Management of patients with membranous nephropathy

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Introduction

Membranous nephropathy (MN) is the most common cause of the nephrotic syndrome in Europe, with an incidence of 5–10/million/year in adults [1]. Although MN can occur secondary to infections, systemic diseases, use of drugs or malignancies, in most patients no underlying cause is identified [idiopathic membranous nephropathy (iMN)]. Recent studies have identified antibodies against the M-type PLA2-receptor, an antigen present on podocytes, in 70% of patients with iMN, thus establishing iMN as an autoimmune disease [2]. These findings were supported by a genome wide association study that found an association between PLA2R and iMN [3]. In this comment, we describe the management of patients with MN (Figure 1).

Exclude secondary causes of MN

Secondary causes of MN are listed in Table 1. Most causes can be excluded by detailed medical history, a review of the patient’s drug history, physical examination and laboratory studies (Table 1). Awareness of a malignancy is particularly important in the elderly [1, 4]. The prevalence of a malignancy was 4.1% in patients <60 years and 19.4% in patients >60 years of age [5]. Studies have suggested that iMN can be differentiated from malignancy-related MN. Japanese investigators reported that glomerular staining for IgG1 was significantly stronger in malignancy-related MN, and equal to IgG4, whereas in iMN, there was predominant staining for IgG4 [6]. The French group reported an increased number of inflammatory cells in the glomerulus of patients with a malignancy [4]. Using a cutoff value of eight cells per glomerulus, specificity and sensitivity were 75 and 92%, respectively. Although promising, these data need validation. Preliminary data indicate that antibodies against PLA2R are absent in patients with secondary MN [2]. If confirmed, there would be no need to search for a malignancy in anti-PLA2R-positive patients.

Risk prediction in iMN

Patients who never develop nephrotic proteinuria do not develop renal failure [7]. These patients should be treated with conservative (non-immunosuppressive) therapy only (Figure 1). Alternatively, patients with a deteriorating renal function will almost invariably progress to end-stage renal disease (ESRD) and should be considered for immunosuppressive therapy. Prognosis is variable in patients with a nephrotic syndrome. Two recent studies showed that 48–54% of patients with iMN and a nephrotic syndrome needed immunosuppressive therapy over a follow-up period of 63–80 months [8, 9]. Thus, accurate risk prediction is needed in these patients.

Proteinuria is an independent predictor of renal function deterioration in patients with iMN [10]. However, baseline proteinuria is not an accurate predictor of prognosis. Up to 21.5% of patients with baseline proteinuria >12 g/day developed a spontaneous remission [9]. Risk factors other than serum creatinine or baseline proteinuria are age, sex, HLA, race, blood pressure, glomerulosclerosis, tubulointerstitial fibrosis, selectivity index and urinary excretion of complement C3dg and C5b-9. All these factors lack clinical utility because of their low sensitivity or specificity (reviewed in ref. [10]). Since then more promising predictors have been proposed [11, 12, 13]. Pei et al. [11] showed that a model that included the duration and magnitude of proteinuria improved predictive accuracy. They studied 184 patients; proteinuria was >4 g/day in 127 patients. During follow-up, 47 patients showed evidence of disease progression. A cutoff value of proteinuria >8 g/day for a period of >6 months provided a specificity of 88% and a sensitivity of 66%. The Toronto group developed a renal risk score, which was based on baseline creatinine clearance, the magnitude of proteinuria in the 6-month period with minimal persistent proteinuria, and the change in creatinine clearance over this 6-month period. This risk score was validated in three independent patient cohorts and provided good accuracy of 79–87% [12]. The use of the risk score has some disadvantages since patients need to be followed for a prolonged period of time and repeated 24 h urine collections are needed. Bazzi et al. [14] used sodium dodecyl sulphate–polyacrylamide gel electrophoresis and showed that increased excretion of low-molecular weight (LMW) proteins predicted outcome. We extended these findings by quantitating urinary β2microglobulin (β2M) [15]. These data were validated in a study that included 57 patients [13]. A threshold value of 0.5 µg/min predicted outcome with a sensitivity of 88% and specificity of 91%. A recent analysis of our data indicates that in the current era sensitivity and specificity are between 75 and 80%.

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Treatment of iMN

Conservative therapy

Patients with oedema should be treated with diuretics and sodium restriction [16]. Drugs that interfere with the renin-angiotensin-aldosterone system effectively lower proteinuria and have improved outcome in patients with kidney diseases [17]. Thus, it is advised that all patients with iMN be treated with angiotensin converting enzyme inhibitor (ACEi). However, the efficacy of ACEi treatment in patients with a severe nephrotic syndrome is limited [9, 18] and the use of ACEi has not dramatically changed the natural history of iMN [19, 20]. Although randomized controlled trials are lacking, most authors advise the use of cholesterol-lowering drugs in patients with long-standing proteinuria. The use of statins in patients with CKD is supported by the SHARP study, which showed a reduction of cardiovascular events [21].

Patients with iMN are at increased risk for thrombosis. It is advised to consider prophylactic anticoagulant therapy in patients with serum albumin <20 g/L. Obviously, risks and benefits must be weighed in the individual patients, considering a history of thrombosis, immobilization, increased bleeding tendency, etc. We advise the use of prophylactic anticoagulation with LMW heparin in patients who start treatment with high-dose prednisone, which might predispose to thrombosis [22].

Immunosuppressive therapy

Many authors are reluctant to advise immunosuppressive therapy in high-risk patients with iMN. Some doubt the efficacy of such therapy, whereas others emphasize the side effects. We recently reviewed the evidence that supports the efficacy of alkylating agents in preventing ESRD in patients with iMN [23]. Two large controlled trials with long follow-up demonstrated improved renal survival after treatment with chlorambucil or cyclophosphamide alternated with high-dose steroids [24, 25]. Benefits were confirmed in cohort studies [26, 27]. Cyclophosphamide is preferred over chlorambucil [28]. Treatment schedules are depicted in Table 2. The optimal duration of therapy is debated. A 3-month regimen of cyclophosphamide is effective, however, only used in patients in the early stage of disease. We have used cyclophosphamide 1.5–2 mg/kg/day for 12 months (cumulative dose 36 g) in high-risk patients and reported a favourable outcome [26]. However, recent literature questioned the safety of a cumulative dose of 36 g [29]. Therefore, we now limit the duration of treatment with cyclophosphamide to a period of 6 months. We caution against a further reduction of the duration of treatment. Based on our experience, a 3-month course may be too short in high-risk patients. This has also been suggested in a recent study that reported resistance to cyclophosphamide used in a dose of 1–2 mg/kg/day for 12 months (cumulative dose 36 g) in high-risk patients and reported a favourable outcome [26]. However, recent literature questioned the safety of a cumulative dose of 36 g [29]. Therefore, we now limit the duration of treatment with cyclophosphamide to a period of 6 months. We caution against a further reduction of the duration of treatment. Based on our experience, a 3-month course may be too short in high-risk patients. This has also been suggested in a recent study that reported resistance to cyclophosphamide used in a dose of 1–2 mg/kg/day for 3–6 months [30]. Overall, in studies with alkylating agents, 5-year renal survival is 86–92%, remission rates range from 65 to 85% and relapse rate is 25% after 5 years [23]. Obviously, the use of alkylating agents is complicated by serious side effects, particularly infertility and risk of late malignancies. This has stimulated the search for alternative treatment modalities.

Calcineurin inhibitors (CNI) are successfully used in patients with iMN and a nephrotic syndrome. Although
remissions occur in 75–88% of patients, the efficacy on renal end points remains unclear. Since 50–72% of patients relapse after stopping treatment [31, 32, 33], and multiple relapses predict ESRD [34], patients may need treatment for many years (CNI dependent). Mycophenolate mofetil (MMF) used as monotherapy is not effective [35]. MMF in a dose of 2 g/day and combined with steroids may induce remissions as effectively as cyclophosphamide or chlorambucil [36]. However, many (75%) patients relapse within 2 years after the end of treatment and benefits on renal end points have not been documented. Therefore, we suggest that MMF be considered only in patients who cannot use or are intolerant to cyclophosphamide or CNI.

Rituximab has received great interest. This antibody, which targets CD-20-positive B cells has been used in different dosing schedules, varying from one bolus of 1 g or two biweekly doses of 1 g/day to 4 weekly doses of 375 mg/m². The use of rituximab was associated with a high incidence of remissions. However, the best outcome was reported in female patients with normal renal function and moderate proteinuria [37]. No benefits were seen in patients with moderate tubulointerstitial fibrosis [38]. These data suggested that rituximab may not be effective in high-risk patients. However, a recent cohort study in 20 patients with iMN, which included 11 patients who had failed prior immunosuppressive therapy, showed a remission rate of 89% [39]. A recent study suggested that rituximab also may allow successful withdrawal in CNI-dependent patients [40].

Several studies showed beneficial effects of synthetic adrenocorticotropic hormone (ACTH) in patients with iMN [41, 42]. Its proposed mechanism of action is through activation of the melancortin receptor MCR1 in podocytes, leading to reduction of oxidative stress and proteinuria and improved podocyte morphology [43]. In a randomized controlled trial, synthetic ACTH proved to be as effective as combined cytotoxic agent/steroid therapy in inducing a remission and was associated with very few side effects [44]. A recent retrospective case series of 11 patients with iMN that were treated with the natural highly purified ACTH gel formulation showed a remission rate of 82% in patients who had previously failed a mean of 2.4 immunosuppressive therapies [45]. We argue against the use of ACTH in view of the lack of sufficient evidence, the short follow-up in the reported studies and the lack of data on hard renal end points. Furthermore, the ACTH gel brings enormous costs.

**Individualized therapy**

The search for markers that accurately predict prognosis in iMN was based on the idea that starting immunosuppressive therapy in the early stage of the disease, i.e. at the time of normal renal function, would be beneficial. However, this has not been proven. We recently reported data of a small-randomized study that compared early start of therapy (shortly after renal biopsy) with a strategy in which treatment was started at the time that there was evident deterioration of renal function [46]. The study included 26 patients with iMN, a nephrotic syndrome and elevated urinary protein/creatinine ratio [47]. Treatment started at the time of renal biopsy showed a higher remission rate (85%) compared to therapy started at the time of evident deterioration of renal function (68%). However, there were no differences in estimated glomerular filtration rate at the end of follow-up [46].

**References**


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**Table 2. Treatment schedules for idiopathic MN**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Agents</th>
<th>Dosage of therapy</th>
<th>Treatment period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard cyclical therapy</td>
<td>Cyclophosphamide</td>
<td>2.0 mg/kg/day</td>
<td>Months 2, 4 and 6</td>
</tr>
<tr>
<td></td>
<td>Prednisolone</td>
<td>0.5 mg/kg/day</td>
<td>Months 1, 3 and 5</td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone</td>
<td>1 g i.v.</td>
<td>3 consecutive days, at start</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>of Months 1, 3 and 5</td>
</tr>
<tr>
<td>Our schedule for</td>
<td>Cyclophosphamide</td>
<td>1.5 mg/kg/day</td>
<td>Months 1–6</td>
</tr>
<tr>
<td>high-risk patients</td>
<td>Prednisolone</td>
<td>0.5 mg/kg/qod</td>
<td>Months 1–5, then taper</td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone</td>
<td>1 g i.v.</td>
<td>3 months, at start of Months 1,3 and 5</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Cyclosporine</td>
<td>Start with 3.5 mg/kg/day, achieve level 125–225 μg/L</td>
<td>Months 1–6, then taper by 25% per month; continue treatment at 50% of dose until 12 months, then taper to lowest possible maintenance doseb</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Prednisolone</td>
<td>0.15 mg/kg/day, maximum 15 mg</td>
<td>Months 1–6, then taper</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus</td>
<td>Start with 0.05 mg/kg/day, achieve level 7–9 ng/L in first 3 months and level 5–9 ng/L afterwards Months 3–6</td>
<td>Months 1–12, then taper to lowest possible maintenance doseb</td>
</tr>
<tr>
<td></td>
<td>Prednisolone</td>
<td>0.15 mg/kg/day, maximum 15 mg</td>
<td>Months 1–6, then taper</td>
</tr>
</tbody>
</table>

aIt is unknown if prednisolone coadministration is needed. Most studies with cyclosporine have used prednisolone.

bHigh relapse rate, treatment must be continued in the majority of patients.

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