Pharmacological treatment of primary membranous nephropathy in 2016

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ABSTRACT

Introduction: Therapy in patients with primary membranous nephropathy is debated. The discovery of anti-PLA2R antibodies provides opportunities for new treatment strategies.

Areas covered: The PubMed database and Cochrane library were searched for full-text articles published in English before March 2016. The search terms included ‘Glomerulonephritis, Membranous’ [MESH], ‘membranous glomerulonephritis’ [tiab] and, ‘idiopathic membranous nephropathy’ [tiab] and ‘membranous nephropathy’ [tiab], in combination with ‘Therapeutics’ [MESH], ‘therapeutic’ [tiab], ‘immunosuppression’ [MESH] and ‘immunosuppression’ [tiab]. All randomized trials were included, cohort trials were included dependent of study design and sufficient number of patients. Expert commentary: With the current available immunosuppressive therapies less than 10% of patients will progress to end stage renal disease. Various treatment options are available and can be used adapted to the clinical characteristics of the patient. Treatment in patients with membranous nephropathy can be individualized using measurement of anti-PLA2R antibodies.

1. Introduction

Membranous nephropathy is the most common cause of nephrotic syndrome in Caucasian adults [1]. In about one-third of patients, an underlying cause, such as an infection, malignancy, systemic autoimmune disease, or use of drugs such as nonsteroidal anti-inflammatory agents, can be identified [2]. In the remaining 70% of patients, the disease is considered to be primary, and the term primary membranous nephropathy (PN) is used.

Our understanding of the pathogenesis of MN has greatly increased during the last decade. A major breakthrough came with the discovery of circulating antibodies against the M-type phospholipase A2 receptor (PLA2R) in the majority of patients with MN [3]. This finding not only proved the immune etiology of the disease, but also established MN as an autoimmune disease. Studies in cohorts of various ethnicities have confirmed the presence of anti-PLA2R antibodies (aPLA2R) in approximately 70% of patients [4–6]. In 2014, another antigen, thrombospondin type-1 domain-containing 7A (THSD7A) was identified. Antibodies against THSDA were present in 8–14% of patients with MN who were seronegative for aPLA2R [7].

Immunosuppressive therapy, consisting of high-dose prednisone, was already used more than 30 years ago to treat nephrotic syndrome in MN [8]. Since then, many different immunosuppressive regimens have been proposed. Still, the use of immunosuppressive therapy is heavily debated. This is partly explained by the variable clinical course of the disease. Overall, up to 50% of patients may develop a spontaneous remission of proteinuria [9], and the unrestricted use of immunosuppressive therapy will expose these many patients unnecessarily to immunosuppressive drugs. In addition, there is a paucity of well-controlled, randomized clinical trials, and as a consequence hard evidence to support treatment protocols is lacking.

In 2012, a working group of ‘Kidney Disease Improving Global Outcomes’ (KDIGO) published guidelines for the treatment of MN [10]. All patients with MN and nephrotic syndrome should receive optimal conservative treatment. Edema should be treated with sodium restriction and diuretics, and blood pressure should be targeted to 125/75 mmHg [10,11]. It is suggested that all patients should be treated with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), as these agents more effectively lower proteinuria than conventional blood-pressure-lowering drugs and improve outcome in patients with chronic proteinuric kidney disease [12,13]. However, evidence for the beneficial effect of these agents in MN is weak; the antiproteinuric effect of ACEIs and ARBs is more modest in these patients (resulting in <30% decrease from baseline) and is mainly observed in those with lower levels of proteinuria [14,15]. Because of the increased risk of cardiovascular events, treatment with cholesterol-lowering drugs is advised in patients with long-standing proteinuria. This is in line with data from the SHARP study that support the use of statins for prevention of cardiovascular events in patients with chronic kidney disease and estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m² [16]. Patients with nephrotic syndrome are at increased risk for arterial and venous thromboembolic events and this risk is especially high in those with MN [17]. The KDIGO guideline suggests that in patients with marked reductions in serum albumin (<25 g/L) and additional risks for

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thrombosis, prophylactic anticoagulant therapy might be considered [10]. Lee et al. developed a useful tool to provide a more personalized decision about the initiation of prophylactic anticoagulation [18]. Recently, it became clear that the risk of arterial thrombosis is also high [19]. Prevention with platelet aggregation inhibition must be considered [20].

In addition to optimal conservative treatment, the guidelines advocate the use of cyclophosphamide and prednisone in patients with high risk of disease progression. High risk is defined as patients with a persisting nephrotic syndrome (>6 months) despite optimal conservative treatment, or deteriorating kidney function, or severe symptoms related to the nephrotic syndrome. In non-high-risk patients, conservative treatment only might induce spontaneous remissions.

In the current review, we summarize the various immunosuppressive treatment options and discuss the quality and strength of evidence. We emphasize the new developments since the publication of the guidelines [10]. Especially, we will highlight the opportunity of applying a more individualized treatment schedule adapted to the course of aPLA2R.

2. Immunosuppressive therapy in primary MN

2.1. Corticosteroids

In 1979, the first randomized controlled trial (RCT) of treatment in patients with MN was published [8]. In this trial, 72 nephrotic patients with MN without renal insufficiency were randomly allocated to either 8 weeks of alternate day high-dose prednisone (125 mg, n = 34), or placebo (n = 38). The rate of renal function deterioration was significantly reduced in the patients treated with prednisone. This study was criticized because of the unexpectedly low renal survival in the placebo group during the short period of follow-up (mean 23 months) [21]. After publication of two other negative RCTs [22,23], prednisone monotherapy was regarded as ineffective in patients with MN. However, these studies have used either long-term, fairly low-dose prednisone (45 mg/m² on alternate days for 6 months) [22], or a short course of high-dose prednisone (125–150 mg on alternate days for 8 weeks) [23]. Therefore, a potential positive effect of prednisone administered for a longer period in a higher dose cannot be excluded [24,25]. However, high-dose steroid regimens are highly toxic and alternatives are available, therefore, we do not consider prednisone monotherapy as a reasonable treatment option.

2.2. Alkylating agents

The KDIGO guidelines recommend initial treatment with an alkylating agent. Cyclophosphamide is preferred over chlorambucil [10]. This recommendation is supported by grade A level of evidence based on two randomized clinical trials that demonstrated that alkylating agents are effective and can improve renal outcome in patients with MN [26,27]. Ponticelli et al. randomly assigned a group of 81 patients with new-onset MN, nephrotic syndrome, and normal renal function to receive either conservative therapy (39 patients) or treatment with chlorambucil, i.v. methylprednisolone, and oral prednisone (42 patients) [28]. The treatment schedule is illustrated in Table 1. Immunosuppressive therapy significantly increased remission rate and improved renal survival compared to standard treatment (Table 2). The study of Ponticelli and colleagues thus established a 6-month course of immunosuppressive therapy with chlorambucil and prednisone (the ‘Ponticelli regimen’) as golden standard of treatment in MN patients. The efficacy of alkylating agents was confirmed in 2007 in a study by Jha et al. [41]. Patients with MN, a nephrotic syndrome of at least 6-month duration and normal renal function were randomly assigned to treatment with cyclophosphamide (replacing chlorambucil in the Ponticelli regimen) and steroids (n = 47) or conservative care only (n = 46). Again, immunosuppressive therapy increased remission rate and improved renal survival. Although these studies thus unequivocally proved the efficacy of cyclophosphamide or chlorambucil in the treatment of patients with MN, a note of caution is needed. Both studies included patients with recent-onset nephrotic syndrome, thus, including patients with lower risk for disease progression. This is illustrated by the data: >60% of patients treated with placebo were alive and off dialysis at 10 years after diagnosis.

Therefore, the guidelines advise to restrict start of immunosuppressive therapy to patients with high risk of disease progression [10]. At the time of writing of the guidelines, there was limited data to support such a restrictive treatment strategy, derived from two cohort studies that used a historical control group (Table 2) [30,43]. Since then, new information has become available. Howman et al. compared chlorambucil with placebo (and cyclosporine (CsA), see below) in an RCT that included 108 patients with MN and established renal insufficiency (defined as a decline of eGFR >20% before start of the study). Patients were randomly assigned to receive conservative treatment only, conservative treatment plus 6 months of alternating cycles of prednisolone and chlorambucil, or conservative treatment plus 12 months of CsA [42]. Of note, this study has been criticized because the starting dose of CsA (5 mg/kg, goal through level 100–200 µg/mL) might have been too high in patients with renal insufficiency at baseline. In the chlorambucil group, the risk for achieving the primary end point (a further 20% decline in renal function) was significantly lower, than in the conservative care only group (Table 2). Still, 58% of patients in the chlorambucil group had disease progression, which is high in comparison with the observed 5–8% end-stage renal disease (ESRD) rate in the treatment groups in the previous mentioned RCTs [28,41]. This study thus raises the concern that late start of immunosuppressive therapy is less effective than immediate start. We therefore analyzed the efficacy of a restrictive treatment strategy in a cohort of 254 patients with MN and nephrotic syndrome. Immunosuppressive therapy predominantly consisted of oral cyclophosphamide, i.v. methylprednisolone and oral prednisone, and was initiated in case of deteriorating renal function or untreated nephrotic syndrome. After a median duration of follow-up of 57 (32–90) months, 124 patients (49%) received immunosuppressive therapy. Long-term outcomes were favorable with an overall renal survival of 86% after 10 years and remission of proteinuria in 83% of all
of future studies. Still, although the efficacy of the Ponticelli regimen is well proven, most physicians are doubtful about the use of cyclophosphamide in the treatment of patients with MN. This is largely explained by the side effects. The increased risk of cancer is likely the most feared side effect of alkylating agents. In a retrospective cohort study, data of 272 patients with MN were available, of whom 127 patients were treated with cyclophosphamide with a median cumulative dose of 37 grams. After a median duration of follow-up of 6 years, the incidence of malignancy in cyclophosphamide-treated MN patients was approximately three times higher compared to patients not exposed to cyclophosphamide. When weighing the risks and benefits of cyclophosphamide, other complications should also be considered. Shortly after start of therapy, approximately one-third of patients suffer from a serious adverse event, being mostly leucopenia, infections, and thrombotic complications. Infertility is another feared side effect. Infertility already becomes evident using a limited dose of cyclophosphamide (± 10 grams). Therefore, for therapy in patients who are planning to have a family, we suggest a maximum cumulative dose of 10 grams of cyclophosphamide meaning a dose of 2.5 mg/kg per day for 8 weeks or 1.5 mg/kg/day for 12 weeks. Thereafter, cyclophosphamide should be replaced by mycophenolic acid (MMF). Of note, the real incidence of side effects with cyclophosphamide therapy might even be higher, since in older studies side effects are likely underreported. Moreover, cyclophosphamide is administered in combination with high doses of steroids. Therefore, the adverse effects of steroids should also be taken in consideration, such as steroid-induced diabetes, bone fractures, thromboembolic complications, and others.

### 2.3. Antimetabolites

The KDIGO guidelines provide no support for the primary use of azathioprine or MMF in patients with MN. The few studies with these agents have been reviewed in detail previously, and no new studies have been published since 2012. A recent analysis of the data of our study with MMF and prednisone provided a possible explanation for the inferior efficacy of MMF as compared to cyclophosphamide. In this observational study, 48 patients with progressive disease (a serum creatinine concentration of ≥1.5 mg/dL or a severe nephrotic syndrome) were treated with cyclophosphamide (n = 26) or MMF (n = 22) both in combination with...
corticosteroids for 12 months. All patients were prospectively followed and final outcome was established 5 years after completion of immunosuppressive therapy. In 34 patients (71%), aPLA2R were present at baseline. In these patients, MMF was less effective than cyclophosphamide in inducing a remission (in 9 of 15 patients treated with MMF vs. 16 of 18 patients treated with cyclophosphamide). A possible explanation for this was noted during measurement of aPLA2R during therapy in a subset of patients. MMF was less effective in clearing aPLA2R at 2 months (aPLA2R negative in 4 of 9 patients treated with MMF, in comparison with 11 of 13 patients treated with cyclophosphamide). And, also at the end of therapy significantly more patients treated with cyclophosphamide were aPLA2R negative (16 of 18 (89%) with cyclophosphamide vs. 8 of 15 (53%) with MMF) [49].

It is possible that higher dosages of MMF might be needed to stop production of aPLA2R and induce persistent remission in MN. In our center, we always have used MMF in a dose of 1000 mg bid. In the ALMS trial, induction therapy with MMF was as effective as intravenous cyclophosphamide in patients with SLE [50]. In this study, the target dosage of MMF was higher, 3 grams/day. In 2013, Gellermann et al. presented results from a randomized trial in which 60 children with frequently relapsing steroid-sensitive nephrotic syndrome were treated with either MMF (target through level 1.5–2.5 µg/mL) or CsA (target through level of 80–100 ng/mL) [51]. In a post hoc analysis, patients with low mycophenolic acid exposure (area under the curve (AUC) <50 µg*h/mL) experienced significantly more relapses than those with high exposure (AUC >50 µg*h/mL). We suggest that future studies could evaluate the efficacy of high-dose MMF in MN.

### 2.4. Calcineurin inhibitors

Calcineurin inhibitors (CNIs) were introduced in the early eighties of the last century for the prevention of allograft rejection. These drugs primarily affect T cell function. Already back then, it was apparent that CNIs reduce proteinuria. Since it was assumed that CNIs do not affect B cell function and thus do not reduce antibody production, the antiproteinuric effects were attributed to hemodynamic effects (decreased glomerular perfusion), decreased T cell-derived lymphokine production, or a direct effect on the podocyte [52]. It is now clear that T cells regulate B cells, thus, explaining attenuation of antibody production by CNIs.

The KDIGO guidelines recommend the use of CsA or tacrolimus in patients with MN who do not tolerate or who refuse treatment with alkylating agents. This advice was primarily based on studies that reported high remission rates during treatment with CNIs. However, there are no studies with sufficient follow-up (>5 years) that report beneficial effects of CNIs on hard renal end points such as doubling of serum creatinine or development of ESRD. An overview of the studies is given in Table 3. Of note, the treatment regimens have been variable.

| Treatment | Follow-up (months) | Remission rate (%) | Relapse rate (%) | Renal function end point |
|-----------|-------------------|-------------------|-----------------|-------------------------|
| Ponticelli [40] | Treatment | 120 | 83 | 26 | Dialysis-free 10 yr-survival: 92% |
| Control | | 120 | 38 | NA | Dialysis-free 10 yr-survival: 60% |
| Jha [41] | Treatment | 132 (126–144) | 72 | 24 | Dialysis-free 10 yr-survival: 89% |
| Control | | 132 (126–144) | 35 | 25 | Dialysis-free 10 yr-survival: 65% |
| Howman [42] | Control | 36 | NA | 20% decline in eGFR in 58% and ESRD in 3% of patients |
| Treatment | 36 | NA | NA | 20% decline in eGFR in 84% and ESRD in 11% of patients |
| Torres [43] | Treatment | 52 ± 37 | 42 | 25 | Dialysis-free 7 yr-survival: 90% |
| Control | 47 ± 38 | 0 | - | Dialysis-free 7 yr-survival: 20% |
| Du Buf [30] | Treatment | 51 (5–132) | 86 | 20 | Dialysis-free 5 yr-survival: 86% |
| Control | 48 (12–65) | 20 | 50 | Dialysis-free 5 yr-survival: 32% |

*Definitions of remission as used by the authors.

Relapse rate: percentage of relapses in patients with previous remission.

eGFR calculated using the Cockcroft–Gault equation.

### Table 2. Alkylating agents in primary membranous nephropathy: clinical trials.

| Treatment | Type of study | Patients | Sex | Duration MN | sCreat | Proteinuria |
|-----------|---------------|----------|-----|-------------|--------|-------------|
| Ponticelli [40] | ChlA/steroids (6 mo) RCT | 42 | 34/8 | 6 (1–50) | 94 ± 22 | 6.2 ± 3.0 |
| Jha [41] | CP/steroids (6 mo) RCT | 39 | 29/10 | 5 (1–52) | 93 ± 25 | 5.3 ± 2.8 |
| Howman [42] | ChlA/steroids (6 mo) RCT | 46 | 27/19 | 12 ± 6 | 103 ± 20 | 5.9 ± 2.2 |
| Torres [43] | ChlA/steroids (6 mo) Cohort | 33 |  NA | NA | 50 ± 16b | 10.1 ± 5.3 |
| Du Buf [30] | CP/steroids (12 mo) Cohort | 37 |  NA | NA | 50 ± 20b | 9.1 ± 5.3 |

m; number; m/f; male/female; MN: primary membranous nephropathy; sCreat: serum creatinine; ChlA: chlorambucil; CP: cyclophosphamide; mo: months; RCT: randomized controlled trial; NA: data not available. Data are presented as number, mean ± SD or median (range).

1) Data on the third trial arm with cyclosporine are included in Table 3.

2) Estimated glomerular filtration rate calculated using the Cockcroft–Gault equation.

3) Duration MN from biopsy to appearance of renal insufficiency.

4) 11 patients in the historical control group received immunosuppressive therapy, mainly prednisone monotherapy.

5) Proteinuria in g/10 mmol creatinine.
Table 3. Calcineurin inhibitors in primary membranous nephropathy: clinical trials.

| Treatment | Type of study | Patients (n) | Sex (m/f) | Duration MN (months) | sCreat (µmol/L) | Proteinuria (g/24 hours) |
|-----------|---------------|--------------|-----------|----------------------|----------------|------------------------|
| Cattran [53] | CsA (12 mo) | RCT | 9 | 8/1 | >12 | 186 ± 65 | 11.5 (9–18) |
| Supportive | 8 | 6/2 | >12 | 204 ± 81 | 12.8 (4–21) |
| Cattran [31] | CsA/steroids (6 mo) | RCT | 28 | 26/2 | >6 | 115 ± 44 | 9.7 ± 5.3 |
| Praga [32] | Tac (12–18 mo) | RCT | 25 | 20/5 | 58 ± 100 | 87 ± 18 | 7.2 ± 3.3 |
| Supportive | 23 | 16/7 | >6 | 97 ± 27 | 8.8 ± 4.7 |
| Chen [54] | Tac/steroids (6–9 mo) | RCT | 39 | 23/16 | 3 (0–120) | 76 ± 22 | 7.7 ± 3.9 |
| Placebo/steroids (6 mo) | 34 | 18/16 | 2 (1–44) | 85 ± 38 | 7.3 ± 3.9 |
| Howman [42] | CsA (12 mo 5 mg/kg) | RCT | 36 | NA | NA | 49 ± 18<sup>o</sup> | 6.8 ± 4.7 |
| Control | 37 | NA | NA | 50 ± 0<sup>o</sup> | 9.1 ± 5.3 |
| He [55] | Tac/steroids (12 mo) | RCT | 28 | 20/8 | NA | 82 ± 27 | 6.8 ± 2.3 |
| CP(IV)/steroids (6 mo) | 28 | 19/9 | NA | 82 ± 26 | 6.4 ± 2.2 |
| Yuan [56] | Tac long term (24 mo)/steroids | RCT | 22 | 16/6 | NA | 77 ± 15 | 8.1 ± 2.6 |
| Tac short term (6 mo)/steroids | 20 | 13/7 | NA | 73 ± 16 | 9.1 ± 2.7 |
| Ramachandran [57] | Tac/steroids (12 mo) | RCT | 35 | 27/8 | 10 ± 5 | 80 ± 24 | 6.8 ± 3.6 |
| CP/steroids (6 mo) | 35 | 20/15 | 11 ± 3 | 80 ± 23 | 5.4 ± 2.7 |
| Rostoker [58] | CsA (12–30 mo)<sup>c</sup> | Cohort | 15 | 13/2 | 14 (6–120) | 107 (85–185) | 11.7 (5.3–27.0) |
| Goumenos [59] | CsA/steroids (24 mo) | Cohort | 16 | 10/6 | >6 | 94 ± 20<sup>o</sup> | 8.0 ± 4.0 |
| Alexopoulos [60] | CsA/steroids (12 mo)<sup>d</sup> | Cohort | 31 | 19/12 | NA | 106 ± 35 | 5.1 ± 2.5 |
| Alexopoulos [60] | CsA (12 mo)<sup>e</sup> | Cohort | 20 | 12/8 | NA | 88 ± 27 | 4.9 ± 1.5 |
| Goumenos [61] | CsA/steroids (18–24 mo) | Cohort | 46 | 34/12 | >6 | 97 ± 27 | 7.4 ± 4.3 |
| ChlA or CP/steroids (6 mo) | Historical controls | 31 | 21/10 | >6 | 106 ± 33 | 9.3 ± 4.7 |
| Kalliakmani [62] | CsA/steroids (18–48 mo) | Cohort | 32 | 22/10 | >6 | 88 ± 27 | 7 ± 3 |
| Ballarin [33] | Tac/steroids ± MMF (12–15 mo) | Cohort | 21 | 16/5 | 24 ± 16 | 93 ± 7 | 10.7 ± 5.4 |
| Caro [63] | Tac ± steroids (in 8%)<sup>f</sup> | Cohort | 122 | 87/35 | 9 (6–34) | 90 ± 30 | 8.3 ± 4.1 |

<sup>n</sup>: number; m/f: male/female; MN: primary membranous nephropathy; sCreat: serum creatine; mo: months; CsA: Cyclosporine A; Tac: tacrolimus; ChlA: Chlorambucil; CP: cyclophosphamide; MMF: mycophenolate mofetil; RCT: randomized controlled trial; NA: data not available; IV: intravenous. Data are presented as number, mean ± SD or median (range).

<sup>a</sup>Data of the third trial arm with chlorambucil are included in Table 2.

<sup>b</sup>Estimated glomerular filtration rate calculated using the Cockcroft-Gault equation.

<sup>c</sup>In non-responders CsA was withdrawn after 4 months.

<sup>d</sup>Patients responding to CsA after 12 months were placed on long-term low-dose therapy.

<sup>e</sup>if proteinuria >1 g/24 hours after 3 months, MMF 500 mg twice daily was added (n = 9 patients).

<sup>f</sup>Duration of tacrolimus treatment was 17.6 ± 7.2 months.

ESRD: end-stage renal disease. Data are presented as number, mean ± SD or median (range).
| Treatment | Follow-up (months) | Remission rate<sup>a</sup> (%) | Relapse rate<sup>b</sup> (%) | Renal function end point |
|-----------|-------------------|-------------------------------|-----------------------------|--------------------------|
| Cattran [53] | CsA 30 (4–54) | 0 | NA | Slope of creatinine clearance stable |
| Supportive | 31 (4–69) | 0 | NA | ESRD in 50% of patients at end of follow-up |
| Cattran [31] | CsA 17 | 75 | 48 | Doubling sCreat: 7% |
| Placebo/steroids | 17 | 22 | 40 | Doubling sCreat: 9% |
| Praga [32] | Tac 30 | 72 | 47 | 50% sCreat increase 4% |
| Supportive | 30 | 22 | 0 | 50% sCreat increase 26% |
| Chen [54] | Tac/steroids 15 | 85 | 18 | 50% sCreat increase 0% |
| CP/steroids | 15 | 65 | 22 | 50% sCreat increase 0% |
| Howman [42] | CsA 36 | NA | NA | 20% decline in eGFR<sup>c</sup> in 81% and ESRD in 17% of patients |
| Control | 36 | NA | NA | 20% decline in eGFR<sup>c</sup> in 84% and ESRD in 11% of patients |
| He [55] | Tac/steroids 12 | 89 | NA | 50% sCreat increase 0% |
| CP(iv)/steroids | 12 | 64 | NA | 50% sCreat increase 0% |
| Yuan [56] | Tac long term | 24 | 82 | sCreat stable in all |
| Tac short term | 24 | 90 | 45 | sCreat stable in all |
| Ramachandran [57] | Tac/steroids | 12 | 71 | NA |
| CP/steroids | 12 | 77 | 88 | NA |
| Rostoker [58] | CsA 40 (18–66) | 73 | 33 | NA |
| Goumenos [59] | CsA/steroids >36 | 88 | 38 | NA |
| Alexopoulos [60] | CsA/steroids 26 ± 16<sup>d</sup> | 84 | 15 | NA |
| Alexopoulos [60] | CsA 18 ± 7<sup>d</sup> | 85 | 47 | NA |
| Goumenos [61] | CsA/steroids 48 ± 36<sup>e</sup> | 85 | 41 | Doubling sCreat. 26%, ESRD 4% |
| ChAI or CP/steroids | 48 ± 36<sup>e</sup> | 55 | 16 | Doubling sCreat. 23%, ESRD 6% |
| Kalliakmani [62] | CsA/steroids 60 ± 24 | 88 | 46 | Doubling sCreat. 31%, ESRD 19% |
| Ballarin [33] | Tac/steroids ± MMF 23 (3–37) | 71 | 73 | NA |
| Caro [63] | Tac ± steroids 30 (14–66) | 84 | 44 | Relapsing patients: doubling sCreat 17%, ESRD 6% (all non-relapsing patients maintained stable renal function during follow-up) |

ESRD: end-stage renal disease. Data are presented as number, mean ± SD or median (range).
<sup>a</sup>Definitions of remission as used by the authors.
<sup>b</sup>Relapse rate: percentage of relapses in patients with previous remission.
<sup>c</sup>Estimated glomerular filtration rate calculated using the Cockcroft–Gault equation.
<sup>d</sup>Data are only given for responders.
<sup>e</sup>Combined follow-up number for treatment and control group.
with respect to the duration of treatment, the actual drug dose, and the concomitant use of corticosteroids.

In the first small RCT, Catran et al. compared 9 patients with kidney function deterioration and persisting nephrotic range proteinuria that were treated with CsA monotherapy (3.5 mg/kg per day for 12 months) and 8 patients that received a placebo [53]. After 12 months, proteinuria was lower in CsA-treated patients, although no patient developed complete or partial remission. In CsA-treated patients, renal function deterioration was attenuated in comparison with placebo, although real improvement of kidney function was not observed. In the second RCT from the same group, 51 steroid-resistant patients with normal kidney function were studied [31]. Patients were randomized for treatment with CsA 3.5 mg/kg per day (target trough level 125–225 µg/L) and prednisone (0.15 mg/kg per day (n = 28) or placebo and prednisone alone (n = 23) for 26 weeks. At 26 weeks, remission rates were significantly higher in the CsA group (75% vs. 22%). However, relapse rate was high (43% in the CsA-treated group, vs. 40% in the placebo-prednisone group). Sustained remission at week 78 was 39% (11/28) in the CsA group vs. 13% (3/23) in the placebo-prednisone group. Follow-up was too short to allow meaningful conclusions regarding renal end points. After 78 weeks of follow-up, doubling of serum creatinine was observed in 7% of CsA-treated and 9% of control patients.

In a Spanish RCT, tacrolimus proved to be an effective therapeutic option in patients with MN and normal kidney function [32]. In this study, patients were randomized between tacrolimus monotherapy (n = 25) and conservative therapy (n = 23). Tacrolimus was started in a dose of 0.05 mg/kg/day to achieve a trough level of 3–5 µg/L, and 5–8 µg/L, if a remission was not achieved after 2 months. The probability of a remission after 18 months was 94% in the tacrolimus group and 35% in the control group. However, a relapse rate of almost 50% in the treated group was noted. High rates of relapses were noted in most studies with sufficient follow-up duration (Table 3). In the study of Alexopoulos et al., it was suggested that combination therapy with CsA and steroids is more effective in inducing remission and preventing relapses as compared with CsA monotherapy [60]. In this study, 31 patients were treated with a combination of CsA and prednisone and 20 with CsA monotherapy. Patients who were in remission after 12 months of treatment, were placed on long-term treatment with lower doses of CsA and prednisone or CsA alone. A low rate of relapses of 15% was noted during continued therapy with the combination therapy, in comparison with a relapse rate of 47% in the CsA monotherapy group. However, a more detailed analysis showed that relapses were most closely associated with lower CsA trough levels. This indicates that higher CsA levels and not necessarily the added use of corticosteroids were responsible for preventing relapses. In another study by Ballarin et al., remission rate was 71% (15 of 21 patients) after 12 to 15 months of treatment with tacrolimus and steroids (and additional MMF in a part of them) [33]. However, again a high relapse rate of 73% (11 out of 15 patients) was noted at a mean interval of 23 months after discontinuation of treatment.

Since then, several RCTs have been published [54–57] that confirm the previously reported high remission rates. However, these trials lack sufficient follow-up to evaluate relapse rate or draw conclusions regarding hard renal end points.

In the study by Chen et al., patients were followed for only 12 months after start of therapy, and only 3 months after withdrawal of tacrolimus [54]. This explains the rather low 18% relapse rate. In the study by He et al., no information about relapses is provided [55]. In another clinical trial, 42 patients with MN and nephrotic syndrome were randomly assigned to receive tacrolimus combined with prednisone for either a short-term (6 months) or long-term (24 months) period [56]. The hypothesis of the authors was that a prolonged course could help reduce the relapse rate. The target whole blood concentration of tacrolimus was 5–8 ng/mL and after 6 months tacrolimus was stopped in the short-term group, while in the long-term group tacrolimus was tapered down slowly over the following 18 months. All patients received oral prednisone 30 mg/day initially for 8 weeks and prednisone was tapered down thereafter until a dose of 10 mg/day was reached. The probability of remission in both groups was over 80% at 6 months and this figure was stable after 12 and 24 months in the long-term group. Nine patients (45%) relapsed during the 24 months of follow-up in the short-term group. Surprisingly, no follow-up information is available after 24 months. Thus, it remains unknown if the relapse rate is really lower after more prolonged therapy.

Recently, the randomized controlled clinical trial of Ramachandran et al. [57] provided important information, with the first direct comparison between CNIs and cyclophosphamide. In this study, 35 patients treated with tacrolimus (target through level 5–10 ng/mL in the first 6 months and 4–8 ng/mL in the next 6 months) combined with steroids (for 12 months) were compared with 35 patients treated with cyclical cyclophosphamide and steroids according to the modified Ponticelli regimen. Patients with MN, 18–60-year old and persistent nephrotic syndrome after at least 6 months of anti-proteinuric therapy or complications of nephrotic syndrome were included. This study confirmed that tacrolimus was equally effective as cyclophosphamide in inducing a remission (71% vs. 77%, respectively). However, after treatment withdrawal, relapse rate was higher in the tacrolimus group. The rate of sustained remissions in the tacrolimus and cyclophosphamide group after 18 and 24 months were 63 vs. 86% and 64 vs. 88%, respectively [64].

In a relatively large observational cohort study from Spain, 122 nephrotic MN patients with stable renal function were treated with tacrolimus [63]. Duration of treatment was 17 ± 7 months, including a full-dose (mean blood trough level 6.8 ± 1.8 mg/mL) and a tapering period. Only 10 patients (8%) received concomitant treatment with corticosteroids. Forty-three (35%) patients had been treated with other immunosuppressive drugs before; however, the number of patients treated previously with cyclophosphamide/prednisone is unknown. Median follow-up was 30 months (14–66). This study again confirmed the efficacy of
CNIs in inducing remission; after 6, 12, and 18 months of treatment remission rates were 60, 78, and 84% respectively. However, of 79 patients who obtained a remission, 35 patients (44%) developed a relapse after a median follow-up of 40 months (3–87). The presence of a partial remission versus a complete remission at the onset of tacrolimus tapering and a shorter duration of the tapering period were associated with a higher relapse rate. Relapsing patients had an unfavorable outcome. At the end of follow-up, 6 of the relapsing patients (17%) had doubled their baseline serum creatinine and 2 (6%) had reached ESRD. This study confirms that relapses are not innocuous. In a previous study, multiple relapses were associated with doubling of serum creatinine levels and development of ESRD [62].

In view of the high relapse rate after withdrawal of CNIs and the association of multiple relapses with bad renal outcome, we need more evidence to support the efficacy of CNIs in preventing ESRD. The recent study of Howman et al. is not reassuring [42]. In this study, 29 (81%) of 36 patients that were treated with CsA developed a further 20% decline in eGFR (in comparison with 84% in the ‘supportive therapy only group’), which was used as end point and considered as failure of therapy [42]. The proportion of patients with serious side effects was even higher with CsA (32%) than with placebo (21%). There are some important concerns about this surrogate renal end point. The starting dose of CsA (5 mg/kg, goal through level 100–200 µg/mL) might have been too high in patients with renal insufficiency at baseline, with increase of serum creatinine reflecting CNI toxicity rather than disease progression. Many factors might contribute to a reduction in eGFR of ‘only’ 20%; such as lowering of blood pressure and the use of diuretics. The surrogate renal end point may thus have caused overestimation of the rate of progression. With a limited duration of follow-up, unfortunately no data about long-term renal outcomes are available. Still, this study questions the use of CsA in patients with MN and renal insufficiency.

An interesting treatment strategy to overcome dependence of CNI (and thus prevent relapses after drug withdrawal) was proposed by Segarra et al. [65] In a study of 13 patients with at least four previous CNI-responsive relapses of nephrotic proteinuria, rituximab treatment (4 weekly doses of 375 mg/m²) enabled CNIs to be successfully withdrawn in all patients. After CNI withdrawal, only three patients suffered from a relapse (19, 23, and 28 months after rituximab treatment), all of them were successfully treated with a second course of rituximab.

The results of this observational study, together with a good tolerance profile, were the reason for the initiation of the STARMEN trial, which is currently including patients [66]. The STARMEN trial, ‘Sequential therapy with Tacrolimus and Rituximab in primary Membranous Nephropathy’ (NCT01955187 Clinicaltrials.gov) will prospectively compare the modified Ponticelli regimen (alternating corticosteroids and cyclophosphamide for 6 months) versus tacrolimus for 9 months (6 months of full therapy and 3 months of tapering doses) and a single dose of rituximab (1 g before the onset of tacrolimus tapering) and can provide important information about the efficacy of rituximab to prevent relapses. Rationale for this strategy is that by inducing remission by using a CNI first, the efficacy of rituximab will be better, by preventing urinary loss of this monoclonal antibody. The primary outcome is the amount of remissions (complete and partial remission) at 24 months after start of study treatment. The expected final data collection for the primary outcome measure is planned in December 2018.

2.5. Rituximab

The presence of antibodies in MN provides a clear rationale for the use of anti-B cell therapy. The availability of rituximab, a monoclonal antibody against the cell surface antigen CD20 of B cells allowed the exploration of whether specific B cell inhibition would improve the outcome of patients with MN and avoid the side effects of steroids and other immunosuppressants. The KDIGO guidelines do not discuss rituximab as a treatment option for patients with MN, but point to the need for more clinical trials with this drug [10].

Several uncontrolled trials have reported the efficacy of rituximab in MN (Table 4). Different dosing schedules have been used, varying from one single dose of 1 gram or two biweekly doses of 1 g/day, to 4 weekly or monthly doses of 375 mg/m² and B cell-driven protocols. Although rituximab was effective in inducing remissions, with reported remission rates of 70%, the initial small-sized studies lacked information on long-term relapse rate and hard renal end points. Some doubt the efficacy of rituximab, since the initial studies suggested that rituximab might not be effective in high-risk patients, as best outcome was observed in female patients with normal renal function and moderate proteinuria, thus patients who regularly develop spontaneous remission [68,72]. On the other hand, rituximab was used with apparent success, in patients who failed treatment with other immunosuppressive drugs [34,35,73].

In a study from Germany, 14 patients, all of them had failed previous immunosuppressive therapy (including alkylating agents in 50%), were treated with 4 monthly doses of rituximab [69]. Twelve months after the last infusion of rituximab complete remission was achieved in 3 patients (21.4%) and partial remission was achieved in 7 patients (50%). Information about relapses is limited, however, with one relapse occurring within the first year after discontinuation of rituximab and one after 3.5 years; however, after 4-year follow-up information of only 4 patients is available. Although there was no significant change in creatinine clearance during follow-up, information on hard renal end points is lacking.

The Italian group of Remuzzi and colleagues has the largest experience with rituximab in patients with MN [35,68,72,73]. Ruggenenti et al. recently updated their findings and described 132 patients with MN and nephrotic proteinuria who were treated with rituximab [70]. Of these, 49 (37%) had failed previous immunosuppressive therapy. A B cell-driven protocol was used in the majority of patients (n = 102
Table 4. Rituximab in primary membranous nephropathy: clinical trials.

| Treatment                      | Follow-up (months) | Remission rate (%) | Relapse rate (%) | Renal function end point |
|--------------------------------|--------------------|--------------------|------------------|--------------------------|
| Cravedi [67]                  | RTX 1 × 375 mg/m²   | 12                 | 67               | NA                       | NA                       |
| Cravedi [67]                  | RTX 4 × 375 mg/m²   | 12                 | 67               | NA                       | NA                       |
| Fervenza [34]                 | RTX 2 × 1 g        | 12                 | 53               | NA                       | ESRD 13%                 |
| Ruggenenti [68]               | RTX 4 × 375 mg/m²   | 3                  | 0                | NA                       | NA                       |
| Ruggenenti [68]               | RTX 4 × 375 mg/m²   | 12                 | 75               | NA                       | NA                       |
| Ruggenenti [68]               | RTX 4 × 375 mg/m²   | 12                 | 67               | NA                       | NA                       |
| Fervenza [36]                 | RTX 4 × 375 mg/m², repeated after 6 mo. | 24                  | 94               | 6                        | NA                       |
| Segarra [65]                  | RTX 4 × 375 mg/m²  | 30                 | 100              | 23                       | NA                       |
| Ruggenenti [35]               | RTX 4 × 375 mg/m² or B-cell driven | 29                  | 65               | 28                       | ESRD 4%                  |
| Busch [69]                    | RTX 4 × 375 mg      | 36 (12–72)         | 71               | 71                       | NA                       |
| Ruggenenti [70]               | RTX 4 × 375 mg/m² or B-cell driven | 31                  | 64               | 30                       | NA                       |
| Dahan [71]                    | RTX 2 × 375 mg/m², repeated after 6 mo. | 17 (13–24)         | 65               | NA                       | NA                       |
| Supportive                    |                    | 17 (13–23)         | 34               | NA                       | NA                       |

ESRD: end-stage renal disease.

*Definitions of remission as used by the authors.

Relapse rate: percentage of relapses in patients with previous remission after withdrawal of medication.

n = 18 in final analysis.

(77%) (where a second infusion of rituximab was only given when more than five circulating B cells per cubic millimeter were detected 1 week after completion of the first rituximab administration (375 mg/m²)). Median duration of follow-up was 30.8 (6.0–145.4) months. This study confirmed the efficacy of treatment with rituximab, with 84 patients (64%) achieving a remission (complete remission in 43 patients (33%)). Only minor side effects were noted. Although this study suggests that rituximab might be an attractive alternative therapy in patients with MN, longer follow-up and confirmation of the data is needed. In fact, if we consider the nonresponder rate of 36% and the relapse rate of 30% (25 of 84 patients), and assume that nonresponders and part of the relapsing patients will develop renal insufficiency, than overall long-term outcome with rituximab may be less impressive. Of course, these conclusions might be biased, since the study included patients that previously had failed treatment. Therefore, there remains an urgent need for controlled trials with rituximab in new incident patients.

In the ‘GEMRITUX study,’ patients with persisting nephrotic syndrome after 6 months of conservative therapy were randomized between either treatment with rituximab 375 mg/m² at day 1 and 8, or ongoing conservative therapy for 6 months [71]. No difference in the amount of remissions after 6 months (the primary end point) was observed between the two groups (13 of 37 patients (35%) vs. 8 of 38 patients (21%) in
the arm with and without rituximab, respectively). Depletion of aPLA2R occurred much faster in the rituximab group in comparison to the conservative therapy group (14 of 25 patients (56%) vs. 1/23 patients (4%) at months 3 ($p < 0.001$) and 13 of 26 patients (50%) and 3/25 patients (12%) at month 6, respectively). In this trial, serum albumin and aPLA2R were identified as early markers of the efficacy of rituximab, and remission of proteinuria occurred only after 6 months. The amount of remissions in the observational phase, before change of assigned treatment was significantly higher in the rituximab group (24 of 37 (65%) vs. 13 of 38 (34%), respectively ($p < 0.01$). The safety profile of rituximab was reassuring, with the number of serious adverse events being comparable between groups. Follow-up needs to be extended to allow conclusions regarding relapse rate and hard renal end points. A drawback of the ‘GEMRITUX study’ is the lack of a control group treated with standard immunosuppressive therapy.

An RCT in which rituximab is compared with an active comparator group is ongoing. In this study, the ‘Mentor trial,’ ‘MEMbranous Nephropathy Trial Of Rituximab’ (NCT01180036 Clinicaltrials.gov), initiated by the Mayo Clinic and the Toronto group, the primary goal is to determine whether or not rituximab is more effective than CsA in inducing long-term remission of proteinuria. The estimated date of study completion is October 2017. Unfortunately, it is questionable if this study will provide sufficient data on hard renal end points.

With the upcoming RCTs, we might be able to properly value rituximab in the treatment of MN within the next years.

### 2.6. Adrenocorticotropic hormone (ACTH)

The KDIGO guideline states that more powerful randomized trials are needed to allow recommendations regarding the use of ACTH therapy in patients with MN [10]. There has been considerable interest in ACTH for treatment of MN. Historically, ACTH was the only drug next to corticosteroids that was approved by the FDA to treat nephrotic syndrome. In Europe, synthetic ACTH is used, whereas in the USA another formula of ACTH, HP Acthar® gel is used. ACTH gel is obtained from processing porcine pituitary glands and consists of full length ACTH, probably in combination with some unspecified fragments. Synthetic ACTH is a long chain polypeptide composed of the first 24 of 39 amino acids contained in the naturally occurring ACTH (corticotrophin) molecule. It is unknown how ACTH might induce a clinical remission in ACTH; one of the proposed mechanisms of ACTH is activation of the melanocortin receptor (MCR1) on the podocytes [74].

In 1999, Berg et al. described beneficial effects of synthetic ACTH in 14 patients with nephrotic syndrome due to MN [75]. Synthetic ACTH was administered to lower lipids in these patients and this led to the expected changes in serum lipid profile, but in addition there was an unexpected 90% decrease of urinary albumin excretion. The proteinuria-lowering effects of synthetic ACTH were confirmed in further studies of the same group, with prolonged remissions after a 2–11-month course of synthetic ACTH treatment (maximal dose of 1 mg twice a week) in 9 of the 10 patients with MN [37]. In a subsequent RCT, 32 nephrotic patients with MN were treated with either synthetic ACTH for 12 months or with the standard 6 months cyclical regimen with an alkylating agent (chlorambucil or cyclophosphamide) and steroids [76]. Remission rates were similar in both groups (87 and 75% for ACTH and alkylating agents, respectively) (Table 5), and ACTH was associated with very few side effects. Unfortunately, no long-term follow-up data were provided.

Bomback et al. used HP Acthar® gel to treat patients with MN. In a retrospective case, series of 11 patients who previously failed a mean of 2.4 immunosuppressive therapies, 9 patients (81%) achieved a remission, with a complete remission in three of them [77]. In a more recent prospective study, two out of five patients with treatment resistant MN achieved a remission of proteinuria after treatment with HP Acthar® gel [78]. Hladunewich et al. treated twenty patients with MN with 40 or 80 IU HP Acthar® gel twice weekly during 12 weeks [39]. Five patients, all treated with 40 IU Acthar gel daily, were treated for another 12 weeks with a dose of 80 IU daily. After treatment, there was a significant reduction of proteinuria, from 9.1 ± 3.4 g/day at baseline to 6.2 ± 4.8 g/day at completion of ACTH, and to 3.9 ± 4.2 g/day by 12 months of follow-up. At 12 months, complete remission was achieved in only 2 patients (10%) and partial remission in 10 patients (50%). Of note, seven patients had previous exposure to immunosuppressive agents. As patients had to be off prednisone therapy, CNIs or MMF for only 1 month and alkylating agents for only 6 months; a delayed effect of the previous immunosuppressive therapy is not excluded. Clearing of anti-PLA2R antibodies was noted in some, but not all patients, suggesting a possible direct effect on the podocyte. In all of the above-mentioned studies, side effects were relatively mild.

With the exception of the study of Ponticelli et al. [76], all the above-mentioned trials were uncontrolled. Besides, in none of these studies, data about long-term outcome were available. Moreover, the patients in the Ponticelli trial were not selected for their high-risk profile [76]. In fact, many patients might have developed spontaneous remission.

We conducted a prospective cohort study in patients with MN and high risk of progression [38]. This is the first study with a long duration of follow-up. We prospectively selected 20 nephrotic patients with MN and high risk for progression. Patients were treated with synthetic ACTH during 9 months (maximal dose 1 mg twice a week). Cumulative remission rate was 55% (complete remission in 4 patients, partial remission in 7 patients), in comparison with 95% in a historical matched control group treated with cyclophosphamide and prednisone. Moreover, ACTH was associated with a shorter relapse-free survival. In our study, the use of synthetic ACTH was also associated with many adverse events. Thus, in our opinion, there is limited benefit from synthetic ACTH in high-risk MN patients.

ACTH is compared with conservative treatment in the now ongoing ‘CHART’ study, ‘Acthar for treatment of proteinuria in membranous nephropathy patients’ (NCT01386554). In this randomized double-blind study, treatment with HP Acthar® gel 80 U twice a week for 6 months is compared to a placebo that contains the same inactive ingredients as that used for HP Acthar® gel. No active comparator group is included. The duration of follow-up in this study is too short; only a 24-week observation period after completion of study medication is included. In December 2016, final data collection is planned.
Table 5. ACTH in primary membranous nephropathy: clinical trials.

| Treatment                                      | Type of study | Patients | Sex | Duration MN (months) | sCreat (umol/l) | Proteinuria (g/day) |
|------------------------------------------------|---------------|----------|-----|----------------------|-----------------|---------------------|
| Ponticelli [76]                                 | RCT           | 16       | m/f | 12/4                 | NA              | 88 ± 32             |
| CP/steroids (6 mo)                              |               |          |     |                      |                 | 6.7 ± 2.8           |
| Hladunewich [39]                                | Cohort        | 16       | m/f | 7/9                  | NA              | 80 ± 15             |
| HP Acthar®gel (40 or 80 IU twice weekly 3–6 mo) |               |          |     |                      |                 | 5.5 ± 2.0           |
| van de Logt [38]                                | Cohort        | 20       | m/f | 13/7                 | 14 (8.5–47)     | 77 ± 30*            |
| Synthetics ACTH (max 1 mg twice weekly for 9 mo) |               |          |     |                      |                 | 9.1 ± 3.4           |
| CP/steroids (12 mo)                             | Historical controls | 20 | m/f | 16/4                 | 8 (6–13)        | 97 (85–119)         |
|                                                |               |          |     |                      |                 | 9.4 (6.7–12.2)*    |

n: number; m/f: male/female; MN: primary membranous nephropathy; sCreat: serum creatinine; mo: months; NA: data not available. Data are presented as number, mean ± SD or median (range).

*eGFR was estimated using 4 variable Modification of Diet in Renal Disease (MDRD).

**Protein-creatinine ratio (g/10 mmol creatinine).

2.7. Plasmapheresis

The presence of antibodies and their role in the pathogenesis of MN has initiated studies with plasmapheresis therapy. In antibody-mediated diseases such as anti-glomerular basement membrane (GBM) disease, anti-neutrophil cytoplasmic antibodies-associated vasculitis, and humoral rejection, the combined use of plasmapheresis (to remove antibodies) and immunosuppressive drugs (to reduce antibody production) is effective and standard of care. Indeed, a similar regimen has recently been evaluated in patients with severe, treatment-resistant MN. Promising results were described in 10 patients with MN, therapy resistant to all conventional regimens and a urinary protein to creatinine ratio of more than 10 g/g creatinine (11.3 gram/10 mmol creatinine) [79]. This rescue regimen consisted of four plasma exchange (PE) treatments against human albumin, 20 g of intravenous immunoglobulins (IVIGs) and 375 mg/m² of rituximab after the last PE. Partial remission was achieved in 90% of patients, with a mean time to partial remission of 2.1 (0.6–8.0) months. Interestingly, two patients who were aPLA2R negative responded to a therapy with PE, IVIG, and rituximab. The researchers found that although aPLA2R decreased shortly after PE, levels increased to baseline in 24-hour time. These two findings suggest that the beneficial effect of PE is independent or at least not associated with changes in serum aPLA2R. As no follow-up information is provided, information about relapses or long-term renal outcome is lacking.

3. New opportunities for individualized treatment

The variable clinical course and the differences between treatment modalities suggest that patients would benefit from a more individualized therapy approach. The first, critical step would be to be able to predict spontaneous remission with high accuracy. Unfortunately, with the previously suggested predictive markers, the Toronto risk score [80], urinary protein markers [81,82], and the initial change of proteinuria [83], the accuracy is at best 80% [82].

With the identification of PLA2R as a major antigen and the discovery of aPLA2R, in the majority of patients new opportunities arise. It has been shown that levels of circulating aPLA2R correlate with clinical disease activity [4] and their disappearance precedes a subsequent decline in proteinuria [84]. The levels of aPLA2R were associated with the likelihood of spontaneous remission; patients in the highest tertile were less likely to develop a spontaneous remission of proteinuria [85]. We also showed that the level of aPLA2R after 6–12 months of immunosuppressive therapy predicted long-term outcome [49]. In this latter study, we were able to evaluate the course of aPLA2R in several patients and we noted clear differences between patients in the time to disappearance of antibodies. In a majority of patients treated with cyclophosphamide, aPLA2R had disappeared after 2 months; however, some patients were still aPLA2R positive after 12 months of treatment.

The recent study by Ruggenenti et al. further supports that aPLA2R levels might allow more personalized therapy in patients with MN [70]. In this study, the relation between the course of aPLA2R and clinical response during treatment with rituximab was assessed. Most notable was the observation that the efficacy of rituximab was predicted by the level of aPLA2R. Remission rate was high in patients with low antibody levels, and relatively low in patients with high antibody levels. Disappearance of antibodies was associated with outcome; 6 months after rituximab administration, aPLA2R were depleted from the circulation in 46 out of 64 patients (71.9%). In this group, 41 patients (89.1%) subsequently achieved complete or
partial remission, compared with 2 out of 18 patients (11.1%) without antibody depletion. In all of the patients achieving complete remission (n = 25), aPLA2R antibodies disappeared compared with 16 out of the 21 patients achieving partial remission (76.2%). Patients with a complete remission had a significantly reduced risk of relapse. Altogether, these findings suggest that serial evaluation of circulating aPLA2R might help to predict the response to therapy and the risk of a relapse.

Since 2014, we have adapted our treatment protocol and we have individualized treatment in patients with PLA2R related MN [86]. According to our antibody-guided treatment protocol, patients are treated with cyclophosphamide 1.5 mg/kg/day and steroids. After 8, 16, and 24 weeks of treatment, aPLA2R are measured with a commercial immuno-fluorescence test. If antibodies are negative, the cyclophosphamide is stopped and the steroids are tapered. If the aPLA2R antibodies are still positive after 24 weeks of treatment, further treatment with MMF and low-dose steroids is recommended. Thus, far 30 patients are included and monitoring of aPLA2R resulted in shorter duration of therapy in approximately 80% of patients. Clinical remission rate is about 80% with stable kidney function in all patients. Relapse rate is 17% after a median follow-up duration of 11 months. Reemergence of aPLA2R into the circulation after initial depletion predicted disease relapse. Longer follow-up is needed to monitor long-term sustained remission rate and renal outcome. As in some patients, relapses do occur already very soon after discontinuation of cyclophosphamide additional markers are needed to optimize therapy. More studies into immune regulation of aPLA2R are needed and might help improving tailor-made therapy.

As approximately, 30% of patients with MN are anti-PLA2R negative, the search for additional biomarkers continues. A new antigen, THSD7A, was recently identified. Still, this antigen seems to be involved in only a minority of patients (approximately 3% of all MN patients).

4. Expert commentary

In our opinion, treatment in patients with MN should be individualized, carefully weighing the short- and long-term benefits versus the adverse events. The personal situation of the patient should be taken into account.

Treatment with alkylating agents is of proven benefit; in fact, it is the only therapy that has been critically evaluated in RCTs with hard renal end points. Unfortunately, treatment with cyclophosphamide and corticosteroids is associated with many side effects, both in the short term as in the long term. Therefore, this therapy should be restricted to patients with evidence of renal function deterioration. These patients will otherwise progress to ESRD, and are less likely to respond to other immunosuppressive agents. We hope that our currently implemented antibody-guided strategy will allow us to treat the majority of patients with a short 8-week course of cyclophosphamide and steroids, thus reducing the side effects. Obviously, we are reluctant to propose treatment with cyclophosphamide and steroids in patients who are planning to have a family, patients with badly controlled diabetes, patients with infections, and the very elderly.

In patients with preserved renal function, treatment with tacrolimus is a good option. The likelihood of developing a remission is high, and as long as the renal function is stable and remission persists, the risk of renal function deterioration is negligible. Patients should be informed that 12 months of therapy is not enough, and longer treatment duration with slow tapering is necessary to avoid relapses. Still, relapse rate is an issue, and although the patients may respond to a second course of tacrolimus, we often would consider treatment with cyclophosphamide to induce a permanent remission.

In patients who have had multiple relapses, after treatment with cyclophosphamide and CNI, we often propose a trial with MMF. Although guidelines advise against it use, we feel that the literature data should be interpreted differently. Monotherapy with MMF in a dose of 2000 mg/day is not effective. However, MMF in combination with steroids is effective in reducing remissions. Admittedly relapse rate is high, but this might be related to the fact that current dosing regimens are insufficient in reducing antibody levels. Although no formal evidence is available yet, we use MMF targeting a high AUC and continue treatment until antibodies have disappeared.

We advise against the use of synthetic ACTH, this therapy is not without side effects, and efficacy is limited if at all. For ACTHAR gel, no RCTs with an active comparator are available.

Rituximab is offered to patients with persisting antibodies after previous immunosuppressive therapy with alkylating agents, MMF, or tacrolimus. Currently, the combination of induction treatment with tacrolimus (6 months with tapering thereafter) followed by a single dose of rituximab is used as part of the STARMEN study protocol.

We are reluctant to use rituximab as initial therapy, especially in high-risk patients. In these patients, efficacy of rituximab has not been proven. In fact, there are data to suggest that its efficacy is limited in patients with tubulointerstitial fibrosis [68], for instance patients with established renal insufficiency. We would consider rituximab monotherapy in patients with maintained renal function and severe nephrotic syndrome. In these patients, rituximab may effectively induce a remission and shorten the duration of the nephrotic syndrome, which may otherwise have occurred spontaneously. The benefits of developing a remission early could be advantageous, even in patients who eventually would have developed a spontaneous remission. An example is the young female who is planning to have a family.

We are eagerly awaiting the results of ongoing studies with rituximab. The most relevant question is if earlier treatment with rituximab (thus exposing patients unnecessary to treatment) might be more beneficial than late start of cyclophosphamide. The limited number of side effects with rituximab and the rapid regression of nephrotic syndrome might outweigh its unnecessary use in some patients. We envisage that a positive answer to this question will change our treatment strategy.

In most studies, the term ‘treatment resistance’ is used to describe patients that do not fully respond to
immunosuppressive therapy. Often this includes patients who relapse. A failure of a certain treatment to induce remission does not mean that a remission will not occur with another drug of a different pharmacological class.

5. Five-year view

The identification of PLA2R antibodies in the majority of patients with MN has increased our understanding of the pathogenesis of the disease. Assays are available that allow easy and reliable detection of the antibodies.

Because of the high specificity of aPLA2R for the diagnosis of MN [87], it is likely that in five years a kidney biopsy will no longer be required to diagnose MN in patients with detectable anti-PLA2R antibodies.

Although treatment with alkylating agents is effective, their use is associated with many short- and long-term side effects. Thus, it will be important to limit the use of cyclophosphamide. One important step is the development of more accurate predictors of outcome, in order to restrict treatment with cyclophosphamide to patients who will progress. Antibody titers, measured at disease onset, may prove helpful in this respect. Measurement of antibody titers during treatment may also be helpful. We hope that our currently implemented antibody-guided treatment strategy will allow us to treat the majority of patients with a short 8-week course of cyclophosphamide and steroids, thus reducing the side effects.

Even more important will be the use of other, less toxic immunosuppressive agents in patients with MN. In five years, there will be more data on the efficacy of CNIs and rituximab on hard renal end points. Although these agents are effective in inducing remission, the relapse rate is high. It might be that these agents are best suited in patients with recent onset of disease (and low antibody titers). And in five years, we will know if earlier start of treatment with rituximab (thus exposing patients unnecessary to treatment) is more beneficial than late start of cyclophosphamide. The limited number of side effects with rituximab and the rapid regression of nephrotic syndrome might outweigh its unnecessary use in some patients. Alternatively, we might have better strategies to preventing relapses of the disease, and more detailed immunological monitoring, with the evaluation of B and T cell phenotypes, might prove valuable.

Recently, progress has been made with the identification of the epitopes that are recognized by aPLA2R in MN. The most important epitope was recognized [88,89]. Moreover, Seitz-Polski et al. showed that epitope spreading occurred in patients with persistent or progressive disease [90]. Recognition of epitope spreading might influence the timing of initiation of immunosuppression. Hopefully, the identification of the relevant epitopes will also lead to the development and subsequent therapeutic use of ligands that interfere with antibody binding.

As 30% of patients with MN are anti-PLA2R negative, the search for additional antigens will continue. The recent discovery of THSD7A as antigen is an example of this progress.

In five years, several new antigens will have been discovered.

6. Conclusion

It is evident that immunosuppressive therapy is effective in patients with MN. With the current available therapies, less than 10% of patients progress to ESRD. The decision whether and when to start a ‘specific’ therapeutic regimen in a patient with MN needs to take in account the likelihood of a spontaneous remission as well as the potential adverse consequences of a prolonged exposure to a nephrotic state. Various treatment options are available and can be used adapted to the clinical characteristics of the patient.

Key issues

- Primary membranous nephropathy (MN) is an autoimmune disease with anti-PLA2R antibodies identified in 70% of patients.
- Up to 50% of patients with MN will develop a spontaneous remission of proteinuria.
- Whether and when to start immunosuppressive therapy is still heavily debated and no ideal biomarker is currently available.
- Treatment with alkylating agents is of proven benefit, and this is the only therapy tested in studies with hard renal outcomes.
- Treatment with cyclophosphamide is associated with many side effects, hopefully an antibody guided strategy will allow to use a short course of 8 weeks of cyclophosphamide in the majority of patients.
- Calcineurin inhibitors are effective in inducing a remission, however relapse rate is high and longer treatment duration with slower tapering is necessary to avoid relapses.
- In patients with multiple relapses, after treatment with cyclophosphamide and calcineurin inhibitors, mycophenolic acid targeting a high AUC (>50 µg*h/ml) is a treatment option.
- There is no place for treatment with synthetic ACTH.
- Rituximab monotherapy is a good treatment option in patients with maintained renal function and severe nephrotic syndrome.
- The most relevant question is if earlier treatment with rituximab (thus exposing patients unnecessary to treatment) might be more beneficial than late start of cyclophosphamide.

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