Membranous Nephropathy: Approaches to Treatment

Andrew S. Bomback^a Fernando C. Fervenza^b

^aDepartment of Medicine, Division of Nephrology, Columbia University, New York, NY, USA;

^bDivision of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA

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Abstract

Background: Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults. This review focuses on mechanisms involved in the pathogenesis of MN and approaches to treatment of this disease. **Summary:** Our understanding of the pathogenesis of primary MN has advanced greatly with the identification of M-type phospholipase A₂ receptor and thrombospondin type-1 domain-containing 7A as target antigens whose antibodies serve as biomarkers of this disease. Additional research, including investigations into the roles of complement and melanocortin receptors on the podocyte, may further improve our understanding of how best to treat this condition. Immunosuppressive therapies, including corticosteroids alternating with alkylating agents, and calcineurin inhibitors are partially successful in reducing proteinuria in MN, but their use may be associated with significant adverse effects and a high relapse rate. Novel interventions, including targeting B cells with rituximab

as well as treatment with adrenocorticotrophic hormone (ACTH), are being investigated. **Key Messages:** The understanding of treatment targets and availability of new biomarkers has facilitated diagnosis and improved risk stratification for MN and may also be useful for individualizing treatment with a wider range of therapeutic options for patients with MN. Considerable evidence supports the use of B-cell depletion as initial therapy in nephrotic patients with MN. ACTH should be considered for patients who do not respond to traditional therapies such as alkylating agents and calcineurin inhibitors.

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Introduction

Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in white adults [1]. It is typically characterized by very high levels of protein in urine, edema, hypoalbuminemia, and elevated serum lipids [2]. Renal pathology in patients with MN includes thickening of the glomerular basement membrane on light microscopy, granular deposits of immunoglobulins (Ig, usually IgG4) and complement (C3) along the capillary walls on

immunofluorescence, and subepithelial deposits on electron microscopy examination [1]. MN is a chronic disease, and its course includes spontaneous remissions (occurring in about 30% of patients, usually within the first 2 years after diagnosis in those with milder presentations) and frequent relapses. Nephrotic patients who do not go into remission are likely to progress to end-stage renal disease [1].

A systematic review of the literature from 1980 to 2010 indicated an overall global incidence of MN of 1.2 per 100,000 per year, with a trend toward more men than women being affected [3]. MN is associated with significant morbidity and mortality. Evaluating the outcomes for 348 patients with MN who had complete, partial, or no remission (either spontaneous or with treatment) over 15 years of follow-up, Troyanov et al. [4] reported renal survival of 30% for those with no remission versus 100 and >70% for those with complete or partial remissions, respectively.

This review discusses underlying causes of primary MN and focuses on approaches to treatment. It is one of a series of articles summarizing presentations and discussions from a roundtable discussion focused on proteinuria in nephrotic syndrome [5].

Primary and Secondary MN

Thanks to recent advances, we now know that approximately 75% of the patients with MN have antibodies to the M-type phospholipase A2 receptor (PLA₂R) present in podocytes [6–8]. An additional 5% of patients who are negative for anti-PLA₂R antibodies may have antibodies against another podocyte antigen – the thrombospondin type-1 domain-containing 7A [9]. Taken together, approximately 80% of patients with MN have antibodies directed against a specific, identifiable podocyte antigen and, as such, should be designated as having primary MN. Approximately 20–25% of MN cases are secondary to autoimmune disease, malignancy, infection, drugs (e.g., gold, penicillamine, non-steroidal anti-inflammatory drugs), or other non-identified autoantibodies [10, 11].

A genome-wide association study of single-nucleotide polymorphisms in patients with idiopathic MN from 3 different white populations (75 French, 146 Dutch, and 335 British patients) identified significant alleles at 2 genomic loci associated with idiopathic MN: chromosome 2q24 containing the gene encoding PLA₂R and chromosome 6p21 containing the gene encoding HLA-DQA1. The OR for idiopathic MN with homozygosity for both

risk alleles was 78.5 [12]. Genotype-phenotype correlations have shown that those who carry a high-risk haplotype in the HLA-DQA1 and PLA₂R1 genes have a much higher prevalence of circulating anti-PLA₂R [13]. Patients who carry 1 or 2 alleles for HLA-DQA1*05:01 or for DQB1*02:01 showed higher anti-PLA₂R titers than those with neither of these HLA alleles [14]. It is important to recognize that the “risk” alleles at the PLA₂R1 locus are actually the major alleles, indicating that a large proportion of the population might be at risk for the disease. It has been proposed that the rare confluence of several relatively common factors (e.g., a particular isoform of HLA-DQA1 conferring susceptibility to autoimmunity, polymorphisms in PLA₂R1 that alter expression and/or create a unique conformation identified by HLA class II on antigen-presenting cells, environmental factors, and perhaps age-related changes in Ig glycosylation) is necessary for activation of the lectin pathway of complement and development of MN [15].

Anti-PLA₂R Antibodies as a Marker for Prognosis and Response to Therapy

There is considerable evidence showing that anti-PLA₂R antibodies correlate with disease activity, provide prognostic information about severity of disease, and can serve as a useful biomarker for assessing treatment efficacy [16].

The occurrence of spontaneous remission is more common in patients with low antibody titers compared with those with high antibody titers [17]. High antibody titers are associated with lower response to immunosuppressive therapy and longer time to remission [18]. Relapse rate is also correlated with the level of antibodies at the time of clinical remission, with patients who become anti-PLA₂R negative having lower relapse rates than patients who remain anti-PLA₂R positive at the end of immunosuppression. Anti-PLA₂R levels may also predict progression from subnephrotic proteinuria to full nephrotic syndrome [19]. Furthermore, high antibody levels are associated with high risk of progressive kidney failure [14, 20].

In general, there is strong correlation between staining renal biopsies for PLA₂R and circulating anti-PLA₂R antibodies [21–23]. This is particularly true when the antibody levels are measured in close proximity to the time of biopsy [24]. However, glomerular staining for PLA₂R is more sensitive than circulating anti-PLA₂R antibodies in diagnosing PLA₂R-associated MN [21].

Treatment of MN

There remains an unmet need for effective therapy with a favorable risk-benefit profile that can support earlier initiation of therapy for patients with MN. There is also a need for a more personalized approach to management of these patients. Patients with MN who go into complete remission of proteinuria have excellent long-term renal survival. Even a partial remission is associated with favorable long-term outcomes [4]. As such, treatment goals for patients with MN should be aimed at achieving remission of proteinuria, since this will prevent decline of renal function [25].

Initial Conservative Treatment

Patients diagnosed with MN should receive conservative treatment directed toward decreasing blood pressure, reducing edema, and limiting the risks for cardiovascular events and thromboembolism. The management of fluid retention and edema formation that typically accompanies patients with nephrotic syndrome has evolved with novel insights into the pathologic mechanisms of edema formation. Under conditions of increased glomerular permeability, serum plasminogen is abnormally filtered into the urine where it is converted to active plasmin by tubular urokinase-type plasminogen activators [26]. Active plasmin subsequently degrades inhibitory peptides to the γ subunit of the amiloride-sensitive Na^+ channel, leading to enhanced Na^+ reabsorption [27]. These observations suggest that combining the Na^+ channel blocker amiloride with loop and thiazide diuretics could be an effective means of controlling edema formation in proteinuric states including MN [27, 28].

Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are recommended for controlling blood pressure. These agents are preferred over other classes of antihypertensive medications because they are renoprotective and have been shown to reduce proteinuria [25, 29]. However, the decrease in proteinuria is unlikely to exceed 30% as compared with pretreatment values, a critical point, particularly in patients with proteinuria >10 g/24 h. These are the patients who are at high risk of disease progression but who are unlikely to benefit from angiotensin II blockade alone. Patients with hypercholesterolemia should also receive a statin. Prophylactic anticoagulant therapy might also be considered in patients with MN and nephrotic syndrome, particularly those with albumin <2.2 g/dL, since they are at high risk of arterial and venous thromboembolic events [25].

Traditionally, conservative treatment was recommended for at least 6 months, unless kidney function was worsening or potentially life-threatening nephrotic symptoms occurred [29].

If Initial Conservative Treatment is Not Completely Effective

Several approaches have been employed to manage patients with MN who are not fully responsive to conservative treatment.

Alkylating Agents (Cyclophosphamide or Chlorambucil) Plus Corticosteroids

Ponticelli et al. [30] demonstrated that a 6-month cyclical regimen of alternating alkylating agents (cyclophosphamide or chlorambucil) plus intravenous pulse and oral corticosteroids was effective for achieving remission in patients with MN and nephrotic syndrome [30–32]. However, cumulative risks associated with this approach include opportunistic infection, reactivation of viral hepatitis, alopecia, gonadal damage (aspermato-genesis, ovulation failure), hemorrhagic cystitis (cyclophosphamide only), neoplasia (myelodysplastic syndrome; acute myelogenous leukemia; transitional cell carcinoma of the bladder, ureter, or pelvis), and toxic hepatitis [29]. It should be considered, however, that monitoring of serious adverse events was included in the guidelines for good clinical practice as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) only in 1996. Thus, it is possible that there was under-reporting in early studies, which may have contributed to a general underestimation of the risks associated with this type of immunosuppression.

Indeed, a more recent study using steroids and cyclophosphamide for 6–12 months showed that severe adverse events were remarkably more frequent in patients who underwent this form of immunosuppression. In particular, 15% of the 91 patients given cyclophosphamide developed a malignancy compared with only 3% of the 130 who received conservative therapy. This difference was statistically significant and, during follow-up, 8 of the patients with a malignancy died, 5 as a result of the cancer. Moreover, patients receiving cyclophosphamide had higher rates of hospitalization, infection, bone marrow and liver toxicity, and cardiovascular and thrombotic events than the group treated conservatively [33]. Although in this study, the cumulative cyclophosphamide dose of 36–46 g over 12 months [33] exceeded the cumulative exposure associated with the traditional cyclical cyclophosphamide

regimen, the high risk for severe adverse events remained when analysis was restricted to patients receiving a cumulative dose of <20 g cyclophosphamide or when the observation period was restricted to the first 3 or 6 months of immunosuppressive therapy [34]. Furthermore, cyclophosphamide has been associated with an increased risk of malignancy even at cumulative doses of 12 g [35].

Based on a more favorable side-effect profile, it has been suggested that cyclophosphamide should be preferred over chlorambucil for treatment of patients with MN and that doses should be limited to minimize the occurrence of adverse drug reactions [25, 32]. To minimize the subsequent development of malignancy, the recommendation is to keep total cumulative cyclophosphamide dose to <20 g.

Calcineurin Inhibitor Monotherapy

Calcineurin inhibitors are often employed in patients with MN. These agents have significant antiproteinuric effects. While their mechanism(s) of action are not fully understood, recent studies have suggested that inhibition of calcineurin phosphatase activity stabilizes cell cytoskeletal structures and improves slit-pore function. Pre-clinical studies have shown that under conditions of increased intracellular calcium, calcineurin stimulates the degradation of synaptopodin, a cell cytoskeletal protein that is central to footplate formation [36]. Moreover, recent studies have indicated that calcineurin regulates expression and function of the slit pore, including nephrin and ZO-1, a slit-diaphragm marker [37]. This effect, however, appears to be of little clinical significance, otherwise clinical recurrence of MN post-transplant with massive proteinuria would not occur in patients on calcineurin inhibitors as maintenance therapy post kidney transplantation [38]. The same is true in another primary podocytopathy, namely focal segmental glomerulosclerosis (FSGS), where use of calcineurin inhibitors does not prevent clinical recurrence post transplantation [39].

Cattran et al. [40] initially showed that cyclosporine was effective in improving proteinuria and slowing the rate of kidney function decline in patients with progressive loss of kidney function. In a subsequent landmark study, these investigators showed that a 6-month course of cyclosporine (3–5 mg/kg per day, orally) plus low-dose prednisone induced complete or partial remission of proteinuria in ~70% of patients, a response similar to cyclical steroid/cytotoxic therapy [41]. However, short-term use of cyclosporine was associated with a close to 50% relapse rate at 2 years, which is basically double the rate seen with the use of cyclical steroid/cytotoxic therapy. A 12-month course of cyclosporine (2–4 mg/kg per day) followed by reduced maintenance

dose of low-dose steroids (1.5 mg/kg/day) was associated with a much lower relapse rate than in cyclosporine monotherapy [42]. However, cyclosporine levels were higher in the group receiving combined therapy, suggesting that it was the higher cyclosporine levels rather than concomitant steroid use that was associated with lower rate of relapses.

In fact, in a prospective, randomized placebo-controlled trial, Praga et al. [43] showed that tacrolimus monotherapy (0.05 mg/kg/day for 12 months with a subsequent 6-month taper period) was also effective in inducing remission of proteinuria in patients with MN. In this study, 76% of tacrolimus-treated patients achieved complete or partial remission by 18 months versus 30% of those who received the control treatment. However, after tacrolimus withdrawal, proteinuria relapse occurred in ~50% of patients [43]. Thus, calcineurin inhibitors are effective – and can be used as monotherapy (i.e., without steroids) – for induction of remission in patients with MN. However, because proteinuria relapse occurs frequently once treatment is discontinued, a significant number of patients will become calcineurin-dependent and will require long-term use of a calcineurin-inhibitor, which will significantly increase the risk of nephrotoxicity [25, 44].

More recently, the results of a UK randomized controlled trial suggest that therapy with cyclosporine has no long-term benefit compared with conservative therapy alone [45].

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) monotherapy is not recommended as first-line treatment for patients with MN [29]. MMF combined with high-dose corticosteroids appeared effective in the short-term as a treatment for patients with MN ($n = 64$) in a comparative study versus historic cyclophosphamide (1.5 mg/kg/day), each administered for 12 months along with intermittent methylprednisolone and alternate-day prednisone. At 12 months, remission of proteinuria occurred in 66% of patients who received MMF versus 72% for cyclophosphamide ($p = \text{NS}$). However, 12 MMF-treated patients (38%) experienced a relapse and 9 (31%) were retreated; the respective values for cyclophosphamide for a comparable follow-up period were 4 (13%) and 2 (6%; $p < 0.01$ and $p = 0.024$) [46]. Results from a subsequent randomized trial in 36 drug-naïve patients with MN indicated conservative therapy (renin-angiotensin system blockade, statins, low-salt and low-protein diet, and diuretics) plus MMF monotherapy was not significantly more effective than conservative therapy alone for decreasing proteinuria or increasing complete or partial remissions after 12 months [29, 47].

Fig. 1. Decline in proteinuria in patients treated with 4 doses of rituximab (375 mg/m²), with re-treatment at 6 months [53]. CR, complete remission; LR, limited response; NR, no response; PR, partial remission; REL, relapsed. Adapted with permission of the American Society of Nephrology, from Fervenza et al. [53]; permission conveyed through Copyright Clearance Center, Inc.

Addressing Unmet Needs in Patients with MN

There remains an unmet need for effective therapy with a favorable risk-benefit profile that can support earlier initiation of therapy for patients with MN. There is also a need for a more personalized approach to management of these patients.

Targeting B Cells in MN

Treatment with cyclophosphamide has been shown to decrease B-cell activity, including spontaneous secretion of Ig [48]. Animal studies have shown further that agents that interfere with B-cell activation provide protection against glomerulonephritis [49]. However, as discussed above, cyclophosphamide-based regimens are associated with significant toxicity and long-term risk for malignancy. Moreover, the toxicities are cumulative and, in diseases that tend to be relapsing, these side effects are much more likely to occur. Therefore, there has long been a desire to find a less toxic but equally effective treatment for these diseases. In the late 1990s, the availability of genetically engineered antibodies to the CD20 antigen found on B lymphocytes provided a novel and targeted therapy capable of causing a rapid and sustained depletion of peripheral and tissue B lymphocytes, and provided the basis for the use of these agents in the treatment of MN.

Rituximab for the Treatment of MN

Rituximab is a mouse/human IgG1k chimeric monoclonal antibody directed against CD20, a receptor on the surface of immature, mature, and activated B cells, but

not on stem cells or long-lived plasma cells. Rituximab depletes B cells by antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and apoptosis [50].

The first study of rituximab in MN evaluated the effects of an infusion (375 mg/m²) every 4 weeks in 8 patients who had treatment-refractory primary MN and nephrotic syndrome. Mean urinary protein decreased from 8.6 g/day at baseline to 3.7 g/day at 20 weeks' follow-up [51]. Two patients achieved full remission, and 3 achieved partial remission [51]. Reduction in proteinuria >50% was seen in all patients.

In a subsequent open-label study from the Mayo Clinic, 15 patients with primary MN were treated with 1 g rituximab at time 0 and again after 15 days, with re-treatment at 6 months. Proteinuria decreased by 50% and, at 1-year follow-up, 2 and 6 patients achieved complete and partial remission, respectively [52]. A subsequent study performed by the same group in 20 patients with MN and proteinuria (>5 g/day) treated with 4 doses of rituximab (375 mg/m²), with re-treatment at 6 months, showed that proteinuria declined from 11.9 g/day at baseline to 4.2 g/day at 12 months, and further to 2.0 g/day at 24 months. By the end of 24 months, complete or partial remission was achieved in 4 and 12 patients, respectively. The decline in proteinuria was gradual in both of these groups of patients (Fig. 1) [53]. Comparison of these results with those from the earlier study [52] showed that the 4 doses of rituximab resulted in more effective B-cell depletion, but not an increased benefit in decreasing proteinuria [53].

Beck et al. [7] measured anti-PLA₂R antibody levels in serial serum samples from the 35 patients treated with

Fig. 2. Anti-M-type phospholipase A₂ receptor (PLA₂R; **a**) declines in advance of a more gradual decline of proteinuria (**b**) in those patients who cleared anti-PLA₂R [7]. **a, b** Represent median (line), and 25th and 75th percentiles, with whiskers to the 10th and 90th

percentiles. Outliers are represented by filled circles. Republished with permission of the American Society of Nephrology, from Beck et al. [7]; permission conveyed through Copyright Clearance Center, Inc.

rituximab included in these 2 studies. Prior to treatment, samples from 71% of these patients contained anti-PLA₂R antibodies, and they were reduced or fell below the level of detection in 68% of these patients within 12 months of rituximab treatment. Clinical results indicated that 88% of patients with a drop in antibody levels had complete or partial remission by 24 months versus 33% for those with no significant immunologic response to rituximab treatment. It was noteworthy that the decline in anti-PLA₂R almost always preceded the decline in proteinuria by months (Fig. 2) [7]. Subsequent studies showed that antibody levels decrease independently of the type of immunosuppressive therapy [20].

More recently, results for 100 consecutive patients with primary MN and persistent nephrotic syndrome who received rituximab (initially, 4 weekly doses of 375 mg/m²; after 2005, patients received a second rituximab infusion only when >5 circulating B cells/mm³ were detected after completion of the first rituximab administration) also support the efficacy of this treatment. At a median follow-up of 29 months, 65 patients achieved complete or partial remission at a median time of 7.1 months. Lower 24-h urinary protein excretion and serum creatinine levels were significant predictors of remission. All 24 patients who were followed for >4 years achieved complete or partial remission [54]. As initially reported by Beck et al. [7], anti-PLA₂R antibody levels predicted response to rituximab therapy [55]. Also, as previously demonstrated with the use of cyclic steroids/cytotoxic therapy [56], in patients who respond

to therapy, improvement of proteinuria continues with longer duration of follow-up, and proteinuria nadir may not be reached until after 24–36 months from the start of therapy.

This effect was also demonstrated in a multicenter, randomized, controlled trial carried out at 31 French hospitals that included 75 patients with biopsy-proven MN and nephrotic syndrome after 6 months of conservative antiproteinuric therapy. Patients in this study were randomized to 6 additional months of treatment with conservative therapy plus 375 mg/m² of rituximab on days 1 and 8 (*n* = 37), or continued on conservative therapy alone (*n* = 38). The primary endpoint was a composite of complete or partial remission of proteinuria at 6 months. At this time point, 35% of patients in the rituximab group and 21% of those in the conservative therapy only group achieved remission. However, the respective values at follow-up (median, 17 months) were 64.9 and 34.2% [57].

The safety profile of rituximab has been remarkable, and a recent retrospective analysis comparing time to any adverse event and serious or non-serious adverse events suggests that rituximab might replace regimens using steroids plus alkylating agents as first-line immunosuppressive therapy in patients with MN [34].

The efficacy and safety of rituximab for the treatment of MN is currently being evaluated by 2 ongoing randomized controlled trials. The MEMbranous Nephropathy Trial Of Rituximab (MENTOR) study (NCT01180036) is an open-label, randomized controlled trial designed to compare efficacy and safety of rituximab (1 g IV on day 1

and 15 followed by re-treatment at 6 months) versus cyclosporine (3.5–5 mg/kg/day for 12 months) in inducing and maintaining remission in patients with primary MN. The efficacy of treatment is being assessed by remission status (based on changes in proteinuria) at 24 months from randomization. The study was completed in September 2017 and results are awaited [57, 58]. The STARMEN trial (NCT01955187) will evaluate tacrolimus monotherapy for 9 months (initial dose of 0.05 mg/kg/day, adjusted to achieve blood trough levels of 5–7 ng/mL for 6 months, with a single dose of rituximab 1 g IV at day 180 before the beginning of tacrolimus dose tapering) in terms of rates of remission, relapse rate, maintenance of renal function, and adverse effects during a 2-year follow-up [59].

Adrenocorticotrophic Hormone for the Treatment of MN

Adrenocorticotrophic hormone (ACTH) has been evaluated in patients with MN, and a growing body of evidence supports its efficacy in patients with this condition.

Synthetic ACTH Analog

A study carried out over 20 years ago evaluated the efficacy of a synthetic ACTH analog for improving the serum lipid profile in hyperlipidemic patients with renal disease. Results from this trial indicated that this treatment was effective in lowering lipids after 30 days of treatment, with stable renal function [60]. In 1999, the same group again reported that this analog not only yielded substantial reductions in serum lipid values but, more importantly, also led to decreases in both urinary protein and serum creatinine with concomitant rise in estimated glomerular filtration rate in 14 patients with primary MN. When ACTH was discontinued after a treatment duration of 56 days, all 14 patients relapsed [61]. This group then studied a treatment regimen for ACTH analog administration in patients with renal disease (1 mg twice a week for 2–11 months, continued until the patient demonstrated a sustained remission of proteinuria) and employed it in 23 patients with proteinuria associated with minimal change disease (MCD), primary MN, FSGS, membranoproliferative glomerulonephritis, mesangioproliferative glomerulonephritis, diabetic nephropathy, or hereditary nephropathy. All of the patients reported in this series demonstrated significant and prolonged remissions of proteinuria with ACTH analog therapy [62].

Twelve months of treatment with the synthetic ACTH analog was compared with the 6-month regimen of cyclophosphamide or chlorambucil alternated with methylprednisolone in a non-inferiority trial that included 32

patients with biopsy-proven MN and nephrotic syndrome. After a median 24 months of follow-up, 14 of the 16 patients who received ACTH analog had complete or partial remission versus 12 of the 16 patients who were treated with a cytotoxic drug plus methylprednisolone. Median proteinuria at last follow-up visit decreased from 5.1 to 2.1 g/day in the patients who received ACTH analog and from 6.0 to 0.3 g/day in those treated with a cytotoxic drug plus methylprednisolone [63].

Natural ACTH Gel

More recently conducted studies have provided support for the efficacy of a natural ACTH gel (typically 80 U administered subcutaneously [SC] twice-weekly for 6 months) for the treatment of primary MN. One retrospective analysis included results from 21 patients with nephrotic syndrome (11 with primary MN, 4 with membranoproliferative glomerulonephritis, 1 with FSGS, 1 with MCD, 1 with immunoglobulin A (IgA) nephropathy, 1 with class V systemic lupus erythematosus glomerulonephritis, 1 with monoclonal diffuse proliferative glomerulonephritis, and 1 with non-biopsied nephrotic syndrome) who were treated with ACTH gel in non-research settings and followed for ≥ 6 months. Complete remission was defined as stable renal function and proteinuria < 500 mg/day, and partial remission as stable renal function with $> 50\%$ reduction in proteinuria from 500 to 3,500 mg/day. Eleven patients achieved a complete or partial remission, including 9 with primary MN [64]. It is noteworthy that, among those patients with MN, all but one had received prior immunosuppressive therapy and had been considered refractory to treatment.

A prospective, open-label study included 15 patients with resistant glomerular diseases (MN, MCD, IgA nephropathy, and FSGS) who were treated with ACTH gel (80 U administered SC twice weekly) for 6 months. Complete remission was defined as stable or improved renal function with $\geq 50\%$ reduction in proteinuria to < 0.5 g/g urine protein:creatinine ratio, and partial remission was defined as above with a urine protein:creatinine ratio of 0.5–3.5 g/g. A total of 2 of 5 resistant MN patients had partial remissions with ACTH, and 3 achieved immunologic remission (loss of anti-PLA₂R antibodies). While study results demonstrated a clear benefit of ACTH in decreasing urinary protein for 2 patients (Fig. 3), they also suggested that responses to ACTH gel might not become apparent until the patient had had 3–4 months of treatment [65]. An even longer period may be needed for demonstration of the full benefit of this treatment.

Fig. 3. Changes in urine protein:creatinine ratio (UPCR) over a 6-month adrenocorticotrophic hormone (ACTH) treatment period in patients with MN. Republished with permission of S. Karger AG, from Bomback et al. [65]; permission conveyed through Copyright Clearance Center, Inc.

In a second prospective study, 20 patients with biopsy-proven primary MN were treated with either 40 or 80 U ACTH gel SC twice weekly for 12 weeks. The primary outcome measures included improvements in proteinuria, serum albumin, and the lipid profile, as well as safety and tolerability. The proportion of patients achieving complete remission (proteinuria <0.3 g/day) and partial remission (reduction in proteinuria by $>50\%$ with a final urine protein <3.5 g/day, but >0.3 g/day) were secondary endpoints. Changes in serum anti-PLA₂R antibodies were assessed at baseline and on treatment. At the end of ACTH therapy, 50% of patients had a $>50\%$ reduction in urinary protein, increasing to 65% of patients by 1 year of follow-up. At this evaluation, there was a significant improvement in proteinuria in the entire cohort, with a mean reduction of 3.87 g/day. The 80 U ACTH dose was significantly superior to the 40 U dose. At the end of 12 weeks of treatment, there was no clinically meaningful change in proteinuria in any patients who received 40 U. In contrast, 5 of 11 patients treated with the 80 U dose demonstrated a $\geq 30\%$ decline in urinary protein. Of the 16 patients who received a full course of 80 U ACTH, 2 achieved complete remission and 9 had partial remission. In the 15 patients with anti-PLA₂R antibodies at baseline, antibodies were cleared completely in 3 patients and reduced in another 4 patients by the completion of the ACTH treatment. Antibody clearance typically preceded or paralleled improvement in proteinuria (Fig. 4) [66].

In summary, clinical trial results from Europe with a synthetic ACTH analog and studies carried out in the

United States with a natural ACTH gel formulation support the efficacy of this treatment for patients with MN, as well as for those with other renal diseases that result in nephrotic syndrome. Importantly, this medication has been shown to be effective in patients with disease resistant to other therapies. Results also highlight the need for adequate periods of follow-up, extending beyond 6 months, to assess response and adjust treatments.

Potential Therapies for MN

As some B cells may be resistant to rituximab therapy, research into other options has been considered. Second- and third-generation anti-CD20 antibodies (obinutuzumab, ofatumumab) that bind to different epitopes on the CD20 molecule have been developed. Preliminary reports have shown efficacy of ofatumumab in rescuing patients with MN resistant to rituximab [67]. It is also possible that inhibition of factors that activate autoreactive B cells might play a role in the treatment of MN. Belimumab targets soluble B lymphocyte stimulator and might induce apoptosis of autoreactive B cells [67]. In a study of 14 patients with anti-PLA₂R-positive MN, administration of belimumab significantly decreased anti-PLA₂R antibody levels, decreased proteinuria, and normalized serum albumin levels [68].

Failure to respond to anti-CD20 B-cell targeted therapy may be due to antibody production by plasma cells, since these cells are devoid of the CD20 molecule and, as such, are not depleted by rituximab. Bortezomib, a proteasome inhibitor, has been shown to deplete autoreactive plasma cells and reduces antineutrophil cytoplasmic antibodies and anti-double-stranded DNA antibody titers in experimental models of antineutrophil cytoplasmic antibody-associated nephritis, and may be considered for the treatment of resistant MN [67, 69]. The use of bortezomib can be associated with significant toxicity, but second-generation proteasome inhibitors with equal efficacy but improved safety profile, such as delanzomib and carfilzomib, are now available. Research into whether these new proteasome inhibitors will have a beneficial impact on resistant MN is needed [67].

Complement itself is another potential target for MN treatment. Results from an unpublished trial of 117 patients with MN did not demonstrate any antiproteinuric effect of eculizumab therapy (8 mg/kg delivered every 2 or 4 weeks for 4 months). However, eculizumab was underdosed in this study and complement was not effec-

Fig. 4. Association between proteinuria and anti-M-type phospholipase A₂ receptor (PLA₂R) antibody. In antibody-positive patients, the association between proteinuria (black squares) and the anti-PLA₂R antibody (gray circles) versus time is plotted: (a) patients in whom a response was noted; (b) patients who did

not respond either clinically or immunologically to adrenocorticotrophic hormone therapy. Adapted with permission of Oxford University Press, from Hladunewich et al. [66]; permission conveyed through Copyright Clearance Center, Inc.

tively inhibited [70]. New complement inhibitors including oral agents are now available and are likely to be evaluated in future clinical trials.

A Novel Approach to the Management of Patients with MN

The traditional approach for predicting patient outcomes has been based on the Toronto model, a semi-quantitative method that considers the initial creatinine clearance, the slope of the creatinine clearance, and the lowest level of proteinuria during a 6-month observation period [71]. The advantage of this model is that it only requires assessing kidney function and proteinuria, and the risk can be calculated repeatedly during the period of follow-up.

However, we now know that proteinuria and serum creatinine may not accurately reflect disease activity and do not discriminate between immunologically active disease and irreversible structural glomerular damage. As discussed above, changes in anti-PLA₂R levels typically precede reduction of proteinuria by several months. In patients with high anti-PLA₂R levels, the observation period required to use proteinuria to assess the risk of progression may delay treatment, resulting in significant kidney damage.

As previously discussed, patients with low levels of anti-PLA₂R antibodies are more likely to undergo spontaneous remission and should be treated initially with conservative therapy. On the other hand, patients with per-

sistently high or increasing anti-PLA₂R antibody levels have lower rates of spontaneous remission and an increased risk of progressive loss of kidney function, and should be considered for earlier initiation of immunosuppressive treatment.

As such, a new individualized serology-based approach that complements and refines the traditional proteinuria-driven approach has recently been proposed (Fig. 5) [72] and has been the subject of recent reviews [73, 74]. Increasing or persistently elevated anti-PLA₂R levels suggest that development of spontaneous remission is unlikely and support early initiation of immunosuppressive treatment. Similarly, a rapid and profound reduction in PLA₂R antibody levels (>90% in <6 months) would support consideration of stopping immunosuppressive treatment. Conversely, a PLA₂R antibody reduction <50% at 6 months would suggest that a change in treatment is needed (Fig. 6) [72].

The hope is that such a personalized approach can improve prognostic accuracy and provide individualized treatment for patients with PLA₂R-associated MN while limiting unnecessary exposure to immunosuppressive therapy. However, it remains to be validated by results from a prospective study [72].

The best approach to the management of patients with primary MN who are antibody-negative is unclear. Considering the high rate of spontaneous remission observed in patients who are anti-PLA₂R and antithrombospondin type-1 domain-containing 7A-negative, maximizing conservative therapy seems to be a reasonable initial approach [8].

Fig. 5. Prognostic algorithm for membranous nephropathy. Ab, antibody; eGFR, estimated glomerular filtration rate; IS, immunosuppression; PLA₂R, M-type phospholipase A₂ receptor; SCreat, serum creatinine. Adapted with permission of the American Society of Nephrology, from De Vriese et al. [72]; permission conveyed through Copyright Clearance Center, Inc.

Fig. 6. Therapeutic algorithm for membranous nephropathy. Ab, antibody; IS, immunosuppression; PLA₂R, M-type phospholipase A₂ receptor. It should be recognized that stopping such therapies while anti-PLA₂R antibodies remain positive is mainly applicable to therapies other than rituximab and cyclophosphamide as both of these agents induce sustained B-cell depletion for variable periods of time that cannot be reversed once the drug is administered. Conversion to an alternative therapy should be considered in those who do not show a significant reduction in antibody titers. Patients with high baseline PLA₂R antibodies may require a longer duration of therapy to achieve immunologic remission and may need to be treated with more intensive and prolonged immunosuppression, possibly including plasma exchange. Adapted with permission of the American Society of Nephrology, from De Vriese et al. [72]; permission conveyed through Copyright Clearance Center, Inc.

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