Treatment of idiopathic membranous nephropathy: the dilemma of who, when, and how

C. A. Stegeman, D. de Zeeuw and P. E. de Jong

Department of Internal Medicine, Division of Nephrology, State University Hospital Groningen, The Netherlands.

Introduction

Membranous nephropathy is the most common histological diagnosis in adult patients with nephrotic syndrome. In most patients no underlying cause for the disease can be identified and the term idiopathic or primary membranous nephropathy is used [1]. It is suspected that idiopathic membranous nephropathy is immunologically mediated and caused by deposition or in situ formation of immune complexes at the epithelial side of the glomerular basement membrane. The trigger for the occurrence of these immune complexes or the antigen(s) involved remain currently unclear [2].

The natural course of idiopathic membranous nephropathy

At the moment of diagnosis most patients with idiopathic membranous nephropathy have normal or only moderately impaired renal function. The subsequent course varies: approximately one-third of the patients show progression to end-stage renal failure within 5–10 years, another third have spontaneous clinical remission of the disease, and the final third show stable renal function with persistent proteinuria. Factors that seem to predict a more unfavourable course are male sex, older age at diagnosis, heavy initial proteinuria, increased serum creatinine at diagnosis, hypertension, and more advanced glomerular or interstitial changes on renal biopsy. Combining some or all of these prognostic factors at the moment of diagnosis will, however, not enable the clinician to identify patients who will develop renal failure during subsequent years with certainty [3]. During follow-up persistent heavy proteinuria increases the likelihood of progressive renal function loss. On the other hand patients who show a partial or complete remission of proteinuria during follow-up have an excellent prognosis with regard to renal function. It therefore seems that the magnitude and duration of proteinuria are linked to the development of progressive renal failure.

What causes progressive renal function loss in idiopathic membranous nephropathy?

Proteinuria in membranous nephropathy is probably the result of the damage to the glomerular basement membrane and glomerular epithelium caused by the subepithelial immune complexes. In an animal model for membranous nephropathy, Heymann nephritis, complement activation at the subepithelial side of the glomerular basement membrane is a prerequisite for proteinuria to occur. Moreover, the amount of proteinuria in this animal model is correlated with the extent of glomerular complement activation as reflected by depositions of activated complement products in the glomeruli and by the levels of urinary C5b-9 [4]. In human membranous nephropathy urinary levels of C3d and C5b-9 are also related to more ‘active’ membranous nephropathy [5]. Since in human membranous nephropathy the proliferative and mesangial glomerular changes are usually mild and renal failure is related to tubulointerstitial damage, it is questionable whether the immunological attack on the glomerulus is directly involved in the progression of renal failure. The level and duration of proteinuria appears to be associated with the development of renal failure. It is tempting to conclude that proteinuria is involved in the pathogenesis of progressive renal failure in membranous nephropathy. Support for this view can be derived from animal studies suggesting a relation between the extent of non-immune mediated proteinuria, tubulointerstitial damage and progressive renal failure [6]. Furthermore, pharmacologically induced reduction in proteinuria attenuates the progressive renal failure in human subjects even with glomerular diseases that are thought to be immunologically mediated [7].
Do we have effective treatment for prevention of renal failure in membranous nephropathy?

According to the above, two different treatment options are possible. First, immunosuppressive therapy could be of help by attenuating or abrogating the immunological attack on the glomerulus. Several randomized controlled studies have been performed with steroids alone or in combination with alkylating or other immunosuppressive drugs. Mean follow-up in these trials varied considerably between 1 and 4.5 years. Thus most trials could not detect a difference in the occurrence of renal failure, but have used other surrogate end-points such as an increase in serum creatinine or the response of proteinuria to evaluate the possible efficacy of treatment. A meta-analysis including five controlled studies involving a total of 228 patients demonstrated a clear benefit of treatment with cytotoxic agents with regard to the occurrence of partial or complete remission of the nephrotic range proteinuria in idiopathic membranous nephropathy [8]. However, no significant effect was detected with regard to renal function outcome. Another meta-analysis including eight controlled studies involving 526 patients that compared corticosteroids or immunosuppressive agents to no treatment claimed benefit of active treatment not only with respect to response of proteinuria but also with respect to renal function outcome [9]. Given the difficulties in proving a beneficial effect of potential toxic therapies with corticosteroids alone or in combination with other immunosuppressive drugs on the course of idiopathic membranous nephropathy, there is understandable hesitation in using these therapies in all patients. A possible alternative may be treatment with cyclosporin A, since a recent study showed a decrease in the rate of decline of renal function in patients treated for 1 year with this drug [10].

Second, a therapy aimed at reducing proteinuria and thereby preventing progression of renal function decline in membranous nephropathy could be a less toxic alternative. Results of prospective controlled studies on the antiproteinuric treatment with ACE inhibitors or NSAIDs with regard to preservation of renal function in membranous nephropathy are, however, not currently available.

Can we identify the patient with idiopathic membranous nephropathy who will benefit from treatment?

It is clear that the patient with a declining GFR and/or persistent nephrotic range proteinuria is eligible for therapeutic intervention. Some reports have found that prolonged treatment with immunosuppression can reduce proteinuria and at least slow or even partially reverse the development of renal failure [11]. Waiting until a decline in renal function occurs will, however, lead to the presence of probably irreversible tubulointerstitial or glomerular lesions. Moreover, it has been suggested that patients with these lesions are less likely to respond to immunosuppressive treatment, thereby limiting the potential benefit of treatment [12]. However, no studies comparing an approach with early immunosuppressive treatment as compared to postponed treatment of only those patients who show progressive decline in renal function are currently available. So the physician caring for a patient with newly diagnosed idiopathic membranous nephropathy with nephrotic range proteinuria and normal renal function faces a serious dilemma. As long as alternative less toxic treatments are of unproven value, should all patients be treated with immunosuppressive therapy? In this case half or even more of the patients, who have a good outcome with regard to renal function anyway, will be exposed to the potential hazards of this toxic therapy. Or should one withhold immunosuppressive therapy until, during follow-up, patients with an unfavourable prognosis can be identified, with the possibility of a less than optimal treatment response?

Are there future perspectives in the treatment of idiopathic membranous nephropathy?

Since idiopathic membranous nephropathy is a rather infrequent diagnosis, only large multicentre studies will be able to answer some of the clinically important questions. In addition, when our main goal is to evaluate interventions with regard to preservation of renal function, an adequate duration of follow-up in these studies is essential. When data on several studies with a non-treated non-selected control group are combined it can be concluded that a maximum of 30–50% of the patients in this group will show a doubling of serum creatinine as compared to the baseline value within 5 years. This means that a study evaluating the effect of an intervention that has to lead to a 50% reduction in patients reaching a doubling of serum creatinine within 5 years to be clinically relevant, will need 70–100 patients in both the control and treatment group for 5 years to have a power of at least 80%. This number is not so easily obtained!

Recently the initiative has been taken for two large scale prospective randomized and controlled European multicentre studies. The first will evaluate the efficacy with regard to preservation of renal function of treatment with the ACE inhibitor enalapril as compared with a 6 months course of alternate-day corticosteroid treatment, or with supportive treatment only, in patients with newly diagnosed idiopathic membranous nephropathy and preserved renal function (creatinine clearance ≥ 60 ml/min/1.73 m²) [13]. This study, called ACIMEN (ACE inhibition versus Corticosteroids In MEMbranous Nephropathy), which is supported by a grant from the European Community (Biomed 1 program) for its coordination, aims to include 240 patients (80 per group) with a follow-up of 5 years. The second study (CYCLOMEN: CYCLOsporin in MEMbranous
Nephropathy) will evaluate the effect of cyclosporin A versus no immunosuppressive treatment in 186 patients with idiopathic membranous nephropathy, reduced renal function (creatinine clearance < 60 ml/min/1.73 m²) and persistent nephrotic syndrome with a follow-up of 3.5 years [14]. Participation of many centres is warmly welcomed in order to achieve the goals of these studies so that some parts of the dilemma of the treatment of idiopathic membranous nephropathy can be solved in a collaborative European effort.

References


Parathyroid-hormone-related protein: a previously unrecognized renal vasodilator

T. Massfelder¹, A. F. Stewart² and J. J. Helwig¹

¹Laboratoire de Physiologie Cellulaire Renale, CJF INSERM 94-09, Université Louis Pasteur, Strasbourg, France; and ²Division of Endocrinology, West Haven VA Medical Center, West Haven, Connecticut 06516, and Yale University School of Medicine, New Haven, CT 06520, USA

Introduction

Parathyroid-hormone-(PTH)-related protein, or PTHrP, is now widely recognized as the factor primarily responsible for the syndrome of humoral hypercalcaemia of malignancy (HHM) [1]. A key structural characteristic of PTHrP is a stretch of 13 amino acids at the amino-terminus which shares 70% homology with PTH which accounts for the ability of PTHrP to cause the clinical features of HHM. Indeed, since its discovery in 1987 in tumours associated with hypercalcaemia, PTHrP has been shown to be produced by a broad array of normal tissues in which it exerts both classic PTH-like as well as PTH-unlike effects. PTHrP is initially translated as a precursor or pro-hormone which is subsequently posttranslationally cleaved into a family of daughter peptides, each of which is likely to have different physiological functions. In this way PTHrP is closely analogous to other neuroendocrine peptide hormone precursors. For example, pro-opiomelanocortin serves as the initial translation product from which ACTH, MSH, beta-endorphin, and lipotrophin are derived. In the normal tissues, which produce PTHrP, it appears to function along three thematic roles: PTHrP acts as a regulator of cellular growth, differentiation, and development; it acts as a regulator of transepithelial calcium transport; and it acts as a relaxant of smooth muscle [2].

Correspondence and offprint requests to: Dr J. J. Helwig, Laboratoire de Physiologie Cellulaire Renale, CJF INSERM 94-09, EA MESR 1314, Pavillon Poincaré, Hôpitaux Universitaires de Strasbourg, B.P. 426, F-67091 Strasbourg Cedex, France.