Membranous nephropathy: Quo vadis?

Idiopathic membranous nephropathy remains the most common cause of the nephrotic syndrome in adults in the world [1]. Because of its frequency, it remains the second or third most common cause of end-stage renal disease within the primary glomerulonephritis group, despite its unusual natural history in which many patients have a spontaneous and complete recovery [2]. The debate over its management has raged since the early 1970s and reached epidemic proportions in the 1980s following contrary reports on the effectiveness of corticosteroid therapy [3, 4]. An editorial at that time suggested that who to treat and at what stage were as relevant as what to use [5].

The debate continues today for several reasons. One relates to the marked variability of its natural history. The rule of thirds (about the one thing that medical students seem to remember about the disease), still seems to apply with up to one-third of patients spontaneously remitting, one-third remaining proteinuric but with stable renal function, and one-third progressing to renal failure over a period of 5 to 10 years. This outcome has not changed much over the past 3 decades as indicated by a recent publication reporting a 30% spontaneous complete remission rate at 5 years and 25% proceeding to end-stage renal disease by the end of 8 years [6]. This is despite our advances in surveillance, lower blood pressure targets, and better antihypertensive agents, some with the additional capacity to drive down proteinuria. Thus, it is clear that if we have an effective and safe treatment, we should use it, since an end-stage renal disease rate of 25% at 8 years is unacceptable.

The second area of controversy is composed of two parts. First, can we accurately predict those patients who will progress to end-stage renal disease? And, second, can we accomplish it early enough that the kidney will still retain the ability to improve with treatment, but late enough to avoid therapy in those patients who will remit spontaneously? The concern of many is that if we wait for the clearest sign of progression, that is, deterioration in renal function, the opportunity for effective treatment will be blunted or prevented. Currently, there are a number of factors, including advanced age, male sex, severity of initial proteinuria and renal insufficiency, plus histologic changes, such as tubular interstitial damage and glomerulosclerosis, that do predict a worse outcome. Unfortunately, these factors are all qualitative and not sufficiently precise for the physician when he or she sits across the desk from an asymptomatic young woman with proteinuria who not only wants to be completely better but also does not want to risk any adverse effects. We and others have suggested that time must be added to the prognostic mix to improve prediction. Our algorithm, which uses only the presenting creatinine level, the quantity of proteinuria, and change in renal function over the initial 6 months of observation, will substantially improve the ability to separate those individuals with a poor outcome from those with a good prognosis [7]. A patient, for example, with 8 g per day or more proteinuria that persists for 6 months has an increased likelihood of developing chronic renal insufficiency from 33% at presentation to over 80% at the end of the observation period. We subsequently validated the overall accuracy of predicting outcome on a similar group of idiopathic membranous nephrology patients from Finland and Italy [8]. This would indicate that the first part of this question has been answered, that is, we can now semi-quantitatively predict outcome within 6 to 12 months of presentation in most patients.

The second part of this controversial area is whether we lose our ability to effectively treat patients by waiting. This is at least partially answered by the article by Torres et al [9] in this issue of *Kidney International*. Although retrospective in nature, with all its attendant problems of case mix and different time frames, none of those in the treatment group received any therapy until their creatinine levels were >1.5 mg/dL or creatinine clearance was <60 mL/minute measured on at least three occasions. As well, the time to reach this point was, on average, 14 months after their biopsy. All patients received the same therapy, oral prednisone beginning at 0.5 mg/kg/day tapered slowly over 6 months plus chlorambucil 0.15 mg/kg/day for 14 weeks. Despite the elevated creatinine level and time delay, the treatment was associated with a decreasing serum creatinine level in 60% of the treated patients and was associated with decreasing proteinuria. Only 30% went on to develop chronic renal insufficiency compared to 75% of patients treated conservatively. This report would suggest that we can safely wait and observe the patient before beginning treatment and still effect a change in its natural history.

This paper by Torres et al [9] also lends some support...
for specific treatment. This is the last area of controversy, do we have effective therapy? He and his colleagues have shown that, despite initial renal insufficiency, almost 60% of patients improved their renal function and reduced their proteinuria level with treatment. Previously published prospective controlled trials have also focused on such progressive cases. One compared the addition of monthly pulse cyclophosphamide plus corticosteroid therapy to corticosteroid therapy alone and failed to show any improvement after a mean follow-up time of 2 years [10]. The other tested 1 year of cyclosporine therapy versus placebo and found a substantial improvement with both a slowing of the rate of progression of the renal disease and reduced proteinuria [11]. Thus, at least in part, we can answer that effective treatment is available, even after a substantial time delay and clear evidence that the disease has progressed.

Do we have anything left to debate or do we now know we are going (quo vadis?) with regard to the management of idiopathic membranous nephropathy? Of course, many questions remain, including what are the causes, how influential are genetic factors, and why do young women do so well? Can we find a more benign and/or specific therapy so all patients could be treated from the beginning?

Perhaps much of the hesitancy about implementing even the known information into patient care plans is related to our insecurity about the strength of the evidence. We have not been able, for many reasons, to mount the large-scale treatment trials in idiopathic membranous nephropathy (or any other type of glomerulonephritis) seen in other medical disciplines. However, recent successes in diabetic nephropathy studies [12, 13] are encouraging and indicate that with the proper question, good design, infrastructure support and funding, nephrologists can and, I believe, will move to address these questions and others in the management of this ubiquitous and fascinating disease.

Correspondence to Daniel C. Cattran, M.D., the Toronto General Hospital, University Health Network, 101 College Street, CCRW3-884, M5G IL7 Toronto, Ontario, Canada.
E-mail: daniel.cattran@uhn.on.ca

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