Controversies in the treatment of idiopathic membranous nephropathy

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Abstract | Optimum treatment of idiopathic membranous nephropathy is both controversial and challenging. The most extensively studied and frequently used immunosuppressive regimens for this disease comprise alkylating agents plus corticosteroids or ciclosporin. All of these treatment options have inherent problems: they are not effective in all patients, partial—rather than complete—remissions are common, adverse effects are worrisome, and relapses after treatment cessation remain problematic. Alternative immunosuppressive agents have been tested in an effort to overcome these unresolved issues. This paper reviews the available evidence regarding both established and new agents for the treatment of patients with idiopathic membranous nephropathy, with an emphasis on the results of the most recent clinical trials.

Introduction

Membranous nephropathy accounts for about one-third of cases of adult-onset nephrotic syndrome.[1,2] Renal biopsy typically reveals diffuse glomerular capillary wall thickening and subepithelial and/or intramembranous immune deposits. In developed countries, approximately 20% of cases are due to rheumatic, neoplastic or infectious diseases, medications or toxins;[3] in this article, however, we focus on idiopathic rather than secondary forms of the disease.

The nephrologist must consider several questions when faced with a patient who has a new diagnosis of idiopathic membranous nephropathy (IMN): should the patient be treated immediately? For how long should I observe the patient before deciding on management? What treatment should be given and for how long? These important and controversial questions do not have straightforward answers. Ultimately, decisions about treatment must integrate what is known about the individual patient with what is known about the risks and benefits of the available treatments and what is known about the natural history of this glomerular disease.

The goal of this Review is to provide an update on the treatment of IMN. Evidence from relatively recent trials is presented, with an emphasis on agents that have been studied as alternatives to cytotoxic drugs and ciclosporin. This article is not meant to be a comprehensive review of membranous nephropathy. We refer readers to several excellent publications and chapters which fulfill that purpose.[4–6]

Who to treat

Estimates of renal survival vary widely among published studies of IMN, which partly reflects differences in baseline prognostic features among the participants. Variation in the numbers of patients without the nephrotic syndrome enrolled in studies of the natural history of IMN makes it difficult to determine the renal prognosis of patients that do have this syndrome. To address this issue, du Buf-Vereijken *et al.*[6] pooled data from 10 studies published over 25 years, excluding those with short follow-up, and calculated the risk of renal failure among patients with the nephrotic syndrome by assuming that renal survival was 100% in patients without this syndrome. Overall, nearly half of the patients with the nephrotic syndrome experienced marked declines in glomerular filtration rate (GFR). Without treatment, end-stage renal disease (ESRD) is estimated to occur in 10–30% of patients with IMN within 10 years.[6–14] In a cohort from France[15] that had median proteinuria of 6 g per day and median estimated GFR of 79 ml/min/1.73 m^2 at baseline, 7-year renal survival was 88%. Almost all patients were treated with an angiotensin receptor blocker or an angiotensin-converting-enzyme antagonist, in contrast to earlier epidemiologic studies, in which use of these agents was inconsistent.

In a pooled analysis of IMN studies, Hogan *et al.*[14] reported that the probability of renal survival (that is, of not progressing to ESRD and not succumbing to death from kidney disease or from cardiovascular events related to the nephrotic syndrome) was 86% at 5 years, 65% at 10 years and 59% at 15 years. Even in patients with IMN who do not progress to renal failure, complications related to the nephrotic syndrome can lead to considerable morbidity and mortality. Individuals with the nephrotic syndrome have an increased risk of thromboembolic complications[16] and experience accelerated cardiovascular disease.[17]

In view of the highly variable clinical course of patients with IMN, investigators have sought to identify

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predictors that can identify high-risk patients for whom the hazards of immunosuppressive drug therapies are justified. Several clinical and biochemical parameters at presentation have been associated with poor outcomes. These include advanced age, male gender, high degrees of proteinuria, reduced GFR, severe glomerulosclerosis and tubulointerstitial changes on renal biopsy, as well as elevated levels of certain urinary proteins (urinary IgG, α_1 microglobulin and β_2 microglobulin).[18,19] More information is needed to fully evaluate the prognostic value of these and other urinary markers in patients with IMN.

Cattran, Pei and colleagues[4,20,21] have derived a robust model that incorporates clinical observations that are acquired over time to predict the renal outcome of IMN. Patients with normal renal function and proteinuria of <4 g per day during a 6-month observation period are classified as low-risk (<5% risk of renal function deterioration during the next 5 years) and are not usually treated with immunosuppressive regimens. Patients with stable, normal renal function and persistent moderate nephrotic proteinuria (>4 g per day but <8 g per day) during the 6-month observation period are at medium risk of progression. Individuals who have declining renal function or persistent high-grade proteinuria (>8 g per day, regardless of the level of renal function), during the 6-month period are at the highest risk of a poor renal outcome.

When to treat

Opinions differ regarding how long medium-risk and high-risk patients should be observed before they are offered immunosuppressive treatment. Patients with impaired or declining renal function or serious complications of the nephrotic syndrome are usually treated without delay. Other patients with the nephrotic syndrome tend to be observed for variable periods of time whilst receiving conservative treatments that typically include angiotensin receptor blockers or angiotensin-converting-enzyme antagonists, and statins. One treatment algorithm proposes immunosuppression for patients who have had the nephrotic syndrome for 6 or more months despite conservative treatment, in view of the risk of renal function deterioration.[4]

Other researchers propose a more restrictive policy whereby treatment is postponed until renal function declines, on the basis of evidence that therapeutic efficacy is not sacrificed by the delay.[6,22,23] This point is illustrated by the results of a small, randomized, controlled trial from The Netherlands, in which 26 patients were randomized either to immediate treatment with cyclophosphamide plus steroids for 12 months or to delayed treatment with the same regimen upon detection of declining renal function (defined as an increase in serum creatinine level of ≥25% to ≥135 μmol/l).[24] At baseline, patients had normal renal function, mean proteinuria of 12–14 g per day, and were considered to be at high risk of progression to ESRD in view of their elevated urinary levels of β_2 microglobulin and IgG. Overall, the cumulative incidence of remissions was comparable (>90%) between the two groups, but immediate treatment led to more-rapid remission. At final follow-up (mean 70 months), neither renal function nor proteinuria differed between the patients who had received immediate treatment and those who had undergone delayed treatment. Although these results are reassuring, whether such a delay has detrimental effects on long-term renal survival remains to be determined. Prolonged follow-up of large treatment groups will be required to evaluate the possible equivalence of immediate and delayed treatment of IMN.

How to treat

Investigators have explored a range of immunosuppressive regimens for patients with IMN in an effort to optimize the balance between efficacy and toxic effects.

Corticosteroids

Controlled trials have not demonstrated a consistent, sustained benefit of corticosteroid monotherapy in the treatment of membranous nephropathy.[7,9,10,25] These findings are supported by two meta-analyses, which showed that corticosteroids did not improve the likelihood of remission or reduce the risk of ESRD or death compared with symptomatic therapy.[14,26] Steroids are often given in conjunction with other immunosuppressants, particularly alkylating agents.

Alkylating agents

A 6-month regimen consisting of alternating months of corticosteroids and alkylating agents has both short-term and long-term beneficial effects on proteinuria and renal survival.[13,27–31] Ponticelli and colleagues[13] found that this regimen increased remission rates at the final follow-up visit from 36% in untreated patients to 76%, and improved 10-year renal survival from 60% to 92%. Substitution of cyclophosphamide for chlorambucil provides similar efficacy with an improved adverse effect profile.[32]

Table 1 | Selected RCTs of cytotoxic drugs in patients with IMN at moderate risk of progression[a]

Study and year	n	Treatment regimens	Follow-up	CR rate (n)	PR rate (n)	Relapse rate (n)	Comments
Ponticelli et al. (1995)[13,27,28]	42	Months 1, 3, 5: intravenous methylprednisolone 1 g per day for 3 days followed by oral prednisone 0.5 mg/kg per day for 27 days; months 2, 4, 6: chlorambucil 0.2 mg/kg per day	Up to 10 years	52% (22/42)[c]	24% (10/42)[c]	24% (8/34)[d]	Treatment with chlorambucil and steroids significantly increased 10-year dialysis-free survival (0.92 vs 0.60; P=0.0038) and the likelihood of remission compared with symptomatic treatment. Adverse events required drug discontinuation in 10% of chlorambucil-treated patients
	39	Symptomatic treatment (no immunosuppression)		5% (2/39)[c]	31% (12/39)[c]	31% (4/13)[d]	
Ponticelli et al. (1998)[32]	44	Months 1, 3, 5: intravenous methylprednisolone 1 g per day for 3 days followed by oral prednisolone 0.4 mg/kg per day for 27 days; months 2, 4, 6: chlorambucil 0.2 mg/kg per day	Median 36 months	27% (12/44)[e]	55% (24/44)[e]	31% (11/36)[e]	No significant difference in number of remissions between chlorambucil and cyclophosphamide groups. Treatments also led to similar improvements in renal function. Chlorambucil was associated with more adverse events than cyclophosphamide
	43	Months 1, 3, 5: intravenous methylprednisolone 1 g per day for 3 days followed by oral prednisolone 0.4 mg/kg per day for 27 days; months 2, 4, 6: oral cyclophosphamide 2.5 mg/kg per day	Median 42 months	37% (16/43)[e]	56% (24/43)[e]	25% (10/40)[e]	
Jha et al. (2007)[29]	47	Months 1, 3, 5: intravenous methylprednisolone 1 g per day for 3 days, followed by oral prednisolone 0.5 mg/kg per day for 27 days; months 2, 4, 6: oral cyclophosphamide 2 mg/kg per day for 30 days[b]	Median 11 years	32% (15/47)	40% (19/47)	24% (8/34)	Patients treated with steroids and cyclophosphamide had a reduced risk of reaching the composite end point (death, dialysis or doubling of serum creatinine) or progressing to end-stage renal disease
	46	No immunosuppression[b]		11% (5/46)	24% (11/46)	25% (4/16)	

[a]Moderate risk is defined as the presence of nephrotic syndrome and preserved renal function. [b]Angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers were withheld for at least 1 year. [c]Data at the last follow-up visit.[13] [d]Data reported in 1989.[27] [e]Results are based on the 87 of 95 patients who completed 1 year of follow-up. Abbreviations: CR, complete remission; IMN, idiopathic membranous nephropathy; PR, partial remission; RCT, randomized, controlled trial.

The long-term outcomes of a randomized, controlled trial from India are consistent with the above data. Jha and colleagues[29] randomized patients to receive either supportive treatment or 6 months of alternating prednisolone and oral cyclophosphamide therapy. Crossover to the immunosuppressive treatment arm was permitted 24 months after randomization. Compared with patients randomized to receive supportive therapy, those randomized to undergo immunosuppressive treatment had higher rates of remission (72% versus 35%; P <0.0001), higher 10-year dialysis-free survival (89% versus 65%; P = 0.016) and a higher likelihood of survival free of dialysis or doubling of serum creatinine level (79% versus 44%; P = 0.0006). Relapse occurred in approximately one-quarter of patients in both groups, on average 6 months after remission was achieved. Notably, remission rates were lower among patients who switched to immunosuppression as rescue therapy (47%) than among those who were initially randomized to such treatment (72%). This finding contrasts with the results of the Dutch study, which indicated that a delay in therapy did not lead to differences in efficacy.[24]

The aforementioned trials included predominantly medium-risk patients with preserved renal function (Table 1). Several randomized, controlled trials (Table 2) and small, prospective studies have evaluated cytotoxic drug regimens in the high-risk population of patients with reduced or declining GFR.[22,23,30,33–37] A 2004 study from The Netherlands compared renal outcomes between 65 high-risk patients who were treated for 1 year with oral cyclophosphamide plus steroids, and 24 historical matched control patients.[23] The control patients received either no immunosuppressive treatment or treatments that have subsequently proven to be ineffective (prednisone monotherapy or intravenous cyclophosphamide, or both). At baseline, patients in both groups had renal insufficiency (serum creatinine level >135 µmol/l, creatinine clearance <70 ml/min or rise in serum creatinine >50%) and high-grade proteinuria. Approximately 25% of patients treated with the extended regimen of oral cyclophosphamide experienced complete remission and another 60% achieved partial remission. The cumulative incidence of relapse 5 years after remission in the cyclophosphamide group was almost 30%. Nevertheless, immunosuppressive therapy markedly lessened the decline in renal function: more than 90% of patients showed a reduction in serum creatinine level of at least 10% during the first year of treatment. Renal survival at 5 years was significantly higher in the oral cyclophosphamide arm than in the historic controls (86% versus 32%; P <0.001). Infection occurred in 26% of patients who received oral cyclophosphamide.

Despite the favorable results of alkylating agents in IMN, many physicians are reluctant to use these drugs,

Table 2 | Selected immunosuppressive treatment comparisons in patients with IMN at high risk of progression

Study, year and design	n	Treatment regimens	Follow-up (months)	Comments
Falk et al. (1992);[33] RCT	26	Intravenous monthly pulse cyclophosphamide 0.5–1.0 g/m² for 6 months plus pulse methylprednisolone and oral prednisone 1 mg/kg for 2 months, then tapered Alternate-day oral prednisone (2 mg/kg) for 2 months, then tapered	Mean 29	Pulse intravenous cyclophosphamide plus corticosteroids does not improve renal function or renal survival compared with corticosteroids alone
Reichert et al. (1994);[30] RCT	18	Months 2, 4, 6: oral chlorambucil 0.15 mg/kg per day; months 1, 3, 5: pulse methylprednisolone 1 g per day for 3 days, then oral prednisone 0.5 mg/kg per day for 27 days Monthly intravenous pulse cyclophosphamide 750 mg/m² for 6 months plus intravenous methylprednisolone as three 1 g doses in months 1, 3 and 5	Median 15	Oral chlorambucil, but not intermittent pulse cyclophosphamide, improves renal function
Branten et al. (1998);[22] partially randomized	32	Oral cyclophosphamide 1.5–2 mg/kg per day for 12 months, plus steroids (oral prednisone in all cases; 10 patients also received pulse methylprednisolone 1 g per day for 3 days at the start of months 1, 3 and 5) Months 2, 4, 6: oral chlorambucil 0.15 mg/kg per day; months 1, 3, 5: pulse methylprednisolone 1 g per day for 3 days, then oral prednisone 0.5 mg/kg per day for 27 days	Median 26 Median 38	Improvement or stabilization of renal function and remission of proteinuria more frequent with cyclophosphamide regimen than with chlorambucil regimen. Chlorambucil was associated with more adverse events than cyclophosphamide
Cattran et al. (1995);[41] RCT	17	Oral ciclosporin for 12 months (initial dose 3.5 mg/kg per day) Placebo	Mean 48	Ciclosporin was associated with slowing in rate of decline in renal function compared with placebo

Abbreviations: IMN, idiopathic membranous nephropathy; RCT, randomized, controlled trial.

because of concerns that patients, particularly those with reduced GFR, are at increased risk of infection and myelosuppression. Cancer risk is of particular concern when alkylating agents are used for an extended period. An analysis of patients with Wegener granulomatosis reported that cumulative doses of more than 36 g of cyclophosphamide (equivalent to 100 mg daily for one year) were associated with a 9.5-fold increased risk of bladder cancer.[38] Extended courses of cyclophosphamide have also been associated with an increased risk of lymphoproliferative disorders.[38,39]

Relapses occur in 25–30% of patients within 5 years of discontinuation of therapy with alkylating agents. This rate of relapse is lower than that observed after discontinuation of ciclosporin (as discussed below); however, it is still disconcerting since relapses generally necessitate increased immunosuppression, with its attendant adverse effects.[13,23,29,32] Finally, some clinicians doubt the efficacy of alkylating agents in IMN, because a meta-analysis failed to show that these drugs have a beneficial effect on overall mortality or risk of ESRD despite inducing remission of proteinuria.[26] This finding is interesting and curious as it seems to belie the notion that reduction of proteinuria is a surrogate end point for reduction of ESRD risk. However, the average durations of follow-up in most of the trials included in the meta-analysis were too short to observe an effect on the hard end point of renal survival. Furthermore, meta-analyses do not take into account subtle variations in study design that can affect outcomes.

Calcineurin inhibitors
Ciclosporin
Ciclosporin reduces proteinuria and the rate of decline in renal function in patients with IMN. These effects have been demonstrated in patients with preserved renal function, in those with declining or impaired renal function and also in patients resistant to other immuno-suppressants,[40–50] as summarized elsewhere (Tables 2 and 3).[51,52] Several issues deserve to be highlighted. In patients with preserved renal function (Table 3), treatment with ciclosporin for 26 weeks led to more total remissions and complete remissions than placebo. However, high rates of relapse occurred after drug discontinuation: almost 50% of patients who had achieved remission relapsed within 1 year of ciclosporin withdrawal (the majority within 6 months).[40] In high-risk patients with declining renal function (Table 2), 12 months of ciclosporin treatment led to a 50% reduction in proteinuria in half of the patients, and slowed the rate of renal deterioration compared with placebo.[41]

Notably, no prospective, randomized, head-to-head comparisons of ciclosporin and alkylating agents have been conducted in IMN. A retrospective study by Goumenos et al.[48] attempted to address this issue by comparing the outcomes of patients who were treated with the 6-month Ponticelli protocol (steroids plus chlor-ambucil or cyclophosphamide; n = 31) with the outcomes of patients who received ciclosporin (for 2 years) plus steroids (n = 46). The use of the two different therapeutic regimens reflects the change in institutional treatment preference over a 10-year period. Baseline characteristics of the groups were similar. More remissions occurred among the ciclosporin-treated patients than among those treated with the cytotoxic regimen (85% versus 55%; P = 0.004); however, relapses tended to occur more often after ciclosporin treatment than after cytotoxic therapy (41% versus 29%; P = nonsignificant). The design and retrospective nature of the study precludes the drawing of

Table 3 | Selected RCTs of calcineurin inhibitors in patients with IMN at moderate risk of progression[a]

Study and year	Patient profile	n	Treatment regimens	Follow-up (months)	CR rate (n)	PR rate (n)	Relapse rate (n)	Comments
Cattran et al. (2001)[40]	All steroid-resistant; 35% failed cytotoxic drugs; mean proteinuria ~9 g per day; mean CrCl ≥90 ml/min/1.73 m²	28	Ciclosporin (initial dose 3.5 mg/kg per day; target trough level 125–225 μg/l) for 26 weeks, then tapered over 4 weeks; prednisone 0.15 mg/kg per day	Up to 19	7% (2/28)	68% (19/28)	48% (10/21)	More remissions in ciclosporin vs placebo group at 26 weeks (75% vs 22%; P=0.001) and at final follow-up (39% vs 13%; P=0.007). High rate of relapse after ciclosporin discontinuation. Two patients in each group experienced 50% reduction in CrCl by 78 weeks. More cases and greater severity of hypertension in ciclosporin arm
		23	Placebo plus prednisone 0.15 mg/kg per day		4% (1/23)	17% (4/23)	60% (3/5)	
Praga et al. (2007)[53]	Total of 40% previously failed steroids or steroids plus cytotoxic agents; mean proteinuria 7–8 g per day; mean eGFR >100 ml/min/1.73 m²	25	Tacrolimus (initial dose 0.05 mg/kg per day; target trough level 5–8 ng/ml) for 12 months then tapered over 6 months	Up to 30	32% (8/25)	44% (11/25)	47% (9/19)	Tacrolimus-treated patients more likely than conservatively treated controls to achieve remission by 18 months. High rate of relapse after tacrolimus discontinuation
		23	Conservative therapy		13% (3/23)	13% (3/23)	0	

[a]Moderate risk is defined as the presence of nephrotic syndrome and preserved renal function. Abbreviations: CR, complete remission; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; IMN, idiopathic membranous nephropathy; PR, partial remission; RCT, randomized, controlled trial.

definitive conclusions regarding the comparative effects of ciclosporin and alkylating agents in IMN.

The optimal dose and duration of treatment with ciclosporin has been difficult to establish. On the basis of the available data, extended therapy seems to enhance the likelihood of remission. In one analysis, the majority of complete remissions occurred after at least 6 months of therapy, and the number increased as treatment continued for more than 12 months.[43] Thereafter, the combination of low-dose ciclosporin (1.4–1.5 mg/kg per day; trough levels >100 ng/ml) and prednisolone (0.1 mg/kg per day) might be more beneficial than ciclosporin monotherapy for maintaining remission and preventing relapse.[50] Guidelines for the use of ciclosporin in IMN have been published on the basis of recommendations from an international conference.[52]

Tacrolimus
Several investigators have evaluated whether tacrolimus could provide similar efficacy to ciclosporin in IMN.[53–55] Tacrolimus is considered to be more potent than ciclosporin, has a more favorable cardiovascular risk profile and leads to better long-term renal function after renal transplantation.[56–58] In a multicenter study in Spain, Praga et al.[53] randomized 48 medium-risk patients to receive either conservative therapy (controls) or tacrolimus monotherapy for 18 months (Table 3). Patients had preserved renal function and persistent nephrotic syndrome of more than 9 months' duration despite receiving maximal doses of angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers. After 18 months of treatment, the tacrolimus group had a higher percentage of remissions than the control group (76% versus 26%; P=0.003). The overall remission rate achieved with tacrolimus is similar to that reported with ciclosporin

but the rate of complete remissions is greater with tacrolimus. This difference might be, in part, related to the long duration of therapy used in this study (18 months, compared with 26 weeks in the study of ciclosporin by Cattran[40]). Nevertheless, as with ciclosporin, relapses were frequent, occurring in 47% of treated patients within an average of 4 months following discontinuation of tacrolimus.[53] Thus, at final follow-up (30 months), the numbers of remissions were not markedly different between the treatment arms.

Aside from the high incidence of relapse after drug discontinuation (up to 48%), the nephrotoxic effects of calcineurin inhibitors are of concern, particularly if long-term treatment is required as a result of relapses. Managing the use of these agents in patients with reduced GFR can be difficult. In light of this issue, Ponticelli and Villa[59] recommend alternative agents in patients with impaired renal function (creatinine clearance <60 ml/min), severe hypertension or severe interstitial fibrosis and tubular atrophy. Finally, the extent to which calcineurin inhibitors affect the underlying immune process rather than merely modifying disease expression is unclear.[49]

In view of the broad range of toxic effects and the high rates of relapse associated with the use of steroids, alkylating agents and calcineurin inhibitors, alternative treatments have been investigated.

Antimetabolites
Mycophenolate mofetil
Clinical efficacy studies of mycophenolate mofetil (MMF) in IMN have produced mixed results (Table 4).[60–68] In a multicenter study in China, Chan et al.[66] randomized 20 newly diagnosed patients with persistent proteinuria ≥3 g per day to undergo 6 months of treatment with

Table 4 | Selected studies of MMF in patients with IMN

Study, year and design	Patient profile	n	Treatment regimens	Follow-up (months)	CR rate (n)	PR rate (n)	Relapse rate (n)	Comments
Chan et al. (2007);[66] RCT	Treatment-naïve; proteinuria ≥3g per day and preserved renal function	11	MMF 2g per day for 6 months and prednisolone 0.8mg/kg per day, then tapered off by ~6 months	Up to 15	27.2% (3/11)	36.4% (4/11)	29% (2/7)	MMF regimen had comparable efficacy to chlorambucil regimen: similar rate of total remissions (64% vs 67%) and overall proteinuria reduction (4.9g per day to 1.5g per day vs 5.8g per day to 1g per day)
		9	Alternating treatment with steroids (months 1, 3, 5: intravenous methylprednisolone 1g per day for 3 days followed by oral prednisolone 0.4mg/kg per day for 21 days, then 0.2mg/kg per day for 6 days) and oral chlorambucil (0.2mg/kg per day during months 2, 4, 6)		33.3% (3/9)	33.3% (3/9)	17% (1/6)	
Branten et al. (2007);[67] matched historical comparison	High risk; median proteinuria >8g/g creatinine; median eGFR 40ml/min/1.73m²	32	MMF 2g per day for 12 months plus steroids (months 1, 3, 5: intravenous methylprednisolone 1g per day for 3 days; oral prednisone 0.5mg/kg on alternate days for 6 months, followed by tapering)	Median 23	NR	66% (21/32)	57% (12/21) at 2 years	At last follow-up, patients in MMF group were less likely to be in remission than historic controls treated with cyclophosphamide (P=0.021). Similar frequency of infections in the two groups. Nine patients in MMF group and two in cyclophosphamide group were treated after relapse with cyclophosphamide
		32	Daily oral cyclophosphamide 1.5mg/kg per day for 12 months plus similar steroid regimen as MMF group		NR	84% (27/32)	15% (4/27) at 2 years	
Dussol et al. (2008);[68] RCT	Treatment-naïve; nephrotic syndrome; preserved renal function	19	MMF 2g per day plus conservative treatment for 12 months	Up to 12	5% (1/19)	32% (6/19)	NR	No major difference in probability of CR or PR between groups. Kidney function was stable and not different between groups
		17	Conservative treatment for 12 months		12% (2/17)	29% (5/17)	NR	

Abbreviations: CR, complete remission; eGFR, estimated glomerular filtration rate; IMN, idiopathic membranous nephropathy; MMF, mycophenolate mofetil; NR, not reported; PR, partial remission; RCT, randomized, controlled trial.

either MMF plus prednisolone or with a regimen of chlorambucil alternating monthly with corticosteroids. The groups achieved similar remission rates (~65%) and experienced few relapses, which suggests that MMF in conjunction with steroids has similar efficacy to a modified Ponticelli regimen. However, the study was not powered to demonstrate equivalency or non-inferiority, follow-up was limited and only patients with a favorable risk profile were enrolled. Furthermore, the study included only Asian patients; therefore, the favorable results might not be generalizable to other patient populations. Studies of other primary glomerulopathies indicate that ethnicity can influence both prognosis and responsiveness to certain immunosuppressants.[69–71] In support of this concept, a retrospective analysis from Japan suggested that a 4-week course of steroids in patients with IMN led to improved renal survival,[72] which contrasts with the absence of benefit of steroid monotherapy in other ethnic populations.[7,9,10,25]

An open-label trial in The Netherlands evaluated the efficacy of MMF in patients considered to be at high risk of disease progression.[67] The outcomes of 32 patients treated for 1 year with MMF (2 g per day) and steroids were compared with those of historic matched controls treated with oral cyclophosphamide plus corticosteroids for 1 year. Patients in both groups had reduced GFR at baseline (median approximately 40 ml/min) and median proteinuria was >8 g/g creatinine. The two groups achieved similar remission rates (approximately 70%). However, the risk of post-treatment relapse was considerably higher in the MMF group such that by the end of follow-up (median 23 months), patients in the MMF arm were less likely to be in remission than those in the cyclophosphamide control arm (44% versus 75%; P = 0.02). Nevertheless, both treatments resulted in stabilization or improvement of renal function in the majority of patients, and infections and hospitalization occurred at a similar frequency in the two groups. Although the investigators concluded that MMF did not seem to be as effective as nor any better tolerated than cyclophosphamide, this study does suggest that a prolonged course of MMF might be of benefit even in patients with unfavorable baseline characteristics.

In contrast to the above-mentioned studies, responses to MMF in a multicenter randomized, controlled trial in France were poor. Dussol et al.[68] randomized 36 patients to conservative treatment alone (angiotensin-converting-enzyme inhibitors, statins, low-salt and low-protein diet and loop diuretics as needed) or to MMF (2 g per day) plus conservative measures for 12 months. Patients were treatment-naïve, recently diagnosed (<6 months), and had the nephrotic syndrome and preserved renal function. At 1 year, the proportion of remissions was approximately 40% in both groups.

In summary, MMF might have a place in the treatment of IMN, but given its limited and conflicting efficacy

Table 5 | Selected pilot trials of rituximab monotherapy in patients with IMN

Study and year	n	Patient profile	Treatment regimen	Follow-up (months)	CR rate	PR rate	Comments
Remuzzi et al. (2002)[77] Ruggenenti et al. (2003)[78]	8	Mean proteinuria 8.6 g per day; mean CrCl 69 ml/min; all receiving ACE inhibitors	Four doses of 375 mg/m² per week	12	25% (2/8)[a]	50% (4/8)[b]	Mean reduction in proteinuria was 66%
Fervenza et al. (2008)[80]	15	Mean proteinuria 13 g per day; mean CrCl 85 ml/min; all receiving ACE inhibitors or ARBs for at least 4 months	Two 1 g doses (on days 1 and 15); repeated at 6 months if proteinuria >3 g per day and CD19⁺ B cells >15/μl (n=10)	12	14% (2/14)[c,d]	43% (6/14)[d,e]	Mean reduction in proteinuria was 48%

[a]CR was defined as proteinuria ≤0.5 g/24 h. [b]PR was defined as proteinuria ≤3.5 g/24 h or >50% reduction in proteinuria. [c]CR was defined as proteinuria <0.3 g/24 h. [d]Results are based on the 14 patients who completed the trial. [e]PR was defined as proteinuria ≤3 g/24 h and >50% reduction in proteinuria. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CR, complete remission; CrCl, creatinine clearance; IMN, idiopathic membranous nephropathy; PR, partial remission.

data, firm recommendations regarding the use of this agent as initial therapy are difficult to make. MMF might be a reasonable option when the toxic effects of alkylating agents and high-dose steroids are of particular concern or when severe azotemia prohibits use of calcineurin inhibitors. Studies in large numbers of patients with prolonged follow-up are needed to determine the long-term effectiveness of MMF for maintenance of remission and preservation of renal function. Additional information is also needed to fully evaluate the adverse effect profile of MMF. FDA 'black box' warnings indicate that MMF is associated with pregnancy loss and congenital malformations; furthermore, MMF can increase the risk of lymphoma and infection. Cases of JC-virus-associated progressive multifocal leukoencephalopathy in patients with systemic lupus erythematosus receiving MMF have elicited concern. All these considerations must be weighed in the decision to use MMF in IMN.

Azathioprine

Before the use of MMF became widespread, azathioprine was tested as a treatment for IMN in several small studies, with mixed results. A combination of azathioprine and corticosteroids was reported to be beneficial in high-risk patients with declining renal function.[73–75] Some patients experienced reduction in proteinuria and stabilization or improvement of renal function. However, these studies were case series with no control groups and the combined number of patients analyzed (29) was small. In contrast to these favorable findings, a retrospective review from Greece indicated that azathioprine had no long-term benefit in IMN.[76] A total of 33 medium-risk patients with IMN who were treated with azathioprine (for a mean of 26 months) plus prednisone (for approximately 12 months) were compared with 17 patients at the same institution who received no treatment; the decision to treat was based on individual physician preference. Baseline characteristics in the two groups were similar. After 10 years of follow-up, the rates of remission in the treated and untreated groups were not substantially different (51% versus 58%). The risks of doubling of serum creatinine level (42% versus 35%) or reaching ESRD (21% versus 18%) were also similar.

In light of the conflicting evidence regarding the efficacy of azathioprine in IMN and the popularity of MMF, azathioprine is unlikely to be tested in future randomized trials in this setting.

Rituximab

Clinical experience with use of the anti-CD20 antibody, rituximab, in IMN is growing (Table 5).[77–83] Remuzzi, Ruggenenti and colleagues[77,78] in Italy administered four weekly intravenous doses of rituximab (375 mg/m²) to eight high-risk patients who remained nephrotic after 6 months of angiotensin-converting-enzyme inhibitor therapy. Mean proteinuria at baseline was 8.6 g per day and mean creatinine clearance was 69 ml/min. Mean proteinuria decreased by 51% at 3 months and by 66% 1 year after treatment.[78] These investigators subsequently treated 50 consecutive medium-risk or high-risk patients with the same regimen; remission (proteinuria <0.5 g per day) was achieved in 20% and was associated with improvement in ultrastructural findings on repeat renal biopsies.[84]

In a pilot trial, Fervenza et al.[80] used an intravenous rituximab regimen of 1 g on days 1 and 15 to treat 15 patients with IMN who had severe proteinuria (mean 13 g per day, range 8–24 g per day). Half of the patients had failed previous immunosuppressive treatments. After 6 months, 4 patients (27%) achieved partial remission. Ten patients were treated with a second course of rituximab, because they exhibited persistent nephrotic-range proteinuria and recovery of B-cell counts. By 12 months, of the 14 patients who completed the trial, 2 (14%) had achieved complete remission and 6 (43%) had experienced partial remission. Overall, proteinuria was reduced by 48% from baseline to month 12. Five patients showed no response to two full courses of rituximab; two of these individuals progressed to ESRD.

Although the effect of rituximab on CD20-expressing B cells is rapid, the reduction in proteinuria can occur gradually over many months.[78,82] Furthermore, changes in circulating B-lymphocyte counts are not consistently associated with remission or relapse of proteinuria. Nonimmune factors might contribute to the variability in responses to rituximab. In one study, patients with

modest tubulointerstitial injury and fibrosis—as indicated by tubulointerstitial injury scores of <1.7—showed halving of baseline proteinuria within 3 months of rituximab treatment, whereas those with tubulointerstitial injury scores of ≥1.7 did not experience meaningful improvements in proteinuria.[82] On the other hand, Fervenza et al. did not find substantial differences in renal pathology between responders and nonresponders.[80] The discordance in findings between these two studies might be related to baseline differences in the degree of tubulointerstitial disease in the study populations. In the latter trial,[80] patients had more-limited tubulointerstitial disease; thus, detection of differences in response rates on the basis of this histological feature might have been difficult.

The optimal dosing and frequency of rituximab for the treatment of IMN need to be defined. The currently used regimens have been adapted from those approved for non-Hodgkin lymphoma (four weekly infusions of 375 mg/m²) and rheumatoid arthritis (two 1 g doses given two weeks apart), but the pharmacokinetics of rituximab might be different in patients with IMN. High-grade non-selective proteinuria could theoretically lead to loss of rituximab in the urine and thereby decrease the drug's efficacy.[80]

A balanced perspective regarding the toxicity profile of rituximab is needed. Although infusion reactions (including fever, chills, pruritus and skin rash) are often mild and manageable, more severe and potentially fatal reactions have occurred (including acute respiratory distress syndrome, bronchospasm, angioedema, shock and myocardial infarction). The FDA black box warning also indicates that potentially fatal mucocutaneous reactions, such as Stevens–Johnson syndrome and toxic epidermal necrolysis, can occur following rituximab exposure. Severe infections are infrequent, occurring in only 1–2% of patients. Of great concern, rare cases of progressive multifocal leukoencephalopathy have been reported with rituximab use, particularly as part of a multidrug immunosuppressive regimen. Physicians and patients need to be aware of the presenting features of this devastating demyelinating disease of the central nervous system, which include altered mental status, visual symptoms, motor deficits and ataxia.

The preliminary results of rituximab treatment are encouraging, but much remains to be learnt before this agent can be recommended for routine use in IMN. So far, no randomized, controlled trials have been conducted to clarify the role of rituximab in the therapeutic armamentarium for IMN. Adequately powered, randomized, controlled trials with prolonged follow-up are needed to determine the long-term course of the disease following B-cell reconstitution; rates of relapse; subsequent re-dosing regimens; and effects on renal survival. Further studies must clarify whether rituximab should be used as monotherapy or in combination with other immunosuppressive drugs to achieve maximum antiproteinuric effect and durable remission. The preliminary results

of a small, uncontrolled study in Spain suggest that the addition of rituximab to tacrolimus can induce sustained remission of the nephrotic syndrome, allowing early tacrolimus withdrawal and thereby overcoming the issue of tacrolimus dependence.[85]

Adrenocorticotropic hormone

Several small, uncontrolled trials have reported beneficial effects of synthetic adrenocorticotropic hormone (ACTH) in patients with IMN.[86–88] One small, randomized, controlled trial by Ponticelli et al.[89] compared treatment with ACTH for 1 year to a 6-month regimen of methylprednisolone alternating monthly with a cytotoxic agent in 32 (mostly medium-risk) patients with IMN. The probability of complete or partial remission did not differ substantially between the groups (87% versus 93%), and the number of remissions, mean time to response and number of relapses were also comparable between the groups. The small size and limited follow-up of the study (mean 21 months) make it difficult to determine the true risk of relapse and the long-term effect of ACTH on kidney function. Nevertheless, the results suggest that prolonged ACTH treatment could be equivalent to the combined use of cytotoxic drugs and steroids. Adverse effects of ACTH include glucose intolerance, fluid retention, hypertension, diarrhea, bronze discoloration of the skin, dizziness and fatigue, all of which resolve after discontinuation of treatment.

Extensive studies with long follow-up are needed to confirm the preliminary data on the use of ACTH in IMN. Further investigation is also required to elucidate the mechanisms by which ACTH seems to decrease proteinuria and alter apolipoprotein metabolism.[86] These effects are probably not entirely attributable to an increase in endogenous cortisol synthesis, since steroid monotherapy has not been shown to be effective in IMN. Moreover, ACTH therapy can be effective even in patients who are unresponsive to steroids. On the other hand, the endogenous cortisol liberated by the actions of exogenous ACTH might act differently and perhaps more effectively than orally administered steroids.

Sirolimus

The role of sirolimus in IMN has been evaluated in two small pilot studies, with unfavorable results.[90,91] Austin et al.[90] studied the effects of sirolimus in nine patients with IMN and high-grade proteinuria (mean 11.9 g per day). No remissions occurred during therapy, but one patient achieved a partial remission after cessation of therapy. Severe adverse events, including pneumonitis, infection, persistent proteinuria and azotemia, necessitated discontinuation of the drug in the majority of cases. This trial was prematurely terminated owing to the unfavorable risk–benefit ratio. Fervenza et al.[91] had previously conducted an open-label trial of sirolimus in 11 patients with a variety of chronic glomerulopathies and declining renal function, including three with membranous nephropathy. Treatment was associated with

acute kidney injury in more than half of the patients; this event generally occurred within weeks of starting sirolimus. Thus, sirolimus does not seem to have a role in the treatment of IMN.

Conclusions

Cytotoxic agents and calcineurin inhibitors are the most extensively studied agents for the treatment of IMN. Nevertheless, rituximab, ACTH and MMF might have a role in the management of this disease and are appealing options in view of their lack of toxic gonadal, bladder and renal effects. In the future, adequately powered, prospective, randomized studies should compare such alternative agents to standard therapy rather than to placebo, to provide more convincing information about optimal therapy. Unfortunately, as is true for many of the glomerular diseases, randomized controlled trials are difficult to conduct in IMN because of the rarity of the disease and the need to have prolonged follow-up to assess the effect of treatment on renal survival. Up to date information regarding new and ongoing clinical trials in IMN can be found at http://www.clinicaltrials.gov.

Meanwhile, progress continues to be made towards elucidation of the pathogenesis of IMN, including identification of the pathogenic autoantigens.[92–94] Hopefully, an improved understanding of the disease will facilitate the development of targeted therapy to directly modulate the immune process and inhibit disease progression.

Review criteria

Articles were identified from PubMed using the search terms "idiopathic membranous nephropathy" and "treatment" in various combinations with "cyclophosphamide", "chlorambucil", "ACTH", "rituximab", "tacrolimus", "cyclosporine", "mycophenolate mofetil", "azathioprine" and "sirolimus". Relevant abstracts from the most recent meetings of the American Society of Nephrology were also reviewed. Only material published in English was considered.

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