Treatment of idiopathic membranous nephropathy

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Abstract | Immunosuppressive treatment of patients with idiopathic membranous nephropathy (iMN) is heavily debated. The controversy is mainly related to the toxicity of the therapy and the variable natural course of the disease—spontaneous remission occurs in 40–50% of patients. The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Glomerulonephritis provides guidance for the treatment of iMN. The guideline suggests that immunosuppressive therapy should be restricted to patients with nephrotic syndrome and persistent proteinuria, deteriorating renal function or severe symptoms. Alkylating agents are the preferred therapy because of their proven efficacy in preventing end-stage renal disease. Calcineurin inhibitors can be used as an alternative although efficacy data on hard renal end points are limited. In this Review, we summarize the KDIGO guideline and address remaining areas of uncertainty. Better risk prediction is needed to identify patients who will benefit from immunosuppressive therapy, and the optimal timing and duration of this therapy is unknown because most of the randomized controlled trials were performed in low-risk or medium-risk patients. Alternative therapies, directed at B cells, are under study. The discovery of anti-M type phospholipase A2 receptor-antibodies is a major breakthrough and we envisage that in the near future, antibody-driven therapy will enable more individualized treatment of patients with iMN.

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Introduction

Membranous nephropathy is a common cause of nephrotic syndrome in adults, with a reported incidence in northern Europe of 5–10 cases per million population per year.[1] In about one-third of patients an underlying cause—such as infection, solid or haematological malignancy, systemic autoimmune disease or use of drugs such as nonsteroidal anti-inflammatories, penicillamine and gold injections—can be identified.[2] In the remaining 70% of patients the disease is considered to be primary or idiopathic membranous nephropathy (iMN). Most patients with iMN present with nephrotic syndrome and normal renal function.

Membranous nephropathy was first described in 1957 by David Jones, who noted the typical basement membrane extrusions in kidney biopsy samples using light microscopy.[3] The characteristic finding of subepithelial deposits consisting of IgG and complement suggested an immunological disease ontology. Unravelling the pathogenesis of the disease started in 1959 with the description of Heymann's nephritis, a rat model of membranous nephropathy.[4] In this model, proteinuria was induced by injecting an extract of proximal tubular cells, and kidney biopsy samples showed subepithelial immune complexes, which contained IgG antibodies targeting megalin, a protein expressed on both rat tubuli and podocytes.[5] As megalin is not present on human podocytes, other pathophysiological mechanisms and antigenic targets were considered. Debiec *et al.* were the first researchers to identify a target antigen in humans. They described a case of neonatal membranous nephropathy in a baby whose mother had a neutral endopeptidase (NEP) deficiency. During pregnancy, the mother formed alloantibodies against NEP that crossed the placenta and bound to NEP expressed on the podocytes of the foetus.[6] A major breakthrough came with the discovery of circulating autoantibodies against the M-type phospholipase A_2 receptor (PLA2R) in the majority of patients with iMN.[7] Cumulative data in cohorts of various ethnicities have confirmed that antibodies against PLA2R, primarily of the IgG4 subclass, are present in ~70% of patients.[8,9] The important role of PLA2R in the pathogenesis of iMN was supported by the observation of highly significant associations between single nucleotide polymorphisms in the PLA2R gene and the development of the disease.[10] Thus iMN should now be considered a renal-limited autoimmune disease.

Treatment of iMN is a matter of fierce debate. Treatment goals include preventing and/or treating complications of nephrotic syndrome, preventing deterioration in renal function and limiting the adverse effects of therapy. Although immunosuppressive therapy has been used to treat patients with iMN for more than four decades, the rationale for this strategy and evidence for its efficacy were lacking for many years. The discovery of autoantibodies in patients with iMN[7] provided retrospective support for the use of immunosuppressive drugs to treat the disease and efficacy data has now been provided

Competing interests
The authors declare no competing interests

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Key points

- Immunosuppressive treatment of idiopathic membranous nephropathy (iMN) should be restricted to patients at high risk of developing end-stage renal disease (ESRD)
- Current tools for predicting prognosis in iMN are inaccurate and up to one-third of patients may receive unnecessary treatment—better risk predictors are required
- The KDIGO guideline suggests use of alkylating agents as a first-line therapy because of their proven efficacy in preventing ESRD, calcineurin inhibitors are an alternative option
- Less-toxic, alternative immunosuppressive therapies, such as rituximab, that could potentially be used to treat patients with iMN are currently being evaluated in randomized controlled trials with hard renal end points
- In the near future, antibody-driven therapies may enable more individualized treatment of patients with anti-PLA2R-related membranous nephropathy

by clinical trials. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group published an evidence-based guideline for the treatment of iMN (Figure 1).[11] In this Review, we summarize current treatment strategies for the disease (Table 1), outline the unanswered questions and propose future developments in therapy.

Identification of patients

As appropriate treatment of membranous nephropathy is governed by the underlying disease, accurate identification of patients is important and guidelines for screening for secondary causes of membranous nephropathy have previously been published.[12] The KDIGO guideline states that appropriate investigations should be performed to exclude secondary causes in all patients with biopsy-proven membranous nephropathy.[11] Secondary causes can mostly be excluded using a detailed medical history (including history of drugs used), physical examination and laboratory studies but some uncertainty always remains, especially in elderly patients in whom malignancy is a common cause of the disease. Therefore, additional tools for patient identification have been considered. A study of the distribution of glomerular IgG subclass deposits in kidney biopsy samples showed that in patients with secondary membranous nephropathy these deposits predominantly contained IgG1, whereas IgG4 dominated in patients with iMN.[13] These findings were confirmed in two subsequent small studies.[14,15] The number of inflammatory cells in the glomeruli has also proven discriminative, with significantly higher numbers reported in patients with cancer-associated membranous nephropathy than in those with iMN ($P = 0.001$).[16] A cut-off value of eight cells per glomerulus was suggested for distinguishing between the two conditions.[16] These preliminary studies showed a predictive accuracy for iMN of over 80%, but further validation is required.

The discovery of antibodies against PLA2R may also provide a new diagnostic tool for iMN. However, it is too early to conclude that the presence of anti-PLA2R antibodies is pathognomonic for the disease as a small number of patients with concurrent anti-PLA2R-positive membranous nephropathy and a malignancy have been described.[9] These patients, in whom antibody titres were low and proteinuria did not resolve after tumour resection, may be an exception to the rule or rather reflect the possibility that patients with iMN may carry a malignancy as a chance finding.[17,18] A larger amount of more accurate data is required to clarify this issue. Such data are expected to become available in the near future.

Supportive care

Up to 27% of patients with iMN present with non-nephrotic proteinuria and many remain nonnephrotic during follow-up.[19] These patients have an excellent prognosis and should be treated in accordance with the current guidelines for the management of chronic kidney disease (CKD)[20] and monitored for the development of nephrotic syndrome, which usually occurs within 2 years of disease onset[19] and may herald more rapid disease progression. Prognosis in patients with iMN and nephrotic syndrome is more variable. Around 30% of patients, including those with fairly high levels of initial proteinuria, develop spontaneous remission 1–2 years after diagnosis.[21] As follow-up time increases, an additional 20% of patients develop remission, leading to a proposed 'rule of halves'; after a follow-up of 5–10 years almost 50% of patients develop spontaneous remission, whereas the remaining patients show disease progression and deterioration of renal function.[22]

The finding that 50% of patients with iMN and nephrotic syndrome develop spontaneous remission and the principle of *primum non nocere* (first, do no harm) has led to the advice that toxic, immunosuppressive therapy should be restricted to patients at high risk of development of end-stage renal disease (ESRD). However, evidence that late start of immunosuppressive therapy is as effective as early start is limited. According to the KDIGO guideline, all patients with iMN and nephrotic syndrome should receive optimal conservative therapy directed at reducing oedema, lowering blood pressure and preventing cardiovascular and thromboembolic events.[11,23] Those with oedema should be treated with diuretics and dietary sodium restriction and blood pressure should be targeted to 125/75 mmHg. Treatment with angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin-II-receptor blockers (ARBs) is preferred, as these agents more effectively lower proteinuria than conventional blood-pressure-lowering therapy alone and improve outcome in patients with chronic proteinuric kidney disease.[24,25] However, evidence that such therapy is beneficial in patients with iMN 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.[26–28] Notably, in patients with severe nephrotic syndrome and normal blood pressure, early initiation of ACEI or ARB therapy may result in acute kidney injury (AKI), probably as a result of existing intravascular volume depletion.[29] We, therefore, advise caution when using ACEIs or ARBs in the first weeks and months after diagnosis in patients presenting with such characteristics. Use of ACEI or ARB therapy has been reported to not be independently related to prognosis in patients with iMN.[30,31]

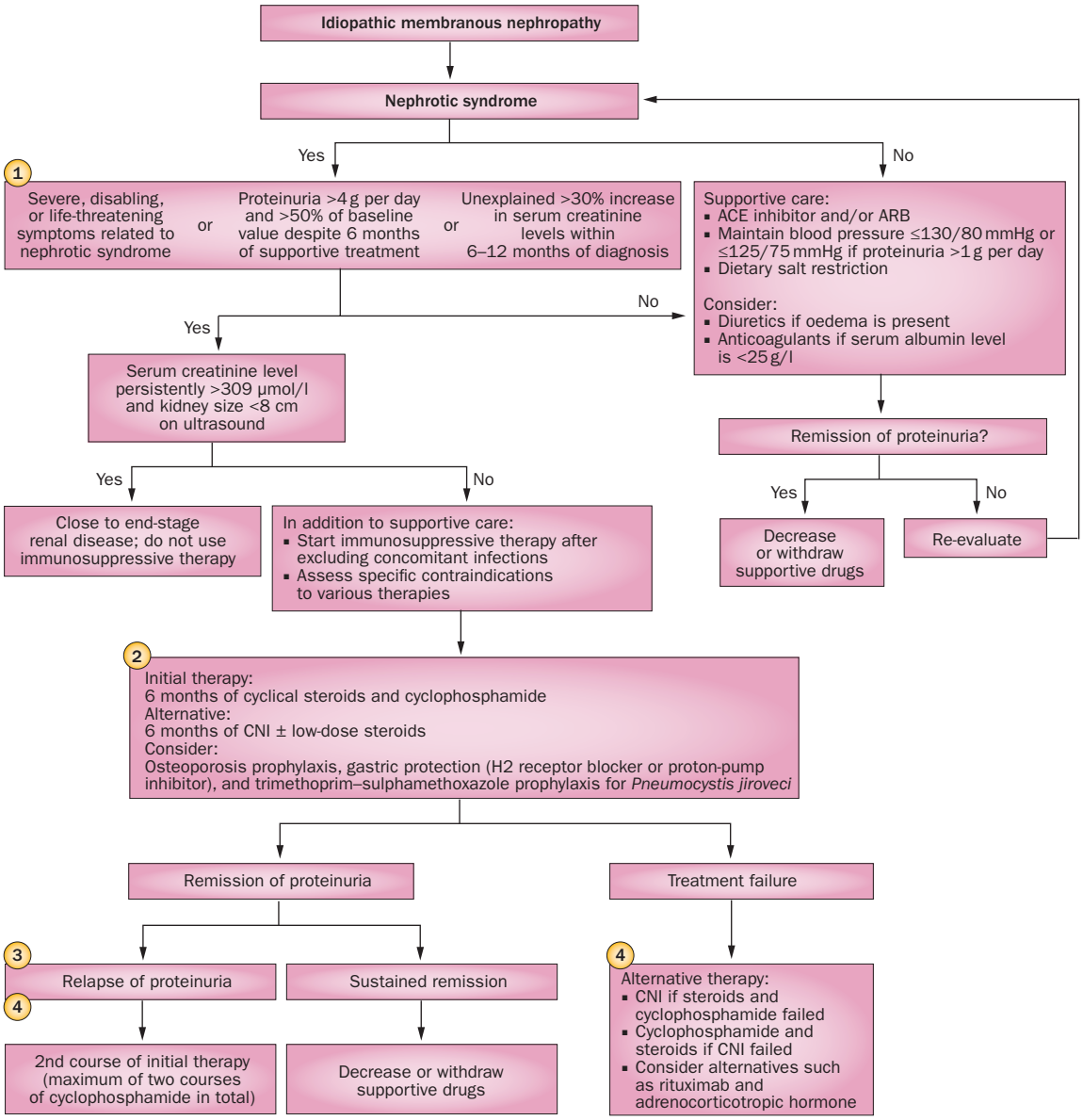

Figure 1 | Treatment algorithm for membranous nephropathy based on the 2012 Kidney Disease: Improving Global Outcomes guideline.[11] The KDIGO guideline provides guidance for the treatment of membranous nephropathy but several areas of uncertainty remain. (1) Better tools for predicting risk of disease progression are required. (2) The optimal duration of alkylating agent therapy is unclear. (3) Further investigation of the potential of antibody-guided therapy for prevention of relapse is required. (4) Further research into the use of alternative therapies after treatment failure is needed. Abbreviations: ACE, angiotensin-converting-enzyme; ARB, angiotensin-II-receptor blocker; CNI, calcineurin inhibitor.

In patients with primary glomerulonephritis, additional beneficial effects of dual blockade of the renin–angiotensin–aldosterone (RAAS) system (that is, ACEI plus ARB) versus ACEI or ARB monotherapy in lowering proteinuria have been reported.[32,33] Although outcome data in patients with iMN are lacking, in our opinion low-dose dual RAAS blockade may be an alternative treatment option for these patients if high-dose ACEI or ARB monotherapy is not tolerated. The ONTARGET study showed that dual RAAS blockade was associated with an increased risk of adverse events without an increase in benefit in patients with vascular disease or diabetes at high risk of cardiovascular events[34] and the KDIGO guideline does not include any suggestions about combining ACEI and ARB therapy in patients with iMN.[11] However, we find no contraindication for use of dual RAAS blockade in these patients as they do not have diabetes, do not have significant cardiovascular disease and are usually younger and have higher levels of proteinuria than the ONTARGET study participants.

The effect of statin therapy on cardiovascular outcomes in patients with iMN has not been investigated in clinical trials. However, most researchers advise treating hypercholesterolaemia in patients with longstanding proteinuria because of their increased cardiovascular risk. The SHARP study findings support the use of statins for

Table 1 | Treatment schedules for idiopathic membranous nephropathy*

Treatment	Dose	Schedule
Chlorambucil cyclical therapy[55]		
Chlorambucil	0.2 mg/kg per day	Months 2,4 and 6
Prednisolone	0.5 mg/kg per day	Months 1,3 and 5
Methylprednisolone	1 g IV	3 consecutive days at start of months 1,3 and 5
Cyclophosphamide cyclical therapy[65]		
Cyclophosphamide	2.5 mg/kg per day‡	Months 2,4 and 6
Prednisolone	0.5 mg/kg per day	Months 1,3 and 5
Methylprednisolone	1 g IV	3 consecutive days at start of months 1,3 and 5
Cyclophosphamide daily therapy[58]		
Cyclophosphamide	1.5 mg/kg per day	Months 1–6§
Prednisolone	0.5 mg/kg every second day	Months 1–5, then taper dose to stop in 6–8 weeks
Methylprednisolone	1 g IV	3 consecutive days at start of months 1,3 and 5
Ciclosporin[91]		
Ciclosporin	Initial dose 3.5 mg/kg per day, trough level 125–225 μg/l	Months 1–6, then taper dose by 25% each month; continue treatment at 50% of dose until 12 months, then taper to lowest possible maintenance dose‖
Prednisolone (if used)¶	0.15 mg/kg per day (maximum of 15 mg)	Months 1–6, then taper dose
Tacrolimus[93,117]		
Tacrolimus	Initial dose 0.05 mg/kg per day, achieve trough level 3–5 ng/l; if remission is not achieved after 2 months, increase to 5–8 ng/l	Months 1–12, then taper to lowest possible maintenance dose‖
Prednisolone (if used)¶	0.15 mg/kg per day (maximum of 15 mg)	Months 1–6, then taper dose
Rituximab[96–99]		
Rituximab	1,000 mg IV Or 375 mg/m^2	Days 1 and 15 1–4 weekly doses

*Some immunosuppressive regimens require prophylactic measures to prevent adverse effects. ‡The KDIGO guideline advises 2 mg/kg per day.[11] §du Buf-Vereijken *et al.* used cyclophosphamide for 12 months;[58] treatment duration is now limited to 6 months. ‖Incidence of relapse is high; treatment must be continued in the majority of patients. ¶It is not known whether prednisolone coadministration is needed. Abbreviation: IV, intravenous.

prevention of cardiovascular events in patients with CKD and estimated glomerular filtration rate (eGFR) <45 ml/min/1.73 m^2,[35] and data from animal studies suggest that these agents may reduce or even reverse podocyte damage.[36–38] In clinical studies, statin therapy has not been proven to lower proteinuria or attenuate deterioration in renal function.[35] The KDIGO guideline[11] suggests that clinicians who treat patients with iMN should refer to the recommendations on statin use in the KDIGO guideline for management of CKD.[20]

The use of anticoagulant therapy in patients with membranous nephropathy should be considered. Patients with nephrotic syndrome are at high risk of arterial and venous thromboembolic events and (for unknown reasons) this risk is especially high in those with membranous nephropathy.[39] In a study of 898 patients with iMN, the incidence of clinically apparent venous thromboembolic events was 7%.[40] Such events mostly occurred in the first 2 years after diagnosis and the only independent risk predictor was level of serum albumin at diagnosis (with an increased risk in patients with serum albumin levels <28 g/l). Whether anticoagulant drugs should be prophylactically administered to patients with iMN has not yet been investigated in a clinical trial. The decision on whether to start prophylactic anticoagulant therapy in an individual patient with iMN should, therefore, be based on the balance between risk of thrombotic events and risk of bleeding. In patients at high risk of thromboembolic events (that is, those with a positive family history, those with a previous thromboembolic event and/or those who are immobile), the physician should consider starting prophylactic anticoagulation when serum albumin levels are fairly high (<28 g/l). In light of the severe morbidity associated with thromboembolic events, our current practice is to start anticoagulation in any patient with low bleeding risk and serum albumin levels <20 g/l. We do not use anticoagulation in patients with high bleeding risk unless the estimated risk of thrombosis clearly outweighs the risk of bleeding. Notably, in patients with nephrotic syndrome who start treatment with high-dose prednisone, the risk of thromboembolic events may increase even further owing to the potential additional thrombogenic effect of the glucocorticoids themselves.[41] In these patients, prophylactic use of low-molecular-weight heparin during initiation of treatment should be considered. An active search for bilateral renal vein thrombosis should be considered in patients with abrupt, sudden AKI but should not be undertaken routinely.

Immunosuppressive therapy

Physicians are faced with a dilemma when considering immunosuppressive therapy in patients with iMN and nephrotic syndrome because early start of immunosuppressive therapy could cause unnecessary harm in patients who would otherwise develop spontaneous remission. Ideally, treatment should be restricted to the 50% of patients with persistent and progressive disease activity. Theoretically, physicians could wait until 2–3 years after diagnosis and then start therapy in those patients who remain severely nephrotic or develop renal insufficiency—the best predictor of ESRD—during follow-up. However, this strategy is controversial for a number of reasons: patients may remain in doubt for a long time as to whether they will need immunosuppressive therapy, the risks of complications such as thromboembolic events are highest during the initial period of nephrotic syndrome, and use of immunosuppressive therapy in patients with established renal insufficiency is associated with more severe adverse effects. Moreover, waiting for spontaneous remission may be disadvantageous in patients who do not remit, especially if immunosuppressive therapy is postponed for too long.

In a small randomized controlled trial, patients with iMN, nephrotic syndrome, normal renal function and high risk of progression were randomly assigned to receive immediate ($n = 14$) or postponed

($n = 12$) immunosuppressive treatment.[42] In the latter group, therapy was initiated at onset of mild deterioration in renal function (that is, when serum creatinine increased to >135 μmol/l). Only eight of the 12 patients in the delayed start immunosuppression group eventually needed immunosuppressive therapy. However, early initiation of therapy was associated with a more rapid onset of remission, thus reducing the period of nephrotic syndrome. At the end of follow-up (median 72 ± 22 months), serum creatinine levels were not significantly higher in the postponed treatment group than in the immediate treatment group (105 μmol/l versus 93 μmol/l, respectively). Although these data might suggest that early immunosuppressive therapy does not result in better preservation of renal function, the study was underpowered to address this issue. In a retrospective study of 328 patients with iMN and nephrotic syndrome who initially received conservative therapy, serum creatinine levels at final follow-up were significantly higher in patients who did not develop spontaneous remission (183 ± 168 μmol/l at 69 ± 51 months) than in those who did develop spontaneous remission (84 ± 31 μmol/l at 91 ± 61 months, $P < 0.0001$).[21] Therefore, accurate prediction of disease progression is utterly relevant.

Identification of patients with poor prognosis

An extensive search for tools to enable early differentiation between patients with iMN and favourable prognosis from those with poor prognosis has been carried out.[43,44] Although histological markers, gender, age, blood pressure, urinary complement levels, and patient HLA type have all been shown to predict prognosis, none of these parameters can be used reliably.[43] By contrast, persistent proteinuria, initial creatinine clearance and the change in creatinine clearance over time have reasonable predictive value.[45] These parameters were incorporated in the Toronto Risk Score, a tool developed to calculate the risk of disease progression in individual patients with iMN.[46] Levels of β2-microglobulin and IgG in urine have also been shown to predict patient prognosis.[47] The Toronto risk score and levels of low-molecular-weight proteins in urine have a comparable predictive accuracy of around 80%.[48] Although reasonable, this level of accuracy may be insufficient to guide treatment decisions in individual patients with iMN. Repeated measurements of urinary markers may improve their predictive performance. We found that repeated measurement of urinary β2-microglobulin had a negative predictive value for progression of iMN of 100% and a positive predictive value of 89%.[22] Although promising, these findings have yet to be validated.

The level of anti-PLA2R antibodies may reflect disease severity in patients with PLA2R-related iMN, and a weak but statistically significant correlation between anti-PLA2R titres and proteinuria has been reported.[49,50] In patients with PLA2R-related iMN, remission of proteinuria was preceded by the disappearance of circulating anti-PLA2R antibodies[8,51] and spontaneous remissions occurred less frequently in patients who had high antibody titres at baseline (4% versus 38% in the highest versus the lowest tertile).[49] However, a decrease in proteinuria may occur independently of anti-PLA2R antibody status and in some cases anti-PLA2R antibodies may persist at least during partial remission.[8] Prospective studies are, therefore, required to determine the prognostic value of anti-PLA2R antibody levels in patients with iMN. In the future, identification of additional autoantibodies that have a role in the pathogenesis of iMN may provide new prognostic markers for those patients in whom no anti-PLA2R antibodies are present at diagnosis.

In the absence of a perfect prognostic marker for iMN, the KDIGO guideline proposes that immunosuppressive therapy should be considered for patients with nephrotic syndrome and persistent proteinuria (defined as >4 g per day for 6 months with no substantial [>50%] decrease in response to optimized conservative treatment) and/or an otherwise unexplained increase in serum creatinine of ≥30% during the first 6–12 months after diagnosis and/or severe, disabling or life-threatening symptoms related to nephrotic syndrome (Figure 1).[11] In our opinion, this definition of persistent proteinuria is rather conservative and may inaccurately identify some patients as being at high risk of progression.

Corticosteroids

Evidence-based treatment of iMN began in 1979 with the report of the first randomized controlled clinical trial in patients with the disease.[52] This study compared 8 weeks of treatment with high-dose (125 mg) alternate-day prednisone monotherapy ($n = 34$) with placebo ($n = 32$). Although prednisone treatment significantly reduced the rate of deterioration in renal function, the poor rate of renal survival in the placebo group during the short follow-up (mean 23 months) was criticized. Indeed, two subsequent randomized controlled trials of prednisone monotherapy failed to confirm beneficial effects of prednisone on renal function and proteinuria.[53,54] As the first of these studies evaluated long-term, fairly low-dose prednisone treatment (45 mg/m^2 on alternate days for 6 months)[53] and the second a short course of high-dose prednisone (125 mg on alternate days for 8 weeks)[54] a positive effect of long-term, high-dose prednisone therapy cannot be excluded. However, we do not consider long-term, high-dose steroid monotherapy to be a treatment option for patients with iMN because such regimens are highly toxic and alternatives are available. The KDIGO guideline recommends that corticosteroid monotherapy is not used as an initial therapy in patients with iMN.[11]

Alkylating agents

The efficacy of alkylating agents in patients with iMN at medium risk of progression (average proteinuria ~7g per 24 h) has been proven with a grade A level of evidence (Table 2). Two randomized controlled trials have shown a clear benefit on hard renal end points in patients treated with chlorambucil or cyclophosphamide. In a landmark trial by Ponticelli *et al.*, 81 patients with recent-onset iMN, nephrotic syndrome and normal renal function were treated with either supportive care

Table 2 | Alkylating agents in idiopathic membranous nephropathy—major clinical trials

Therapy	No of patients (male/female)	Baseline serum creatinine (μmol/l)*	Baseline proteinuria (g per day)*	Follow-up (months)*	Rate of remission (%)‡	Rate of relapse (%)§	Outcome
Ponticelli et al. (randomized controlled trial)[55]							
6 months of chlorambucil and steroids	42 (24/8)	94±22	6.2±3.0	120	83	26	10-year dialysis-free survival in 92% of patients
Supportive care	39 (29/10)	93±25	5.3±2.8	120	38	NA	10-year dialysis-free survival in 60% of patients
Torres et al. (cohort study with historical controls)[57]							
6 months of chlorambucil and steroids	19 (11/8)	124±62	8.9±3.6	52±37	42	25	7-year dialysis-free survival in 90% of patients
Supportive care	20 (15/5)	124±88	6.9±3.1	47±38	0	NA	7-year dialysis-free survival in 20% of patients
Du Buf et al. (cohort study with historical controls)[58]							
12 months of cyclophosphamide and steroids	65 (55/10)	171 (106–512)	10.0 (2.0–23.0)‖	51 (5–132)	86	20	5-year dialysis-free survival in 86% of patients
Supportive care¶	24 (20/4)	173 (137–360)	8.5 (0–19.6)‖	48 (12–65)	20	50	5-year dialysis-free survival in 32% of patients
Jha et al. (randomized controlled trial)[56]							
6 months of cyclophosphamide and steroids	47 (30/17)	108±27	6.2±2.1	132 (126–144)	72	24	10-year dialysis-free survival in 89% of patients
Supportive care	46 (27/19)	103±20	5.9±2.2	132 (126–144)	35	25	10-year dialysis-free survival in 65% of patients
Howman et al. (randomized controlled trial)[62]#							
6 months of chlorambucil and steroids	33 (NA)	50±16**	10.1±5.3	36	NA	NA	20% decline in eGFR** in 58% and ESRD in 3% of patients
Supportive care	37 (NA)	50±20**	9.1±5.3	36	NA	NA	20% decline in eGFR** in 84% and ESRD in 11% of patients

*Mean±SD or median (range). ‡As defined in the study. §As defined in the study in patients with previous remission. ‖Proteinuria reported as g/10 mmol creatinine. ¶11 patients in this group received ineffective immunosuppressive therapy (mainly prednisone monotherapy). #Data on the third trial arm with ciclosporin are included in Table 3. **eGFR calculated using the Cockcroft–Gault equation. Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; NA, not available.

or chlorambucil and glucocorticoids in an alternating schedule for 6 months.[55] Patients in the treatment group had higher rates of remission and dialysis-free survival after 10 years than those in the control group (83% versus 38% and 92% versus 60%, respectively). These findings paved the way for immunosuppressive therapy in patients with iMN and many physicians adopted the so-called Ponticelli regimen. The beneficial effects of alkylating agents were confirmed in a subsequent randomized controlled trial in which patients with iMN, normal renal function and nephrotic syndrome were randomly assigned to treatment with cyclophosphamide (replacing chlorambucil in the Ponticelli regimen) and steroids ($n=47$) or supportive care only ($n=46$).[56] Again, the rates of remission and renal survival were higher in the treatment group than in the placebo group; rates of remission and 10-year dialysis-free survival were 72% and 89%, respectively, in the treatment group compared with 35% and 65%, respectively, in the control group (Table 2). Both studies clearly illustrate the dilemma faced by clinicians; although treatment with alkylating agents was effective, dialysis-free survival after 10 years was ≥60% in untreated patients. Adoption of this treatment strategy for all patients with iMN would unnecessarily expose many patients to the toxic adverse effects of alkylating agents; therefore, a more restrictive use of these agents in patients with iMN is advocated in the KDIGO guideline.[11]

Some evidence supports the efficacy of such a restrictive strategy. Two small cohort studies showed better renal survival in patients with iMN and established renal insufficiency who were treated with either chlorambucil or cyclophosphamide than in historical controls (Table 2).[57,58] The overall efficacy of a restrictive treatment policy was also evaluated in a cohort of 60 patients with iMN and nephrotic syndrome.[59] In this study, immunosuppressive therapy was started only in patients with renal insufficiency or severe, longstanding nephrotic syndrome. During 66 months of follow-up, 22 patients (37%) developed spontaneous remission and

33 patients (48%) received immunosuppressive therapy. Patient survival at 7 years was 100% and renal survival was 88%. Thus, the restrictive treatment strategy assured a favourable long-term outcome, whilst avoiding unnecessary exposure to toxic therapy in around 50% of the patients. Additional evidence that a restrictive treatment strategy improves outcomes in patients with iMN was provided by an epidemiological study in The Netherlands that showed that the incidence of ESRD in patients with iMN decreased by 75% after the introduction of restrictive treatment with cyclophosphamide, whereas the incidence remained unchanged in regions that did not regularly use such therapy.[60] An analysis of data from the Toronto Glomerulonephritis Registry confirmed that an improvement in outcome in patients with iMN has occurred in the past 30 years and that this improvement is related to the implementation of restrictive immunosuppressive therapy.[61] In this study, propensity scoring was used to match 39 patients who received immunosuppressant therapy with 39 untreated controls; 5-year renal survival was ~70% in the control group compared with >95% in the treated patients.

In a UK trial published in 2013, 108 patients with iMN and deterioration in renal function (defined as a 20% decline in eGFR before study entry) were randomly assigned to treatment with either alternating chlorambucil and steroids for 6 months, ciclosporin monotherapy for 12 months or supportive care only.[62] The researchers found that the risk of reaching the primary end point (a further 20% decline in eGFR) was significantly lower in the chlorambucil group, but not in the ciclosporin group, when compared with supportive care only (Table 2). Although these data support the use of chlorambucil in patients with deterioration in renal function, the high rate of progression in patients treated with chlorambucil (58%) compared with the low rate of progression (5–8%) reported in the treatment groups in previous randomized controlled trials,[55,56] may again cause concern that late start of immunosuppressive therapy is less effective than immediate start. We believe such conclusions would be premature for several reasons. The UK trial may be limited by the use of low-dose chlorambucil (starting dose 0.15 mg/kg per day) for a fairly short period of time. Moreover, the surrogate renal end point was a reduction in eGFR of only 20%, although lowering of blood pressure, use of diuretics, and changes in kidney creatinine handling during nephrosis might all contribute to slight changes in serum creatinine levels.[63] The number of patients enrolled in the study who had unusually rapid loss of renal function is also unclear. The inclusion criteria included a decline in eGFR of ≥20% based on at least three measurements over a period of at least 3 months within 2 years before study entry. Thus patients whose eGFR decreased rapidly during a 3–6-month period may have been enrolled in the study even though such a decrease is atypical for iMN, and superimposed events, including acute renal vein thrombosis and interstitial nephritis, would have to be ruled out. We, therefore, suggest that the surrogate renal end point is invalid and may have caused overestimation of the rate of progression to ESRD. Unfortunately, owing to limited follow-up, the UK study does not provide data on long-term renal outcomes.

With regard to the choice of the best alkylating agent, uncontrolled data from our group suggest that cyclophosphamide is more effective and less toxic than chlorambucil.[64] Our review of the literature supports this conclusion but we could not exclude that differences in drug efficacy were caused by differences in treatment duration in the various studies.[30,64] A randomized controlled trial in which 87 patients with iMN were treated with an alternating schedule of either chlorambucil or cyclophosphamide showed no significant difference in efficacy parameters, such as incidence of remission (82% in the chlorambucil group versus 93% in the cyclophosphamide group), incidence of relapse (30% in the chlorambucil group versus 25% in the cyclophosphamide group) or deterioration in renal function (defined as an increase in plasma creatinine level of ≥50% from baseline, an end point reached by 1 of 41 (2%) chlorambucil-treated patients and 2 of 43 (5%) cyclophosphamide-treated patients).[65] However, adverse effects, such as nausea, bone marrow suppression and infectious complications were more frequent in patients who received chlorambucil. Thus, this study also supports the use of cyclophosphamide as the preferred agent for patients with iMN, as stated in the KDIGO guideline.[11]

Malignancy is one of the most feared adverse effects of alkylating agents. The risk of malignancy associated with use of cyclophosphamide is substantial and correlates with the cumulative dose.[66–68] In a study of patients with Wegener's granulomatosis ($n = 293$), risk of malignancy was not increased in patients who had never received cyclophosphamide or in those treated with a cumulative dose of ≤36 g.[69] However, the risks of leukaemia and bladder cancer were increased in patients treated with a cumulative dose of cyclophosphamide of >36 g. A patient weighing 80 kg who receives 2.5 mg/kg cyclophosphamide per day would exceed this threshold after two courses of the Ponticelli regimen. Cyclophosphamide is, therefore, of limited utility when frequent relapses occur. Infertility is another notorious side effect of alkylating agents. The risk of ovarian failure is dependent on cumulative dose and patient age. However, amenorrhoea has been reported in female patients of any age receiving a cumulative dose of 10–15 g of cyclophosphamide.[70–72] In male patients, doses of cyclophosphamide greater than 7.5 g/m^2 can result in permanent oligospermia.[73,74] We advise limiting the use of cyclophosphamide in young patients to 2.5 mg/kg per day for 8 weeks or 1.5 mg/kg per day for 12 weeks (resulting in a cumulative dose of ~10 g).

In summary, grade A evidence suggests that alkylating agents are effective in patients with iMN and normal or decreased renal function. The available data strongly suggest that treatment with these agents should be restricted to patients at high-risk of disease progression. Of note, the centres in Toronto and The Netherlands that reported a favourable outcome of restricted therapy[60,61] are known for their use of risk predictors, which may help to avoid therapy being started too late. In our opinion,

cyclophosphamide should be the preferred alkylating agent for patients with iMN; however, the dose must be carefully limited to reduce the risk of adverse effects.

Antimetabolites

The antimetabolites azathioprine and mycophenolate mofetil (MMF) have been successfully used as a replacement for cyclophosphamide in patients with lupus nephritis and in patients with vasculitis[75,76] and have also been used to treat patients with iMN. Several studies, including a small randomized controlled trial, failed to demonstrate an overall benefit of azathioprine therapy in patients with iMN.[77,78] However, these studies included patients with normal renal function and the event rate was low, so some beneficial effects of the agent cannot be totally excluded. Indeed, two studies in which a total of 34 patients were treated with azathioprine and steroids suggested that azathioprine improved renal outcome in patients with iMN and renal insufficiency.[79,80] In these studies, the majority of patients developed partial remission of proteinuria and renal function stabilized in 28 patients. However, relapse of proteinuria occurred during tapering of drugs in all but four patients, suggesting that treatment needs to be continued for many years (perhaps even for life). A subsequent trial did not show beneficial effects of azathioprine on hard renal end points after 10 years of follow-up.[81]

MMF is a comparatively new immunosuppressive agent with mild adverse effects in comparison to cyclophosphamide. Initial case reports and small cohort studies supported the efficacy of MMF in patients with iMN[82] and many physicians were eager to use this drug as a replacement for cyclophosphamide. However, the results of a randomized controlled trial in which MMF monotherapy was compared to placebo in 36 patients with iMN were disappointing because the rates of remission in the treatment and control groups were not significantly different (both ~37%).[83] A second study of MMF monotherapy also failed to demonstrate efficacy of the drug in inducing remission in patients with iMN.[84] Some data suggest that MMF may be more effective in inducing remission in patients with iMN when used in combination with steroids rather than as a monotherapy. We prospectively treated 32 high-risk patients with iMN and evidence of renal insufficiency (that is, plasma creatinine level >135 μmol/l, endogenous creatinine clearance <70 ml/min or an increase in plasma creatinine >50% from baseline) with MMF (2 g per day) and steroids for 12 months and found no difference in the initial response rate between the MMF group and historical controls treated with cyclophosphamide, with a cumulative remission rate after 12 months of 66% and 72%, respectively.[85] Similarly, in two small Asian randomized controlled trials, MMF and prednisone were as effective as alkylating agents and steroids at inducing remission of iMN.[86,87] Although these data suggest that MMF combined with high-dose corticosteroids is effective in inducing remission of iMN, some concerns remain. A higher primary nonresponse with MMF than with cyclophosphamide was observed in several studies[85,86] and relapse rates after treatment with MMF were high. In our study, the cumulative relapse rate 2 years after the end of therapy was 70% in the MMF group compared to 20% in the cyclophosphamide group.[85]

Consistent evidence that azathioprine has beneficial effects on renal outcome in patients with iMN is lacking and MMF monotherapy is not effective in inducing remission in these patients. Although MMF in combination with steroids is effective in inducing remission of iMN, data on hard renal end points are lacking and as relapse rates are high, treatment must likely be continued for a long period. Therefore, in line with the KDIGO guideline, we do not suggest the use of antimetabolites for initial treatment of iMN.[11]

Calcineurin inhibitors

Calcineurin inhibitors (CNIs) are widely used in patients with iMN. Although the antiproteinuric effects of CNIs have been extensively documented, the exact mechanism of action remains unclear. As CNIs do not directly affect antibody production, their antiproteinuric effects were initially attributed to decreased glomerular perfusion and altered T-cell function.[88] However, Faul *et al.* demonstrated that CNIs could also directly influence podocyte function.[89] Moreover, T-cell and B-cell interactions are an important component of immune regulation and CNIs may modulate antibody production through this mechanism.

Many clinical trials have evaluated the effects of CNIs in patients with iMN but most were uncontrolled, with comparatively short follow-up and limited data on hard renal end points (Table 3). In the first small randomized controlled trial, in which nine patients with progressive iMN were treated with ciclosporin monotherapy (3.5 mg/kg per day for 12 months) and eight received placebo, ciclosporin significantly decreased proteinuria and attenuated decrease in eGFR.[90] A second randomized controlled trial included 51 patients with steroid-resistant iMN, nephrotic-range proteinuria and normal renal function who were randomly assigned to treatment with either ciclosporin 3.5 mg/kg per day (target trough level 125–225 μg/l) and prednisone 0.15 mg/kg per day ($n = 28$) or prednisone alone ($n = 23$) for 26 weeks.[91] The incidence of remission at 26 weeks of follow-up was significantly higher in the ciclosporin group than in the control group (75% versus 22%, respectively, $P < 0.001$), but in most patients remission was not sustained; relapse occurred in almost 50% of patients within 12 months after withdrawal of ciclosporin and doubling of serum creatinine was noted in 7% of treated and 9% of control patients. In the UK trial, 29 (81%) of 36 patients with progressive iMN who were treated with ciclosporin reached the primary end point of a further 20% decline in eGFR.[62] However, the ciclosporin starting dose used in this study (5 mg/kg, goal trough level 100–200 μg/ml) may have been too high, particularly in patients who already showed a degree of renal compromise, and might have prompted a sudden decrease in eGFR, which was considered as failure of therapy. The results of the UK study might thus underestimate the efficacy of ciclosporin, and in the absence

Table 3 | Calcineurin inhibitors in idiopathic membranous nephropathy—major clinical trials

Therapy	No of patients (male/female)	Baseline serum creatinine (μmol/l)*	Baseline proteinuria (g per day)*	Follow-up (months)*	Rate of remission (%)‡	Rate of relapse (%)§	Outcome
Rostoker et al. (cohort study)[118]							
12–30 months of ciclosporin‖	15 (13/2)	107 (85–185)	11.7 (5.3–27.0)	40 (18–66)	73	33	NA
Cattran et al. (randomized controlled trial)[90]							
12 months of ciclosporin	9 (8/1)	186±65	11.5 (9–18)	30 (4–54)	0	NA	Slope of creatinine clearance stable
Supportive care	8 (6/2)	204±81	12.8 (4–21)	31 (4–69)	0	NA	ESRD in 50% of patients at end of follow-up
Cattran et al. (randomized controlled trial)[91]							
6 months of ciclosporin and steroids	28 (26/2)	115±44	9.7±5.3	17	75	48	Doubling of serum creatinine levels in 7% of patients
6 months of placebo and steroids	23 (16/7)	97±27	8.8±4.7	17	22	40	Doubling of serum creatinine levels in 9% of patients
Goumenos et al. (cohort study)[119]							
24 months of ciclosporin and steroids	16 (10/6)	94±20¶	8.0±4.0	>36	88	38	NA
Alexopoulos et al. (cohort study)[92]							
12 months of ciclosporin and steroids#	31 (19/12)	106±35	5.1±2.5	26±16**	84	15	NA
12 months of ciclosporin#	20 (12/8)	88±27	4.9±1.5	18±7**	85	47	NA
Goumenos et al. (cohort study with historical controls)[120]							
18–24 months of ciclosporin and steroids	46 (34/12)	97±27	7.4±4.3	48±36‡‡	85	41	Renal function deterioration in 26% of patients
6 months of chlorambucil or cyclophosphamide and steroids	31 (21/10)	106±53	9.3±4.7	48±36‡‡	55	16	Renal function deterioration in 23% of patients
Kalliakmani et al. (cohort study)[94]							
18–48 months of ciclosporin and steroids	32 (22/10)	88±27	7±3	60±24	88	46	Doubling of serum creatinine levels in 31% and ESRD in 19% of patients
Praga et al. (randomized controlled trial)[93]							
12–18 months of tacrolimus	25 (20/5)	87±18	7.2±3.3	30	72	47	50% increase in serum creatinine levels in 4% of patients
Supportive care	23 (20/3)	97±27	8.4±5.3	30	22	0	50% increase in serum creatinine levels in 26% of patients
Ballarin et al. (cohort study)[117]							
12–15 months of tacrolimus and steroids ± MMF§§	21 (16/5)	93±7	10.7±5.4	23 (3–37)	71	73	NA
Chen et al. (randomized controlled trial)[121]							
6–9 months of tacrolimus and steroids	39 (23/16)	76±22	7.7±3.9	15	85	18	50% increase in serum creatinine levels in 0% of patients
6 months of cyclophosphamide and steroids	34 (18/16)	85±38	7.3±3.9	15	65	22	50% increase in serum creatinine levels in 0% of patients
Howman et al. (randomized controlled trial)[62]‖‖							
12 months of ciclosporin 5 mg/kg per day	36 (NA)	49±18¶	6.8±4.7	36	NA	NA	20% decline in eGFR¶ in 81% and ESRD in 17% of patients
Supportive care	37 (NA)	50±20¶	9.1±5.3	36	NA	NA	20% decline in eGFR¶ in 84% and ESRD in 11% of patients

*Mean ± SD or median (range). ‡As defined in the study. §As defined in the study in patients with previous remission. ‖In nonresponders, ciclosporin therapy was withdrawn after 4 months. ¶eGFR calculated using the Cockcroft–Gault equation. #Patients who responded to ciclosporin after 12 months were placed on long-term, low-dose therapy. **Data for responders only. ‡‡Combined data for treatment and control group. §§MMF (500 mg twice daily) was used in patients with proteinuria >1 g per day after 3 months of therapy ($n = 9$). ‖‖Data on the third trial arm with chlorambucil are included in Table 2. Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; MMF, mycophenolate mofetil; NA, not available.

of data on hard renal end points, no definite conclusions can be made.

Alexopoulos *et al.* suggested that combination therapy with ciclosporin and steroids could induce remission and prevent relapse in patients with membranous nephropathy.[92] They found that after remission, patients who received ciclosporin monotherapy ($n = 17$) had a higher rate of relapse during long-term treatment than those treated with ciclosporin and prednisolone ($n = 26$; 47% versus 15% respectively, $P < 0.05$). However, careful

Table 4 | Rituximab in idiopathic membranous nephropathy—major clinical trials

Rituximab therapy	No of patients (male/female)	Baseline serum creatinine (μmol/l)*	Baseline proteinuria (g per day)*	Follow-up (months)*	Rate of remission (%)‡	Rate of relapse (%)§	Outcome
Cravedi et al. (cohort study)[98]							
1×375 mg/m² (B-cell-driven protocol)‖	12 (8/4)	124±44	10.3±8.9	12	67	NA	NA
4×375 mg/m²	24 (16/8)	133±62	9.1±3.8	12	67	NA	NA
Fervenza et al. (cohort study)[96]							
2×1 g¶	15 (13/2)	124±44	13.0±5.7	12	53	NA	ESRD in 13% of patients
Ruggenenti et al. (cohort study)[99]							
4×375 mg/m²#	6 (5/1)	186±88	9.4±4.0	3	0	NA	NA
4×375 mg/m²**	8 (3/5)	115±35	9.1±40	12	75	NA	NA
4×375 mg/m²‡‡	9 (4/5)	88±27	8.9±5.3	12	67	NA	NA
Fervenza et al. (cohort study)[97]							
4×375 mg/m², repeated after 6 months	20 (17/3)¶¶	133±44	11.9±4.9	24	80	5	NA
Segarra et al. (cohort study)[102]							
4×375 mg/m²##	13 (11/2)	91 (75–128)	2.3 (0.7–3.2)	30	100	23	NA
Ruggenenti et al. (cohort)[100]							
1×375 mg/m² or 4×375 mg/m²	100 (72/28)	107 (86–150)	9.1 (5.8–12.8)	31	65	~25	ESRD in 4% of patients

*Mean±SD or median (range). ‡As defined in the study. §As defined in the study in patients with previous remission. ‖Treatment repeated if B cells >5/mm³ (n=1). ¶Treatment repeated after 6 months if proteinuria >3 g per day and B cells >5×106/l (n=10). #Retrospective cohort with tubule–interstitial score >1.7. **Retrospective cohort with tubule–interstitial score <1.7. ‡‡Prospective cohort with tubule–interstitial score <1.7. ¶¶18 patients were included in the final analysis. ##Patients were initially treated with calcineurin inhibitors; these were withdrawn when remission was induced by rituximab. Abbreviations: ESRD, end-stage renal disease; NA, not available.

review of their data suggests that patients who remained in remission following tapering of ciclosporin had substantially higher trough levels than those who relapsed, both in the monotherapy group and in the ciclosporin plus prednisone group. This finding suggests that higher levels of ciclosporin may be associated with maintenance of remission in patients with iMN.

Further evidence that CNI monotherapy is effective in inducing remission in patients with membranous nephropathy came from a Spanish multicentre randomized controlled trial in which the efficacy of tacrolimus (n=25) was compared with that of standard therapy (n=23).[93] Tacrolimus was started at 0.05 mg/kg per day and the dose adjusted to achieve a trough level of 3–5 ng/ml, and 5-8 ng/ml if remission was not achieved after 2 months. After 12 months of therapy, tacrolimus dose was gradually tapered for a further 6 months. Although rates of remission at 18 months of follow-up were high (76% in the tacrolimus group versus 30% in the control group), almost 50% of treated patients relapsed within 18 months of tacrolimus withdrawal. High rates of relapse associated with use of CNIs have been reported in most studies with sufficient follow-up (Table 3). These relapses are not innocuous as multiple relapses are associated with doubling of serum creatinine levels and the development of ESRD.[94]

Although CNIs are an effective therapy for inducing remission in the majority of patients with iMN and nephrotic syndrome, relapse rates after treatment withdrawal are high, necessitating continued treatment for many years. The lack of data on renal outcomes is a major limitation and renal toxicity is a concern. To date, no randomized controlled trials have compared the serious adverse events of CNIs versus alkylating agents when used as an initial therapy for iMN, and formal studies with sufficiently long follow-up on hard renal end points are urgently needed. Despite the lack of data, and in line with the KDIGO guideline,[11] we consider CNIs to be an alternative initial therapy for patients with iMN who do not tolerate treatment with alkylating agents.

Rituximab

The chimeric anti-CD20 monoclonal antibody rituximab has now been used to treat patients with iMN for more than a decade. As iMN is considered to be an antibody-driven autoimmune disease, a rationale for rituximab therapy certainly exists. Results of randomized clinical trials of rituximab in patients with iMN are expected in the next few years and data from several cohort studies are already available (Table 4). In 2002, Remuzzi *et al.* reported that rituximab therapy (375 mg/m² once weekly for 4 weeks) significantly decreased mean urinary protein excretion from 8.6 g to 3.8 g per 24 h in eight patients with iMN and persistent nephrotic syndrome despite standard supportive care; remission occurred in five of these patients.[95] Two subsequent studies involving a total of 35 patients with

iMN (about 50% of whom were refractory to standard therapy) treated with intravenous rituximab (initial regimen of two 1 g infusions 2 weeks apart or four once-weekly infusions of 375 mg/m^2) showed 50% complete or partial remission of proteinuria at 1 year and 80% at 2 years.[96,97] The proteinuria response was gradual and sustained with no difference in the effectiveness of the two dosing regimens at 1 year. Total B-cell counts started to recover after 3 months (faster than has been reported in patients with antineutrophil cytoplasmic antibody [ANCA]-associated vasculitis, rheumatoid arthritis or non-Hodgkin's lymphoma[97]), suggesting that as the drug is lost in the urine, heavy proteinuria may result in decreased levels of rituximab. However, no correlation between rituximab levels, degree of proteinuria or drug response was observed. A B-cell-titrated protocol in which patients initially receive a single dose of rituximab (375 mg/m^2) followed by a second infusion when ≥5 B cells/mm^3 are detected in the circulation during follow-up has been shown to have similar effectiveness to the four-dose protocol but at a lower cost.[98] However, protocols using higher rituximab doses were associated with significantly lower relapse rates than was the B-cell-titrated protocol,[96,97] suggesting that use of the latter strategy may result in a higher rate of relapse. Rituximab therapy may be less beneficial in patients with iMN and moderate tubulointerstitial fibrosis than in those with mild or no interstitial fibrosis,[99] but this has not been confirmed.

An immunological effect of rituximab in patients with iMN was confirmed in a study that showed that anti-PLA2R antibodies disappeared in 17 of 25 (68%) patients who were treated with the drug.[51] A decline in antibody levels preceded a decrease in proteinuria, and disappearance of anti-PLAR2 antibodies was associated with a higher rate of remission of proteinuria. In a cohort of 100 consecutive patients who were treated with rituximab (almost one-third of whom had previously been treated with other immunosuppressive agents), proteinuria decreased over time from a median of 9.1 g per day to ~4 g per day, ~2 g per day and ~1.5 g per day at 1 year, 2 years and 3 years of follow-up, respectively.[100] Although these data support the efficacy of rituximab, some caveats exist. Firstly, the number of patients who would have developed spontaneous remission without rituximab therapy is unknown. Secondly, although the cumulative incidence of remission was 94%, these data should be interpreted with caution in view of the censoring of patients who failed therapy; remission was not achieved in 35 patients and approximately 25% of remitting patients relapsed during follow-up. Lastly, the study does not prove that rituximab was effective on hard renal end points: four patients died and four developed ESRD after a mean follow-up of 31 months. A randomized controlled trial of rituximab versus ciclosporin in patients with iMN that should provide data on hard renal end points is currently recruiting.[101]

Rituximab therapy may enable successful withdrawal of CNIs in CNI-dependent patients with membranous nephropathy. In a study of 13 patients with at least four previous CNI-responsive relapses of nephrotic proteinuria, rituximab therapy (375 mg/m^2) enabled CNIs to be successfully withdrawn in all patients.[102] Moreover, CNI withdrawal after administration of rituximab was accompanied by an improvement in eGFR and further reduction in proteinuria. Three patients relapsed during a mean follow-up of 35 months but were successfully treated with a second course of rituximab therapy. Notably, several studies have shown rituximab-induced remission of iMN in patients who previously failed other treatments.[95,96,100] In light of these data and the favourable adverse effect profile, we support the use of rituximab as a rescue therapy in patients who have already been exposed to the toxicity of other immunosuppressive drugs. However, evidence for the efficacy of rituximab in patients with low GFR (<45 ml/min) is lacking.

In summary, rituximab is associated with high remission rates and only mild adverse effects have been reported. Relapse rates are fairly low, and comparable to those seen with cyclophosphamide, and a B-cell-titrated treatment regimen seems most cost-effective. Until the eagerly awaited results of upcoming randomized controlled trials with hard renal end points are available, we advise the use of rituximab in patients with iMN as a second-line or third-line treatment only. The KDIGO guideline does not discuss rituximab as a treatment option for patients with iMN but does state that there is a need for clinical trials of this drug in these patients.[11]

Adrenocorticotropic hormone

Several studies have shown a decrease in proteinuria in patients with iMN in response to treatment with synthetic adrenocorticotropic hormone (ACTH).[103,104] Consistent with the hypothesis that this drug acts through a direct renal mechanism, treatment with a melanocortin-receptor agonist reduced proteinuria and oxidative stress and improved podocyte morphology in rats with passive Heymann's nephritis.[105] In patients with iMN, ACTH may exert similar beneficial effects through activation of the melanocortin receptor MCR1 in podocytes.[105] A randomized controlled trial showed that synthetic ACTH (which is not available in the USA) was as effective in inducing remission of iMN as was combined therapy with an alkylating agent and steroid, and was associated with very few adverse effects.[106] A retrospective case series showed a remission rate of 82% in 11 patients with iMN who were treated with the highly purified ACTH gel formulation and had previously failed a mean of 2.4 immunosuppressive therapies.[107] A subsequent prospective open-label study included five patients with iMN and eGFR <45 ml/min who were resistant to previous immunosuppressive treatment.[108] In three of these patients, ACTH gel induced immunological remission, that is, disappearance of anti-PLA2R antibodies, which was accompanied by clinical remission in two of the patients. In a study in which 20 patients with iMN were randomly assigned to receive either 40 IU or 80 IU of ACTH gel twice weekly for 120 days, ACTH therapy resulted in a significant reduction in median proteinuria from

9.1 ± 3.4 g per day at baseline to 3.8 ± 4.3 g per day at 12 months of follow-up (P <0.001).[109] At 12 months of follow-up, 65% of the patients showed a >50% decrease in proteinuria. A clear dose–response relationship was also reported, with 80 IU twice weekly for at least 4 months seeming necessary for maximal effect. Clearing of serum anti-PLA2R antibodies in parallel with a reduction in proteinuria was noted in some, but not all, patients, suggesting a possible direct effect on the podocyte; no serious adverse effects were reported.

Although promising, evidence for the efficacy of ACTH in improving long-term renal outcomes in patients with iMN is lacking, as none of the current studies provided sufficient follow-up. In addition, ACTH gel is extremely costly. We, therefore, recommend that ACTH should not be used for the initial treatment of iMN. The KDIGO guideline states that until more powerful randomized trials are performed, no recommendations can be made regarding the use of ACTH therapy in patients with iMN.[11]

Prevention of adverse effects

Many immunosuppressive drugs are associated with adverse effects and existing guidelines recommend or suggest prophylactic measures to reduce the risk of these effects. In the case of treatment with high-dose steroids for longer than 3 months, prophylactic osteoporosis treatment should be started according to current guidelines[11] and in our opinion, gastric protection should be provided using H2-receptor blockers or proton pump inhibitors. In addition, prophylactic treatment for *Pneumocystis jiroveci* using trimethoprim–sulfamethoxazole (or an alternative in the case of allergy resistant to sulfa desensitization) should be considered for all patients receiving alkylating agents and rituximab.

Areas of concern

The KDIGO guideline provides guidance for the use of immunosuppressive treatment in patients with iMN but some areas of uncertainty remain. Strategies for the identification of patients at high-risk of progression are insufficient and many patients will receive unnecessary immunosuppressive therapy if KDIGO definitions are applied. For example, in a cohort of 104 patients with iMN, we identified 48 patients with persistent proteinuria defined according to the KDIGO guideline.[11,48] After a mean follow-up of 32 months, spontaneous remission had occurred in 18 of these patients (38%). Although patients in this cohort were classified as low or high risk with reasonable accuracy (~80%) using both the Toronto risk score and urinary β2-microglobulin excretion, we suggest repeated measurement of the levels of low-molecular-weight proteins in urine as these are better predictors of renal disease progression.[22] However, quantification of these urinary markers might not help to predict response to immunosuppressive therapy[110,111] and new biomarkers are needed. Measurement of anti-PLA2R antibody titres might be valuable not only for diagnosis of iMN but also for prediction of outcomes and titration of immunosuppressive therapy (Figure 2).

Late start of immunosuppressive therapy avoids unnecessary drug exposure; however, immunosuppressants may be less effective in patients with established renal injury, a late start might mean that patients are exposed to complications of nephrotic syndrome and adverse effects of therapy might be more severe in patients with renal insufficiency. Treatment with cyclophosphamide and steroids is preferred but is not without risks, and careful weighing of the risks and benefits for individual patients is needed. The optimal duration of alkylating agent therapy is subject to discussion. The KDIGO guideline recommends a 6-month alternating Ponticelli treatment regimen that effectively leads to 3 months of treatment with steroids and 3 months of treatment with alkylating agents.[11] However, this regimen has proven beneficial only in randomized controlled trials that included patients with recent-onset disease and normal renal function. In the UK randomized controlled trial, the Ponticelli regimen seemed to be less effective in high-risk patients.[62] Beneficial effects of alkylating agents in patients with renal insufficiency have been obtained with protocols that used cyclophosphamide 1.5 mg/kg per day for 12 months (cumulative dose of 44 g in a person weighing 80 kg).[58,85] We suggest that in patients with renal insufficiency, treatment may be extended to 1.5 mg/kg per day for a period of 6 months (resulting in a total dose of 22 g in a 80 kg patient). In the near future, treatment duration might be individualized and guided by measurement of anti-PLA2R antibody levels (Figure 2)[51] and future studies should address the efficacy of antibody-driven treatment strategies.

Adverse effects of alkylating agents preclude their injudicious, early and prolonged use in patients with iMN and the search for safer, equally effective alternatives is warranted. CNIs are an alternative option, either used as a monotherapy or in combination with low-dose prednisone. Unfortunately, treatment with these agents must be continued long-term to avoid relapse, and nephrotoxicity is a serious concern that will often preclude use of CNIs in patients with moderate to severe renal insufficiency. Rituximab might be a good alternative to alkylating agents but no evidence that rituximab has beneficial effects on hard renal end points is currently available. Ongoing randomized clinical trials should provide definite answers. For example, the ERA-EDTA-supported STARMEN trial will compare cyclophosphamide and steroids with a combination of tacrolimus and rituximab.[112] Another potential new treatment option is the monoclonal antibody belimumab. This inhibitor of soluble B lymphocyte stimulator decreases B-cell survival and prevents the development of plasma cells.[113] In theory, treatment with belumimab should decrease autoantibody levels in patients with iMN. The therapy has already been shown to decrease levels of anti-double-stranded DNA and rheumatoid factor in patients with systemic lupus erythematosus and rheumatoid arthritis, respectively.[113] Phase II studies of belumimab in patients with iMN are currently underway.[114]

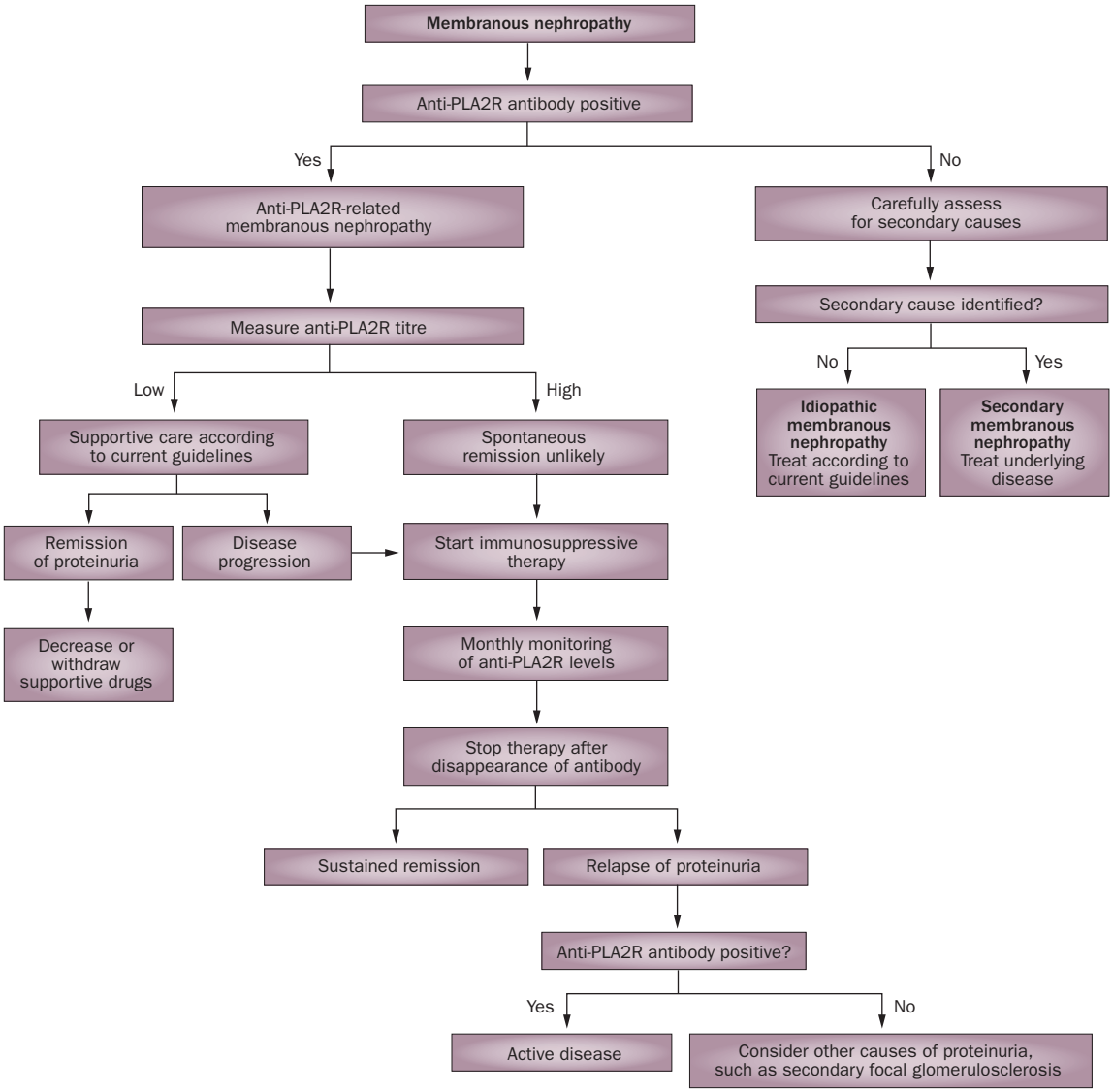

Figure 2 | Potential role of anti-PLA2R antibody assessment in guiding diagnosis and therapy in membranous nephropathy. If ongoing prospective studies confirm the high specificity of anti-PLA2R antibodies for diagnosis of idiopathic membranous nephropathy and the predictive value of antibody titres for patient prognosis, anti-PLA2R levels might be used to aid diagnosis and treatment decisions. Low and high antibody titres have not yet been defined. An increase in anti-PLA2R titre over time may suggest that spontaneous remission is unlikely. Abbreviation: anti-PLA2R, autoantibodies against the M-type phospholipase A_2 receptor.

To date, no clinical trials with any therapeutic regimen have been carried out in patients with iMN who failed their initial therapy or relapsed. In general, patients who fail a certain therapy might benefit from treatment with an agent from another class. Patients who relapse could also be treated with a second course of their original therapy although no more than two courses of the Ponticelli regimen should be used. In patients with increasing proteinuria and/or progressive loss of renal function, recurrence of disease activity must be differentiated from secondary focal glomerulosclerosis. In such patients a renal biopsy may be helpful and might disclose that the glomerular basement membrane architecture is still greatly disrupted although antibody deposits have been reabsorbed.[115] The absence of antibody deposits and/or the presence of severe glomerulosclerosis and/or interstitial fibrosis with tubular atrophy would argue against renewed treatment with immunosuppressive therapy.

Conclusions

Treatment of iMN has been a matter of fierce debate for decades and some clinicians still doubt the efficacy of established immunosuppressive therapies. However, the 2012 KDIGO guideline[11] reflects the sense that major progress in treatment of iMN has been made. We can now use clinical criteria to identify patients who might need immunosuppressive therapy and several treatment options exist. In line with the KDIGO guideline, we advocate cyclophosphamide combined with steroids

as the initial therapy for patients with iMN. Obviously, many open questions remain and the risks and benefits of each therapy should be considered for each individual patient when making treatment decisions—this is the art of being a physician. Immunosuppressive therapy is associated with an increased risk of adverse effects but could reduce the duration of nephrotic syndrome, which is associated with increased risk of infection, thrombosis, cardiovascular events and ultimately progressive renal failure. The identification of PLA2R as a major antigen in patients with iMN may change the diagnosis and treatment of the disease in the near future and studies directed at optimizing therapy using anti-PLA2R antibody titres should be developed. However, approximately 30% of patients with iMN are anti-PLA2R negative and the search for additional autoantibodies continues.[116] The most important lesson of the KDIGO guideline is the need for further randomized controlled trials of immunosuppressants in patients with glomerular diseases.[11] Global collaborations are needed to enable considerable improvements.

Review criteria

The PubMed database and Cochrane library were searched for full-text articles published in English before February 2013. The search terms included "membranous nephropathy" and "idiopathic membranous nephropathy" in combination with the terms "treatment" and "immunosuppressive therapy", using the filters "randomized controlled trial" and "clinical trial". All randomized trials were included, cohort trials were judged on study design and sufficient number of patients. In areas where clinical trials are lacking, review articles were included. Furthermore, the reference lists of key articles, including the recent KDIGO guideline on membranous nephropathy, were searched to identify further relevant articles.

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Author contributions

J. M. Hofstra researched data for the article and wrote the manuscript. J. F. M. Wetzels wrote and reviewed and/or edited the manuscript before submission. F. C. Fervenza reviewed and/or edited the manuscript before submission. All authors made a substantial contribution to discussions of the content.