

# Idiopathic Membranous Nephropathy: Outline and Rationale of a Treatment Strategy

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● Idiopathic membranous nephropathy is a common cause of nephrotic syndrome. The treatment of patients with idiopathic membranous nephropathy is heavily debated. Based on literature data and our own experience, we propose a rational treatment strategy. Patients with renal insufficiency (serum creatinine level > 1.5 mg/dL [ $>135 \mu\text{mol/L}$ ]) are at greatest risk for the development of end-stage renal disease and should receive immunosuppressive therapy. In patients with normal renal function (serum creatinine level < 1.5 mg/dL [ $<135 \mu\text{mol/L}$ ]), risk for developing end-stage renal disease can be estimated by measuring urinary excretion of  $\beta_2$ -microglobulin or  $\alpha_1$ -microglobulin and immunoglobulin G. For low-risk patients, a wait-and-see policy is advised. High-risk patients likely benefit from immunosuppressive therapy. Currently, combinations of steroids with chlorambucil or cyclophosphamide are the best studied. We prefer cyclophosphamide in view of its fewer side effects. Cyclosporine may be an alternative option in patients with well-preserved renal function, although long-term data are lacking. Other immunosuppressive agents, such as mycophenolate mofetil or rituximab, currently are under study; however, data are insufficient to support their routine use. *Am J Kidney Dis* 46:1012-1029.

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**INDEX WORDS:** Membranous nephropathy; nephrotic syndrome; cyclophosphamide; chlorambucil; treatment; immunosuppressive therapy.

**I**DIOPATHIC MEMBRANOUS nephropathy (IMN) is one of the most common causes of nephrotic syndrome in adult patients.<sup>1</sup> The natural history varies from a spontaneous complete remission of proteinuria to rapid progression to end-stage renal disease (ESRD). The treatment of patients with IMN has been a regular theme for debate. Opinions of various investigators are as diverse as reported data on the natural history. Some emphasize the high rate of spontaneous remissions and argue against the use of immunosuppressive drugs,<sup>2</sup> whereas others point to the high rate of ESRD and favor immunosuppressive therapy.<sup>3</sup> The titles of editorial reviews written

during the past 25 years clearly reflect the uncertainty in this field, from Cameron's<sup>4</sup> "Membranous Nephropathy: The Treatment Dilemma" in 1982 and "Membranous Nephropathy—Still a Treatment Dilemma"<sup>5</sup> in 1992 to Glasscock's<sup>6</sup> "The Treatment of Idiopathic Membranous Nephropathy: A Dilemma or a Conundrum" in 2004.

In the current era of evidence-based medicine, some might argue that the discussion can end with the publication of a recent meta-analysis on immunosuppressive therapy for patients with IMN.<sup>7</sup> Based on data derived from 18 randomized controlled trials (RCTs) including more than 1,000 patients, the investigators concluded that immunosuppressive treatment had no benefit in terms of patient and/or renal survival. There was weak evidence in favor of regimens containing alkylating agents in inducing complete remission of proteinuria; however, only when considering patients with relatively well-preserved renal function. Because the use of immunosuppressive therapy in especially this latter group of patients is most questionable, this finding also seems to argue against the use of immunosuppressive therapy. However, conclusions of the meta-analysis are debatable and must not lead to therapeutic nihilism. Specifically, the meta-analysis included RCTs of limited size and quality. Conclusions based on a systematic review, which includes many trials of limited quality, are not necessarily better than conclusions based on results of 1 large, carefully conducted RCT.

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Furthermore, in view of the limited number of large high-quality RCTs, we must not neglect important and relevant information that can be obtained from carefully conducted observational studies.<sup>8,9</sup>

During the past 2 decades, we have systematically studied patients with IMN; our database now includes 279 patients.<sup>8,10-18</sup> These studies have enabled us to define risk factors and develop a treatment strategy tailored to the individual patient. Our treatment strategy is shown in Fig 1. In this review, we discuss treatment modalities for patients with IMN and provide arguments based on the literature data and our experience in favor of our strategy. We specifically address the following questions: (1) Has the natural history of IMN changed during the past decades? (2) Is immunosuppressive therapy of proven benefit in patients with IMN when considering hard end points? (3) Should all patients with IMN and nephrotic syndrome be treated with immunosuppressive therapy? (4) Are all immunosuppressive agents equally effective? (5) Which parameters can be used to identify patients at risk for progressive renal insufficiency?

A detailed discussion of supportive (nonimmunosuppressive) treatment of patients with membranous nephropathy is beyond the scope of this review. However, it is evident that proteinuric patients

should be administered antihypertensive drugs, aiming at target blood pressures of 125/75 mm Hg. Because of their additional antiproteinuric effects, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II type 1 receptor antagonists (ARBs) are the preferred agents, although there is no evidence that these agents have changed the natural history of IMN (vide infra). A sodium-restricted diet and diuretics are needed to limit edema formation and enhance the antiproteinuric effects of ACE inhibitors. Hypercholesterolemia is often present in patients with nephrotic syndrome and should be treated according to established guidelines. There is debate over the use of prophylactic anticoagulation. Patients with IMN and nephrotic syndrome are at increased risk for thromboembolic complications. Using a decision-analysis model, Sarasin and Schifferli<sup>19</sup> showed that prophylactic anticoagulation increased quality-adjusted life expectancy. We advise oral anticoagulant drugs in patients with a serum albumin level less than 2 g/dL (<20 g/L) or patients who are immobilized. Notably, we are unaware of studies that documented beneficial effects of anticoagulant treatment on the long-term course of renal function in patients with IMN.

#### NATURAL HISTORY OF IMN

It is important to define the natural history of IMN. Most probably agree that the overall prog-

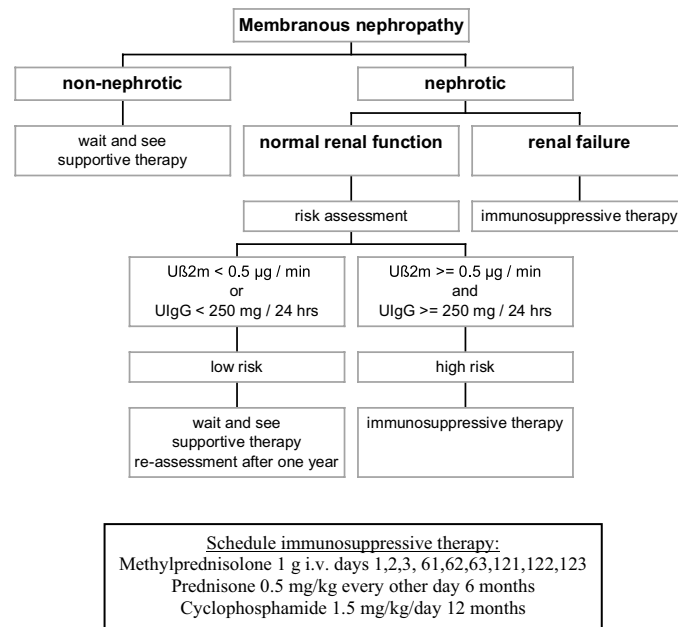


Fig 1. Outline of proposed treatment strategy in patients with IMN.

nosis determines whether one would ever consider the (early) use of aggressive therapy. In this respect, descriptions of the natural history of IMN are divergent and thus have laid the ground for heavy disputes on the use of immunosuppressive therapy. Schieppati et al<sup>2</sup> pointed to the relatively benign course of IMN in untreated patients; 65% of patients followed up for more than 5 years developed spontaneous remission of proteinuria and had an estimated renal survival rate of 88% at 5 years. Conversely, Ponticelli et al<sup>3</sup> stressed the poor outcome, observing permanent remission in only 33% of untreated patients followed up for more than 10 years and a renal survival rate of 60% at 10 years. It is no surprise that the first investigators claim that symptomatic treatment is still the best option for patients with IMN, whereas the latter argue that all patients with IMN and nephrotic syndrome should receive immunosuppressive therapy.

The short-term outcome (<5 years) of membranous nephropathy already was reported extensively before 1980.<sup>20-27</sup> However, it is difficult to compare results because most of these older studies have the handicap that they included not only patients with IMN and secondary membranous nephropathy, but also treated and untreated patients. In these studies, complete remission of proteinuria occurred in approximately 16% to 29% of patients, whereas in approximately 40% to 60% of patients, there was evidence of progressive renal insufficiency.

To better appreciate the natural history of patients with IMN, we analyzed studies published during the past 25 years. An overview is listed in Tables 1 and 2.<sup>2,3,28-37</sup> When possible, we used data from untreated patients. The reported studies still vary considerably with respect to patient characteristics, time of follow-up, and definition of renal failure. Therefore, it may be no surprise that reported outcomes are variable. However, we must take into account that many studies included patients with nonnephrotic proteinuria. Outcome in never-nephrotic patients with IMN invariably is good, with reported 10-year renal survival rates approximating 100%.<sup>32,36,38-40</sup> The confounding effect of including up to 37% of nonnephrotic patients in studies of the natural history of IMN is shown in Fig 2. Therefore, we recalculated data from the studies in Table 1 by attributing a 100% renal survival rate to nonnephrotic patients (Table 2).

Table 1. Natural History of Patients With IMN

Reference	Publication Year	No. of Patients	Sex (M/F)	Serum Creatinine (mg/dL)	Proteinuria (g/d)	Nephrotic Syndrome (%)	Treated (%)	Follow-Up (y)	Complete Remission (%)	Partial Remission (%)	Renal Function Deterioration (%)	ESRD (%)
Collaborative Study <sup>28</sup>	1979	38	20/18	1.0 ± 0.2	8.3 ± 4	100	0	2	13	16	29	21
Davison et al <sup>29</sup>	1984	64	47/17	1.24	Not available	81	0	2-15	Not available	Not available	50	??
MacTier et al <sup>30</sup>	1986	37	31/6	1.47	10.5	93	0	5.3	22	8	41	22
Zuchelli et al <sup>31</sup>	1987	49	37/12	1.18 ± 0.27	Not available	100	0	9.5	14.3	40	45	27
Donadio et al <sup>32</sup>	1988	89	56/33	1.3 ± 0.6	8.2 ± 5.2	83	0	6.1	Not available	Not available	33	18
Cattran et al <sup>33</sup>	1989	77	44/33	1.17 ± 0.1	5.2 ± 0.9	73	0	4	35	23*	25	5
Wehrmann et al <sup>34</sup>	1989	334	223/111	7.4/334 > 1.3	Not available	73	35	4	Not available	Not available	31	14
Cameron et al <sup>35</sup>	1990	51	43/8	1.3 ± 0.49	10.4 ± 5.3	100	0	4.3	14	14	52	29
Durin et al <sup>36</sup>	1990	82	48/34	9/82 > 1.5	Not available	68	0	8.5	39	39	38	20
Schieppati et al <sup>2</sup>	1993	100	68/32	1.1 ± 0.5	5.1 ± 3.6	63	0	3.3	22	44	32	14
Ponticelli et al <sup>3</sup>	1995	39	29/10	1.05 ± 0.29	5.3 ± 2.8	100	0	>10	5	28	47	25

NOTE. To convert serum creatinine in mg/dL to  $\mu\text{mol/L}$ , multiply by 88.4. Durin et al<sup>36</sup> provided long-term outcome of a patient cohort originally described by Noel et al<sup>37</sup> in 1979.

\*Remission at 3 years of follow-up.

**Table 2. Calculated Outcomes in Patients With IMN and Nephrotic Syndrome**

Reference	Publication Year	No. of Patients	Nephrotic (%)	Treated (%)	Follow-Up (y)	Corrected Renal Function Deterioration (%)	Corrected Renal Survival (%/y)
Davison et al <sup>29</sup>	1984	64	81	0	7	62	Not available
MacTier et al <sup>30</sup>	1986	37	93	0	5.3	44	46
Zuchelli et al <sup>31</sup>	1987	49	100	0	9.5	45	52/10
Donadio et al <sup>32</sup>	1988	89	83	0	6.1	39	49/10
Cattran et al <sup>33</sup>	1989	77	73	0	4	34	88/8*
Wehrmann et al <sup>34</sup>	1989	334	73	35	4	42	59/4
Cameron et al <sup>35</sup>	1990	51	100	0	4.3	52	Not available
Durin et al <sup>36</sup>	1990	82	68	0	8	56	63/10
Schieppati et al <sup>2</sup>	1993	100	63	0	3.3	51	57/8
Ponticelli et al <sup>3</sup>	1995	39	100	0	>10	47	60/10

NOTE. We calculated percentage of renal function deterioration and renal survival after correction for percentage of patients without nephrotic syndrome, assuming 100% survival in nonnephrotic patients. Correction factor = 100/(% nephrotic patients). For this analysis, we excluded studies with a follow-up less than 3 years.<sup>28</sup>

\*The projected 8-year renal survival is not reliable because 22% of patients were lost to follow-up and median follow-up was only 4 years.

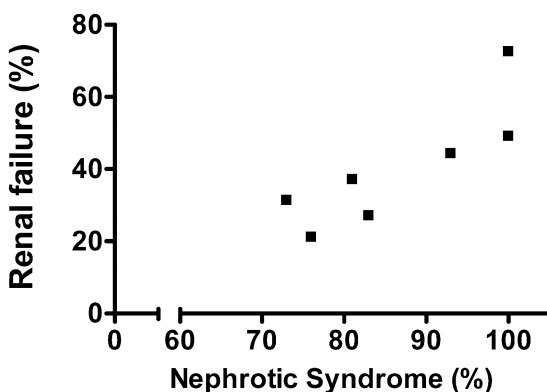
Furthermore, we not only included reported data on the percentage of patients with ESRD, because these figures are not always corrected for patient death and are not informative for studies with follow-up less than 5 years, but to circumvent this problem and allow good comparisons between studies, we calculated the percentage of patients with evidence of renal function deterioration, which is a very specific predictor of ESRD.<sup>38</sup> From Table 2, it is evident that data become more homogeneous. Overall, nearly half the patients with IMN and nephrotic syndrome developed renal failure. Our conclusion is emphasized by the good agreement between calculated

percentage of renal function deterioration and reported overall renal survival rate (Table 2).

Obviously, conservative treatment of patients with proteinuria has changed dramatically in the past decade. Nowadays, all patients with proteinuria are treated with ACE inhibitors or ARBs. These agents decrease proteinuria and attenuate the deterioration in renal function in patients with diabetic and nondiabetic proteinuric renal diseases.<sup>41-44</sup> Therefore, one might question the relevance of the data listed in Tables 1 and 2, which are derived largely from studies that included many patients not administered ACE inhibitors or ARBs. We must consider whether the natural history of IMN has changed with the venue of ACE inhibitors and ARBs.

The prospect of the use of ACE inhibitors as effective treatment in patients with IMN stimulated the initiative of a randomized study in the early 1990s. In this study, called ACE Inhibition versus Corticosteroids in Membranous Nephropathy, it was intended to compare treatment with the ACE inhibitor enalapril with a 6-month course of alternate-day prednisone or placebo treatment.<sup>45</sup> Unfortunately, this study was not completed because of the low rate of patient accrual; however, an interim analysis did not show a particular benefit of ACE inhibitor over placebo.

To determine whether use of ACE inhibitors could have substantially changed the prognosis in patients with IMN, we analyzed outcomes in patients with IMN entered in our database since



**Fig 2. Outcome in studies of patients with IMN is dependent on the prevalence of nephrotic syndrome. Relation of the calculated percentage of patients with progressive renal insufficiency during 5-year follow-up and the percentage of patients with nephrotic syndrome in studies of membranous nephropathy.**<sup>28-30,32,33,37,62</sup>

1988. For this analysis, we included all patients with biopsy-proven IMN, normal renal function (serum creatinine level  $< 1.25$  mg/dL [ $< 110$   $\mu\text{mol/L}$ ]) at the time of biopsy, and treated with an ACE inhibitor or ARB (start of treatment before or within 6 months after biopsy). Ninety-one patients (61 men, 30 women) fulfilled the entry criteria. Median age was 49 years (range, 18 to 78 years), serum creatinine level was 0.98 mg/dL (range, 0.54 to 1.24 mg/dL [ $87$   $\mu\text{mol/L}$ ; range, 48 to 110  $\mu\text{mol/L}$ ]), and proteinuria showed protein of 6.1 g/10 mmol creatinine (range, 0.7 to 32 g/10 mmol creatinine). Nephrotic syndrome was present in 87% of patients. Median follow-up was 46 months (range, 3 to 167 months). During follow-up, 39 patients (43%) developed renal death, defined by criteria that we have regularly used to allow the start of immunosuppressive therapy.<sup>8,15</sup> Thus, our data indicate that use of ACE inhibitors or ARBs has not greatly improved the prognosis in patients with IMN. Our data support the findings of Troyanov et al,<sup>46</sup> who assessed the role of ACE inhibitors as an independent predictor of outcome in their cohort of patients with IMN. In multivariate analysis, use of ACE inhibitors was not related to outcome. Possible benefits of ACE-inhibitor treatment in patients with IMN also were challenged by the studies of Praga et al,<sup>47</sup> who clearly showed that antiproteinuric effects of ACE inhibitors were particularly evident in patients with renal diseases characterized by secondary focal segmental glomerulosclerosis caused by hyperfiltration. In these patients, proteinuria decreased from protein of  $7.1 \pm 1.7$  g/d at baseline to  $3.7 \pm 1.7$  g/d after 6 months of treatment with ACE inhibitors. Conversely, in patients with nephrotic syndrome (the majority caused by IMN), proteinuria remained unchanged, with protein of approximately 8 g/d. In a subsequent study, it was shown that this poorer antiproteinuric response in patients with primary glomerulopathies also heralded a worse outcome with respect to renal function.<sup>48</sup>

From studies that reported the natural history, important information can be obtained on the time course of events in patients with IMN. This knowledge is pivotal to allow evaluation of the quality of RCTs conducted in patients with IMN, in particular, to determine whether suitable end points were used in relation to the time of follow-up. In general, development of ESRD takes more than 5 years, and as a consequence, studies that use ESRD as an end

point need a follow-up of 7 to 10 years. Conversely, patients with evidence of renal function deterioration (a specific predictor of ESRD, discussed next) can be identified at an earlier time. In various studies, median time to the development of renal insufficiency was 2 to 2.5 years, with no patient with normal renal function at 5-year follow-up showing deterioration in renal function thereafter.<sup>29,36</sup> Thus, renal function deterioration can be used as an estimate of treatment efficacy in studies with a follow-up of 3 to 4 years.

Remission rate cannot be evaluated at a much earlier time. Median time to partial remission ranges from 11 to 23 months, and to complete remission, from 16 to 40 months.<sup>8,39,46,49</sup> Although remissions occurred earlier in treated patients, median times to complete remission in the study of Ponticelli et al<sup>3</sup> and our study were 18 and 22 months, respectively. Thus, studies with a limited follow-up ( $< 2$  to 3 years) cannot be used to evaluate remission rate.

Admittedly, it can be questioned whether renal function deterioration and remission rate can be used as reliable surrogate end points in studies of patients with IMN. Use of renal function deterioration as an end point is supported by studies showing low renal survival in untreated patients with IMN with established renal insufficiency.<sup>8,9</sup> Furthermore, patients with evidence of renal function deterioration (increase in serum creatinine level) almost invariably progress to ESRD.<sup>29,38,50</sup> Likewise, the development of remission can be used as a surrogate end point of a study because most studies documented a good overall prognosis in patients who entered partial or complete remission of proteinuria, independent of treatment.<sup>39,46,49,51</sup> In the study of Troyanov et al,<sup>46</sup> the hazard ratio for developing ESRD was 0 for patients with complete remission and 0.08 for patients with partial remission.

#### IS IMMUNOSUPPRESSIVE THERAPY OF PROVEN BENEFIT?

In 1960 to 1970, membranous nephropathy was considered a slowly progressive disease that was totally unresponsive to steroid treatment (reviewed by Rastogi et al<sup>52</sup>). Uncontrolled studies suggested some benefit from prednisone treatment: of 108 treated patients, 29 patients developed complete remission of proteinuria and 19 patients developed partial remission.<sup>52</sup>

A subsequent RCT provided promising results.<sup>28</sup> A treatment regimen consisting of high-dose alternate-day prednisone (125 mg every other day for 8 weeks) significantly reduced the rate of renal function deterioration. This study was criticized because of the high rate of doubling of serum creatinine level that occurred within 2 years of follow-up in the placebo group (29% versus 6%). Two subsequent RCTs unequivocally proved that prednisone did not prevent deterioration in renal function.<sup>33,35</sup> Apparently, publication of these RCTs has settled the issue, and prednisone monotherapy since then is regarded as ineffective in patients with IMN. However, it is important to realize that these conclusions only hold for the use of prednisone in limited dosage or during a limited period. The mentioned studies used either 125 to 150 mg of prednisone on alternate days for 8 weeks<sup>28,35</sup> or 45 mg/m<sup>2</sup> on alternate days for 6 months,<sup>33</sup> thus providing cumulative doses of prednisone of 4.2 and 7.0 g, respectively. It is possible that a greater dose of prednisone administered for a longer period may be more effective. Hopper et al.<sup>53</sup> used prednisone in a dose of 100 to 200 mg every other day for 7.5 months, followed by a gradual dose reduction during another 6 months. The cumulative dose of prednisone averaged greater than 25 g. They reported 15 patients with progressive disease during an observation period of 8 to 66 months before the start of therapy. After treatment, 7 patients developed complete remission, and 4 patients, partial remission, of proteinuria. Before the start of therapy, renal function was severely decreased in 9 patients (all with serum creatinine levels > 1.8 mg/dL [ $>160 \mu\text{mol/L}$ ]). At the end of follow-up, renal function had improved in 7 of these 9 patients. Other uncontrolled studies that reported some benefit from steroid therapy used prednisone in cumulative dosages of 9 to 10 g.<sup>21,54,55</sup> Admittedly, the high-dose prednisone regimen as used by Hopper et al.<sup>53</sup> is toxic, and its efficacy is not adequately proven. Therefore, it is realistic to consider alternative treatment options.

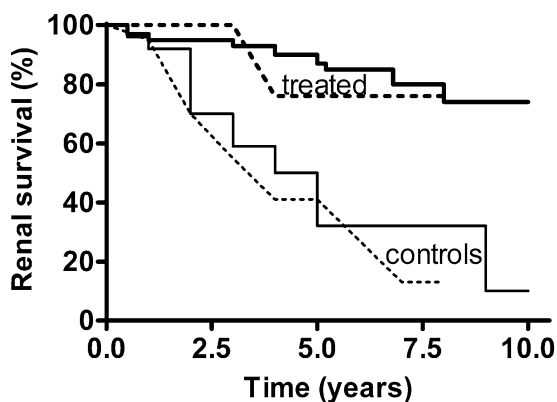
Other immunosuppressive agents have been used in patients with IMN. Most studies used a combination of an alkylating agent and prednisone.<sup>3,8,9,14,15,56-65</sup>

The best study on the efficacy of aggressive immunosuppressive therapy in patients with IMN undoubtedly is the RCT conducted by Ponticelli

et al.<sup>3,62,63</sup> These Italian investigators randomized patients with IMN with nephrotic syndrome and normal renal function (average serum creatinine level, 1.06 mg/dL [ $94 \mu\text{mol/L}$ ]) for treatment with alternating monthly cycles of prednisone and chlorambucil versus no treatment. Duration of treatment was 6 months. Patients were followed up for more than 10 years.<sup>3</sup> The data unambiguously showed the beneficial effect of immunosuppressive therapy. Treatment increased remission rate (at the end of follow-up, 63% versus 33%) and improved renal survival (92% versus 60%).

Unfortunately, results of 1 RCT cannot be used to draw conclusions with the highest level of evidence. In the recently published Cochrane meta-analysis, results provided by the study of Ponticelli et al.<sup>3,62,63</sup> are virtually annihilated by reports of 3 other RCTs. However, 2 RCTs were small sized and had a limited follow-up of 12 and 24 months.<sup>66,67</sup> In view of these characteristics of the natural course in IMN, these latter studies cannot be used to analyze the effect of treatment on renal function. Notably, even within the short period of follow-up, both studies documented significantly lower proteinuria in treated patients. The third RCT was only published in abstract form.<sup>68</sup> However, additional information is provided in the report by Risler et al.<sup>69</sup> The investigators specifically stated that for statistical purposes, retrospectively studied control patients were added, thus invalidating this study as an RCT. The efficacy of alkylating agents in patients with IMN is supported by other studies. In a small RCT, we showed that the Ponticelli regimen is more effective than intravenous cyclophosphamide and methylprednisolone.<sup>10</sup> Furthermore, 2 cohort studies showed the efficacy of alkylating agents.<sup>8,9</sup> In these studies, historical controls were used for comparison. Data from these studies are strengthened because only patients with renal function deterioration were included; thus, patients with an unfavorable renal prognosis and low likelihood of spontaneous remissions. Torres et al.<sup>9</sup> treated patients with IMN and renal insufficiency with chlorambucil and prednisone. We performed a similar study using a cyclophosphamide-based regimen. Results were similar, with favorable renal survival in treated patients compared with historical controls (Fig 3).

In conclusion, a high-quality RCT and 2 cohort studies with historical controls of adequate size and long follow-up provide evidence for the



**Fig 3.** Renal survival in patients with IMN and renal insufficiency treated with alkylating agents (treated) compared with historic controls (controls). Data adapted from du Buf-Vereijken et al<sup>8</sup> (cyclophosphamide; straight lines) and Torres et al<sup>9</sup> (chlorambucil; dotted lines). Data from Torres et al<sup>9</sup> were recalculated to provide overall renal survival without censoring for death.

efficacy of immunosuppressive therapy consisting of alkylating agents and prednisone in patients with IMN.

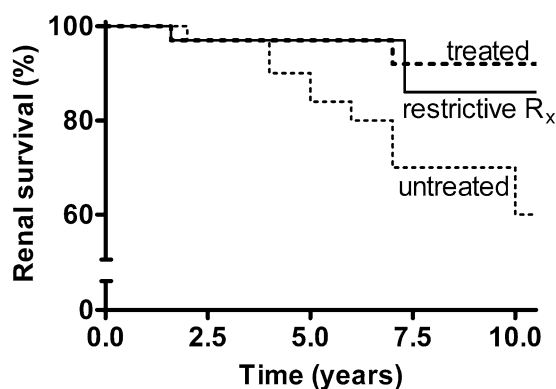
#### SHOULD ALL PATIENTS WITH MEMBRANOUS NEPHROPATHY AND NEPHROTIC SYNDROME BE TREATED?

Based on results from their controlled trials, Ponticelli et al<sup>62</sup> concluded that treatment with chlorambucil and prednisone improved survival in patients with IMN, nephrotic syndrome, and normal renal function. Although we fully appreciated their findings, we and others were not convinced that the data proved that all patients should receive immediate treatment. Adoption of such an approach would unnecessarily expose up to 40% of patients to toxic immunosuppressive agents.

From the late 1980s, we have adopted a restricted treatment policy in which immunosuppressive therapy was given to patients with IMN, nephrotic syndrome, and evidence of renal function deterioration, reflected by a serum creatinine level greater than 1.5 mg/dL ( $>135 \mu\text{mol/L}$ ) or an increase in serum creatinine level greater than 50%.<sup>13,14,70</sup> We found support for this strategy in studies by Mathieson et al<sup>61</sup> and Warwick and Boulton-Jones,<sup>65</sup> who reported improvement in renal function in patients with renal insufficiency. We recently reported our experience with a cyclophosphamide-based treatment regimen in 65 patients with IMN. Serum creatinine level at

the start of therapy was 1.9 mg/dL ( $171 \mu\text{mol/L}$ ).<sup>8</sup> Renal function improved, at least temporarily, in greater than 90% of patients, and the cumulative incidence of complete and partial remissions of proteinuria was 92% at 5 years. If we calculated renal survival from the time of biopsy, renal survival rates were 93% and 81% at 5 and 10 years, respectively.

Although these results were favorable and supported the efficacy of immunosuppressive therapy when started in patients with renal insufficiency, these data could not answer the question of whether start of therapy can be delayed safely until renal insufficiency has developed. Our survival data must be compared with results obtained by Ponticelli et al,<sup>3</sup> who reported a 10-year renal survival rate of 92% (Fig 4). It is obvious that the comparison is biased in view of the high-risk profile of our treated patients. Therefore, we formally analyzed results of our restrictive treatment policy in an unbiased cohort of patients with IMN, nephrotic syndrome, and serum creatinine level less than 1.5 mg/dL ( $<135 \mu\text{mol/L}$ ) at the time of biopsy.<sup>16</sup> We advised to restrict immunosuppressive treatment to patients with evidence of renal function deterioration (discussed previously). The cohort included 69 patients with a serum creatinine level of  $1.0 \pm 0.2 \text{ mg/dL}$  ( $88 \pm 16 \mu\text{mol/L}$ ) and proteinuria with protein of  $6.7 \pm 3.0 \text{ g/d}$ . Follow-up was 5.4 years (range, 0.5 to 14.1 years). To date, 33 patients (48%) have received immunosuppres-



**Fig 4.** Renal survival in patients with IMN, nephrotic syndrome, and normal renal function using a restrictive treatment policy.<sup>16</sup> Overall, 48% of patients needed immunosuppressive treatment during follow-up. For comparison, renal survival is shown for patients included in the RCT of Ponticelli et al<sup>3</sup> comparing chlorambucil and steroids (treated) with no treatment (untreated).

sive therapy, which confirms the general idea that approximately half the patients will not need therapy. If we calculate renal survival for patients who were treated according to the protocol, 5-year renal survival was 97%, similar to results obtained by Ponticelli et al<sup>3</sup> in patients treated from the onset of disease (Fig 4). There was a small survival difference at 10 years of follow-up. However, it is important to realize that the average serum creatinine level in our treated patients was  $1.7 \pm 0.6$  mg/dL ( $150 \pm 54$   $\mu$ mol/L) at the start of therapy, whereas in the study of Ponticelli et al,<sup>3</sup> serum creatinine level was  $1.05 \pm 0.25$  mg/dL ( $93 \pm 22$   $\mu$ mol/L). It is likely that our results would have been even better if treatment in high-risk patients had started earlier, which may become possible with the use of sensitive and specific predictors of progression (vide infra).

To date, we and other investigators have regularly used serum creatinine values to define renal function. We realized that the often used threshold value of 1.5 mg/dL (135  $\mu$ mol/L) in reality already indicated the presence of renal impairment, especially in elderly patients. Use of this threshold value enabled us to limit immunosuppressive therapy to patients at greatest risk for ESRD. However, in the past years, it became evident that use of serum creatinine level as a marker of glomerular filtration rate (GFR) is problematic in patients with nephrotic syndrome. We observed that creatinine secretion is increased in patients with nephrotic syndrome, thus leading to marked overestimation of GFR.<sup>71</sup> Using the 6-point Modification of Diet in Renal Disease formula, we calculated a median GFR of 68 mL/min/1.73 m<sup>2</sup> (range, 49 to 83 mL/min/1.73 m<sup>2</sup> [1.13 mL/s/1.73 m<sup>2</sup>; range, 0.82 to 1.28 mL/s/1.73 m<sup>2</sup>]) in our group of patients with a median serum creatinine level of 1.2 mg/dL (range, 1.0 to 1.6 mg/dL [103  $\mu$ mol/L; range, 84 to 143  $\mu$ mol/L]). In our current practice, we now consider even slight increases in serum creatinine level as indicative of renal impairment. Moreover, we calculate Modification of Diet in Renal Disease GFR and assess renal function by means of other markers, such as  $\beta_2$ -microglobulin ( $\beta_2$ M). The finding of a specific risk marker for disease progression (vide infra) also has the advantage that we no longer are dependent solely on renal function assessment to guide treatment start. Thus, we now are inclined to start immunosuppressive therapy at lower serum creatinine values.

Conversely, it can be questioned whether treatment is still effective in patients with severe renal impairment. We have no evidence that there really is a point of no return, although we are somewhat reluctant in treating patients with a serum creatinine level greater than 3 mg/dL ( $>265$   $\mu$ mol/L). However, we have successfully treated patients with serum creatinine values up to 5 mg/dL (445  $\mu$ mol/L). In retrospect, patients with disease that did not respond to therapy were characterized by greater serum albumin levels and lesser increments in serum creatinine levels in the 6 months preceding the start of therapy. Most importantly, patients with disease that responds to treatment will show a response within 3 months. Thus, if in doubt, we advise patients for a trial of immunosuppressive therapy for 3 months. If at that point renal function has not improved, treatment will be stopped.

#### ARE ALL IMMUNOSUPPRESSIVE AGENTS EQUALLY EFFECTIVE?

Various immunosuppressive agents have been used in the treatment of patients with IMN, including chlorambucil, cyclophosphamide, azathioprine, cyclosporine (CsA), mycophenolate mofetil (MMF), tacrolimus, corticotropin, and, most recently, the anti-CD20 monoclonal antibody rituximab and the anti-C5a monoclonal antibody eculizumab.<sup>3,8,9,14,15,56-61,63,64,66,67,69,72-89</sup> Relevant data from the most important studies are listed in Tables 3 and 4.

There are no randomized trials that compared the various classes of agents. It therefore is difficult to draw hard conclusions. From reviewing the literature, some conclusions emerge.

Most studies used oral chlorambucil or oral cyclophosphamide. Our experience with both agents has been reported previously.<sup>14</sup> In our hands, a regimen based on chlorambucil was less effective and more toxic than a cyclophosphamide-based regimen. An overview of studies performed in patients with renal insufficiency supports this notion (Table 3). Admittedly, we cannot exclude that the better efficacy of cyclophosphamide is explained because cyclophosphamide therapy usually is given for a more prolonged period (12 months of cyclophosphamide compared with 6 months of chlorambucil). However, despite this shorter treatment period, side effects occurred more frequently with chlorambucil. It was suggested that side effects of



chlorambucil might be particularly prominent in patients with renal insufficiency. However, a similar difference in side effects was noted by Ponticelli et al,<sup>90</sup> who compared chlorambucil and cyclophosphamide administered in monthly alternating cycles with prednisone for 6 months in patients with normal renal function. Side effects occurred more frequently during chlorambucil therapy: herpes zoster infections occurred in 8% of chlorambucil-treated patients and 0% of cyclophosphamide-treated patients, other side effects necessitated withdrawal of therapy in 12% of patients on chlorambucil versus 4% on cyclophosphamide therapy.

Of note, these studies all used orally administered cyclophosphamide. To date, treatment schedules that used intravenous pulses of cyclophosphamide have been ineffective.<sup>10,59</sup>

Azathioprine often is considered a good replacement for cyclophosphamide, and recent studies of patients with vasculitis provided evidence that after the induction phase (3 months), cyclophosphamide can be replaced safely by azathioprine.<sup>91</sup> We switch from cyclophosphamide to azathioprine after 3 months in patients of young age because of infertility risks associated with the use of cyclophosphamide.<sup>92</sup> Although our experience is limited, we have the impression that the few treatment failures we observed during the past 10 years were confined mainly to patients who used cyclophosphamide for only 3 months. In the literature, azathioprine was used with variable success.<sup>72,74-76,85,86</sup> Not surprisingly, there was no proven benefit of azathioprine in studies with short follow-up or that included many patients with a good prognosis.<sup>72,85</sup> Other studies focused on patients with progressive renal failure and reported more promising results (Table 4).<sup>74-76,86</sup> Bone et al<sup>74</sup> evaluated outcome after the start of azathioprine therapy in 21 patients with evidence of progressive renal insufficiency, reflected by a mean decrease in creatinine clearance of 23 mL/min/y. These patients were followed up for 10 years. Treatment resulted in improvement or stabilization in renal function in all except 3 patients and a decrease in proteinuria, although protein levels less than 1 g/d were reached in only 6 patients. At the end of follow-up, 4 patients had progressed to dialysis therapy; however, 14 patients were alive with functioning kidneys. Of note, treatment with low-dose azathioprine and prednisone needed to be continued lifelong, with re-

lapses occurring during decreases in prednisone dose.

Similar results were reported by Brown et al.<sup>76</sup> These investigators treated 13 patients with azathioprine and prednisone. All patients had evidence of renal failure (Table 4). Overall treatment improved renal function with a decrease in serum creatinine level greater than 15% in 10 patients and resulted in complete or partial remission in 7 patients. Continued treatment was needed to maintain efficacy during follow-up. Only 4 patients were able to successfully discontinue azathioprine and prednisone therapy at the end of follow-up. The latter studies at least suggest that a combination of azathioprine and prednisone exerts beneficial effects in patients with IMN and renal insufficiency. However, data also indicate that azathioprine-containing regimens may be effective only if treatment is continued for life, in contrast to the experience with cyclophosphamide.

CsA was used with success in patients with minimal change disease. The efficacy of CsA was attributed to the ability of CsA to decrease lymphokine or cytokine production. Subsequently, it was noted that CsA also decreased proteinuria in patients with such nonimmunologic glomerular diseases as Alport syndrome.<sup>93</sup> In the latter patients, the decrease in proteinuria was considered the consequence of the hemodynamic effects of CsA, which decreased GFR. Animal studies clearly proved a direct effect of CsA on glomerular permeability,<sup>94,95</sup> which was confirmed in humans. Zietse et al<sup>96</sup> studied patients with IMN and observed a decrease in proteinuria within 1 to 3 months. Because fractional excretion of albumin decreased, it was suggested that hemodynamic effects were not the only cause of decrease in proteinuria. In subsequent studies, both Zietse et al<sup>96</sup> and Ambalavanan et al,<sup>97</sup> by using dextran-sieving experiments, confirmed that CsA improved glomerular permselectivity, with a decrease in shunt flow.<sup>96,97</sup> Unfortunately, proteinuria returned to baseline values within 4 to 8 weeks after stopping CsA therapy.

Many studies showed the short-term antiproteinuric effect of CsA in patients with IMN. Most investigators agree that the effect is evident within 3 months after the start of therapy, and continued use of CsA beyond 4 months is not useful in nonresponders. It remains unclear whether use of CsA could have long-term benefits. Rostoker et al<sup>83</sup> treated patients for a median of 15 months

**Table 3. Results of Treatment With Cyclophosphamide or Chlorambucil in Patients With IMN**

Reference	No. of Patients	Sex (M/F)	Serum Creatinine (mg/dL)	Proteinuria (g/d)	Follow-Up (mo)	Remission Proteinuria				Renal Function		
						Initial		Final		Improved	Stable	Deteriorated
						Complete	Partial	Complete	Partial			
<b>Renal insufficiency</b>												
<b>Cyclophosphamide</b>												
Bruns et al <sup>57</sup>	11	9/2	2.24 (1.80-4.20)	11.9 (6.2-22)	34 (12-54)	4	5	3	4	7	4	0
Jindal et al <sup>60</sup>	9	7/2	2.51 (1.24-3.74)	11.1 ± 7.6	83 ± 13	4	4	3	4	3	3	3
Alexopoulos et al <sup>73</sup>	17	12/5	1.30 ± 0.5	5.1 ± 1.4	58.9 (12-156)	5	7	3	4	1	12	4
du Buf-Vereijken et al <sup>8</sup>	65	55/10	1.93 (1.20-5.79)	10 (2-23)	51 (5-132)	17	39	16	31	35	20	10
Total	102					30 (29)	55 (54)	25 (25)	43 (41)	46 (45)	39 (38)	17 (17)
<b>Chlorambucil</b>												
Mathieson et al <sup>61</sup>	8	7/1	2.19 ± 0.7	15.3 (8.8-23.9)	17 (9-32)	1	3	0	4	6	1	1
Brunkhorst et al <sup>56</sup>	9	6/3	2.57 ± 0.44	>10	20 (12-24)	NA	NA	NA	NA	5	2	2
Warwick et al <sup>64</sup>	21	19/2	2.71 (2.04-5.43)	14.1 (1.4-30.4)	39 (4-68)	NA	NA	2	4	7	5	9
Stirling et al <sup>84</sup>	19	17/2	3.02	12.5	54	NA	NA	2	3	5	2	12
Branten et al <sup>14</sup>	15	15/0	2.48 ± 0.83	9 ± 2.6	38 (8-71)	0	5	0	2	3	3	9
Torres et al <sup>9</sup>	19	11/8	2.3 ± 0.94	11.2 ± 3.3	51.8 ± 36.5	5	3	5	2	11	2	6
Total	91					6 (14)	11 (26)	9* (11)	15* (18)	37 (41)	15 (16)	39 (43)
<b>Normal renal function</b>												
<b>Cyclophosphamide</b>												
Ponticelli et al <sup>90</sup>	45 (43)†	29/16	1.04 ± 0.27	6.85 ± 3.51	42 (12-72)	16	24	16	24	0	41	2
<b>Chlorambucil</b>												
Ponticelli et al <sup>90</sup>	50 (44)†	37/13	1.06 ± 0.27	7.96 ± 5.19	36 (12-78)	12	24	12	24	0	43	1

NOTE. Data expressed as mean ± SD, median (range), or number (percent). To convert serum creatinine in mg/dL to  $\mu$ mol/L, multiply by 88.4.

Abbreviation: NA, not available.

\*Percentage of patients in remission calculated for n = 82 evaluated patients.

†Number of patients at final assessment in parentheses.

Table 4. Results of Treatment With Azathioprine, CsA, or MMF in Patients With IMN

Reference	No. of Patients	Sex (M/F)	Serum Creatinine (mg/dL)	Proteinuria (g/d)	Follow-Up (mo)	Remission Proteinuria				Renal Function		
						Initial		Final		Improved	Stable	Deteriorated
						Complete	Partial	Complete	Partial			
<b>Renal insufficiency</b>												
<b>Azathioprine</b>												
Bone et al <sup>74</sup>	21	15/6	3.0 ± 0.19	12.2 ± 1.4	120 (36-240)	8	6	6	12	14	2	5
Brown et al <sup>76</sup>	13	10/3	2.38 (1.89-3.96)	11.8 (4.3-21.7)	73 (24-103)	6	6	7	11	11	1	1
<b>Cyclosporine</b>												
Cattran et al <sup>77</sup>	9	8/1	2.1 ± 0.74	11.5 (9-18)	26 (3-36)	0	0	0	0	1	4	4
<b>MMF</b>												
Miller et al <sup>81</sup>	16	11/5	2.1 ± 1.3	9.2 ± 4.2	8	0	2	0	2	2	13	1
Choi et al <sup>79</sup>	17	10/7	1.5 ± 0.8	7.8 ± 4.8	12 ± 7	2	5	3	4	3	14	0
<b>CsA RCT</b>												
Cattran et al <sup>78</sup>	28	26/2	1.3 ± 0.5	9.7 ± 5.3	17	2	19	2	9	0	26	2
CsA	23	16/7	1.1 ± 0.3	8.8 ± 4.7	17	1	4	1	2	0	21	2

NOTE. Data provided for studies that included high-risk patients (patients with renal failure) or for RCTs. To convert serum creatinine in mg/dL to  $\mu\text{mol/L}$ , multiply by 88.4.

and observed that several patients remained in remission after discontinuation of the drug. Obviously, in this study, it was not excluded that most sustained remissions could have occurred spontaneously. Most importantly, the data did not prove or even suggest that CsA would benefit patients with IMN in terms of attenuating the development of renal failure.

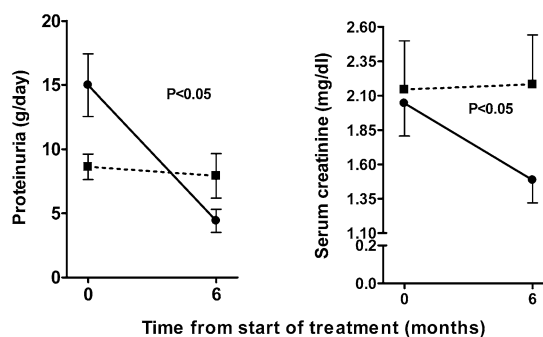
Cattran et al<sup>77</sup> reported results of a small RCT (including 18 patients total) with IMN and renal insufficiency. They observed that CsA attenuated renal function deterioration compared with placebo, with a decrease in the slope of creatinine clearance from 2.1 to 0.7 mL/min/month. Remarkably, treatment with CsA did not result in improvement in renal function, and no patient developed complete remission of proteinuria, in contrast to observed effects of alkylating agents. To date, these data have not been confirmed. Others noted that CsA was not very effective in patients with renal insufficiency and even often caused progression to ESRD.<sup>80</sup> Furthermore, the Cyclosporine in Membranous Nephropathy Study Group compared CsA with conservative treatment in patients with IMN and renal function deterioration.<sup>98</sup> In this controlled trial, which was terminated too early, CsA failed to exert long-term benefits. This and other observations led Ponticelli and Villa<sup>99</sup> to advise against the use of CsA in patients with a creatinine clearance less than 60 mL/min (<1.00 mL/s) and/or severe hypertension and/or severe tubulointerstitial fibrosis and tubular atrophy at renal biopsy.

The situation may be different in patients without renal failure. The efficacy of CsA was studied in an RCT of patients with IMN and normal renal function.<sup>78</sup> Eligible patients had steroid-resistant disease, defined as nonresponsiveness to 8 weeks of prednisone treatment. Obviously, this definition can be questioned because prednisone is not considered effective therapy and 8 weeks is too short to document remissions in patients with IMN. Nonetheless, CsA significantly decreased proteinuria compared with placebo. At the end of the 26-week treatment of 28 CsA-treated patients, 2 patients were in complete remission and 19 patients were in partial remission, significantly different from results in 23 untreated patients (complete remission in 1 patient, partial remission in 4 patients). However, after ending treatment, many relapses occurred, and at the end of follow-up, differences

in remission rates were not impressive (Table 4). Follow-up of this study was too short, only 18 months, to allow conclusions with respect to renal function. Furthermore, 9 patients (30%) experienced a temporary increase in serum creatinine levels during treatment with CsA, necessitating dose reduction or even discontinuation of the drug, suggesting that CsA therapy might be difficult to handle in clinical practice.

MMF was introduced as an effective immunosuppressive agent in transplant recipients. The drug caused few side effects. Efficacy has since been shown in patients with systemic lupus erythematosus, and some studies suggested equipotency compared with cyclophosphamide. Because cyclophosphamide and azathioprine are considered effective in patients with IMN, it seems logical to consider MMF in these patients. To date, experience with MMF in patients with IMN is limited. After their anecdotal report of 3 patients, Choi et al<sup>79</sup> continued to use MMF in patients with IMN. Their experience has been published in detail. The study included 17 patients with IMN and proteinuria. Only 6 patients had evidence of renal insufficiency. Treatment consisted of MMF, 0.5 to 1.0 g twice daily, for 12 months (range, 4 to 25 months), combined with steroids in most patients. Overall, proteinuria decreased, and, in 2 patients, complete remission (protein < 0.2 g/d), and, in 5 patients, partial remission (protein < 2 g/d), was noted. Renal function improved in 3 of 6 patients with renal failure. The heterogeneity of patients precludes us from drawing hard conclusions. In another study, Miller et al<sup>81</sup> treated 16 patients with IMN, the majority with evidence of renal failure and thus high-risk patients. MMF was used in dosages of 500 to 2,000 mg/d, and only 5 patients were administered steroids concomitantly. Therapy was continued for only 8 months (range, 2 to 10 months). Partial remission of proteinuria was achieved in 2 patients.

We also evaluated effects of MMF in a pilot study of patients with IMN and renal insufficiency.<sup>100</sup> Our treatment regimen consisted of MMF, 1,000 mg twice daily, combined with steroids, as in our cyclophosphamide protocol. We observed a significant decrease in serum creatinine and proteinuria levels, in contrast to the findings of Miller et al<sup>81</sup> (Fig 5). Differences in efficacy most likely are explained by differences in dose and duration of MMF therapy (we



**Fig 5. Efficacy of MMF in patients with IMN. Serum creatinine levels at baseline and after 6 months are shown as reported by Miller et al<sup>81</sup> (dotted lines) and du Buf-Vereijken and Wetzels<sup>100</sup> (straight lines). Differences are significant, likely explained by the greater dose of MMF, longer duration of therapy, and concomitant use of prednisone in all patients in the latter study. To convert creatinine in mg/dL to  $\mu\text{mol/L}$ , multiply by 88.4.**

consistently used 2,000 mg/d for 1 year) and the use of steroids (all our patients were administered methylprednisolone pulses and oral prednisone according to our schedule with cyclophosphamide). Although we consider our data promising, data are too limited to advise regular use of MMF as standard therapy in patients with IMN.

The anti-CD20 antibody rituximab has proved effective in the treatment of B cell lymphomas. The effectiveness of this agent in decreasing the number of B cells and attenuating antibody production has led to the introduction of this drug in such immune-mediated kidney diseases as IMN. Remuzzi et al<sup>82</sup> and Ruggenti et al<sup>101</sup> described results after 1 year of treatment. They treated 8 patients (3 men, 5 women) with IMN and nephrotic syndrome. Renal function was normal in 5 patients. During follow-up, creatinine levels remained stable and proteinuria decreased to some extent; however, only 3 patients developed partial remission and no patient developed complete remission. Thus, this study included low-risk patients (women and patients with normal renal function) and follow-up was too short to allow meaningful conclusions on the efficacy of the drug. Subsequent data published in abstract form even suggested that efficacy may be very limited.<sup>102</sup> In this abstract, it was shown that rituximab was ineffective in patients with tubulointerstitial injury; a decrease in proteinuria was observed only in patients without tubulointerstitial injury. Because the latter patients usually develop spontaneous remissions,

these data suggest that rituximab is ineffective in patients at risk for ESRD.

The potential use of corticotropin in patients with IMN has received little attention. Long-acting corticotropin administered intramuscularly 2 to 3 times weekly decreased serum lipid levels and proteinuria within 8 weeks.<sup>88</sup> Relapses occurred after ending treatment. However, continued treatment for 1 year in 5 patients resulted in improvement in renal function and remission of proteinuria. Unfortunately, these data have not been confirmed; effectiveness was evaluated only in patients with recent-onset IMN, normal renal function, and moderate proteinuria.<sup>89</sup>

It generally is accepted that the complement system is involved in IMN. Activation of the complement system with the formation of the C5b-9 membrane attack complex is held responsible for the podocyte injury and proteinuria. Development of a monoclonal antibody directed at C5a held the promise of rational treatment targeting 1 of the effector molecules. A humanized antibody allowed studies of patients with IMN. The first study showed no obvious benefits.<sup>87</sup> Admittedly, this may have been caused by the inability of the regimen used to continuously block complement generation. Thus, additional studies are needed to better define adequate timing of drug administration.

#### WHICH PARAMETERS CAN BE USED TO IDENTIFY PATIENTS AT RISK FOR DISEASE PROGRESSION?

Ideally, immunosuppressive therapy should be restricted to patients with IMN who will develop ESRD. In such patients, treatment preferably should be started before severe renal insufficiency develops. Admittedly, there still is no evidence that an early start of treatment will lead to better preservation of renal function. However, early start of treatment will decrease the time patients spend in a nephrotic phase, with its associated risks for thromboembolic complications and premature vascular disease.<sup>30,31,36</sup> To allow an early start of treatment, it is necessary to be able to identify patients at risk for ESRD with high sensitivity and specificity. If a prognostic marker is used to guide treatment, its specificity must be high, preferably greater than 90%. In such a case, less than 10% of patients will receive treatment unnecessarily. Furthermore,

sensitivity also must be high to ensure that patients are detected.

In the literature, several risk markers have been identified that are associated with disease progression. We reviewed the literature and calculated sensitivities and specificities for various factors.<sup>50</sup> Examples of risk factors are advanced age, male sex, white race, disturbed renal function at baseline, hypertension, higher glomerular stage, and more extensive area of tubulointerstitial fibrosis. Unfortunately, these parameters lack sufficient sensitivity and specificity and do not allow their use to guide treatment. As recently as 1994, Honkanen et al<sup>38</sup> stated that "the prediction of renal outcome on clinical basis is hopeless in IMN patients showing a nephrotic syndrome at biopsy."

Although proteinuria is a well-known predictor of progressive renal injury, the magnitude of proteinuria at baseline is not very discriminative.<sup>74</sup> This is explained readily by the lack of association between level of proteinuria and extent of tubulointerstitial injury in renal biopsy specimens.<sup>34</sup> By combining magnitude and duration of proteinuria, risk for renal function deterioration can be better estimated. Pei et al<sup>103</sup> observed a 47% risk for progression in patients with proteinuria with protein greater than 4 g for longer than 18 months and a 66% risk in patients with protein greater than 8 g for longer than 6 months. Sensitivity and specificity improved when using a model that included level of proteinuria during the 6-month period with the greatest proteinuria, as well as serum creatinine level at the start of this period and change in creatinine clearance during this 6-month period (Table 5).<sup>104</sup>

Some investigators advocated measurement of urinary complement products based on the hypothesis that renal injury in patients with IMN is mediated by complement.<sup>105</sup> Initial studies suggested high sensitivity and specificity (Table 5).<sup>106</sup> We and others studied the predictive value of specific urinary proteins, such as immunoglobulin G (IgG; as a marker of glomerular size selectivity) and the low-molecular-weight proteins  $\beta$ 2M or  $\alpha$ <sub>1</sub>-microglobulin (markers of tubulointerstitial injury).<sup>11,12,107,108</sup> Both urinary IgG excretion and urinary excretion of low-molecular-weight proteins proved valuable markers (Table 5).

It is important to realize that initial studies often provide a too-optimistic view of the value of risk markers. To evaluate these risk markers,

**Table 5. Overview of Accuracy of Predictors of ESRD in Patients With IMN**

Original Study	Parameter and Threshold	Original Study		Validation Study	
		Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Pei et al <sup>103</sup>	Proteinuria > 8 g > 6 mo	66	88		
Cattran et al <sup>104</sup>	Model proteinuria and serum creatinine	83	86	58	93
Cattran et al <sup>104</sup>				60	92
Italy <sup>104</sup>				77	89
Finland <sup>104</sup>					
Brenchley et al <sup>106</sup>	Urinary C3dg > 25 U/mg creatinine	80	81	Not available	Not available
Brenchley et al <sup>106</sup>	Urinary C5b-9 > 7 U/mg creatinine	60	86		
Cattran et al <sup>110</sup>				Invalid	
				See comments in text	
Reichert et al <sup>12</sup>	Urinary IgG > 250 mg/24 h	89	85		
Branten et al <sup>18</sup>				88	88
Bazzi et al <sup>107</sup>	Urinary IgG > 110 mg/g creatinine	100	58	Not available	Not available
Reichert et al <sup>11</sup>	Urinary $\beta$ 2M > 0.5 $\mu$ g/min	85	82		
Branten et al <sup>18</sup>				88	91
Bazzi et al <sup>107</sup>	Urinary $\alpha$ 1M > 33 mg/g creatinine	100	84	Not available	Not available
Branten et al <sup>18</sup>	Urinary $\alpha$ 1M > 40 $\mu$ g/min	84	94	Not available	Not available
Reichert et al <sup>50</sup>	Serum creatinine > 1.5 mg/dL*	52	90		
Honkanen et al <sup>88</sup>				80	92

NOTE. To convert serum creatinine in mg/dL to  $\mu$ mol/L, multiply by 88.4.

Abbreviations: c3dg, complement degradation product c3dg;  $\alpha$ 1M,  $\alpha$ <sub>1</sub>-microglobulin.

\*Threshold for renal insufficiency varied from 1.2 to 1.8 mg/dL (106 to 160  $\mu$ mol/L).

their accuracy at the predefined threshold values must be validated in a new patient cohort. To date, the accuracy of urinary complement C3d has not been validated. We measured urinary C3d in patients with various renal diseases.<sup>109</sup> We observed good correlation between urinary C3d excretion and urinary excretion of IgG and  $\beta$ 2M. We calculated that urinary C3d level was determined by tubular reabsorption processes, as well as glomerular permeability of C3 and local production of C3 and C3d. Corrected for proteinuria, there were no differences between patients with IMN and other glomerular diseases. We did not evaluate the prognostic accuracy of C3d, although we expect that urinary C3d will be predictive in view of the good correlation with IgG and  $\beta$ 2M levels. However, measurement of urinary C3d is difficult in routine clinical practice and requires special sampling conditions (in EDTA-containing tubes, placed on ice, centrifuged in the cold, and stored at  $-70^{\circ}\text{C}$ ). Furthermore, C3 may interfere in the assay, and the coefficient of variation is 7% to 10%.

Accuracy of the urinary C5b-9 membrane attack complex has not been validated formally. However, Cattran et al<sup>110</sup> measured urine C5b-9 in patients with IMN who had participated in the CsA con-

trolled trial. Notably, urinary C5b-9 was not measurable in the majority of patients (11 of 16 patients). Furthermore, the absence or presence of the membrane attack complex did not predict outcome or treatment response in their patients.

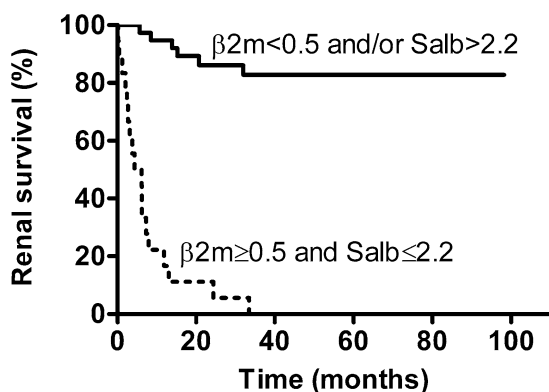
Change in serum creatinine levels during 2 years proved a very specific marker (Table 5).<sup>38</sup> Unfortunately, sensitivity is low, and use of this parameter does not allow the start of treatment before the onset of renal failure.

The model developed by Cattran's group was validated in a Finnish and Italian population.<sup>104</sup> This validation study proved the high specificity and sensitivity of this model (Table 5). Of note, the validation cohort consisted of treated and untreated patients and also included patients with nonnephrotic proteinuria (17% to 23%). It is unclear whether results would have been similar if the validation cohorts had only included untreated patients with nephrotic syndrome. Furthermore, application of the model requires a period of follow-up to identify the 6-month period with the greatest level of persistent proteinuria. In approximately one quarter of patients in the validation study, the period of maximal persistent proteinuria started longer than 12 months after renal biopsy.

We recently validated the use of urinary IgG and  $\beta$ 2M levels in a new cohort of patients with IMN.<sup>18</sup> Data unequivocally proved that these markers predict prognosis, with sensitivities and specificities approximating 90%. Specificity approached 100% when combining urinary  $\beta$ 2M and serum albumin levels. In Fig 6, renal survival is shown for patients with urinary  $\beta$ 2M and serum albumin levels less than or greater than the threshold.

The use of the Toronto model or specific urinary protein analysis should allow us to restrict therapy to patients at greatest risk for disease progression. We prefer measurements of low-molecular-weight proteins, rather than duration and magnitude of proteinuria, because of greater accuracy, easy applicability (no need for 24-hour urine collections), and direct use (no need for a waiting period).

In conclusion, our treatment strategy is intended to allow individualized treatment for patients with IMN. High-risk patients can be identified readily. Patients at risk for developing ESRD should receive immunosuppressive therapy. The optimal time of the start of treatment has not been defined. Potential benefits of early therapy start (shorter nephrotic phase) must be weighed against the potential side effects of treatment and expected gain in renal function. In this respect, the balance may favor immediate treatment in the young and delayed treatment in the elderly or patients with a pregnancy wish. Currently, we prefer a combination of cyclophosphamide and ste-



**Fig 6.** Urinary  $\beta$ 2M excretion and serum albumin level predict renal survival in patients with IMN, nephrotic syndrome, and normal renal function at biopsy. Data adapted from Branten et al.<sup>18</sup> Threshold values were 0.5  $\mu$ g/min for urinary  $\beta$ 2M and 2.2 g/dL (22 g/L) for serum albumin.

roids. Alternative agents include CsA and MMF; however, their efficacy long term remains to be proved.

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