PLA2R/THSD7A positive patients reveals granular and diffuse deposits of IgG4 along the outer surfaces of all capillary wall, but also lesser amounts of IgG1, IgG3 and C3 may be seen. The antigen PLA2R or THSD7A colocalizes with IgG4. Electron microscopy shows subepithelial electron-dense deposits. Additional biopsy findings suggest secondary MN: electron-dense deposits in subendothelial or mesangial locations, dominant staining for IgG1 or IgG3, IgA, IgM, C1q, mesangial or endothelial cell proliferation, tubuloreticular inclusions in the endothelial cells and negative PLA2R staining in the immune deposits[1,2].

Supportive care therapy

Regarding the duration and type of conservative ("supportive care") therapy there is general consensus among experts, that is valid for all patients, regardless of patient's individual risk profile: ACE inhibitors or ARBs or a combination of the two drugs given at the highest tollerate dose obtaining the target blood pressure (<130/80 mmHg), salt restriction, statins for hyperlipidemia, diuretics to control edema, antithrombotic prophylaxis in the presence of severe hypoalbuminemia (serum albumin <25 g/L) and a favorable risk/benefit ratio. Supportive care should be initiated in all patients at the time of diagnosis and continued throghout the course of the disease[5-7].

Immunosuppressive therapy: which patients? When?

According to current KDIGO 2012 guidelines, the decision to start immunosuppressive therapy depends on patient's individual risk profile (Toronto Risk Score)[6-8]. Immunosoppressive therapy is not recommended for low risk patients, meaning those with subnephrotic proteinuria, because they have a good prognosis, with only a 5% risk of progression to chronic renal failure over 5 years. Immunosoppressive therapy is also not recommended in patients with clinical, ultrasound and histological signs of chronic renal disease (eGFR <30 ml/min, small fibrotic kidneys or >50% of sclerotic glomeruli), due to the significant risks associated with immunosuppressive therapy versus the potential benefits.

Immunosoppressive therapy is recommended in moderate (proteinuria 4-8 g/d, stable GFR) and high risk patients (proteinuria >8 g/d, <50% decrease from baseline or >30% decline in GFR from baseline), due to their >50% and 65%-80% probability of developing CKD within 5 years, respectively. In addition, in these patients the risk of developing the clinical complications of nephrotic syndrome is higher. There is general consensus to wait six months, in absence of declining renal function, nephrotic syndrome's complications (such as thromboembolic events), proteinuria >10 g/d or proteinuria > 8 g/d after three months of conservative therapy[2].

About one third of patients undergo spontaneous remission within six months from diagnosis[9,10]. These are those with lower and stable or declining anti PLA2R titer, low proteinuria and normal and stable renal function during the observation period. Patients with higher or increasing anti PLA2R titer, high proteinuria (particularly if >8g/d) and declining renal function probably will not undergo spontaneous remission during the observation period and so they should be treated with immunosoppressive therapy before the end of the observation period[5,8,11,12].

Role of Anti PLA2R: marker of remission and relapse

In the last few years, scientific interest has mainly focused on the role of anti PLA2R not only in the diagnosis of MN and in differential diagnosis between primary and secondary MN[22] but also in the predictive value of the clinical outcome of the antibody titer. Patients with higher or increasing anti PLA2R level at diagnosis probably will not undergo spontaneous remission and the reduction of anti PLA2R titer ("immunological remission") comes before the clinical remission. Similarly, increasing anti PLA2R level after obtaining clinical remission comes before the relapse[12,14-19]. Anti PLA2R therefore should be taken into account in the definition of the patient's individual risk profile (Toronto Risk Score) at the time of diagnosis because they are important prognostic indicator of remission and relapses.

Immunosuppressive therapy: what drugs should be used?

In the last few years scientific interest focused on the search for new more effective and safer therapeutic strategies for the treatment of MN including the type of immunosuppression.

Ponticelli regimen

For many years, Ponticelli regimen has been the first choice for moderate and high risk patients with MN. KDIGO 2012 guidelines recommend this therapeutic regimen (a 6-month cycling of an alkylating agent, cyclophosphamide, with corticosteroids) with the highest level of evidence. 6 It is effective (50-60% and 70-80% probability of remission after 1 and 2-3 years, respectively) and is the only therapeutic regimen of which there is, so far, greatest experience and a long-term follow-up about the progression of kidney disease (reduction risk ESRD after 10 years 40-10%)[2,6,20-22]. Ponticelli regimen is however associated with relatively high adverse event rate, that includes infection, later malignancy and hematologic complications[6,23,24]. In addition, Ponticelli regimen may be relatively contraindicated in presence of diabetes, obesity, osteoporosis or young women in childbearing age. Finally, in case of relapse (about 25%)[22] the regimen should not be repeated for its high oncologic risk due to the cumulative dose of cyclophosphamide (> 36 g)[25].

Calcineurin Inhibitors (CNIs)

Calcineurin inhibitors (cyclosporine and tacrolimus) are recommended as second or first (in presence of controindications to Ponticelli regimen) therapeutic choice by current KDIGO 2012 guidelines[6]. CNIs induce clinical remission in up to 80% of cases of PMN within 12 month[2], but tacrolimus may be more effective than cyclosporine and induces earlier remission[26]. CNIs are well tolerated due to their best adverse effect profile, as has been shown by a Spanish, multicentre and retrospective study[27]. 122 MN patients with nephrotic syndrome and stable renal function were included in the study and treated with tacrolimus (0.05 mg/kg/die) for 17.6 ± 7.2 months, including a full-dose and a tapering period. Partial/complete remission was 60, 78 and 84% after 6, 12 and 18 months of treatment, respectively. Interestingly the study identified the predictors of clinical remission and relapse. The probability of remission, in fact, was higher in patients with lower proteinuria at baseline. A high number of relapses (44%) were evidenced in patients who had achieved partial or complete remission and most of relapses appeared shortly after tacrolimus withdrawal or during the period of tacrolimus tapering. The probability of relapse was higher in patients with higher proteinuria at the beginning of tacrolimus tapering with more relapses for patients who had achieved partial remission. Renal prognosis was good for patients who had achieved persistent clinical remission without relapses. The main disadvantage of CNIs remains the high relapse rate[26,27] during the period of tapering or after withdrawal of therapy. Therefore tapering should be gradual, particularly in presence of predictors of relapse, and a maintenance lowest effective dose may be necessary to maintain remission, despite the risk of chronic nephrotoxicity[28].

Adrenocorticotropic Hormone (ACTH)

Data regarding the use of ACTH in the treatment of MN are conflicting. A small randomized trial in patients with PMN showed that a year of monotherapy with ACTH (given as 1 mg twice a week) was equivalent to the Ponticelli regimen in achieving remission (80% remission at 6 months) with minimal adverse events[29].

A nonrandomized study using this synthetic agent in patients with PMN and high risk for progression found a lower response rate and a higher incidence of adverse events[30]. A recent study using the natural ACTH gel found a significant reduction of proteinuria related to drug exposure in the majority of PMN patients with an acceptable adverse events profile also accompanied by a parallel re-

duction of PLA2R levels[31]. Given its limited evidence base, its high cost and the conflicting results in the above mentioned studies, ACTH should not be used as first line therapy for PMN patients and further studies should be done to clarify the efficacy of ACTH in the treatment of PMN.

Rituximab (RTX)

Promising results have been obtained in the treatment of MN with Rituximab (anti-CD19/20 monoclonal antibody) as monotherapy. A retrospective observational cohort study by Ruggenenti and Remuzzi[32] compared the therapy in terms of safety profile with RTX (100 patients) versus Ponticelli regimen (103 patients). The follow up was 40 months. The incidence rates of serious and nonserious adverse events were three- to fourfold lower in RTX-treated patients than in Ponticelli regimen-treated patients, proving the more favorable RTX's safety profile. There was no difference in terms of complete remission and renal outcome between the two groups (partial remission rate was higher in Ponticelli-group than RTX-group). The effectiveness of RTX in inducing clinical remission in patients with PMN has been demonstrated by GEMRITUX trial[33], a recent RCT in which rituximab in combination with supportive therapy was compared with supportive therapy alone.

There was no difference in terms of remission at 6 months between the two groups, but post hoc analysis showed a significant benefit in the rituximab group at 17 months, with remission rates of 64.9% versus 34.2% for controls, proving a "delayed response" on proteinuria by RTX. In addition, RTX is also more effective than CNIs in maintaining remission, as shown by The membranous nephropathy trial of rituximab (MENTOR) trial[34]. This multicentre RCT compared RTX therapy with cyclosporine therapy in 130 patients with PMN, nephrotic syndrome (proteinuria >5 g/d) and a creatinine clearance >40 ml/min/1.73 m^2 after three months of conservative therapy. 65 patients were treated with RTX (1 g rituximab 14 days apart). At 6 months a second course of RTX was administered in patients with proteinuria reduced from baseline by at least 25% and in patients in partial remission, regardless of the CD19+ B-cell count. A second course of RTX was not given in patients with complete remission and in those with proteinuria reduced less than 25% by 6 months ("treatment failure group"). 65 patients were treated with cyclosporine at an oral dose of 3,5 mg/kg/day divided into two equal doses given at 12-hours intervals. If complete remission was observed at 6 months, cyclosporine was tapered and discontinued over a 2-month period. In patients with partial remission and in those with proteinuria reduced by at least 25%, cyclosporine was continued for an additional 6 months and then slowly tapered until complete withdrawal. As in RTX group, if proteinuria was reduced from baseline by less than 25% at 6 months, was considered as treatment failure and cyclosporine was discontinued. At 12 months, RTX was noninferior to cyclosporine in inducing complete or partial remission of proteinuria, 60% (14% complete and 46% partial) vs. 52% (5% complete and 47% partial), respectively. At 24 months, RTX was better than cyclosporine in preventing relapses and maintaining proteinuria remission, 60% (35% complete and 25% partial) vs. 20% (0% complete and 20% partial), respectively. Immunological remission rate was higher in RTX-group than in cyclosporine-group (66% vs. 13%, respectively) and this is consistent with the fact that immunological remission precedes clinical remission. In addition, the results of the MENTOR trial 34 confirm the "delayed response" on proteinuria by RTX (increasing remission rate from 6 to 12 months, 35% vs. 60%, respectively) and RTX's good safety profile (no difference in terms of adverse events between the two groups).

Rituximab (RTX) plus CNIs

As reported in the above mentioned studies, the goal standard of the treatment of MN should be a therapeutic strategy that is able to obtain clinical remission (preferably a complete remission) as soon as possible and maintain it for as long as possible without relapses and side effects. It has been suggested to consider the ability of CNIs to induce a rapid clinical remission together with the ability of RTX to maintain remission. A pilot study of Waldman and coworkers[35] developed a treatment protocol based on a novel combination of rituximab and cyclosporine. Thirteen high-risk patients defined by sustained high-grade proteinuria (mean 10.8 g/d) received combination induction therapy with rituximab (1 g rituximab 14 days apart) plus cyclosporine (3 mg/kg/d) for 6 months. After 6 months cyclosporine was gradually tapered until withdrawal. RTX was administered "on demand", based on CD19+ B-cell count. After three months, the majority of patients was in clinical remission (61%, 54% partial, 7% complete) and in immunological remission (>75%). After six months, almost all patients were in clinical remis-

sion (85%, 62% partial, 23% complete). After 12 and 24 months, remission was maintained in almost all patients (85%) with > 54% of patients in complete remission. Renal function stabilized and the therapy was well tolerated during follow-up.

Further data will be provided by the ongoing Sequential treatment with Tacrolimus-Rituximab versus steroids plus cyclophosphamide in patients with primary Membranous Nephropathy (STARMEN) trial[36], a randomized controlled trial that compares Ponticelli regimen with tacrolimus plus RTX: tacrolimus is administered at full dose for 6 months and then tapered until withdrawal at the ninth month and RTX is given at 6 months.

Conclusion

The first and second line therapies recommended by the current KDIGO 2012 guidelines for moderate and high risk patients with PMN appear to be outdated. The new available therapies seem as effective as traditional treatment in inducing immunological and clinical remission and preventing relapses with less side effects. The results of MENTOR trial 34 and Waldman and coworkers' study[35] together with the ongoing STARMEN trial[36] open new and promising horizons in the treatment of membranous glomerulonephritis. RTX could become a mainstay in the treatment of membranous glomerulonephritis due to its efficacy, safety profile and superiority to maintain clinical remission in the long term.

The "delayed response" on proteinuria by RTX may be overcomed by the simultaneous use of CNIs, particularly tacrolimus, that seems to be more effective and induce earlier remission than cyclosporine. The simultaneous use of RTX and CNIs could be particularly useful in high risk patients, in whom it is important to achieve a rapid reduction of proteinuria preventing the complications linked with nephrotic syndrome. Recently, a new anti-CD20 antibody, obinutuzumab, has been successfully used in patients with PLA2R-associated PMN that failed to achieve immunological or clinical remission after RTX[37]. It appears to be a promising treatment strategy for patients with PLA2R-associated PMN resistent to RTX, although further studies are needed to confirm these promising results.

Finally, the discovery of antiPLA2R's role has changed the approach to membranous glomerulonephritis, from a traditionally proteinuria-based approach to a serology-based approach. The levels of antibody anti PLA2R are predictors of clinical outcome and correlate with the disease activity, making the levels of these antibodies the guide for therapeutic decisions, limiting unnecessary exposure to immunosoppressive therapy and optimizing efficacy of treatment. Further randomized and controlled trials with a long-term follow-up are required to optimize therapeutic strategies, which, however, should always be tailored for each patient.

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