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REVIEW ARTICLE

Membranous nephropathy: Treatment outline and risk stratification

Ziad Arabi

Department of Nephrology, University of Buffalo, NY, USA

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ABSTRACT

Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in adult. However, the exact etiology and the best treatment approach are still unclear. It is imperative to understand the nature of and prognosis of MN before initiating treatment which may include disease specific therapy based on a careful risk-stratification approach.

Key words: Membranous, nephropathy, proteinuria, cyclophosphamide, ponticelli, ACE inhibitors

INTRODUCTION

Membranous nephropathy (MN) remains the most common cause of nephrotic syndrome in adults age (40–60 years), and it is a leading cause of renal failure within the primary glomerulonephritis group.[1,2] It usually presents as a frank nephrotic syndrome, often with low-grade microhematuria and relatively well-preserved renal function. However, some patients have only asymptomatic low-grade or nephrotic-range proteinuria that is discovered on routine urinalysis. Patients can lose 10–20 g protein per day and experience severe disability. Most cases are idiopathic and patients have M-type phospholipase A2 receptor as a target antigen in about 70% of cases.[3]

In the future, the detection of M-type PLA2R antibodies may help distinguish patients with primary MN who require aggressive immunosuppressive therapy from those with secondary disease.[4] Anti-PLA2R antibodies also appear to predict activity of the disease as well as response to therapy.[5]

MN can be secondary to the use of certain medications, such penicillamine, gold, and rarely, captopril or nonsteroidal agents, or associated with certain viral infections (chronic hepatitis B and C), or with malignancies (of lung, breast, and gastrointestinal origin). Occasionally, patients with autoimmune disease such systemic lupus erythematosus may develop MN (class V lupus glomerular disease).[1,2]

Patients with idiopathic MN typically have normal serum complements and have no pathognomonic, serologic, or clinical features.

Diagnosis is made by kidney biopsy. By light microscopy, the glomeruli typically appear normocellular with thickening of the glomerular basement membrane (GBM). Use of silver methenamine reveals additional "spike-like" protrusions on the epithelial side of the GBM, which represent of basement membrane-like material. Immunofluorescence microscopy demonstrates IgG and C3 along the capillary wall in a "granular" pattern, and electron microscopy reveals that the immune deposits are located in the subepithelial region.[1,2]

NATURAL HISTORY AND PROGNOSIS

Before considering approaches to therapy, which remain controversial, it is imperative to understand the nature of untreated MN and its prognosis.[6-8]

In general, idiopathic MN has a better outcome in women than men. These benefits are mostly mediated through both lower proteinuria and blood pressure at presentation

Address for correspondence: Dr. Ziad Arabi, Department of Nephrology, University of Buffalo, NY, USA, E-mail: ziadarabi@yahoo.com

and throughout follow-up, although females did have an independent advantage at higher levels of proteinuria.[9]

The prognosis in men also depends on the degree of proteinurea. For non-nephrotic patents, the outcome is generally good even without disease-specific therapy with a 10-year renal survival rate of close to 100%.[1,6-8] However, the prognosis is worse in men with nephrotic range proteinurea. After 3 years of follow-up, about 50% of untreated patients develop progressive renal disease. Another 25% of patients eventually have a spontaneous complete remission (normal protein excretion). Another 25% have partial remissions (<2 g/day proteinuria) with persistent proteinuria, but no loss of GFR. About 25% of patients who enter remission suffer a subsequent relapse of nephrotic syndrome. For patients who exhibit remission or maintain normal GFR for >3 years, the prognosis is excellent [Table 1].[6]

Since disease-specific therapy is generally associated with significant side effects, it is important to try to identify patients at substantial risk of progression to receive such treatment and to spare those patients who are likely to have a benign course independent of cytotoxic immunosuppressive therapy.

There are various prognostic factors in identifying patients whose disease will subsequently progress. The best established clinical parameters are the presence of persistent proteinuria (>8 g for >6 months, >6 g for >9 months, or >4 g for >1 year) and increased serum creatinine at the time of diagnosis or during follow-up, which documents that progression is already in progress. Urinary excretion of >250 mg/day of IgG (an index of urine protein selectivity) and >0.5 μg/min of B_2-microglobulin (an index of tubular function that likely reflects severity of interstitial disease) are also strong progressive disease, with an established specificity of about 90%.[8]

THERAPY

Despite the fact that MN is a relatively common glomerular disease and has been subjected to multiple controlled trials of various steroid and immunosuppressive regimens, the therapy of MN is still controversial.[8] Multiple factors complicate interpretation of such studies. These include the limited number of patients or short duration of most studies, and inability to incorporate the likely benefits of current nonspecific therapies such as achieving good blood pressure control, or medications that nonspecifically lower the level of urine protein excretion (such as ACE inhibitors or angiotensin receptor blockers).[8]

Treatment that is not disease specific

Nondisease-specific variables have been shown to affect the prognosis of all glomerular diseases adversely, in general, including MN. Combinations of blood pressure control to values of ≤125/75 mmHg, dietary sodium restriction, diuretics, and the angiotensin converting enzyme inhibitors (ACE inhibitors), and angiotensin receptor blockers (ARB drugs) are appropriate for all patients with MN.

Treatment of hyperlipidemia

Hyperlipidemia so commonly complicates heavy proteinuria that it is part of the definition the nephrotic syndrome. Characteristically, total plasma cholesterol and triglyceride levels are elevated. Increased lipid levels contribute to an increased risk of coronary disease in nephrotic patients. Elevated lipids may also adversely affect renal function. Therefore, the use of statins is appropriate in patients with prolonged elevation in urine protein excretion and secondary hyperlipidemia.[10-12] However, no prospective trials have evaluated the relationship between deranged lipid metabolism and coronary or cerebral artery disease in patients with nephrotic syndrome.

Low protein diet

The degree of proteinuria correlates with the rate progression of renal failure, and proteinuria may be an independent mediator of progression rather than simply being a marker of glomerular dysfunction.[13] Therefore, any measures that can lower levels of proteinuria, even if independent of an effect on the underlying disease process, are likely to slow the rate of progression in patients with more moderate disease.

Moderate dietary protein restriction (usually 0.8 g/kg/day) may reduce proteinuria by 15–25% and slow the progression of renal disease without significant side effects or adverse changes

Table 1: Risk stratification in membranous nephropathy

Risk stratification	Proteinuria	Creatinine clearance	Follow-up	Risk of developing chronic kidney disease over 5 years	Recommended treatment
Low risk	<4 g/day	Remains normal	6 months	<8% over 5 years	Nondisease-specific treatment
Moderate risk	4–8 g/day	Normal or near normal	6 months	50%	Nondisease specific then disease-specific therapy if not better in 6 months
High risk	>8 g/day	Below normal or decreases during the observation period	3 months	75%	Diseasespecific therapy in addition to non-disease specific

in serum protein levels, especially in patients with urinary protein excretion between 2 and 10 g/day.[1] However, the safety of a low protein diet in nephrotic syndrome is uncertain.

The use of ACE I and ARB

ACE inhibitors or ARBs alter glomerular hemodynamics and may also have a direct effect on interstitial fibrotic processes. ACE inhibitors or ARBs can lower protein excretion in early MN by an average of 35% without having adverse effects on blood pressure or GFR.[13] The combination of both an ACE inhibitor and an ARB together can be tried for a further reduction in proteinuria. These agents are titrated to the maximal dose that can be tolerated without adversely effecting systemic blood pressure, GFR, or serum potassium levels. They should be used cautiously in older patients with possible renal vascular disease or significant renal insufficiency.

The use of prophylactic anticoagulation

Patients with MN with massive proteinuria and a serum albumin below 2.0 g/dL (20 g/L) represent the highest risk group for thromboembolism. Prophylactic anticoagulation is indicated for patients with any additional risk factor for thrombosis (e.g., a prior idiopathic thromboembolic event; immobilization; severe heart failure; morbid obesity; or abdominal, orthopedic, or gynecologic surgery).

The advent of better measures to reduce urinary protein excretion nonspecifically, as well as to control blood pressure and to lower lipid levels, almost certainly means that the natural history of MN without disease-specific therapy is better than that discussed previously. However, there are a significant number of patients, particularly males older than age 50 who have persistent nephrotic syndrome will have progressive loss of renal function despite vigorous application of all these nonspecific measures. These patients are candidates for treatment directed specifically at the underlying disease process.

Disease-specific therapy

As mentioned above, the selection of patients of more aggressive therapy, and the efficacy of such therapy remain topics of significant controversy [Table 2].

The use of steroid

The utilization of high-dose oral steroids alone is not beneficial in MN.[14,15] A more promising approach has been the use of oral steroids combined with cytotoxic drugs, usually alkylating agents.

The use of alkylating agents

The best and most convincing studies of this approach have been those of Ponticelli and Passerini,[16] who have studied primarily patients with nephrotic syndrome and normal renal function. They have employed a regimen of a 3-day course of methylprednisolone 1G intravenously followed by (0.4–0.5 mg/kg/day) oral prednisone for 1 month alternating with 1 month of oral chlorambucil (0.2 mg/kg/day) for a total treatment period of 6 months. After 5 years of follow-up, renal function had deteriorated in about 50%

Table 2: Drug-specific treatment

Regimen	Protocol	Advantages	Disadvantages	Comment	Reference
Steroid alone			Not beneficial		[14,15]
Steroid with chlorambucil	A 3-day course of 1G methylprednisolone followed by prednisone (0.4–0.5 mg/kg/day) for 1 month alternating with 1 month of chlorambucil (0.2 mg/kg/day) for a total treatment period of 6 months	After 5 years of follow-up, renal function had deteriorated in about 50% of the control group, but only in 10% of the treated patients	Not widely used in the United States because of bone marrow suppression		[16]
Cyclophosphamide, with low-dose prednisone	Cyclophosphamide (1.5–2.0 mg/kg/day) with prednisone (0.5 mg/kg/day) for 3–6 months	Comparable results to steroid with chlorambucil	Side effects leading to stop therapy in only 10% cases	First-line treatment	[17,18]
Cyclosporine	3.5–5 mg/kg/day (trough levels of 150–225 mg)	70% of patients show occasional complete or partial remission	Prolonged courses (1–2 years) may produce more permanent remission	The best-studied alternative to steroid–cytotoxic drug therapy	[19,20]
Tacrolimus	Tacrolimus (0.05 mg/kg/day) over 12 months with a 6-month taper	Decreases proteinurea in MN	Patients have significant relapse rate		[21,22]
Mycophenolatemofetil	With steroids in a dose of 2 g/day for a year		Limited data	Third alternative in the treatment	[23]
Anti-B cell monoclonal antibody	Four weekly infusions	Proteinuria was significantly reduced and renal function stabilized 1 year later	Limited data		[24]
Adrenocorticotropic hormone		Comparably to a combined regimen of steroids and alkylating agents	Limited data		[25]

of the control group, but only 10% of the treated patients; progression to dialysis occurred in 4 of 39 in the control group and only 1 of 42 treated patients. At 10 years, 88% of treated and only 47% of control patients had complete or partial remission of nephrotic syndrome, and of the treated group, only 8% were in renal failure compared with almost 40% of controls.[16]

Although the Ponticelli and Passerini studies provide strong evidence for the efficacy of combined steroid–cytotoxic drug therapy in MN, the protocol employed has not been widely used in the United States because of problems with bone marrow suppression and infection in chlorambucil-treated patients, particularly renal insufficiency is present. More popular has been oral cyclophosphamide, usually 1.5–2.0 mg/kg/day, in combination with low-dose prednisone (0.5 mg/kg/day), for periods of 3–6 months. Ponticelli and colleagues have compared chlorambucil and cyclophosphamide in their treatment regimen and found them to give comparable results with side effects leading to stop therapy in only about 10% cases.[17,18]

Cyclosporine and tacrolimus

The best-studied alternative to steroid–cytotoxic drug therapy for MN is cyclosporine, usually employed in relatively low doses of 3.5–5 mg/kg/day adjusted to trough levels of 150–225 mg. Cyclosporine does reduce protein excretion in MN, usually by 30–50%, and about 70% of patients show occasional complete or more commonly partial remission.[19] The disease often relapses after short (4–6 months) courses of cyclosporine, but more prolonged courses (1–2 years) may produce more permanent remission.[20] In patients who do respond, a stabilization of renal function has also been reported. Cyclosporine is considered a second choice to cytotoxic drug therapy because of the significantly lower incidence of complete remissions, the tendency to relapse when therapy is discontinued, the potential nephrotoxic effects of the drug itself, and the problems of hypertension and hyperkalemia encountered during treatment. Cyclosporine should not be used in patients with impaired renal function.

While tacrolimus decreases proteinurea in MN, "it might not alter the pathology of the disease" and treated patients have significant relapse rate.[21,22]

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a significantly less toxic immunosuppressive agent than cyclophosphamide or chlorambucil, and is considered to be third alternative in the treatment of MN that may be beneficial in some patients with MN, especially patients intolerant of, or dependent on, cyclophosphamide or cyclosporine. Preliminary results suggest that some patients may respond to MMF used with steroids in a dose of 2 g/day for a year,[23] but insufficient data are available to establish a role for MMF in the treatment of MN.

Anti-B cell monoclonal antibody

More recent data are available on the use of Rituximab, an anti-B cell monoclonal antibody.[24] Given in four weekly infusions to eight patients with resistant MN, proteinuria was significantly reduced and renal function stabilized 1 year later.

Adrenocorticotropic hormone

The initial experience in Europe using synthetic adrenocorticotropic hormone (ACTH) in MN led to a randomized trial in which ACTH performed comparably to a combined regimen of steroids and alkylating agents. Observational data from American patients treated with natural ACTH gel for resistant nephrotic syndrome have also been promising.[25]

RISK STRATIFICATION IN MEMBRANOUS NEPHROPATHY

Low risk

Proteinuria remains less than 4 g/day and creatinine clearance remains normal for 6 months. Such patients have a less than 8% risk of developing chronic renal insufficiency over 5 years and can be treated with non-disease-specific treatment [Table 1].[6,26,27]

Moderate risk

Proteinuria is between 4 and 8 g/day and persists for more than 6 months. Creatinine clearance is normal or near normal and remains stable over 6 months of observation. Chronic renal insufficiency develops over 5 years in approximately 50% of these patients. Patients should receive treatment that is not disease specific then disease-specific therapy if not better in 6 months.[6,26,27]

High risk

Proteinuria is greater than 8 g/day and persists for 3 months and/or renal function that is either below normal due to MN or decreases during the observation period. Approximately 75% of such patients are at risk of progression to chronic renal insufficiency over 5 years. Patients should be started on disease-specific therapy in addition to treatment that is not disease specific.[6,26,27]

Finally, it is important to keep in mind when treating patients with MN, the long lag time between successful

interruption of the immune response and a corresponding reduction in urine protein excretion before declaring a patient resistant to therapy. This averages about 3 months, but may be as long as a year.

In summary, membranous nephropathy is the most common cause of nephrotic syndrome in adults age (40–60 years), and it is a leading cause of renal failure within the primary glomerulonephritis group. However before considering approaches to therapy, which remain controversial, it is imperative to understand the nature of untreated MN and its prognosis.

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