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SPECIAL REPORT

The management of membranous nephropathy—an update

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ABSTRACT

In recent decades, several important advances have taken place in the understanding of the pathogenesis underlying membranous nephropathy (MN) that have sparked renewed interest in its management. Four landmark trials in MN and a fifth clinical trial—which was a pilot study—have been published in recent years. The results from some of these trials have had a significant impact on the recommendations included in the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) Guideline for the Management of Glomerular Diseases, representing a significant step forward compared with the previous guideline in several aspects, including diagnosis, disease monitoring and treatment strategies. However, considering the rapidly evolving advances in the knowledge of MN and the recent publication of the STARMEN and RI-CYCLO trials, several recommendations contained in the guideline warrant updates. This article provides a perspective of the Immunonephrology Working Group of the European Renal Association regarding the management of MN in native kidneys of adult patients.

Keywords: calcineurin inhibitors, cyclophosphamide, membranous nephropathy, remission, rituximab

INTRODUCTION

Membranous nephropathy (MN) represents, rather than a single disease, a histologic pattern of glomerular injury characterized by an accumulation of electron-dense subepithelial deposits composed of immunoglobulins and complement components [1]. MN is the most common cause of adult-onset nephrotic syndrome; even though up to one-third of the patients may reach spontaneous remission at any time during the course of follow-up (the majority within the first 2 years), one-third may persist with nephrotic syndrome, half of which may finally develop end-stage kidney disease (ESKD) [2–7]. In recent decades, several discoveries have increased the understanding of the pathogenesis underlying MN and have sparked renewed interest in the management of this entity [4].

Since the initial description of antibodies targeting the phospholipase A2 receptor (PLA2R) [8], eight additional target antigens have been identified [9–11]: thrombospondin type 1 domain-containing 7A (THSD7A) [12], exostosin 1/exostosin

2 (EXT1/EXT2) [13], neural epidermal growth factor-like 1 protein (NELL-1) [14], semaphorin 3B (SEMA3B) [15], protocadherin 7 (PCDH7) [16], neural cell adhesion molecule 1 (NCAM-1) [17], high temperature recombinant protein A1 (HTRA1) [18] and contactin-1 (CNTN1) [19]. This paradigm shift has led to a recent proposal of a reclassification of MN according to the target antigen and the associated disease, thus leaving behind the distinction between primary/secondary MN [10].

Four landmark randomized controlled trials in MN have been published in recent years—namely the trial by Ramachandran *et al.* [20, 21], the Evaluate Rituximab Treatment for Idiopathic Membranous Nephropathy (GEMRITUX) trial [22], MEmbranous Nephropathy Trial Of Rituximab (MENTOR) [23] and the Sequential Therapy with Tacrolimus and RTX in Primary MN (STARMEN) [24] trial—that have impacted the current management of patients affected with this condition (Table 1). In addition, a fifth trial that was actually a pilot study, the Rituximab Versus Steroids and Cyclophosphamide in the Treatment of Idiopathic Membranous Nephropathy (RI-CYCLO) trial [25], has also been published recently.

Briefly, in the trial by Ramachandran *et al.* [20, 21], the authors compared the efficacy of tacrolimus–corticosteroids with cyclical corticosteroids–cyclophosphamide (i.e. a modified Ponticelli regimen consisting of corticosteroids at months 1, 3 and 5 and cyclophosphamide at months 2, 4 and 6, as opposed to the original Ponticelli regimen that used chlorambucil) at 6 and 12 months, showing comparable results, although with different adverse effect profiles (higher incidence of nephrotoxicity in the tacrolimus–corticosteroids group and amenorrhea in patients receiving corticosteroids–cyclophosphamide) [21].

The GEMRITUX trial evaluated the effects of rituximab (RTX) in MN as compared with placebo [22]. Although no significant differences were observed within the first 6 months (primary endpoint of the trial), in the follow-up period beyond 6 months the remission rate was significantly greater in the RTX arm.

The MENTOR trial compared RTX to cyclosporine, and while no significant differences were observed in the rate of complete or partial remissions at 12 months (60% versus 52%), at 24 months a significantly greater number of patients remained in remission in the RTX group, mostly due to a large number of relapses after the discontinuation of the calcineurin inhibitor [23]. Thus RTX was found to be non-inferior to cyclosporine for induction of remission at 12 months but was statistically superior at 24 months in terms of maintenance of remission.

The STARMEN trial compared a sequential scheme of tacrolimus followed by RTX to that of a cyclical alternating treatment with corticosteroid and oral cyclophosphamide (modified Ponticelli regimen) for the induction of persistent remission in MN [24]. The primary outcome (complete or partial remission at 24 months) occurred in 84% in the corticosteroids–cyclophosphamide group versus 58% in the tacrolimus–RTX group, with the rate of complete remissions being significantly greater in the former as compared with the latter. Remarkably, the number of relapses was also lower in the group of patients treated with corticosteroids–cyclophosphamide. Hence the STARMEN trial failed to support the hypothesis that tacrolimus–RTX was superior to the modified Ponticelli regimen [24].

Finally, the RI-CYCLO trial aimed to assess the effect of RTX as compared with the modified Ponticelli regimen for the induction of remission [25]. At 12 months, the number of patients with complete remission was lower in the RTX arm as compared with corticosteroids–cyclophosphamide (16% versus 32%), while at 24 months these probabilities were similar. Thus the authors concluded that there was no signal of superiority of RTX versus the cyclical regimen in patients with MN and severe proteinuria, although a pragmatic comparison of these two regimens may require a global non-inferiority trial [25].

The results from some of these trials have had a significant impact on the recommendations listed in the recently released KDIGO 2021 Guideline for the Management of Glomerular Diseases [26] (Table 2). Significant changes have been made in the recommendations for the management of MN—including both diagnosis, disease monitoring and therapeutic approach according to the estimated risk—although further research will be needed to address important questions such as the accuracy of different techniques for measuring antibodies in MN, the accuracy of changes in the levels of these antibodies in the prediction of outcomes and the efficacy of alternative therapeutic schemes for the management of the disease, among others.

Considering the rapidly evolving advances in the knowledge of MN and the recent publication of trials result, several recommendations included in the guideline warrant some comments. This article provides remarks and conclusions from the Immunonephrology Working Group (IWG) of the ERA regarding the management of MN in native kidneys of adult patients, following public release of the KDIGO guidelines [26].

RECOMMENDATION TOPICS

Role of kidney biopsy and biomarkers in the diagnosis

Based on the proposal initially made by the Mayo Clinic's group [27, 28], the 2021 KDIGO guideline states that a kidney biopsy may not be required to confirm the diagnosis of MN in patients with a compatible clinical and serological presentation (practice point 3.1.1) [26]. Given the high specificity of PLA2R antibodies in the presence of a pure nephrotic syndrome with normal kidney function and no secondary causes (including diabetes mellitus), a kidney biopsy may not substantially change the diagnosis or management of the disease. However, the guideline stresses that all patients should be evaluated for associated conditions regardless of the positivity of an antibody (practice point 3.1.2) [26]. Since the proposal for a serology-based diagnosis of MN [27] and the published clinical experience showing that the non-invasive approach could provide sufficient information for the management of MN among cases with preserved kidney function and no evidence of secondary causes [28], several nephrology departments have opted for this strategy. Although this approach has not yet

Table 1. Summary of the most recent trials on MN

Study (year)		Ramachandran *et al.* (2016)	GEMRITUX (2017)	MENTOR (2019)	STARMEN (2021)	RI-CYCLO (2021)
Patients, country		$N = 70$, India	$N = 77$, France	$N = 130$, North America	$N = 86$, Spain and The Netherlands	$N = 74$, Italy and Switzerland
Design		Randomized, parallel group, controlled trial	Multicentre, open-label, randomized controlled trial	Multicentre, randomized, non-inferiority trial	Multicentre, prospective, randomized controlled trial with two-parallel-arm design	Open-label, pilot, two-parallel-arm, randomized controlled trial
Inclusion criteria		Adult patients with biopsy-proven MN	Adult patients with biopsy-proven MN	Adult patients with biopsy-proven MN	Adult patients with biopsy-proven MN	All patients with incident MN
Run-in phase		6 months	6 months	3 months	6 months	3 months
Intervention		CS–CYC group: MP at months 1, 3 and 5; CYC at months 2, 4 and 6 CS–TAC group: oral TAC for 12 months and oral prednisone for 6 months	NIAT group RTX ± NIAT group: 375 mg/m^2 RTX on days 1 and 8. At the end of month 6, possibility to reinfuse RTX	RTX group: RTX 1 g on days 1 and 15; second course of RTX at 6 months if no CR. CsA group: oral CsA for 12 months and tapered after 2 months	CS–CYC group: MP at months 1, 3 and 5; CYC at months 2, 4 and 6 TAC–RTX group: Oral TAC for 6 months + RTX 1 g at month 6	CS–CYC group: MP at months 1, 3 and 5; CYC at months 2, 4 and 6 RTX group: RTX 1 g on days 1 and 15
Outcomes		Primary outcome: CR or PR at 6 and 12 months Secondary: eGFR and adverse events	Primary outcome: CR or PR at 6 months Secondary: proteinuria, albumin, creatinine, PLA2Rab	Primary outcome: CR or PR at 24 months Secondary: C/PR at months 6, 12, 18 and time to treatment failure; ESKD	Primary outcome: CR or PR at 24 months Secondary: C/PR at months 3, 6, 12, 18 and 24; relapses; IR.	Primary outcome: CR 12 months Secondary: C/PR at months 6, 12, 18 and 24; proteinuria; SAE
PLA2Rab positivity, *n/N* (%)		48/70 (69)	55/75 (73)	96/130 (74)	53/69 (77)	41/62 (66)
Baseline proteinuria (g/day, or UPCR, mg/g)		CS–CYC group: 5.4 ± 2.7 CS–TAC group: 6.8 ± 3.6	NIAT group: 7195 (5363–8965) RTX + NIAT: 7680 (4584–10 339)	RTX group: 8.9 (6.8–12.3) CsA group: 8.9 (6.7–12.9)	CS–CYC group: 7.4 (4.8–11.3) TAC–RTX group: 7.4 (6.7–11.6)	CS–CYC group: 6 (5–9) RTX group: 6 (4–10)
Results	CR + PR, *n* (%)	At 6 and 12 months: CS–CYC group: 21 (60), and 27 (77) CS–TAC group: 26 (74), and 25 (71)	At 6 months: NIAT group: 8 (21) RTX + NIAT group: 13 (35)	At 24 months: RTX group: 39 (60) CsA group: 13 (20)	At 24 months: CS–CYC group: 36 (84) TAC–RTX group: 25 (58)	At 12 and 24 months: CS–CYC group: 27 (73) and 25 (81) RTX group: 23 (62) and 22 (85)
	CR, *n* (%)	At 6 and 12 months: CS–CYC group: 13 (37) and 18 (51) CS–TAC group: 13 (37) and 19 (54)	–	At 24 months: RTX group: 23 (35) CsA group: 0 (0)	At 24 months: CS–CYC group: 26 (60) TAC–RTX group: 11 (26)	At 12 months: CS–CYC group: 12 (32) RTX group: 6 (16)
	IR, *n* (%)	At 6 and 12 months: CS–CYC group: 83% and 88% CS–TAC group: 86% and 80%	At 6 months: NIAT group: 3 (12) RTX + NIAT group: 13 (50)	At 24 months: RTX group: 33 (66) CsA group: 6 (13)	At 3 and 6 months: CS–CYC group: 77% and 92% TAC–RTX group: 45% and 70%	At 12 months: CS–CYC group: 56% RTX group: 62%
	Relapses, *n* (%)	None[a]	–	RTX group: 2 (5) CsA group: 18 (53)	CS–CYC group: 1 (2) TAC–RTX group: 3 (12)	CS–CYC group: 6 (22) RTX group: 3 (13)
SAE		CS–CYC group: 24 (69) CS–TAC group: 29 (83)	NIAT group: 5 (13) RTX + NIAT group: 6 (16)	RTX group: 11 (17) CsA group: 20 (31)	CS–CYC group: 8 (19) TAC–RTX group: 6 (14)	CS–CYC group: 5 (14) RTX group: 7 (19)

[a]An extended follow-up study by the same group found a relapse rate of 40% and 6.7% in the CS–TAC and CS–CYC groups at 24 months, respectively.

CR, complete remission; CsA, cyclosporine; CS-CYC: corticosteroidscyclophosphamide; CS-TAC: corticosteroids-tacrolimus; IR, immunological response; NIAT, non-immunosuppressive antiproteinuric treatment; PLA2Rab, phospholipase A2 receptor antibodies; PR, partial remission; SAE, serious adverse events; TAC, tacrolimus; UPCR, urinary protein: creatinine ratio.

Table 2. Summary of the most important recommendations for the management of MN in native kidneys of adult patients in 2012 versus 2021 KDIGO guidelines

<table>
<tr><th>Practice Point</th><th>2012 KDIGO Guideline</th><th>2021 KDIGO Guideline</th></tr>
<tr><td>Evaluation of patients with MN</td><td>7.1.1. Perform appropriate investigations to exclude secondary causes in all cases of biopsy-proven MN</td><td>3.1.1. A kidney biopsy is not be required to confirm the diagnosis of MN in patients with nephrotic syndrome and a positive PLA2Rab test..
3.1.2. Patients with MN should be evaluated for associated conditions, regardless of whether PLA2Rab and/or TSHD7Aab are present or absent</td></tr>
<tr><td>Considerations for treatment of patients with MN</td><td>7.2.1. Initial therapy should be started only in patients with nephrotic syndrome AND one of the following conditions:
- Proteinuria >4 g/d AND remains >50% of the baseline value, AND does not show progressive decline during an observation period of at least 6 months.
- Presence of severe, disabling, or life-threatening symptoms related to the nephrotic syndrome
- SCr has risen by 30% or more within 6–12 months from diagnosis but the eGFR is not less than 25–30 ml/min/1.73 m^2 AND this change is not explained by superimposed complications.

7.2.2. Do not use immunosuppressive therapy in patients with a SCr persistently >3.5 mg/dl (or an eGFR <30 ml/min per 1.73 m^2) AND reduction of kidney size on ultrasound OR those with concomitant severe or potentially life-threatening infections.</td><td>3.2.1. In patients with MN, use clinical and laboratory criteria to assess the risk of progressive loss of kidney function:
<table><tr><th>Low Risk</th><th>Moderate Risk</th><th>High Risk</th><th>Very High Risk</th></tr><tr><td>- Normal eGFR, proteinuria <3.5 g/24h or SAlb >30 g/l OR
- Normal eGFR, proteinuria <3.5 g/d or decrease >50% after 6 months conservative therapy with ACEi/ARB</td><td>- Normal eGFR, proteinuria >3.5 g/d and no decrease >50% after 6 mo of conservative therapy. AND- No
- Not fulfilling high-risk criteriaan</td><td>- eGFR <60 ml/min/1.73 m^2 and/or proteinuria >8g/d for >6 mo OR
- Normal eGFR, proteinuria >3.5 g/d and no decrease >50% after 6 mo conservative therapyAND AND at least one of the following:
- SAlb <25 g/l
- PLA2Rab >50 RU/ml
- Urinary alpha1-microglobulin >40 µg/min
- Urinary IgG >1 µg/min
- Urinary ß2-microglobulin >250 mg/d
- Selectivity index >0.2
- No</td><td>- Life-threatening nephrotic syndrome OR
- Rapid deterioration of kidney function</td></tr></table></td></tr>
<tr><td>Initial Treatment</td><td>7.3.1. We recommend that initial therapy consist of a 6-month course of alternating monthly cycles of oral and iv CS, and oral alkylating agents.
7.3.3. Patients should be managed conservatively for at least 6 mo following the completion of this regimen before being considered a treatment failure if there is no remission, unless kidney function is deteriorating or severe, disabling, or potentially life-threatening symptoms related to the nephrotic syndrome are present

7.4.1. We recommend that CsA or TAC be used for a period of at least 6 mo in patients who meet the criteria for initial therapy, but who choose not to receive the cyclical regimen or who have contraindications to this regimen.
7.4.2. CNIs should be discontinued in patients who do not achieve C/PR after 6 mo of treatment.
7.4.3. The dosage of CNI should be reduced at intervals of 4–8 weeks to a level of about 50% of the starting dosage, if remission is maintained and no treatment-limiting CNI-related nephrotoxicity occurs, and continued for at least 12 months.</td><td>3.3.1. All patients with primary MN and proteinuria should receive optimal supportive care. Immunosuppressive therapy should be restricted to patients considered at risk for progressive kidney injury.
For patients with MN and at least one risk factor for disease progression, we recommend using rituximab or cyclophosphamide and alternate month glucocorticoids for 6 months, or CNI-based therapy for ‡6 months, with the choice of treatment depending on the risk estimate.
<table><tr><th>Low Risk</th><th>Moderate Risk</th><th>High Risk</th><th>Very High Risk</th></tr><tr><td>Wait and see</td><td>Wait and see
OR RTXRTX
OR CNI + RTXCNI ± GC</td><td>RTX
OR CYC + GC
OR CNI + RTX</td><td>CYC + GC</td></tr></table>3.3.4. Longitudinal monitoring of PLA2Rab levels at six months after start of therapy may be useful for evaluating treatment response in patients with membranous nephropathy and can be used to guide adjustments to therapy.</td></tr>
<tr><td>Treatment-resistant MN</td><td>7.6.1. We suggest that patients with MN resistant to alkylating agent/steroid-based initial therapy be treated with a CNI.

7.6.2. We suggest that patients with MN resistant to CNI-based initial therapy be treated with an alkylating agent/ steroid-based therapy.</td><td>3.4.2. Management of patients with treatment-resistant membranous nephropathy
<table><tr><th>Initial therapy</th><th>Resistant disease</th><th>Second treatment</th><th>No response after 3 months</th><th></th></tr><tr><td>RTX</td><td>Stable eGFR</td><td>CNI + RTX</td><td rowspan="2">CYC + GC</td><td rowspan="6">Resistant to RTX and CYC+GC
Consult Expert Center</td></tr><tr><td></td><td>Decreasing eGFR</td><td>CYC + GC</td></tr><tr><td>CNI</td><td>Stable eGFR</td><td>RTX</td><td rowspan="2">CYC + GC</td></tr><tr><td></td><td>Decreasing eGFR</td><td>CYC + GC</td></tr><tr><td>CYC</td><td>Stable eGFR</td><td>RTX</td><td rowspan="2">CYC + GC</td></tr><tr><td></td><td>Decreasing eGFR</td><td>CYC + GC</td></tr></table></td></tr>
<tr><td>Treatment of relapses of MN</td><td>7.7.1. We suggest that relapses of nephrotic syndrome in MN be treated by reinstitution of the same therapy that resulted in the initial remission.
7.7.2. We suggest that, if a 6-month cyclical corticosteroid/alkylating-agent regimen was used for initial therapy, the regimen be repeated only once for treatment of a relapse.</td><td>3.4.1. Treatment of patients with MN and initial relapse after therapy.
<table><tr><th>Initial Treatment</th><th>Relapses after remission</th></tr><tr><td>RTX</td><td>Repeat RTX</td></tr><tr><td>CNI ± GC</td><td>RTX
CNI ± RTX</td></tr><tr><td>CYC ± GC</td><td>CYC + GC
RTX
CNI ± RTX</td></tr></table></td></tr>
<tr><td>Prophylactic anticoagulation</td><td>7.9.1: We suggest that patients with MN and NS, with marked reduction in serum albumin (<2.5g/dl) and additional risks for thrombosis, be considered for prophylactic anticoagulant therapy, using oral warfarin</td><td>3.4.5. Prophylactic anticoagulant therapy in patients with membranous nephropathy and nephrotic syndrome should be based on an estimate of the risk of thrombotic events and the risk of bleeding complications.</td></tr>
</table>

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CNI, calcineurin inhibitor; CR, complete remission; CsA, cyclosporine; CYC, cyclophosphamide; GC, glucocorticoids; NS, nephrotic syndrome; PLA2Rab, phospholipase A2 receptor antibodies; PR, partial remission; SAlb, serum albumin; SCr, serum creatinine; TAC, tacrolimus; TSHD7Aab, thrombospondin type I domain-containing 7A antibodies.

been validated in prospective cohorts, it seems prudent to consider this policy on a case-by-case basis and especially when an absolute or relative contraindication for kidney biopsy exists [29, 30] (Table 3). For cases with atypical clinical course, progressive kidney function impairment, concomitant positivity of other serological markers or paraproteinaemia, it is highly advisable to perform a kidney biopsy. PLA2R-antibody-negative patients require a kidney biopsy and immunohistochemical/immunofluorescence staining for PLA2R. Furthermore, the recent description and characterization of novel antigens in MN has raised the possibility of reclassifying the disease towards an antigen-based classification system

Table 3. Suggestions of the IWG regarding the management of MN in native kidneys of adult patients

Evaluation of patients with MN	Consider not performing a kidney biopsy for the diagnosis of the disease in PLA2R-positive patients on a case-by-case basis, especially when an absolute/relative contraindication for kidney biopsy exists. We advocate abandoning the dichotomization of MN into primary and secondary.
Considerations for treatment of patients with MN	We advocate for a close follow-up of patients after the diagnosis of MN—especially those with high PLA2R antibody titres—for earlier identification of cases with progressive kidney impairment or severe persistent nephrotic syndrome that may require the initiation of immunosuppressive therapy despite an initial supportive care. Cardiovascular risk should be carefully evaluated in patients with MN and preventive measures aimed at slowing down CKD progression should be universally implemented. Lifestyle modifications and weight loss, especially in overweight/obese patients with MN. Consider dual RAS/SGLT2 blockade in selected cases.
Treatment with RTX	In highly proteinuric patients, a complete B-cell depletion should be documented and additional dose of RTX may be needed. It is advisable to monitor serum immunoglobulin levels after RTX infusion.
Treatment with CYC	Adjust dose of CYC by age and kidney function. Monitor cumulative doses.
Treatment with CNI	When CNIs are prescribed, patients need closer monitoring of serum levels to ensure that the target therapeutic levels are achieved. Consider using extended-release tacrolimus to facilitate treatment compliance and more stable serum levels. Once remission is reached, CNIs should be tapered slowly. Consider the addition of RTX at the onset of CNI tapering to prevent relapses.
Disease monitoring	A biomarker combination consisting of PLA2R antibody titres, serum albumin and proteinuria and their dynamic changes over time may provide clinicians a more accurate assessment of patients with MN rather than relying only on PLA2R antibody titres.

CNI, calcineurin inhibitor; CYC, cyclophosphamide.

[10]. The implementation of this classification system will be complex in clinical practice until validated and standardized diagnostic tests become widely available [31]. In addition, it is yet unknown whether this reclassification could affect clinical decisions regarding treatment strategies. Nevertheless, we advocate abandoning the dichotomization of MN into primary and secondary.

Risk stratification and risk-based treatment: towards a personalized approach

Practice point 3.2.1 suggests the use of clinical and laboratory criteria to assess the risk of progressive loss of kidney function, although some limitations are raised concerning the individual evaluation of risk in clinical practice in patients with MN [26]. For instance, the guideline acknowledges that no predictive model has yet evaluated the added value of each risk factor and thus it is probable that a combination of factors may help identify those patients at higher risk for a progressive disease. We advocate for a close follow-up of patients after the diagnosis of MN—especially those with high PLA2R antibody titres—for an earlier identification of cases with progressive kidney impairment, or severe persistent nephrotic syndrome within the first months after diagnosis (e.g. anasarca despite diuretics, together with heavy proteinuria and/or severe hypoalbuminaemia), which may require the initiation of immunosuppressive therapy despite initial supportive care [32, 33].

As with other kidney diseases, cardiovascular risk should be carefully evaluated in patients with MN and preventive measures aimed at curtailing chronic kidney disease (CKD) progression should be universally implemented. Renin–angiotensin system (RAS) blockade—either angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers—is a mainstay of therapy both for blood pressure control and albuminuria reduction [34–36]. The importance of a low-salt diet should also be emphasized. Moreover, the recent findings that sodium–glucose cotransporter-2 (SGLT2) inhibitors can attenuate the progression of non-diabetic CKD with proteinuria and also reduce cardiovascular mortality [37–42] have been a major breakthrough in the management of glomerular diseases. Although precise information is not yet available in patients with MN, the similarities in the mechanisms of kidney damage and progression with other immune complex diseases support its potential use in patients with MN at risk for CKD progression. On the other hand, careful attention should be given to overweight/obese patients, since these conditions are well-recognized risk factors for hyperfiltration and proteinuria [43–45]. Additionally, persistent proteinuria in obese patients may be misinterpreted as a resistant disease in certain clinical scenarios. Thus it is essential to control or avoid obesity in these patients in order to limit the haemodynamic and metabolic deleterious effects in the kidneys. This goal may be particularly difficult to achieve after treatment with high-dose corticosteroids, but in the medium- to long-term follow-up it is necessary to make the patient aware of its importance. Hence all these reasons suggest that dual RAS–SGLT2 blockade could be beneficial in a subset of MN patients—particularly those with persistent residual proteinuria despite immunosuppressive therapy and RAS blockade—although future prospective studies are warranted

to explore this hypothesis. In fact, it is likely that in the coming years this combination could become the new standard of care for patients with any type of glomerular disease, independent of the underlying pathogenic mechanism involved [41].

Practice point 3.3 suggests different therapeutic approaches according to risk stratification [26]. It is important to note, however, that some of these risk factors are based on low-quality evidence and some parameters are not routinely available in clinical settings. The guideline states that immunosuppressive therapy may not be required in cases at low risk [proteinuria <3.5 g/day, serum albumin >30 g/L and estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2]. In addition, immunosuppressive therapy may not be required in those patients with nephrotic syndrome and normal eGFR, unless one additional risk factor for disease progression is present or serious complications of the nephrotic syndrome have occurred (e.g. thromboembolic events or acute kidney injury), an aspect on which there is broad consensus.

For patients at moderate risk, the guideline suggests a wait-and-see approach or immunosuppressive therapy based on RTX or calcineurin inhibitor ± glucocorticoids. Conversely, for high-risk patients, RTX, cyclophosphamide plus glucocorticoids or calcineurin inhibitor plus RTX are suggested.

We acknowledge that this point may be subject to controversy since the publication of the latest trials on MN, namely the MENTOR and STARMEN trials [23, 24]. Calcineurin inhibitors (cyclosporine or tacrolimus) have proven to be effective in achieving remission in MN [21, 24, 46–48], although these drugs have never been shown to prevent ESKD in MN patients. In addition, there are two major concerns with calcineurin inhibitors in MN: the risk of nephrotoxicity and the risk of relapse after its discontinuation [49]. In the MENTOR trial, cyclosporine was effective in inducing remission at 12 months, although the number of relapses was high in this treatment arm after its discontinuation [23]. Additionally, patients in this arm presented a decline in creatinine clearance that persisted at all time points during the follow-up [23]. In the STARMEN trial, 51% of patients in the tacrolimus–RTX group reached the primary outcome of complete or partial remission at 12 months. Unlike the MENTOR trial, this percentage was similar (58%) at 24 months [24]. It is important to note, however, that in the MENTOR trial the treatment period with cyclosporine was 12 months (plus the tapering phase), while in the STARMEN trial the treatment period with tacrolimus was 6 months. Likewise, patients in the tacrolimus–RTX arm of the STARMEN trial exhibited a trend for lower values of eGFR throughout the study period, which persisted in 12% of cases [24]. Interestingly, the number of relapses was low in the STARMEN trial and not significantly different between the two arms of the study (3% in the modified Ponticelli group and 12% in the tacrolimus–RTX group), suggesting a beneficial effect of RTX, infused at the onset of tacrolimus tapering to prevent relapses (in combination with a slow tapering of tacrolimus over a period of 3 months) [24]. In this regard, the effectiveness of RTX to prevent relapses in corticosteroid-dependent or frequently relapsing cases of minimal change disease or focal and segmental glomerulosclerosis has been demonstrated in several prospective studies [50–54]. In both the MENTOR and STARMEN trials, the decrease in PLA2R antibody titres was slower in the calcineurin inhibitor arms [23, 24].

Hence these results provide further evidence for the effectiveness of calcineurin inhibitors in MN [20, 23, 24], although some caveats must be raised. When calcineurin inhibitors are prescribed, patients need monitoring of trough levels to ensure that the target therapeutic levels are achieved. In addition, in case of choosing tacrolimus, an extended-release formulation to facilitate treatment compliance and more stable serum levels may be considered.

Once remission is reached—and especially when this remission is only partial—calcineurin inhibitors should be tapered slowly or RTX should be added [49]. Observational studies have shown that the duration of the tapering period significantly predicts the risk of relapses in patients with MN treated with tacrolimus [55], although this may be at the expense of an increased risk of nephrotoxicity. The amount of residual proteinuria at the onset of tacrolimus tapering in patients who achieve partial response has also been associated with a higher risk of relapses [55]. Thus, before the RTX era, a more prolonged therapy (up to 1–2 years) or a lower dose of cyclosporine was suggested for long-term maintenance of patients with MN who achieved only a partial remission, especially when the patient was at high risk for relapse or previously had significant adverse effects on full-dose therapy [49, 56]. Such cumulative observational experience would suggest that more prolonged cyclosporine tapering could have influenced the long-term results in the MENTOR trial.

Future studies should evaluate the effectiveness of alternative regimens that combine RTX with calcineurin inhibitors for this subset of patients with moderate to high risk. RTX has proven to be effective in MN [57], but the onset of action is slow. The optimal dose and the need for re-treatment are also a matter of debate [4]. In addition, urinary losses from RTX remain a concern in highly proteinuric patients [58]. In these patients, a complete B-cell depletion should be documented and an additional dose of RTX may be needed. Thus it is likely that the combination of RTX with calcineurin inhibitor could accelerate time to remission in this group of patients. Furthermore, the infusion of RTX at the time of calcineurin inhibitor initiation and at the onset of its tapering, and probably at a higher dose than that used in the STARMEN trial, could provide better results than those obtained in this study [59]. On the other hand, given the experience of obinutuzumab in lupus nephritis, it is likely that this agent could induce a more profound and a faster response in proteinuria in patients with MN [60, 61].

There is broad agreement that in patients with MN at a very high risk of progressive decline in kidney function, cyclophosphamide-based regimens are the most appropriate, as they reduce the risk of CKD progression [26]. However, there is concern regarding the toxicity induced by cyclophosphamide, particularly the long-term complications such as malignancy or infertility [62]. For instance, in the STARMEN trial, there were more adverse events per patient in the corticosteroids–cyclophosphamide arm, especially leukopaenia [24]. Two malignancies occurred in this therapeutic arm

(gastric adenocarcinoma and breast carcinoma) versus one in the tacrolimus–RTX arm (rectal carcinoma). These patients had positive PLA2R antibodies at baseline and, at the time of tumour detection, patients were in clinical remission [24].

Similarly, in the RI-CYCLO trial, leukopaenia was a frequent complication in the group of patients who received the cyclic regimen, requiring a reduction or even temporary cessation of cyclophosphamide [25].

While the cumulative doses of cyclophosphamide with the modified Ponticelli regimen are lower than that of previous cyclophosphamide-based regimens (10 g with modified Ponticelli versus >30 g with the Dutch protocol for a 70-kg adult), there is an ongoing debate about the need to upgrade the current protocol, which should be evaluated in further prospective trials [4]. Potential alternative regimens to be explored might include pulsed intravenous cyclophosphamide [63–65], shorten the length of the corticosteroids–cyclophosphamide regimen up to 4 months according to the type of response achieved or even consider the combination of cyclophosphamide with RTX in rare cases presenting with an aggressive form of the disease [66] (e.g. progressive kidney impairment with severe nephrotic syndrome), as used in ANCA-associated vasculitis [67].

However, no randomized controlled study has yet been conducted that directly compares full-dose RTX (i.e. 4 g/12 months, as in MENTOR trial) with cyclophosphamide in patients at high risk.

Finally, as with other autoimmune diseases, future protocols should address the effectiveness of lower doses of corticosteroids to reduce their associated side effects [62] or even the possible use of enteric-coated budesonide, which has been used in other disorders with reduced associated side effects [68].

Disease monitoring

The 2021 KDIGO guideline states that longitudinal monitoring of PLA2R antibody levels at 6 months after the start of therapy may be useful for evaluating treatment response and can be used to guide adjustments to therapy (practice point 3.3.4) [26]. A number of studies have confirmed the crucial role of serial measurement of PLA2R antibodies for the prediction of outcomes and to help guide the length of treatments [8, 27, 69–72]. Furthermore, it has been suggested that the number of targeted PLA2R epitope regions may determine disease severity and prognosis: those patients whose PLA2R antibody specificity spreads beyond the N-terminal cysteine-rich domain (CysR) toward recognition of the C-type lectin-like domain 1 and/or 7 may have a worse kidney prognosis [73–75]. However, this hypothesis challenged in a recent study that suggested that at the time of clinical diagnosis, patients may already have a broad reactivity to PLA2R [76, 77].

As observed in several studies [22, 70, 78–80] and is commonly seen in clinical experience, serum albumin increases before a reduction in proteinuria is detected in patients who ultimately achieve remission. Thus these changes in serum albumin levels over time provide important information in clinical settings, which can also be beneficial in guiding therapeutic decisions.

Hence a biomarker combination consisting of PLA2R antibody titres, serum albumin and proteinuria and their dynamic changes over time may provide clinicians a more accurate assessment of patients with MN rather than relying only on PLA2R antibody titres.

Finally, for patients receiving RTX, $CD19^{+}$ B-cell counts may be used for drug titration to ensure proper B-cell depletion [81]. However, the clinical usefulness of serial measurement of B-cells (including memory B-cells and T-cell phenotypes) in patients with MN for prediction of outcomes and treatment response remains to be elucidated [26].

Management of relapses and treatment-resistant membranous nephropathy

Practice point 3.4.1 proposes an algorithm for the management of an initial relapse of MN after treatment [26]. For patients who received RTX, a repeated course of RTX may be used. For patients who received calcineurin inhibitor, the guideline suggests considering RTX and/or calcineurin inhibitor. Conversely, for patients who received a cyclophosphamide-based regimen, cyclophosphamide and glucocorticoids may be repeated—with a recommendation of not exceeding a cumulative dose of 10 g if preservation of fertility is required and <25 g to limit the risk of malignancies—or consider RTX and/or calcineurin inhibitor. However, it is important to note that for an average patient of 70–80 kg, the cumulative doses from the first cycle will make it unadvisable to prescribe another course of therapy.

One of the main limitations of this point is the lack of standardization in the definition of relapse across different studies [11]. The guideline suggests using serum albumin and protein:creatinine ratio for the evaluation of relapses to better define whether the increment in proteinuria may be interpreted as a relapse of MN or a resistant disease [26]. As previously stated, we advocate for using the combination of all biochemical parameters (PLA2R antibody titres, serum albumin and proteinuria) for the assessment of disease status and to indicate the start of treatment. This may be particularly important in patients in remission who develop progressive proteinuria without hypoalbuminaemia in the setting of significant weight gain, which could be mistakenly interpreted as a relapse.

In addition, there may be cases with persistent significant residual proteinuria without hypoalbuminaemia despite immunological remission [82]. It is known from clinical experience that the decline in proteinuria in patients with MN is usually slower than that observed in patients with several other glomerular diseases. For these cases, it is highly advisable to optimize RAS blockade or even combine it with an SGLT2 inhibitor [83].

The 2021 KDIGO guideline defines resistant MN as when nephrotic syndrome persists after immunosuppressive therapy [26]. In PLA2R-associated MN, the guideline advises waiting 6–12 months after the disappearance of the antibody before evaluating treatment response. A detailed algorithm for the management of resistant MN is presented according to the previous immunosuppressive regimen received and the trend

in eGFR. For patients with stable eGFR, calcineurin inhibitor and/or RTX-based regimens are proposed, whereas in cases with decreasing eGFR, cyclophosphamide-based regimens are suggested. We recommend assessing proper treatment compliance when the initial therapy included oral drugs. The latest clinical trials published have not revealed additional data regarding this topic.

Finally, for patients who did not respond to either RTX or cyclophosphamide, the guideline recommends referral to expert centres to be recruited to ongoing trials with newer experimental therapies (e.g. ofatumumab [84, 85], obinutuzumab [60, 61], bortezomib, daratumumab, belimumab and newer anti-complement drugs). The IWG strongly endorses this suggestion.

Prophylactic anticoagulation in primary MN

The 2021 KDIGO guideline recommends assessing the risk of thrombotic events and bleeding complications in patients with MN and nephrotic syndrome according to the levels of serum albumin [26]. However, it is also pointed out that the threshold values of serum albumin at which to consider anticoagulant therapy in MN may be different according to the biochemical assay (<20 g/L for bromocresol purple versus <25 g/L for bromocresol green). In addition, the use of online clinical tools for the individual assessment of risk of venous thrombosis and risk of bleeding is advocated.

CONCLUSIONS

In the last decade, several important efforts have led to a better understanding of the pathogenesis of MN and its best management in clinical practice. However, some of the advances described in MN have not yet been shown to translate into improved outcomes and therefore more studies are needed to address these issues. In this respect, conducting pragmatic trials involving the participation of different centres around the globe could represent an interesting alternative to help consolidate evidence-based treatment strategies in MN in real-life routine practice conditions.

The recommendations for the management of MN contained in the 2021 Guideline for the Management of Glomerular Diseases represent a significant step forward compared with the previous 2012 KDIGO guidelines. Yet further research is warranted to evaluate several aspects of diagnosis, disease monitoring and treatment strategies, which may ultimately contribute to more personalized treatment of the disease.

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CONFLICT OF INTEREST STATEMENT

AK reports personal fees from Novartis, TerumoBCT, Miltenyi Biotech, Vifor Pharma and Alexion. H.-J.A. reports personal fees from Janssen, GlaxoSmithKline, Bayer, Boehringer Ingelheim, AstraZeneca, Novartis, Kezar and Previpharma. J.F. reports personal fees from Amgen, Bayer, Calliditas, Novo Nordisk, Omeros, Travere and Vifor Fresenius. A.B. reports personal fees from AstraZeneca, ChemoCentryx, Merck/MSD, Vifor and AbbVie. M.S. reports personal fees from Hansa Biopharma, Chemocentryx and Vifor Fresenius. The rest of the authors declare no conflict of interests.

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