

Treatment of Idiopathic Membranous Nephropathy

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ABSTRACT

Exciting progress recently has been made in our understanding of idiopathic membranous nephropathy, as well as treatment of this disease. Here, we review important advances regarding the pathogenesis of membranous nephropathy. We will also review the current approach to treatment and its limitations and will highlight new therapies that are currently being explored for this disease including Rituximab, mycophenolate mofetil, and adrenocorticotropic hormone, with an emphasis on results of the most recent clinical trials.

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This is an especially exciting time in the history of idiopathic membranous nephropathy (IMN). Our understanding of its natural history and pathogenetic mechanisms has been slowly evolving over several decades but has recently gained more momentum. This, in conjunction with data from recent clinical trials, makes it an ideal time to revisit our approach to patients with IMN.

The recent identification of the M-type phospholipase A₂ receptor (PLA₂R) as the first major human antigenic target in adult onset IMN represents a major milestone in understanding of the pathogenesis of this disease. In 2009, Beck *et al.* reported that the majority of IMN patients (70%) have circulating antibodies against PLA₂R, a cell surface transmembrane receptor expressed on the surface of podocytes.¹ Compelling work from Beck *et al.* suggests that the subepithelium-like deposits, characteristic of IMN, are formed from *in situ* binding of circulating anti-PLA₂R autoantibodies to the PLA₂R antigen. From a historical perspective, the findings of Beck *et al.* come 50 years after Heymann *et al.* first described an experimental model of membranous disease known as Heymann nephritis by

injecting rats with an antigenic preparation of kidney extracts.² Elegant work over several decades on this now well established rat model shed light on the immune events and molecular basis for podocyte injury in membranous lesions and generated hypotheses regarding their relevance in human disease.^{3–9} Indeed, the findings of Beck *et al.* are in agreement with a critical prediction of the Heymann model that circulating autoantibodies directed against a podocyte moiety cause IMN.

The precise biologic function of PLA₂R in the kidney and the effect of anti-PLA₂R on podocytes are still unknown.¹⁰ However, the existing body of evidence supports the following important concepts: autoantibodies reactive to PLA₂R are both sensitive and specific for the disease,^{11,12} autoantibodies seem to discriminate between primary and secondary forms of membranous disease,¹ and there seems to be a relationship (in most, but not all patients) between the titer of circulating anti-PLA₂R and clinical disease activity defined by proteinuria.^{13,14} Moreover, changes in titers of anti-PLA₂R antibody precede corresponding changes in proteinuria.^{13,14} These observations

strengthen the relevance of this antigen-autoantibody pair in IMN. However, it is important to note that causation has yet to be definitively proven.¹⁵

Additional podocyte autoantigens including SOD2,¹⁶ aldose reductase,¹⁶ α-enolase,¹⁷ and neutral endopeptidase¹⁸ are also implicated as targets for specific autoantibodies in some IMN patients. Antibodies to these targets may be relevant in patients who are negative for PLA₂R antibody. Unlike the anti-PLA₂R antibody, correlation of antibody titers for these antigens with disease activity has not been reported to date.

What incites the immune response and triggers the development of these and other autoantibodies remain a mystery.¹⁹ Genetics may play a role. Results of a recent genome-wide association study in a large European cohort suggest that sequence variants within HLA-DQA1 and PLA₂R1 alleles might confer an increased risk of membranous nephropathy in some populations.²⁰

We have only touched the tip of the iceberg, and there is still so much to learn. Nevertheless, what has been uncovered thus far is certainly provocative and will advance our approach to diagnosis, monitoring, and treatment of patients with

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this disease in the near future. Application of new technology is allowing for a much faster transition of these bench-side findings to the bedside, and progress has already been made in developing standardized immunoassays for anti-PLA₂R for use in clinical practice. One can envision how integrating information obtained from genetic testing and antigen-antibody profiling might potentially be applied for individual patient management and in future clinical trials in that it may help to better classify subsets of patients with different prognoses or to predict response to treatment. Measurement of circulating anti-PLA₂R and other antibodies may be used in conjunction with proteinuria to better assess disease activity and provide a more informative definition of clinical remission. Such information might provide insight as to whether persistent proteinuria in patients is related to ongoing immunologic activity, amenable to more immunosuppression, or due to fixed structural damage to glomeruli or tubulointerstitium. Future clinical trials might use such information to identify and enroll a more homogenous population of patients at higher risk of disease progression who would most benefit from immunosuppression. In addition, comparison of efficacy of immunosuppressive agents in trials might involve evaluation of their effect on immune activity, including the timing and kinetics of autoantibody clearance from the circulation.

NATURAL HISTORY OF IMN

As we move forward in our understanding of the pathogenesis of disease in IMN, two recent studies re-examine more basic concepts regarding the natural history of IMN.^{21,22} These concepts were largely derived from studies performed 2–3 decades ago, when antiproteinuric strategies and other supportive measures were implemented inconsistently.^{23–26} Moreover, some of the older studies included patients with non-nephrotic-range proteinuria, a group with an invariably good prognosis.^{25,27} In contrast, these contemporary studies include only nephrotic

patients, make greater use of antiproteinuric strategies, and serve as important references to inform management decisions in these patients.

An impressive multicenter study from the Spanish Group for the Study of Glomerular Disease (GLOSEN) examined the course of a large number of nephrotic IMN patients ($n=328$) who were diagnosed between 1975 and 2007 and followed for an extended period of time (approximately 6 years).²¹ Importantly, because of the possibility of spontaneous remission, all patients were initially managed conservatively; immunosuppressive therapy was withheld until complications arose or deterioration of renal function was evident, an approach that provides greater insight into the natural evolution of this disease. Approximately two-thirds of patients received angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). Almost 32% of patients experienced a spontaneous remission, most of which occurred within the first 2 years of diagnosis, comparable with several other studies.^{23,24,26,28}

Two features regarding spontaneous remissions in the Spanish study²¹ deserve consideration. First, among patients destined to experience a spontaneous remission, proteinuria tended to decline gradually. Moreover, a decrease in proteinuria during the first year of follow-up >50% of baseline (even if still nephrotic) significantly predicted spontaneous remission. Second, spontaneous remissions were observed among some high-risk patients, including approximately 25% of those with severe proteinuria (>8 g/24 h) as well as a number of patients with CKD,²⁹ another subset considered unlikely to undergo spontaneous remission. Consequently, careful observation of some high-risk patients may be appropriate before starting immunosuppressive therapy, particularly if they are not experiencing complications of the nephrotic syndrome or declining renal function and if they are manifesting a gradual decline in proteinuria.

Concordant with previous reports,³⁰ the long-term outcome and renal survival of those with spontaneous remission (either complete or partial) is excellent,

with a 0% risk of ESRD and a 2% mortality rate.²¹ In contrast, outcomes in patients who have persistence of nephrotic-range proteinuria are less favorable, with a 11% mortality rate and a 19% risk of ESRD.

A second contemporary natural history study from the United Kingdom by McQuarrie *et al.* analyzed patients diagnosed between 1997 and 2008.²² Almost all patients were treated with ACE inhibitors and/or ARBs. Consistent with the above data and previous reports,³⁰ this study showed that achieving any remission (spontaneous or treatment-induced) independently associated with a reduced risk of requiring renal replacement therapy (hazard ratio, 0.02; 95% confidence interval, 0.0–0.2; $P=0.001$) and reduced risk of death (hazard ratio, 0.07; 95% confidence interval, 0.02–0.3; $P=0.001$).

Although these contemporary retrospective analyses do have greater implementation of ACE inhibitors or ARBs, they were not designed to formally evaluate whether these drugs have significant benefit on renal prognosis or reduction of proteinuria in IMN. Some investigators note that responsiveness to these agents is less impressive in IMN compared with other types of glomerular disorders, which has raised questions about their role in this disorder.^{31–33} In the GLOSEN study, the probability of spontaneous remission was higher in patients taking ACE inhibitors or ARBs than those not receiving these agents ($P=0.009$).²¹ In the study by McQuarrie *et al.* in which there was widespread use of ACE inhibitors/ARBs, the 5-year actuarial rate for spontaneous partial remission was remarkably high at 70%.²² These data hint, but do not prove, that ACE inhibitors and ARBs have favorable effects on the disease. In contrast, other studies failed to demonstrate an effect of ACE inhibitors on renal outcome in IMN.^{30,32,34,35} This issue cannot be definitively answered without a controlled trial. For now, given that treatment with ACE inhibitors and ARBs has proven benefits in other kidney diseases and may result in some improvement in proteinuria, hypoalbuminemia, and hyperlipidemia, these agents should remain as part of standard conservative treatment for IMN.^{36–38}

IMMUNOSUPPRESSION

Immunosuppressive therapies that have received the most attention for IMN include alkylating agents such as cyclophosphamide and chlorambucil, calcineurin inhibitors (CNIs) such as cyclosporine and tacrolimus, mycophenolate mofetil (MMF), rituximab, and adrenocorticotropic hormone (ACTH). Table 1 shows the commonly used regimens, although many variations exist. There is a lack of well powered, randomized, controlled trials that formally compare therapies. The quality of the existing evidence for these different regimens in IMN is variable. Comparisons among studies are hampered by differences in the risk profiles²⁸ of the patients and variable duration of follow-up, among other factors.

Alkylating Agents

Table 2 depicts results of several studies examining the efficacy of two very different approaches to cytotoxic drug therapy for IMN. Ponticelli *et al.* and Jha *et al.* used a 6-month regimen consisting of daily oral chlorambucil or cyclophosphamide, alternating monthly with corticosteroids.^{39–41} Their patients

had nephrotic-range proteinuria and normal or near normal renal function. Conversely, investigators from the Netherlands have described outcomes of an extended course, typically 12 months (Table 1), of daily oral cyclophosphamide and corticosteroids in patients with nephrotic syndrome and deteriorating renal function.^{34,42}

Both Ponticelli *et al.* and Jha *et al.* found that alternating monthly cycles of corticosteroids and an alkylating agent were more effective than supportive therapy alone for inducing remissions of proteinuria and preserving renal function.^{40,41} Ponticelli *et al.* found that substitution of cyclophosphamide for chlorambucil provides similar efficacy with an improved adverse event profile.⁴³

Jha *et al.* permitted crossover to the immunosuppressive treatment arm 24 months after randomization to supportive treatment.⁴¹ It is notable that remission rates were lower among patients who switched to immunosuppression as rescue therapy (47%) than among those who were initially randomized to immunosuppression (72%), suggesting that delay in immunosuppressive therapy until evidence of disease progression diminishes efficacy.

Studies reported by du Buf-Vereijken *et al.* and Hofstra *et al.* from the Netherlands provide additional insights into the effect of delaying cytotoxic drug therapy for IMN until there is evidence of renal function deterioration.^{34,42,44} These investigators favor this restrictive treatment policy because it identifies patients at highest risk of progression and avoids unnecessary immunosuppression in patients with a more favorable prognosis. A beneficial effect of this approach in attenuating deterioration of renal function was shown in the case-controlled study of high-risk IMN patients reported by du Buf-Vereijken *et al.*³⁴ Renal outcomes of 65 patients treated for 1 year with oral cytoxan and steroids were compared with 24 historical matched control patients. Control patients received either no immunosuppression or treatments that have subsequently proven to be ineffective (prednisone monotherapy, intravenous cyclophosphamide, or both). Patients had an impaired GFR at baseline (median creatinine clearance of 42 ml/min per 1.73 m²) and high-grade proteinuria. Remission of proteinuria was achieved in 86% of 65 patients receiving immunosuppressive therapy (Table 2). At 5 years, a

Table 1. Immunosuppressive regimens that have been used in treatment of IMN

Immunosuppression Agent	Regimen
Alkylating agents	Italian Ponticelli protocol
	Months 1, 3, and 5: 1 g/d intravenous methylprednisolone for 3 consecutive d, followed by oral prednisolone 0.4 mg/kg daily or oral prednisone 0.5 mg/kg daily for 27 d
	Months 2, 4, and 6: 0.2 mg/kg oral chlorambucil daily for 30 d
	Modified Ponticelli protocol
Cyclosporine, tacrolimus	Months 1, 3, and 5: 1 g/d intravenous methylprednisolone for 3 consecutive d, followed by oral prednisone 0.5 mg/kg daily for 27 d
	Months 2, 4, and 6: 2–2.5 mg/kg oral cyclophosphamide daily for 30 d
	Dutch protocol ³⁴
	1.5–2 mg/kg oral cyclophosphamide daily for 12 mo plus 0.5 mg/kg oral prednisone daily or every other day for 6 months and then tapered, plus 1 g/d intravenous methylprednisolone for 3 consecutive days for months 1, 3, and 5
MMF	3.5 mg/kg cyclosporine daily, achieving levels of 125–200 μg/L for a minimum of 6–12 mo, then tapered to lowest possible maintenance dose (± low-dose corticosteroids)
	0.05 mg/kg tacrolimus daily achieving levels 7–9 for 6–12 mo, then tapered to lowest possible maintenance dose (± low-dose corticosteroids)
Rituximab	2 g/d MMF for 1 yr ± low-dose corticosteroids
	375 mg/m ² weekly for four doses
ACTH	1 g on days 1 and 15
	375-mg/m ² single doses, titrated to the number of circulating B cells
	1 mg tetracosactrin injected intramuscularly twice weekly for 6–12 mo
	80 U corticotropin injected intramuscularly twice weekly for 6–12 mo

Table 2. Selected studies of alkylating agents in patients with IMN

Study	N	Treatment Regimen	Follow-Up	Initial Remission Rate		Relapse Rate (Timing)	Effect on Renal Survival
				CR	PR		
Ponticelli et al. (1989 and 1995) ^{39,40}	42	Months 1, 3, and 5: steroids ^a ; months 2, 4, and 6: 0.2 mg/kg chlorambucil daily	Up to 10 yr	57 (24/42)	24 (10/42)	24 (8/34)	Dialysis-free 10-yr survival: 92
Ponticelli et al. (1998) ⁴³	39	No immunosuppression	Median 3 yr	18 (7/39)	15 (6/39)	31 (4/13)	Dialysis-free 10-yr survival: 60 1 patient (2%) reached ESRD after 42 mo
	44	Mo 1, 3, and 5: steroids ^b ; months 2, 4, and 6: 0.2 mg/kg chlorambucil daily		27 (12/44)	55 (24/44)	31 (11/36) (between 6 and 30 mo)	
Jha et al. (2007) ⁴¹	43	Mo 1, 3, and 5: steroids ^b ; months 2, 4, and 6: 2.5 mg/kg cyclophosphamide daily	Median 3.5 yr	37 (16/43)	56 (24/43)	25 (10/40) (between 6 and 24 mo)	2 patients (4%) reached ESRD after 36 mo
	47	Mo 1, 3, and 5: steroids ^c ; months 2, 4, and 6: 2 mg/kg cyclophosphamide daily	Median 11 yr	32 (15/47)	40 (19/47)	24 (8/34)	10-yr dialysis-free survival: 89
du Buf-Vereijken (2004) ³⁴ (not randomized; matched historical comparison)	46	No immunosuppression	Median 11 yr	11 (5/46)	24 (11/46)	25 (4/16)	10-yr dialysis-free survival: 65
	65	1.5–2 mg/kg oral cyclophosphamide daily for 12 mo plus steroids ^d	Median 4.3 yr	26 (17/65)	60 (39/65)	20 (11/56)	5-yr dialysis-free survival: 86
Hofstra et al. (2010) ⁴²	24	No treatment or various immunosuppressive agents subsequently considered ineffective	Mean 6 yr	NA	NA	NA	5-yr dialysis-free survival: 32
	14	Early start: 1.5 mg/kg oral cyclophosphamide daily for 12 mo plus steroids ^c		64 (9/14)	29 (4/14)	23 (3/13) (median 36 mo after treatment)	1 patient (7%) reached ESRD
	12	Late start: 1.5 mg/kg oral cyclophosphamide daily for 12 mo plus steroids ^c	Mean 6 yr	67 ^e (8/12)	25 (3/12)	27% (3/11) (median 38 mo after treatment)	0 patients reached ESRD

Data are expressed in percentages unless otherwise indicated. CR, complete remission; PR, partial remission; NA, data not available.

^aDosages at months 1, 3, and 5: 1 g intravenous methylprednisolone daily for 3 days, followed by 0.4 mg/kg oral prednisolone daily or 0.5 mg/kg oral prednisolone daily for 27 d. Dosage at mo 2, 4, 6: 0.2 mg/kg chlorambucil daily.

^bDosages at months 1, 3, and 5: 1 g intravenous methylprednisolone daily for 3 days, followed by 0.4 mg/kg oral prednisolone daily for 27 d.

^cDosages at months 1, 3, and 5: 1 g intravenous methylprednisolone daily for 3 days, followed by 0.5 mg/kg oral prednisolone (or prednisolone) daily.

^dDosages at months 1, 3, and 5: 1 g intravenous methylprednisolone daily for 3 days, followed by 0.5 mg/kg oral prednisolone every other day for 6 mo and then tapered.

^eIncludes four spontaneous remissions that occurred during the observation period.

renal survival advantage was evident in cyclophosphamide-treated patients compared with controls (86% versus 32%; $P < 0.001$). The renal survival of these cyclophosphamide-treated patients at 7 years was 74%, which is somewhat lower than the 10-year renal survival of patients with normal baseline renal function treated with a cytotoxic drug regimen by Ponticelli *et al.*⁴⁰ (92%).

Hofstra *et al.* recently reported the results of a small but well designed study comparing early versus late initiation of immunosuppressive treatment.⁴² Patients were randomized to receive oral cyclophosphamide for 12 months plus corticosteroids early after diagnosis ($n=14$) or later if renal function deteriorated ($n=12$), defined as an increase of serum creatinine $\geq 25\%$ reaching a level of ≥ 135 $\mu\text{mol/L}$ or an increase of serum creatinine $\geq 50\%$. In the late treatment arm, 67% of patients ultimately met criteria for immunosuppression after a median of 14 months from randomization. Overall cumulative incidence of remission was similar in both the early and late treatment arms (93% versus 92%, respectively) but earlier treatment resulted in more rapid onset of remission. Relapse rates were similar. At final follow-up (mean 72 months), there were no differences in clinical status, proteinuria, or renal function in either group, with the latter observation indicating that immunosuppressive treatment led to an improvement in renal function in the late treatment arm (because those patients started out with a lower average GFR). The good overall outcomes do provide reassurance that delaying therapy is justified in some patients. By delaying treatment, 33% of patients avoided unnecessary exposure to immunosuppression. However, delayed treatment was associated with more frequent and severe side effects and more hospitalizations. An individualized approach that considers age, pre-existing comorbidities, and risk of treatment versus risk of complications of the nephrotic syndrome is critical when deciding on therapy.

Despite the favorable results with alkylating agents, there is reluctance to prescribe them due to the short-term and potential long-term adverse effects. Short-term

effects include myelosuppression, especially leucopenia infections, hemorrhagic cystitis, and gastrointestinal problems such as peptic ulcers, nausea, anorexia, and liver dysfunction. Risk of infertility remains a concern for patients in childbearing years. Cancer risk remains a long-term worry, particularly since the cumulative dosage of cyclophosphamide increases if repeat courses are needed after relapse. The Ponticelli regimen entails 3 months of cyclophosphamide (2 mg/kg daily), which is a cumulative dose of approximately 13 g in a 70-kg patient. The 12-month regimen³⁴ (using 1.5 mg/kg daily) represents a cumulative dose of approximately 40 g in a 70-kg patient. Several studies have reported threshold values for cumulative doses of cyclophosphamide, above which is associated with increased risk of malignancies such as bladder cancer, skin cancer, and lymphoproliferative disorders. Older studies report an increased risk of malignancy with cumulative doses > 50 g,^{45,46} whereas more recent studies suggest that exposure to lower cumulative dosages may also pose an increased risk.⁴⁷

CNIs

Cyclosporine is an established option for treatment of IMN patients at moderate or high risk of disease progression.⁴⁸ Tacrolimus, another CNI, is an alternative.^{49,50} Cumulative data indicate that CNIs are effective in inducing a remission of proteinuria in up to 80% of patients (Table 3).^{49–52} CNIs show favorable responses in patients who have been unresponsive to other immunosuppressants, including alkylating agents.^{51–54} In a recent randomized controlled trial in which all patients had previously failed the Ponticelli protocol, treatment with cyclosporine for 2 years (plus low-dose prednisone) led to remissions in 80% of patients and stabilization of renal function.⁵²

The antiproteinuric effect of CNIs is typically evident early. Generally, if some response in proteinuria is not present by 3 months (provided adequate drug levels are achieved), it is unlikely that a significant response will occur later. However, time to maximum reduction of proteinuria takes longer. Although optimal duration of therapy has not been established,

extended therapy for at least a year is recommended for patients who show an initial response to these agents, because the number of remissions and proportion of complete remissions increases with duration of treatment.⁵³

The majority of complete remissions with CNIs occur after at least 6 months of therapy and the number increases as treatment continues for > 12 months. This concept is supported by several studies.^{49,52,53,55} A prospective study by Naumovic *et al.* recently showed that a prolonged course of cyclosporine for 24 months led to a steady increase in cumulative remission rates from 50% at 6 months to 80% by 18 months, and complete remissions increased from 0 at 6 months to 40% by 18 months.⁵² Mean time to partial remission was 9.7 months (range, 3–18 months), and mean time to complete remission was 15 months (range, 9–18 months). These outcomes are consistent with the results of earlier studies reported by Cattran *et al.*⁵¹ and Praga *et al.*⁴⁹ (Table 3). Cattran *et al.* found that a 6-month course of cyclosporine led to complete remissions in only 7% of his patients,⁵¹ whereas Praga *et al.* observed complete remissions in 32% of patients after 18 months of tacrolimus treatment.⁴⁹

Relapse upon drug withdrawal is a well recognized problem with CNIs, occurring in 13% to almost 50% of patients within 1 year of drug withdrawal.⁴⁹ In the above-mentioned study by Praga *et al.*, 47% of patients randomized to tacrolimus relapsed within an average of 4 months after discontinuation of therapy such that by final follow-up, the number of remissions in the tacrolimus arm was not markedly different from the placebo arm.⁴⁹ These data provide additional justification for long-term treatment. Maintenance therapy with low-dose cyclosporine (1.4–1.5 mg/kg daily; trough levels > 100 ng/ml), possibly in conjunction with low-dose steroids (0.1 mg/kg daily), may help to reduce the likelihood of relapses⁵⁵; however, this practice has not been formally tested in randomized controlled trials.

The role of CNIs in attenuating a decline in renal function and the long-term

Table 3. Selected randomized controlled trials of CNIs in patients with IMN and evolution of remissions over time

Study	n	Treatment (Total Duration)	Follow-Up (mo)	Remissions						Relapse Rate (n) [Time to Relapse]			
				6 mo		12 mo		24 mo					
				CR	PR	Total	CR	PR	Total	CR	PR	Total	
Cattran et al. (2001) ⁵¹	28	3.5 mg/kg cyclosporine daily (26 wk); target trough 125–225 µg/ml for 26 wk, then tapered for 4 wk plus 0.15 mg/kg prednisone daily	Up to 19	7 (2/28)	68 (19/28)	75	7 (2/28)	39 (11/28)	46	7 (2/28) ^a	32 (9/28) ^a	39 ^a	48 (10/21) [within 12 mo of drug cessation]
	23	Placebo plus 0.15 mg/kg prednisone daily		4 (1/23)	17 (4/23)	21	4 (1/23)	9 (2/23)	13	4 (1/23)	9 (2/23)	13	40 (2/5)
Naumovic et al. (2011) ⁵²	10	3 mg/kg cyclosporine daily for 6 mo, then adjusted to achieve trough levels of 80–100 ng/ml (24 mo) plus 0.5 mg/kg prednisone daily for 8 wk, then tapered	36	0	50 (5/10)	50	10 (1/10)	40 (4/10)	50	40 (4/10)	40 (4/10)	80	13 (1/8) [within 12 mo of drug cessation]
	13	1.5–2 mg/kg azathioprine daily for 6 mo, then 50 mg daily (24 mo) plus 0.5 mg/kg prednisone daily for 8 wk, then tapered		7 (1/13)	77 (10/13)	84	0	92 (12/13)	92	31 (4/13)	62 (8/13)	92	42 (5/12) [within 12 mo of drug cessation]
Praga et al. (2007) ⁴⁹	25	0.05 mg/kg tacrolimus daily for 12 mo (through level 5–8 ng/ml), then tapered over 6 mo (18 mo)	Up to 30	12 (3/25)	44 (11/25)	56	24 (6/25)	48 (12/25)	72	32 (8/25) ^a	44 (11/25) ^a	76 ^a	47 (9/19) [within 12 mo of drug cessation]
	23	Conservative		9 (2/23)	4 (1/23)	13	17 (4/23)	4 (1/23)	21	13 (3/23) ^a	13 (3/23) ^a	26 ^a	0
Chen et al. (2010) ⁵⁰	39	0.1 mg/kg tacrolimus daily for 6 mo; target trough 5–10 ng/ml, then adjusted for trough 2–5 ng/ml (9 mo) plus 1 mg/kg prednisone daily for 4 wk, then tapered over 8 mo	12	28 (11/39)	56 (22/39)	85	NA	NA	79	NA	NA	NA	18 (6/33) [within 3 mo of drug cessation]
	34	100 mg/d cytoxan (4 mo) plus 1 mg/kg prednisone daily for 4 wk, then tapered over 8 mo		26 (9/34)	38 (13/34)	65	NA	NA	69	NA	NA	NA	22 (5/23)

Data are expressed in percentages unless otherwise indicated. CR, complete remission; PR, partial remission; NA, data not available.

^aRemission rates reported at 18 mo (24-mo remission status not provided).

effect on renal survival in IMN are less clear due to lack of longitudinal studies.^{56,57} Cattran *et al.* reported reduced rates of deterioration of renal function with cyclosporine in one small study of high-risk patients.⁵⁶ In a study design similar to that used by du Buf-Vereijken *et al.*,^{34,44} 65 patients with IMN were initially followed conservatively for 12 months. Only patients with clear evidence of declining renal function and persistent nephrotic-range proteinuria during the observation period were randomized to receive treatment with cyclosporine for 12 months or placebo. Of 65 patients, 23 (36%) met criteria for randomization. Compared with placebo, cyclosporine-treated patients demonstrated significantly reduced proteinuria (halving of proteinuria in 50% of treated patients versus no improvement in placebo patients) and slower rates of decline in kidney function as measured by change in the slope of creatinine clearance. These improvements were sustained in 75% of the patients for up to 2 years post-treatment. Fewer patients in the treated group progressed to end stage (11% versus 50%, respectively). In contrast, a controlled trial by the Cyclosporine in Membranous Nephropathy Study Group failed to demonstrate any long-term benefits of cyclosporine when used in patients with deteriorating renal function.⁵⁸ In light of the nephrotoxic potential of calcineurin inhibitors, caution and close monitoring of blood drug levels and renal function are advised if CNIs are initiated in patients with an impaired GFR at the start of therapy and/or severe tubulointerstitial damage on renal biopsy.

No prospective randomized head-to-head comparisons of cyclosporine (or tacrolimus) to standard regimens of alkylating agents have been conducted. A retrospective study by Goumenos *et al.* attempted to address this issue by comparing the outcomes of patients who were treated with a 6-month Ponticelli protocol (steroids plus chlorambucil or cyclophosphamide; $n=31$) with those treated with cyclosporine for 2 years plus steroids ($n=46$).⁵⁹ The use of different therapeutic regimens in the two groups reflects institutional treatment preferences

over a 10-year period. Baseline characteristics of the groups were similar. More remissions occurred among the cyclosporine-treated patients than among those receiving alkylating agents (85% versus 55%; $P=0.004$). Relapses tended to occur more often in the cyclosporine-treated group but the differences were not significant (41% versus 29%, respectively). During a mean follow-up of 48 ± 36 months there were no differences in rates of doubling of serum creatinine between treatment groups (26% versus 23%, respectively) or requirement for renal replacement therapy. However the design and retrospective nature of the study preclude definitive comparisons of these therapies for IMN.

A recent multicenter randomized controlled trial from China compared efficacy of tacrolimus with an abbreviated course of cytoxan in 73 patients with IMN.⁵⁰ Patients were randomized to receive tacrolimus for 9 months or 4 months of daily oral cytoxan (100 mg/d). Both groups received oral prednisone. Cumulative remission rates at 6 months were greater in the tacrolimus arm than the cytoxan arm (85% versus 65%, $P<0.05$); however, remission rates were comparable by 12 months. Relapse rates between the two groups were similar (18% versus 23%), leading the authors to conclude that short-term efficacy of tacrolimus plus steroids might be better than cyclophosphamide plus steroids. Several issues limit the conclusions that can be drawn from this study. Tacrolimus was not compared with one of the standard cytoxan-containing regimens. Follow-up was very short, which may underestimate true relapse rates. Last, there was inconsistent use of ACE inhibitors and ARBs, which favored the tacrolimus group.

Currently, there is a three-arm randomized controlled trial in progress in the United Kingdom that compares supportive therapy versus 12 months of cyclosporine versus 6 months of alternating prednisolone/chlorambucil in patients with progressive IMN. The results of this trial are eagerly awaited and should provide information regarding this important group of patients.

Rituximab

Of the newer agents being explored for IMN, rituximab has emerged as the most likely candidate to be incorporated into treatment guidelines. Although it has yet to be tested in randomized controlled trials and there is a lack of longitudinal data, important groundwork has been laid since its first reported use for IMN in 2002.⁶⁰ Most of the reported experiences with rituximab are from uncontrolled pilot trials or case series from two centers in Bergamo, Italy, and the Mayo Clinic in the United States.^{60–67}

The following treatment protocols have been tried for IMN (Table 1): four weekly doses of 375 mg/m^2 , which is standard dosing for treatment of lymphoma; two 1000-mg doses given biweekly, which is standard for rheumatoid arthritis; and a B cell–driven protocol in which dosing is titrated to the number of circulating B cells.⁶³ The pharmacokinetics of rituximab in nephrotic patients differ from that in nonproteinuric patients treated with identical protocols,⁶⁵ prompting interesting questions about the optimal dosing regimen for IMN. Compared with nonproteinuric patients, rituximab levels are lower and recovery of CD20-expressing B cells typically occurs earlier in nephrotic patients. However, among nephrotic patients with IMN, the four-dose lymphoma and two-dose arthritis regimens seem to have similar efficacy despite faster B cell recovery after the two-dose regimen.⁶⁶ Consistent with these conclusions, a recent retrospective analysis of banked serum samples showed no detectable differences in the progressive reduction of anti-PLA₂R levels between the two dosing regimens.¹⁴

Regardless of the regimen administered, proteinuria tends to decline slowly and remissions may occur up to 2 years after treatment (Table 4). Interestingly, Beck *et al.* showed that after administration of rituximab, the median time to reach undetectable anti-PLA₂R levels was 9 months (range, 1–18 months).¹⁴ This may explain the delay in remissions, because the reduction in antibody levels seems to precede the decline in proteinuria by months.

Table 4. Selected studies of rituximab for IMN and evolution of remissions over time

Study	n	Treatment Regimen	Remissions						Relapse Rate (n) [Time to Relapse]				
			6 mo		12 mo		24 mo						
			CR	PR	Total	CR	PR	Total		CR	PR	Total	
Remuzzi et al. (2002) ⁶⁰ and Ruggenenti et al. (2003) ^{61,a}	8	Four doses of 375 mg/m ² per wk	0	63 (5/8) ^a	63	0	63 (5/8) ^a	63	NA	NA	NA	NA	NA
Cravedi et al. (2011) ⁶⁴	22 ^b	375 mg/m ² per wk for 4 wk or 375 mg/m ² for 1 wk; redosed when ≥5 B cells/mm ³	0	0	0	18 (2/11)	45 (5/11)	63	27 (3/11)	45 (5/11)	72	13 (1/8) [within 24 mo]	14 (1/7) [within 24 mo]
Fervenza et al. (2008) ⁶⁵	15	Two 1-g doses (on days 1 and 15); repeated at 6 mo if proteinuria > 3 g/d and CD19+B cells > 15/μl	0	29 (4/14)	29	14 (2/14)	43 (6/14)	57	NA	NA	NA	NA	NA
Fervenza et al. (2010) ⁶⁶	20	Four doses of 375 mg/m ² per week; repeated at 6 mo	0	40 (8/20)	40	0	50 (10/20)	50	20 (4/20)	60 (12/20)	80	6 (1/16)	

Data are expressed in percentages unless otherwise indicated. CR, complete remission; PR, partial remission; NA, data not available.

^aRemission status was standardized for ease of comparison. CR defined as proteinuria <0.3 g/d; PR defined as proteinuria ≤3.5 g/d and a 50% reduction from peak value.

^bEleven patients were given rituximab as first-line therapy, and 11 patients were given rituximab as second-line therapy.

It is interesting to note that remissions continue to occur well after the end of therapy with rituximab or alkylating agents; complete remissions can be seen >12 months after the completion of these interventions. This is in contrast to what is observed after cyclosporine or tacrolimus, in which typically no additional remissions occur once treatment stops.

Relapse rates after rituximab therapy are difficult to estimate given the limited longitudinal data. There are two published studies ($n=31$) that followed patients for up to 24 months^{64,66} and relapses were infrequent (6% and 13%, respectively). It is hoped that forthcoming studies with extended follow-up will provide much needed information. Such data may inform decisions regarding role and timing of redosing.

Currently, there are no established guidelines regarding the issue of retreatment and investigators have taken different approaches. In one study, Fervenza *et al.* retreated patients with rituximab after 6 months, only if B cells recovered (B cells $\geq 15/\mu\text{l}$) and patients had nephrotic-range proteinuria.⁶⁵ In another study from the same institution, all patients were retreated 6 months after the first course of rituximab, regardless of clinical status.⁶⁶ Remuzzi *et al.* have redosed rituximab (with single doses of 375 mg/m²) when there is evidence of relapse of nephrotic-range proteinuria (rather than empirical retreatment).⁶³ Whether empirical redosing at 6 months, or other predefined intervals, provides added benefit with respect to durability of remissions or number of remissions is not clear. In light of the preliminary observation that re-emergence of anti-PLA₂R antibody in the circulation precedes recurrence of disease, serial measurements of the antibody may help guide decisions regarding retreatment.

There are several advantages of rituximab that add to its appeal. It appears effective as monotherapy, and the side effect profile may be more favorable than with other agents (*i.e.*, with no hypertension or potential for nephrotoxicity). Conversely, the long delay in reduction of proteinuria may be problematic in patients who suffer from severe complications of nephrotic

syndrome. Combining rituximab with an abbreviated course of another agent that has a quicker onset of antiproteinuric effects (CNIs) is an approach that we are currently investigating.

We do need to have a balanced perspective regarding the toxicity profile of rituximab. Although acute infusion reactions are often mild and manageable (*e.g.*, fever, chills, pruritus, and skin rash), more severe and potentially fatal reactions (*e.g.*, acute respiratory distress syndrome, bronchospasm, angioedema, shock and myocardial infarction) as well as potentially fatal mucocutaneous reactions (*e.g.*, Stevens–Johnson syndrome and toxic epidermal necrolysis) can occur. Rare cases of the devastating demyelinating central nervous system disease, progressive multifocal leukoencephalopathy, have also been reported, although typically when administered as part of multidrug immunosuppressive regimens. Finally, the long-term safety profile of rituximab in glomerular diseases is largely unknown, particularly if repeated courses are needed.

Controlled prospective trials are needed to compare the efficacy and toxicity of rituximab with CNIs and cytotoxic drugs. More data are needed to clarify the role of rituximab in patients with impaired or declining renal function and the effects of rituximab on hard endpoints such as dialysis and death. A randomized controlled trial comparing rituximab with

cyclosporine is underway and hopefully will provide much needed answers.

MMF

Encouraging results from early, uncontrolled series published almost a decade ago indicated a potential role of MMF in the management of high-risk patients with IMN.^{68–72} Subsequent studies have produced mixed results (Table 5).^{73–76} A multicenter randomized controlled trial from France reported cumulative remission rates after 1 year of MMF that were no different from conservative therapy (approximately 40%).⁷³ Two other studies suggested that treatment with MMF had similar efficacy as a regimen consisting of alkylating agents plus steroids.^{74,75} A multicenter trial from China by Chan *et al.* randomized 20 treatment-naïve, newly diagnosed nephrotic patients to undergo 6 months of treatment with MMF (2 g/d) plus prednisolone or with a regimen of chlorambucil alternating with corticosteroids.⁷⁴ The treatment arms achieved similar remission rates (approximately 65%) at 15 months and experienced few relapses. To note, the study was not powered to demonstrate equivalency or noninferiority, follow-up was too short to evaluate relapse or renal survival outcomes, and only patients with a favorable risk profile were enrolled. Furthermore, only Asian patients were included. On the basis of studies of other primary glomerulopathies,

Asian ethnicity may be associated with a relatively favorable prognosis and increased responsiveness to certain immunosuppressive regimens.^{77–79}

A trial from the Netherlands compared outcomes of 32 IMN patients treated with 1 year of MMF plus corticosteroids with historical matched controls treated with oral cyclophosphamide plus corticosteroids for 1 year.⁷⁵ Patients were considered at high risk for progressive disease with reduced GFR at baseline (median approximately 40 ml/min) and high-grade proteinuria. The two groups achieved similar initial remission rates (approximately 70%). Renal function stabilized or improved in the majority of patients during the year of therapy with MMF. However, the post-treatment relapse rate 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 cytoxan arm (44% versus 75%; $P=0.02$).

Post-treatment relapse is problematic. In the trial by Branten *et al.*, 57% of patients relapsed within 2 years and some relapses occurred during active treatment.⁷⁵ Of interest, relapse is also a concern after treatment with the related older antimetabolite, azathioprine.^{80,81} A recent study showed that 12 months of azathioprine induced remissions in a large percentage of patients who had previously been refractory to

Table 5. Selected studies using MMF in IMN

Study	Study Type	n	Treatment Regimen (Duration)	Follow-Up (mo)	Remissions (Initial)			Relapse Rate (n) [Time to Relapse]
					CR	PR	Total	
Chan <i>et al.</i> (2007) ⁷⁴	RCT	11	2 g/d MMF (6 mo) plus prednisone (0.8 mg/kg daily tapered over 6 mo)	Up to 15	27 (3/11)	36 4/11	63	29 (2/7) [within 2–8 mo after achieving remission]
		9	Modified Ponticelli protocol ^a		33 (3/9)	33 3/9	66	
Branten <i>et al.</i> (2007) ⁷⁵	Historical matched comparison	32	2 g/d MMF (12 mo) plus steroids ^b	Median 23	NR	66 (21/32)	66	57 (12/21) [within 2 yr]
		32	1.5 mg/kg oral cytoxan daily (12 mo) plus steroids ^b		NR	84 (27/32)	84	
Dussol <i>et al.</i> (2008) ⁷³	RCT	19	2 g/d MMF (12 mo)	Up to 12	5 (1/19)	32 (6/19)	37	NR
		17	Conservative		12 (2/17)	29 (5/17)	41	NR

Data are expressed in percentages unless otherwise indicated. CR, complete remission; PR, partial remission; RCT, randomized controlled trial. NR, not reported.

^aSteroid dosage during mo 1, 3, and 5: 1 g/d intravenous methylprednisolone for 3 d, 0.4 mg/kg oral prednisolone daily for 21 d, and then 0.2 mg/kg daily for 6 d; mo 2, 4, and 6: 0.2 mg/kg oral chlorambucil daily.

^bDosage of 0.5 mg/kg oral prednisone every other day for 6 mo and then tapered, plus intravenous methylprednisolone 1g/d for 3 days during months 1, 3, and 5.

the Ponticelli protocol.⁵² However, within 6 months of azathioprine withdrawal, 33% relapsed.

Although the initial enthusiasm regarding MMF has quieted, a place for MMF in treatment of IMN cannot be discounted at this point. However, until more data become available, it is difficult to recommend MMF as initial therapy. It may be a reasonable option for patients in whom toxicity of alkylating agents and high-dose steroids are a concern or when significant azotemia prohibits use of CNIs (Figure 1). MMF has been used with some success as rescue therapy in patients resistant to other immunosuppression and has also been tried as adjunctive or maintenance therapy to avoid prolonged exposure to CNIs⁷¹; however, the evidence is too limited to recommend routine use of MMF for these indications. Extended duration of

treatment (>12 months), and possibly the addition of oral corticosteroids, may be necessary to achieve greater anti-proteinuric effects or to prevent relapse. The optimal target dosing of MMF for IMN is not known because the kinetics of MMF in patients with hypoalbuminemia and nephrotic syndrome are not well defined. It is possible that higher drug doses are needed to reach the therapeutic window.

ACTH

ACTH is one of the newer agents being explored for treatment of IMN but it certainly is not a new drug. Historically, ACTH was used decades ago to treat nephrotic syndrome as well as a variety of inflammatory and autoimmune diseases. However, this parenterally administered drug fell out of favor when the greater clinical benefits of oral steroids were

recognized. Its use was recently resurrected after Berg *et al.* in Sweden observed reduction in proteinuria when ACTH was administered for lipid-lowering purposes in patients with IMN.⁸²

Initial experiences with ACTH have been in Europe using ACTH tetracosactide, a synthetic, depot formulation (tetracosactrin; Novartis Pharmaceuticals, Basel, Switzerland). The data are conflicting. Several small case series reported reduction of proteinuria in IMN patients, many of whom were refractory to other therapies.^{83–86} A small multicenter randomized control trial of 32 patients by Ponticelli *et al.* compared efficacy of 6 months of alkylating agents alternating with corticosteroids to tetracosactrin intramuscular injections for 1 year (1 mg twice weekly).⁸⁷ There were no significant differences in cumulative remission rates between the treatment arms initially

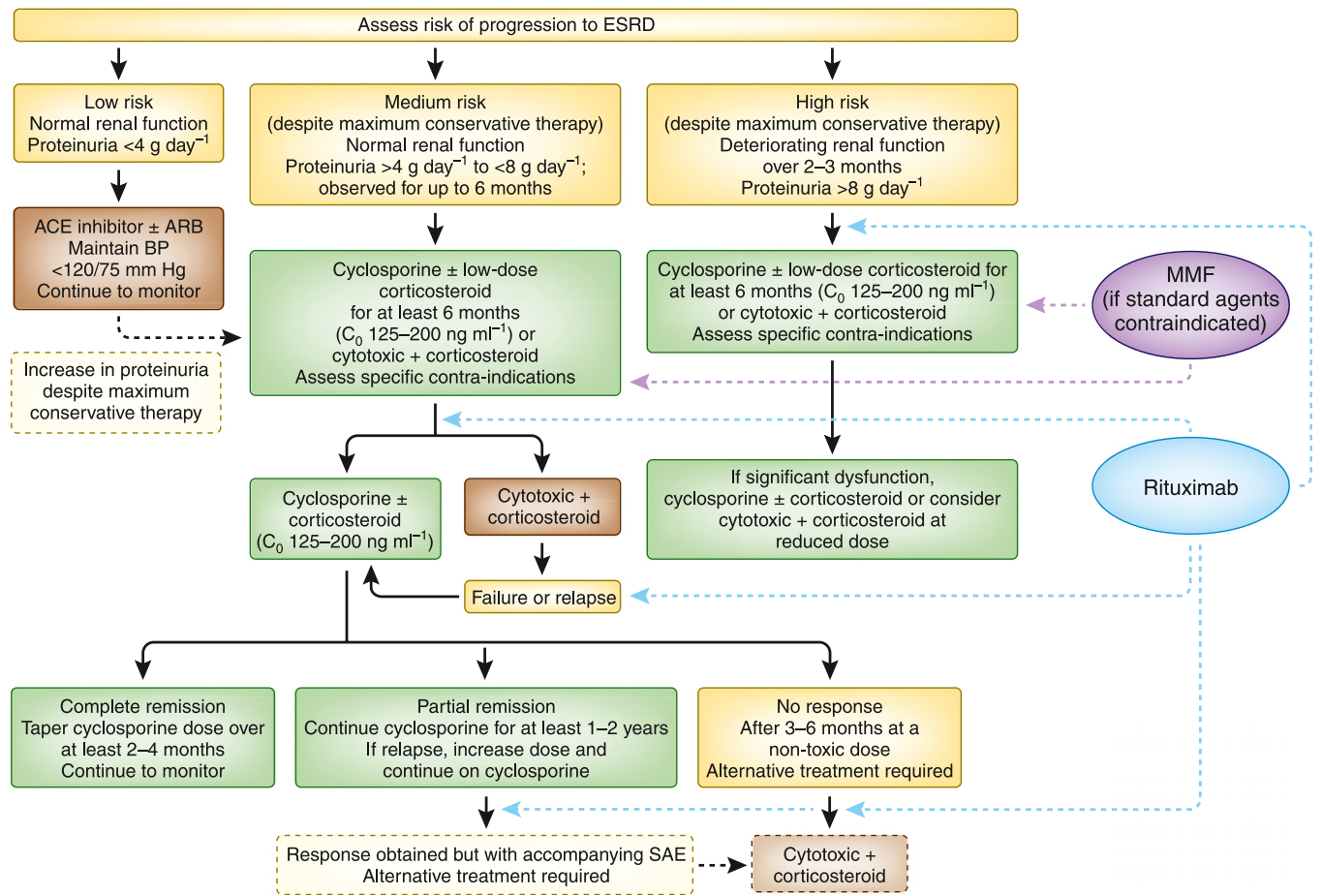


Figure 1. Current consensus guidelines for treatment of IMN, adapted from Cattran *et al.*⁴⁸ Possible positions of MMF and rituximab in treatment scheme based on available data (but not currently in guidelines). SAE, severe adverse event.

(93% versus 87%, respectively) or at final follow-up of 21 months (75% total versus 87%, respectively). However, it is notable that these patients were treatment naïve, with preserved kidney function and low to modest degrees of proteinuria (5–6 g/d)—all of which may lead to an overly optimistic view of remission rates. Outcomes were not as favorable in a recent prospective study from the Netherlands in which tetracosactrin was administered to high-risk IMN patients.⁸⁸ Patients were considered at high risk for progression based on elevated urinary $\beta 2$ microglobulin levels and high-grade proteinuria. After 9 months of treatment, only 44% of patients achieved remission and relapse rates were high (43%). Other investigators have reported similarly high relapse rates after drug discontinuation, particularly after short courses of therapy.⁸²

A different formulation of ACTH, a natural highly purified gel, is available in the United States (corticotropin; Questcor Pharmaceuticals Inc, Anaheim Hills, CA). In a retrospective study of corticotropin in proteinuric glomerular diseases, 9 of 11 (82%) patients with IMN achieved a remission (three complete; six partial). The complete remissions occurred in patients with relatively low levels of baseline proteinuria (2.6–4.8 g/d). Interpretations of the data are limited due to the uncontrolled nature of the study, the variable dosing regimens used, a possible carry-over effect from previously administered immunosuppression, and short follow-up (beyond the active treatment period).

The mechanisms by which ACTH exerts its antiproteinuric effect are not understood. Multiple mechanisms likely contribute and may involve both immune-mediated and immune-independent mechanisms.⁸⁹ The effects are not thought to be mediated by induction of endogenous cortisol from the adrenal glands because administration of corticosteroids as monotherapy has not been effective in IMN. However, it is conceivable that ACTH-induced increases in endogenous steroids might act differently than oral steroid preparations.⁸⁴ More recently, attention has focused on a possible direct

effect of ACTH on podocytes as expression of one of the natural receptors for endogenous ACTH (melanocortin receptor-1) has been identified in human kidney tissue, mainly in the podocyte.⁸⁶ In support of this theory, experimental evidence in a rat model of membranous disease showed that treatment with an agonist of the melanocortin receptor-1 reduced proteinuria and improved podocyte morphology compared with untreated rats.⁸⁶

The experience with ACTH, particularly in the United States, is far too preliminary to consider using this treatment outside of clinical research studies. A trial is currently underway to more formally evaluate the efficacy of ACTH gel as secondary therapy in patients who have failed conventional therapy.

SUMMARY

Figure 1 summarizes two widely used treatment options for immunosuppressive drugs in patients with IMN at moderate to high-risk of renal deterioration. These options, CNIs and cytotoxic drug therapy, have been incorporated into consensus recommendations⁴⁸ on the basis of the clinical studies discussed in this review. Randomized controlled trials are needed to compare the efficacy and toxicity of rituximab with these regimens. Additional studies are needed to identify the optimal rituximab regimen for this condition. Consequently, at the present time, it would be ideal to refer patients to ongoing clinical trials of rituximab in order to address these important issues. MMF is another relatively new immunosuppressive agent that has been used (but not extensively studied) for the treatment of IMN. Therefore, it is difficult to determine its role in the standard approach to IMN. It would be sensible to consider MMF as an alternative therapy when the risk profiles of CNIs or cytotoxic drugs are considered unacceptable. Figure 1 reflects where rituximab and MMF might potentially fit into the treatment scheme on the basis of the available data. As previously discussed, there is too little information to

recommend using ACTH outside of the context of a clinical research study. Ongoing studies of pathogenic mechanisms and innovative treatments will refine our approach to the treatment of membranous nephropathy.

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DISCLOSURES

None.

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