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 μmol/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 μmol/L]), risk for developing end-stage renal disease can be estimated by measuring urinary excretion of β_2-microglobulin or α_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.**

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

IDIOPATHIC MEMBRANOUS nephropathy (IMN) is one of the most common causes of nephrotic syndrome in adult patients.[1] 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,[2] whereas others point to the high rate of ESRD and favor immunosuppressive therapy.[3] The titles of editorial reviews written during the past 25 years clearly reflect the uncertainty in this field, from Cameron's[4] "Membranous Nephropathy: The Treatment Dilemma" in 1982 and "Membranous Nephropathy—Still a Treatment Dilemma"[5] in 1992 to Glassock's[6] "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.[7] 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.[8,9]

During the past 2 decades, we have systematically studied patients with IMN; our database now includes 279 patients.[8,10-18] 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[19] 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-

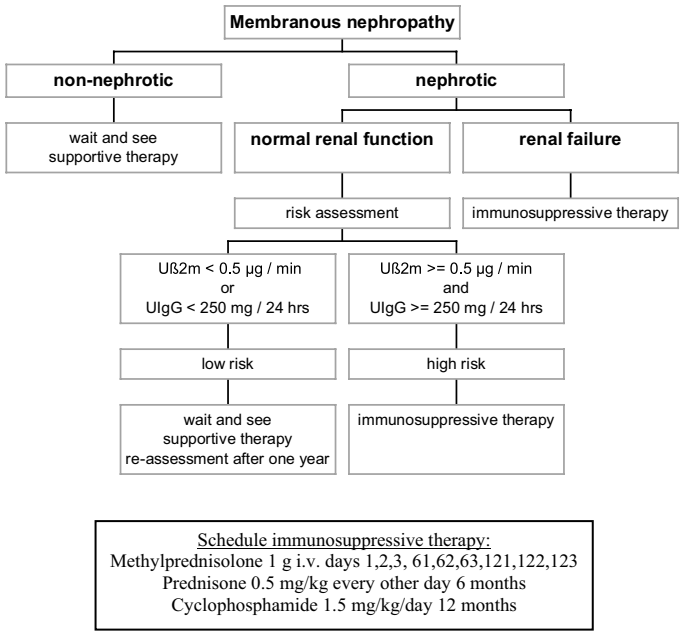

Fig 1. Outline of proposed treatment strategy in patients with IMN.