Kidney International, Vol. 55, Suppl. 70 (1999), pp. S-47–S-55

Management of idiopathic membranous nephropathy: Evidence-based recommendations

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Management of idiopathic membranous nephropathy: Evidence-based recommendations. Membranous nephropathy is a frequent cause of nephrotic syndrome in adults, and in one third of these patients, it leads to end-stage renal disease. Based on an extensive critical review of the literature, the following recommendations are offered. Oral high-dose corticosteroids are ineffective in producing either a sustained remission of nephrotic syndrome or in preserving renal function in patients with membranous nephropathy, and should not be used as the sole therapy (grade A recommendation). The use of azathioprine is not associated with any significant benefits, so its use is not justified (grade C). The alkylating agents cyclophosphamide and chlorambucil are both effective in the management of membranous nephropathy. Because of growing concern about long-term toxicity, especially with cyclophosphamide, these drugs should be reserved for patients who exhibit clinical features, such as severe or prolonged nephrosis, renal insufficiency, or hypertension, that predict a high likelihood of progression to end-stage renal disease. Chlorambucil in conjunction with oral steroids is the drug of first choice (grade A). Cyclophosphamide and oral steroids are alternatives (grade B). Cyclosporine may, in the future, become the agent of choice for membranous nephropathy. Currently, it is recommended (grade B) that cyclosporine use be considered in patients at high risk for progression in membranous nephropathy or if alkylating agents are contraindicated or ineffective.

Membranous nephropathy may occur secondary to conditions such as hepatitis B and other infections, systemic lupus erythematosus (SLE), therapy with various drugs (for example, gold, penicillamine), and malignancies [1]. However, in adults, membranous nephropathy is most often idiopathic. The disease presents most frequently as the nephrotic syndrome (NS) or, less frequently, as asymptomatic proteinuria, with or without hypertension. Membranous nephropathy accounts for approximately 30% of cases of NS in adults [2].

The diagnosis of membranous nephropathy is made by renal biopsy, with thickening of the glomerular basement membrane (GBM) on light microscopy, which is both diffuse and uniform and is accompanied by little in the way of cellular proliferation [3]. Silver staining may reveal the presence of spikes of argyrophilic material projecting out from the GBM toward the epithelial space. With further progression, intense thickening of the glomerular capillary walls occurs, with reduplication of the GBM. Extensive interstitial fibrosis and tubular atrophy are also apparent in advanced disease. Electron microscopy reveals the presence of electron-dense immune deposits, which on immunofluorescence are found to contain IgG, usually accompanied by C_3, in a characteristic granular pattern, outlining the GBM. In very advanced disease, the intensity of IgG staining may be diminished, corresponding to the reduction in immune deposits seen on electron microscopy in late disease.

Natural history and risk factors for progression

Attempts to define the optimal management strategy for membranous nephropathy have been substantially hampered by the extremely variable clinical course that can be seen in the disease. The challenge is to find ways of identifying those patients at highest risk for progressive disease and then using cytotoxic or other therapies such as cyclosporine. Many studies have "identified" risk factors for progression to renal failure, including severe NS, hypertension, age of more than 50 years, male sex, and renal insufficiency at presentation [4–10]. However, few studies have examined such risk factors prospectively.

Recently, Pei, Cattran, and Greenwood reported a predictive model, based on data in the Toronto Glomerulonephritis Registry, for chronic renal insufficiency in patients with idiopathic membranous nephropathy [11]. A variety of models, based on severity and duration of proteinuria and rate of change in renal function, was able to improve the ability to predict the development of chronic renal insufficiency from a baseline level of 26% to a range of 55 to 86%, with a sensitivity of more than 60%. Such a model could be used to anticipate the need for therapy by identifying individual patients at risk for progressive disease, and it could also be used to identify high-risk patients for future clinical trials. The

Key words: nephrotic syndrome, end-stage renal disease, corticosteroids, toxicity, chlorambucil.

inclusion of large numbers of patients with a good prognosis has been one of the major weaknesses of previous clinical trials of therapy in membranous nephropathy.

In a recent update that compares the Canadian data to other patient populations in Italy and Finland, the predictive model outlined above has been validated [12]. The most important factor determining long-term outcome in membranous nephropathy was found to be the highest sustained six-month period of proteinuria. The model was able to predict patients at high risk of progression with an accuracy of more than 85%, despite the differences at baseline.

A number of studies have examined the natural history and outcome of membranous nephropathy, with or without therapy [4–6, 13–15]. Honkanen, Tornroth and Gronhagen-Riska, in a recent review, suggested that overall patient survival was approximately 83% at 10 years compared with 88% for an age- and sex-matched Finnish control population [13]. Other studies have reported similar long-term survival. For patients with NS, Honkanen et al reported a 10-year survival of 70%, irrespective of the treatment given [13].

Schieppati et al reported on the course in 100 patients who received no therapy other than supportive treatment [6]. The incidence of remission of proteinuria increased over time such that at five years, 65% were in complete or partial remission, whereas only 16% progressed to end-stage renal disease (ESRD). The benign course of these patients may, in part, be explained by the modest degree of proteinuria. Fully 37% had nonnephrotic-range proteinuria (that is, less than 3.5 g/day), whereas 56% had less than 5 g/day.

In contrast, the prognosis of membranous nephropathy seems to be much more benign in women, children, younger adults, and those with secondary (drug-induced) disease [8, 16–18]. Patients in whom proteinuria is less than 3.5 g/day or who maintain normal renal function for the first three years also have a good prognosis [4].

METHODS

This article focuses on a critical review of the extensive published literature in the area, with an emphasis on the levels of evidence for the validity of the studies cited, using the guidelines developed by Carruthers et al for studies of treatment [19]. A total of more than 200 articles was identified from a MEDLINE search covering the period from 1970 to 1997, using the key words membranous nephropathy and therapy. Abstracts were reviewed and articles selected for in-depth review using the criteria proposed by Carruthers et al [19].

MANAGEMENT OF IDIOPATHIC MEMBRANOUS NEPHROPATHY

Evaluation of the effectiveness of treatment strategies for idiopathic membranous nephropathy is substantially confounded by the variable course of the disease and, in particular, by the frequent development of spontaneous remissions, sometimes many months or years after the onset of NS, reported in studies of natural history [4–6, 20]. Treatment may be considered in two broad categories: the management of symptoms and signs of NS (for example, edema, hyperlipidemia) and therapies aimed at inducing remission of proteinuria and preventing progression to ESRD.

Thromboembolic complications, especially renal vein thrombosis, are frequent in NS in general and membranous nephropathy in particular. The incidence of renal vein thrombosis in membranous nephropathy has been reported at 5 to 60% [21–23]. This wide range reflects a high incidence of subclinical thrombosis, identified by prophylactic venography [22]. Routine use of prophylactic anticoagulation has not been the norm in most centers [23, 24]. However, an article by Sarasin and Schifferli suggested, using a decision model, that the benefits of prophylactic anticoagulation outweighed the risks and that it should be routine for all patients with NS secondary to idiopathic membranous nephropathy [25]. Prophylactic anticoagulation should certainly be considered in patients felt to be at high risk for venous thrombosis, that is, those with severe or prolonged nephrotic range proteinuria. This has not yet been subjected to a randomized controlled trial. A firm recommendation thus cannot be made.

Over the past 30 years, many different treatment regimens have been recommended for the treatment of idiopathic membranous nephropathy. The heterogeneity of study designs, treatment regimens, enrollment criteria, outcomes, and follow-up data has lead to considerable difficulty in interpreting the results of these many studies. There are a number of prospective, randomized trials addressing a variety of treatment regimens, but with very variable results. The lack of consistent results favoring one treatment over another is what lies behind the current debate on the optimal treatment of idiopathic membranous nephropathy.

Recommendations

Recommendation 1. There is no benefit of either a short or prolonged course of oral, alternate-day steroids for either inducing remission of NS or preserving renal function in patients with membranous nephropathy. Corticosteroids should not be used as sole therapy (grade A).

Evidence. There have been three large, prospective, randomized, placebo-controlled clinical trials (RCTs) of corticosteroid therapy for membranous nephropathy (Table 1) published between 1979 and 1990 [26–28]. These studies are comparable in terms of the clinical and demographic characteristics of the patients. End points were similar, although there were differences in the definitions of partial and complete remissions of the NS.

Table 1. Corticosteroid treatment in idiopathic membranous nephropathy

Author [reference]	Level of evidence	*N*	Treatment regimen	Results/comments
CSAINS [26]	1	72	Prednisone 100–150 mg p.o. on alternate days × 8–12 weeks vs. placebo	Rapid decline in renal function in controls. Prednisone associated with more complete or partial remissions of NS.
Cameron [27]	1	107	Prednisone 125–150 mg p.o. on alternate days × 8 weeks vs. placebo	No difference in renal function or proteinuria at 36 months. Modest early (3 and 6 month) benefit on urinary protein excretion.
Cattran [28]	1	158	Prednisone 45 mg/m^2 on alternate days × 6 months vs. placebo	No difference in remission rates for NS in either short (6 and 12 month) or long (48 month) term. No differences in rates of progression of renal insufficiency.

Abbreviations are: p.o., oral; NS, nephrotic syndrome.

The U.S. Collaborative Study of Adult Idiopathic Nephrotic Syndrome [26], the smallest of the three RCTs, reported that a minimum of eight weeks of high-dose (100 to 150 mg, depending on body weight), alternate-day prednisone resulted in a significant reduction in the rate of progression to renal failure. The short follow-up period and poorer than expected outcome in the placebo group [4, 5] have led to criticism of the results of this study. However, some authors continue to recommend this regime for patients with early histological disease and persistent NS, despite the lack of any evidence for benefit, citing the relative safety of therapy as justification [7].

The British Medical Research Trial [27] duplicated the effort of the U.S. study but with a larger patient population and a longer duration of follow-up (minimum of 3 years). This study was unable to demonstrate any significant effect of a short course of corticosteroids on renal function or urinary protein excretion at three years, although there was a modest early beneficial effect on urinary protein excretion and serum albumin noted at three to six months.

The study of the Toronto Glomerulonephritis Study Group evaluated a much longer (six months) course of oral, alternate-day prednisone in a lower dose (45 mg/m^2) than the earlier studies on the outcome of idiopathic membranous nephropathy [28]. After a median follow-up period of 48 months, there was no difference in the rates of decline in creatinine clearance or in the proportions of patients in either partial or complete remission. No early benefits were noted.

Recommendation 2. Azathioprine should not be used as part of routine care for this condition (grade C).

Evidence. Few studies have addressed the effects of azathioprine either alone or in combination with steroids in membranous nephropathy. Those that have addressed these effects suggest that it is largely ineffective in either inducing remission of NS or preventing renal insufficiency [29, 30]. A recent uncontrolled study did, however, suggest that the addition of oral azathioprine to a regime of intravenous pulse methylprednisolone and oral prednisone could reverse or stabilize progressive renal failure in patients with advanced idiopathic membranous nephropathy [31]. This observation is, as yet, unconfirmed.

Recommendation 3. Treatment with alkylating agents induces prolonged remission of membranous nephropathy. Because most controlled trials have used corticosteroids in combination with alkylating agents, it is recommended that both be used. Specific recommendations regarding timing, dose, and duration of therapy are provided in Table 2 and Figure 1. Given the potential toxicity of these therapies, they should be reserved for patients at high risk of progression to renal failure (grade A).

Evidence. Despite the widespread use of cyclophosphamide and chlorambucil in patients with idiopathic membranous nephropathy, the clinical trial evidence on which these treatments are based consists of a number of small uncontrolled studies [32–36] and just six prospective RCTs [37–42], which vary in study design, entry criteria, and outcomes evaluated (Table 2).

Many of the smaller trials suffer from significant methodological flaws, in that they are either retrospective or lack the statistical power, because of sample size considerations, to allow firm conclusions to be drawn. As such, the data presented in these studies must be interpreted with caution. However, Lagrue et al, in a retrospective study, noted complete or partial remission of proteinuria in 13 out of 16 patients with membranous nephropathy who were treated with chlorambucil compared with just 3 out of 14 on placebo and 1 out of 11 on azathioprine [32]. In contrast, neither Shearman et al nor Alexopoulos et al found any benefits from oral cyclophosphamide compared with either corticosteroids or symptomatic therapy in their retrospective studies [35, 36].

Donadio et al conducted a study of 22 patients randomized to either oral cyclophosphamide of 1.5 to 2.5 mg/kg daily or no specific therapy for a period of 12 months [37]. There was no effect of cyclophosphamide on renal function, proteinuria, or histological stage of disease. Falk et al conducted a randomized controlled trial of intravenous and oral corticosteroids plus intrave-

Table 2. Cytotoxic treatment in idiopathic membranous nephropathy

Author [reference]	Level of evidence	*N*	Treatment regimen	Results/comments
Ponticelli [39]	1	67	MP 1 g i.v. × 3 days; 0.4 mg/kg p.o. × 27 days, then chlorambucil 0.2 mg/kg p.o. × 28 days × 3 cycles vs. symptomatic therapy	Well-conducted study. All patients had NS, but patients with renal insufficiency excluded. Increased rate of partial/complete remission in treatment group vs. declining in controls.
Ponticelli [42]	1	92	MP 1 g i.v. × 3 days; 0.4 mg/kg p.o. × 27 days, then chlorambucil 0.2 mg/kg/day × 28 days for 3 cycles vs. MP alone. On alternate months × 6 months	Chlorambucil associated with earlier remission of NS.
Donadio [37]	2	22	Cyclophosphamide 1.5 to 2.5 mg/kg p.o. × 1 year vs. symptomatic therapy	Small study. No favorable impact of cyclophosphamide on proteinuria, renal function or histology.
Ponticelli [43]	1	67	MP 1 g i.v. × 3 days; 0.4 mg/kg p.o. × 27 days, then chlorambucil 0.2 mg/kg p.o. × 28 days × 3 cycles vs. symptomatic therapy	10 year follow-up data from above study. Significant improvement in renal survival for chlorambucil vs. symptomatic therapy.
Murphy [41]	2	40	Cyclophosphamide 1.5 mg/kg × 6 months + dipyridamole/warfarin × 2 years vs. symptomatic therapy	No differences in renal function at 2 years. Treatment group had significantly less proteinuria and higher serum albumin through follow-up.
Falk [38]	2	26	Prednisone 2 mg/kg vs. cyclophosphamide 0.5 g/m^2 + i.v. pulse and oral steroids (7 mg/kg methylprednisone, then prednisone 2 mg/kg) for 6 months	No impact of cyclophosphamide on renal function, progression to ESRD or level of proteinuria.
West [40]	3	26	Cyclophosphamide 2 mg/kg × 20 ± 4 months ± prednisone vs. prednisone or symptomatic therapy	High-risk patients with significant renal failure and/or prolonged NS. Cyclophosphamide associated with an increased rate of remission of NS and better preservation of renal function.

Abbreviations are: MP, methylprednisolone; NS, nephrotic syndrome; other abbreviations are in Table 1.

nous cyclophosphamide compared with oral corticosteroids alone in 26 patients with idiopathic membranous nephropathy and clinical and laboratory evidence of deterioration [38]. Over a mean follow-up period of 29.2 ± 17.1 months, there were no differences between the rate of progression to ESRD (4 out of 13 in each group) nor in the severity of renal failure or urinary protein excretion. West et al conducted a case-control study of oral cyclophosphamide versus oral corticosteroids (in 15 out of 17 control subjects) in idiopathic membranous nephropathy [40]. They were able to conclude that therapy with cyclophosphamide was associated with improvement in both serum albumin and 24-hour proteinuria, while preserving renal function and delaying progression to ESRD. This study is remarkable for its selection of a group of patients at high risk for progression, that is, persistent proteinuria of more than 3.5 g/day and serum creatinine of more than 135 μmol/liter.

Murphy et al studied 40 patients randomized to either no specific therapy or a treatment regimen consisting of oral cyclophosphamide for six months and oral warfarin and dipyridamole for two years [41]. Renal function was unchanged during two years of follow-up in both groups, but reduced proteinuria and improved serum albumin were found in the cyclophosphamide-treated patients. When only those patients with the NS are considered, a significantly higher proportion of patients in the treatment group achieved a complete remission compared with control patients (9 out of 13 vs. 4 out of 13, $P = 0.05$).

Ponticelli et al have published the results of two separate studies of chlorambucil in the treatment of idiopathic membranous nephropathy. The first of these, published in 1984, was a RCT of six months treatment with chlorambucil plus corticosteroids in monthly cycles versus symptomatic therapy, in patients with nephrotic range proteinuria related to idiopathic membranous nephropathy [39]. Impressive results favoring the treatment group were reported, with 23 out of 32 chlorambucil patients experiencing a complete or partial remission compared with just 9 out of 30 control patients. The second study, published in 1992, compared the chlorambucil/steroid regimen with steroids alone in 92 nephrotic patients with idiopathic membranous nephropathy [42]. None of the patients had participated in the earlier study. Again, a net benefit favoring the chlorambucil-treated patients was apparent, both for remission of NS (66% free of NS at three years vs. 40% in control) and preservation of renal function. This study suggested that treatment with chlorambucil/methylprednisone was less likely to induce a remission in the presence of renal insufficiency or mesangial sclerosis.

Ponticelli et al have recently published data concerning 10-year outcomes in their original cohort of 81 patients prospectively randomized to symptomatic therapy compared with cyclic treatment with intravenous methylprednisolone, oral prednisone, and oral chlorambucil [43]. All of these patients had NS at the time of initial treatment assignment, in contrast to other prospective studies and to studies of untreated patients, in which a variable percentage of patients had non-nephrotic pro-

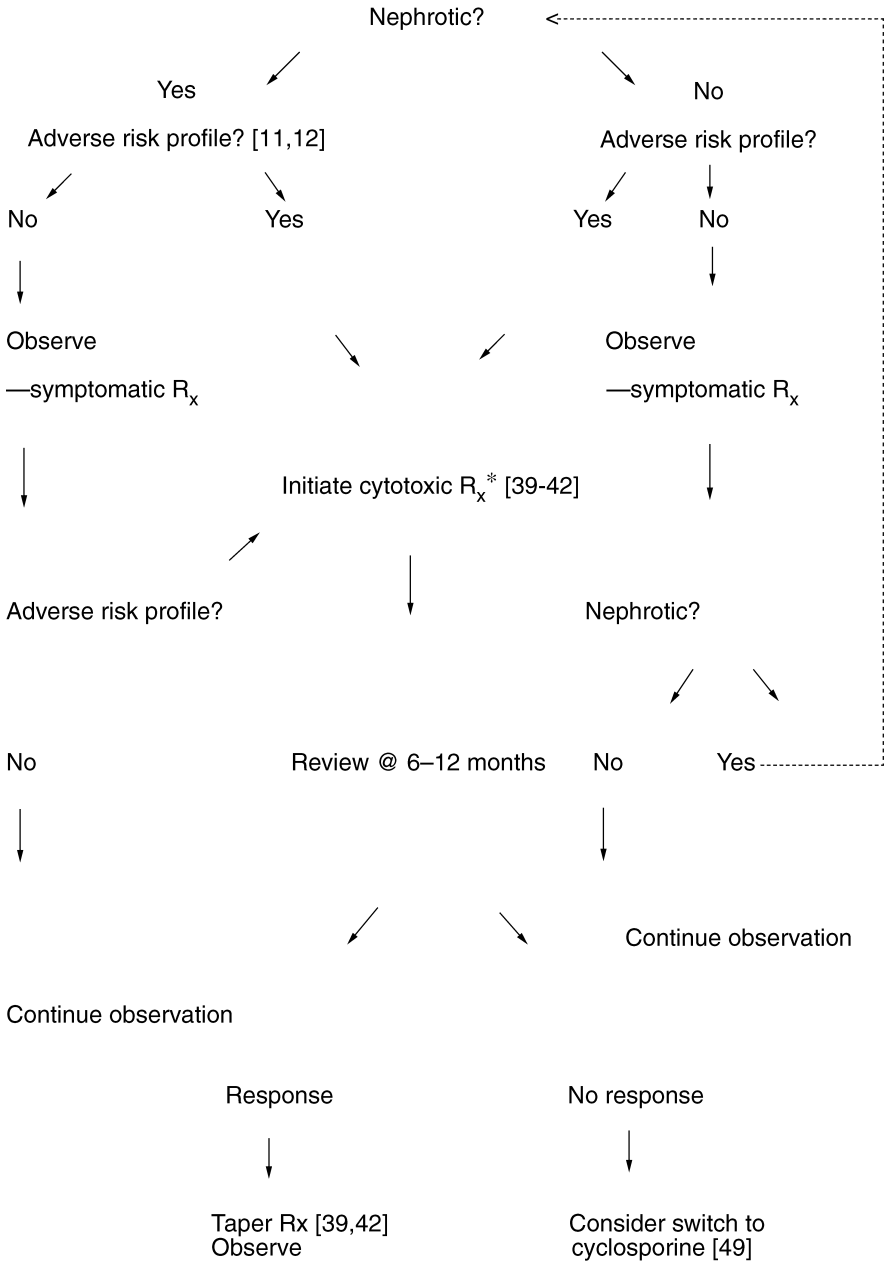

Fig. 1. Treatment algorithm for idiopathic membranous nephropathy. *Chlorambucil may be preferable to cyclophosphamide with respect to toxicity.

teinuria. Ten-year follow-up revealed that the probability of renal survival was 0.92 (95% CI, 0.83 to 1.00) for treated patients compared with 0.60 (95% CI, 0.42 to 0.78) for controls. This raises the question of whether Ponticelli's control patients may have experienced an unduly rapid progression of renal failure. In contrast, Cattran et al reported an actuarial survival, using a creatinine clearance of 0.16 ml/seconds as the end point, of 91 versus 90% at eight years for control versus prednisone-treated patients [28]. Cattran et al's patients were very similar to Ponticelli's in all respects except that patients with renal insufficiency were not excluded [28]. The 10-year renal survival of 72% reported by Schieppati in untreated patients from the same region of Italy as Ponticelli's patients must be interpreted with caution, as 37% of their patients had nonnephrotic range proteinuria and 56% had less than 5 g/day of proteinuria [6]. Massive proteinuria has been identified in a number of studies as an important risk factor for progression [4, 8], although the recent meta-analyses have failed to demonstrate this as an independent risk factor, perhaps because of methodological limitations. The relative rarity of mas-

Table 3. Cyclosporine treatment in idiopathic membranous nephropathy

Author [reference]	Level of evidence	*N*	Treatment regimen	Results/comments
Cattran [49]	2	17	CsA 3.5 mg/kg/day × 12 months vs. placebo	CsA associated with slower rate of decline in renal function. Sustained remission of proteinuria in 6/8 CsA patients.
Rostoker [47]	5	15	CsA 4–5 mg/kg × 12–30 months Prednisone 1–2 mg/kg/day × 2 months	11/15 had complete or partial remission of NS. Relapse seen in 3/9 on CsA withdrawal. No CsA nephrotoxicity.
DeSanto [46]	6	5	CsA 7 mg/kg × 6 months + MP 1–3 mg/kg/day, decreasing to 0.15 mg/kg/day	All had failed prior to chlorambucil/MP therapy. 4/5 had prompt remission of proteinuria. No renal failure. Follow-up brief.
Radhakrishnan [48]	6	10	CsA 4–6 mg/kg × 6–43 months ± prednisone	SLE-associated membranous nephropathy 6/10 had remission of proteinuria. No worsening of renal failure.

Abbreviations are: MP, methylprednisolone; NS, nephrotic syndrome; CsA, cyclosporine.

sive proteinuria (only 10% of patients had proteinuria in excess of 10 g/day) may further explain the relatively benign course undergone by the patients described by Schieppati et al [6].

Several small studies have examined the effects of chlorambucil or cyclophosphamide on the outcome of membranous nephropathy in patients with more advanced disease [44, 45]. In both of these studies, patients had severe and/or persistent NS (24-hr protein of more than 3.5 g for more than six months) and renal insufficiency (serum creatinine of more than 159 μmol/liter) prior to cytotoxic therapy. Both treatments have been associated with an improvement in both the degree of proteinuria and rate of decline in renal function despite the presence of advanced histological disease, severe proteinuria, and renal failure. This observation is important, as most of the patients in the RCTs of both chlorambucil and cyclophosphamide had normal renal function prior to treatment. It may be that patients selected on the basis of a higher risk of progression will be more likely to benefit from alkylating agents. However, this remains to be studied in a clinical trial of adequate size and duration.

Recommendation 4. Cyclosporine therapy shows promise as an effective therapy for patients with membranous nephropathy who are at high risk for progressive renal failure (grade B). Cyclosporine of 4 to 6 mg/kg daily for 12 months is the preferred regimen.

Evidence. A number of trials have addressed the use of cyclosporine, usually in conjunction with steroids, for the treatment of idiopathic membranous nephropathy (Table 3), as well as membranous lupus nephritis [46–49]. The usual dose of cyclosporine used in these studies has been 4 to 6 mg/kg. The majority of studies have been uncontrolled yet have shown promising results with respect to both remission of NS and preservation of renal function, together with freedom from serious cyclosporine nephrotoxicity.

Cattran et al recently reported the results of a randomized trial of cyclosporine in patients with idiopathic membranous nephropathy who were felt to be at high risk of progression [49]. Of 64 patients followed initially on a low-protein diet, 17 had persistent nephrotic range proteinuria and a rate of decline in creatinine clearance in excess of 8 ml/min/year, and were randomized to cyclosporine or placebo. After 12 months of drug therapy, patients on cyclosporine had a significantly slower rate of decline in renal function and less proteinuria than placebo-treated patients. These benefits persisted for up to two years after the withdrawal of cyclosporine. These results are certainly encouraging, but will need to be confirmed by a larger trial with a more prolonged follow-up period, given the natural history of the disease.

Meta-analyses of studies in idiopathic membranous nephropathy

Two meta-analyses of clinical trials in idiopathic membranous nephropathy have recently been published [50, 51]. Imperiale, Goldfarb, and Berns conducted a detailed examination of the five randomized prospective clinical trials of cyclophosphamide and/or chlorambucil in this disease [50]. In contrast to the often very large numbers of patients reported in retrospective studies focused either on therapy or natural history, these five studies collectively involve just 228 patients. Even in this small group of studies, there is still considerable heterogeneity in the doses and duration of drug therapy, mean duration of follow-up, definitions of complete and partial responses to treatment and comparison therapies used. However, despite these shortcomings, this meta-analysis provides evidence suggesting that, for some patients at least, there are benefits to the use of alkylating agents. For all of the trials, the relative risk (RR) of achieving a complete remission in the treatment group (urine protein of less than 0.2 to 0.5 g/day) was 4.6 (95% CI, 3.2 to 8.4). When just the RCTs were included in the meta-analysis, the RR was 3.4 (95% CI, 1.6 to 7.1). There were no qualitative or quantitative differences noted in complete remission rates for cyclophosphamide compared with chlorambucil treatment. Calculation of the number needed to treat (NNT) to produce one complete

remission (calculated as the reciprocal of the absolute difference in event rate between treatment and control groups) yielded a value of 4.7 both for all trials and for trials comparing cytotoxic therapy with symptomatic treatment only. This study did not address the issue of long-term effects of therapy on renal function, owing to the lack of clear renal outcome data in the source material.

Hogan et al conducted a less rigorous yet more extensive examination of 32 studies published between 1968 and 1993 [51]. This analysis comprised a second meta-analysis of the prospective trials noted earlier here, as well as pooled analyses, including many retrospective studies and case series for which relevant outcome data could be gleaned from the published articles. In this way, the analysis was able to include data on close to 2000 patients followed, in most cases, for more than two years. The meta-analysis again found that the RR for complete remission in patients treated with alkylating agents was 4.8 (95% CI, 1.44 to 15.96). The results of the pooled analysis revealed that renal survival, however, was no different at two years between alkylating therapy and either the symptomatic therapy or steroid groups. At five years, there was a lower probability of renal survival in the steroid/no-therapy group (0.80) than in patients receiving alkylating agents (0.99).

Toxicity of cytotoxic therapy

The conclusions that can be drawn from studies of cytotoxic therapy for membranous nephropathy are necessarily tempered by concern regarding the potential toxicities of both chlorambucil and cyclophosphamide, as well as continued anxiety concerning the long-term outcome of therapy. Although Ponticelli et al's most recent follow-up study may allay the latter fear [43, 52], many physicians remain reluctant to commit their patients to cytotoxic therapy, preferring to use corticosteroids despite clear evidence that they are ineffectual.

A recent article highlighted the potential long-term consequences of cyclophosphamide therapy. Talar-Williams et al evaluated the occurrence of bladder cancer in patients who had received cyclophosphamide as therapy for Wegener's granulomatosis at the National Institutes of Health between 1967 and 1993 [53]. They found that prolonged cyclophosphamide therapy, particularly at cumulative doses in excess of 100 g, was associated with an increased rate of development of bladder cancer. The bladder cancer risk was estimated to be 5% at 10 years and 16% at 16 years after first exposure to cyclophosphamide. A cumulative dose of 100 g requires some 19 months of therapy for a 70 g patient on 2.5 mg/kg daily. It remains to be seen what effect, if any, this finding will have on the use of cyclophosphamide for glomerular diseases of all kinds.

Table 4. Recommendations regarding drug therapy in idiopathic membranous nephropathy

1. Cyclophosphamide
   - 1.5 to 2.5 mg/kg/day orally for six to twelve months with 1 to 2 mg/kg/day alternate day prednisone for the first two months [40, 41]. Prednisone should be tapered as soon as a response is evident.
   - The dose of cyclophosphamide should be adjusted to maintain total WBC $> 4.5 \times 10^9$/liter.
   - Intravenous pulse cyclosphosphamide should not be used [54].
2. Chlorambucil
   - Pulse methylprednisolone 1 g i.v. $\times$ three days followed by 0.4 mg/kd/day orally for 27 days. Chlorambucil 0.2 mg/kg/day for 28 days.
   - Cycle repeated $\times$ three for a total duration of six months [39, 42].
   - Chlorambucil dose should be adjusted to maintain total WBC $> 4.5 \times 10^9$/liter.

     The dose of both cyclophosphamide and chlorambucil should be based on an estimate of 'dry' or pre-nephrotic weight to avoid marrow toxicity.
3. Cyclosporine
   - 4 to 6 mg/kg/day in two divided doses for six to twelve months [46–49]. Dose should be adjusted to maintain monoclonal whole blood trough level of 120 to 200 ng/ml.
   - Prednisone 1 to 2 mg/kg on alternate days may be added [46–48] as above, but should be tapered as soon as a response is evident.

Abbreviations are: WBC, white blood cells; i.v., intravenous.

CONCLUSIONS

Despite the large number of clinical studies with variable outcome measures and treatment regimes, it is possible to draw some reasonably firm conclusions (Table 4 and Fig. 1). First, data from the three randomized controlled trials suggest that, on balance, there is no justification for the continued use of corticosteroids alone as primary therapy for patients with NS caused by idiopathic membranous nephropathy. There is even less justification to use corticosteroids in patients without NS.

Second, the spontaneous favorable outcome in many patients with idiopathic membranous nephropathy and NS, with up to 40% of patients entering complete remission, often delayed, does not justify the routine use of cytotoxic therapy for all patients even with NS. However, a meta-analysis of the RCTs of cytotoxic therapy for membranous nephropathy indicates that there are long-term benefits on both the remission of NS and the rate of progression of renal failure. Cytotoxic therapy should therefore be offered to all patients who are felt to be at high risk of progression based on clinical factors such as age, male gender, renal function, blood pressure, severity and persistence of NS, or histological presence of severe tubulointerstitial disease. Meta-analysis of RCTs does not indicate a preference for chlorambucil over cyclophosphamide. The recent publication by Ponticelli et al of a randomized comparison of cyclophosphamide versus chlorambucil suggests that the therapies should be considered equivalent in terms of efficacy [52]. Both drugs are associated with significant short- and long-term toxicity. The recent report of a significant increase in the risk

of bladder cancer many years after initiation of treatment with cyclophosphamide [53] suggests that chlorambucil may ultimately prove to be the less toxic alternative. Intravenous cyclophosphamide has been shown in one small recent study to be less effective than oral chlorambucil [54], suggesting that it may not be prudent to switch to the intravenous route for cyclophosphamide in an effort to avoid toxicity.

Finally, cyclosporine has been shown to benefit some patients with severe and/or persistent and progressive disease. The quality of evidence for benefit of cyclosporine is not as good as for cytotoxic drugs, but if larger scale trials confirm efficacy, cyclosporine has the potential to become a treatment of choice for many nephrologists who harbor lingering concerns about the long-term consequences of cytotoxic drugs, particularly the late cancer risk.

Based on the data available from the literature, it is now possible to suggest a treatment algorithm for the management of patients with idiopathic membranous nephropathy (Fig. 1). This algorithm reflects the known risk factors for progression, as well as the known tendency for the development of late spontaneous remissions. Patients without NS would not be offered therapy unless they had other adverse prognostic indicators such as renal insufficiency, hypertension, or marked interstitial fibrosis on renal biopsy. Patients with the NS would only be offered therapy if other risk indicators were present or developed during follow-up.

The assessment of risk in the application of such a treatment algorithm could rely simply on clinical determinants such as those noted earlier in this article. A more detailed assessment of risk could, however, be made by applying the criteria of Pei, Cattran, and Greenwood [11].

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