


See related article, “siRNA-Based Therapy Ameliorates Glomerulonephritis,” on pages 622–633.

**Idiopathic Membranous Nephropathy: Getting Better by Itself**

Richard J. Glassock
David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California


Understanding the natural history of a disease is crucial in determining whether therapy will be appropriate or useful. Idiopathic membranous nephropathy is a prime example of this guiding principle. It has been known for decades, from studies out of France, Italy, and elsewhere, that without treatment, membranous nephropathy follows a course punctuated by spontaneous remission and relapse. In this issue of *JASN*, this point is revisited in a large, well-conducted study from Spain. Polanco et al. from the Spanish Group for the Study of Glomerular Disease (GLOSEN) managed to gain cooperation from many participating physicians at 14 centers throughout Spain to withhold initial steroid or other immunosuppressive drugs from patients with renal biopsy-proven idiopathic membranous nephropathy, at least until complications ensued or an unsatisfactory evolution of the disease was evident. This approach allowed them to determine the spontaneous remission rate of disease.

The authors wisely limited the study to patients with membranous nephropathy presenting with nephrotic syndrome, because those with initial and persisting non-nephrotic proteinuria would have not required intervention in any case. Although observed remissions were judged to be spontaneous, two thirds of the patients received potentially disease-modifying treatment in the form of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), given both to reduce BP and to diminish proteinuria. Because treatment with these agents was not carried out in a randomized, controlled manner, it was not possible to conclude definitively that nonimmunosuppressive drugs had an impact on the frequency of spontaneous remissions; however, analysis of the observational data does generate a testable hypothesis that ACEIs or ARBs have antiproteinuric actions in membranous nephropathy and may alter the long-term course of the disease, at least in some patients. The strengths of this landmark study are the large number of patients, the strict definitions of remission, and the duration of follow-up, averaging approximately 6 years.

From the perspective of a physician who is seeking guidance as to when to initiate specific immunosuppressive therapy, with its attendant risks for patients with membranous nephropathy and nephrotic syndrome, these data are rather sobering. Almost one third developed a spontaneous complete or partial remission, usually within the first 2 years of observation, but with wide variation in onset; 1 to 66 months for a partial remission and 4 to 120 months for a complete remission. Four features tended to associate with remissions: Female gender, lower proteinuria at baseline, those with initial and persisting non-nephrotic proteinuria would to when to initiate specific immunosuppressive therapy, with its attendant risks for patients with membranous nephropathy and nephrotic syndrome, these data are rather sobering. Almost one third developed a spontaneous complete or partial remission, usually within the first 2 years of observation, but with wide variation in onset; 1 to 66 months for a partial remission and 4 to 120 months for a complete remission. Four features tended to associate with remissions: Female gender, lower proteinuria at baseline, lower serum creatinine at baseline, and treatment with an ACEI or ARB. Histologic predictions of remission were not examined in this study, although previous studies hinted that early morphologic stages of the disease have a greater propensity for spontaneous remission, but this is controversial. Remarkably, one in five patients with initial proteinuria >12 g/d underwent spontaneous remission. Most patients exhibited a slow decline in the magnitude of proteinuria over time, and a ≥50% decline in proteinuria during the first year frequently heralded a spontaneous remission.

These humbling observations raise important questions about when to consider immunosuppressive therapy. Patients with declining proteinuria, even if nephrosis remains, are more likely to undergo spontaneous remission and thus not require any specific
treatment. In the end, almost 80% of patients without remission did receive immunosuppressive therapy, largely as a result of worsening renal function or complications of nephrotic syndrome. Taken together with recent findings from a controlled clinical trial of early versus late initiation of immunosuppressive therapy in membranous nephropathy, it seems that it is not necessary to initiate specific treatment upon confirmation of the diagnosis by renal biopsy, unless severe symptoms of nephrotic syndrome are present or renal function is on the decline. The seeming lack of benefit from ACEI or ARB therapy in patients with baseline proteinuria of ≥8 g/d is remarkable, but this needs confirmation in a randomized, controlled trial. At present, although ACEIs and ARBs are often recommended as part of the nonimmunosuppressive management of membranous nephropathy, this is not evidence-based guidance.

Not surprising, the long-term outcome of those with complete or partial spontaneous remissions is excellent: Mortality rate was 2%, and ESRD risk was 0%. Conversely, the risks of persistent nephrotic syndrome in membranous nephropathy are considerable: Mortality rate was 11%, and ESRD risk was 19%. Relapses after a spontaneous remission seem quite infrequent (5.7%) and easy to manage. For unclear reasons, this relapse rate after a spontaneous remission is substantially lower than when a remission is therapeutically induced with immunosuppressive drugs.

The GLOSEN study offers much in the way of reassurance and guidance to the treating physician but does not shed much light on the mechanisms underlying the behavior of membranous nephropathy as a self-limiting disease in many patients. More questions naturally arise as we enter a new era of understanding the pathogenesis of membranous nephropathy as a podocytopathy induced by circulating autoantibodies to well-defined antigens intrinsic to visceral epithelial cells along the glomerulus. What triggers the appearance of these autoantibodies, and are spontaneous remissions associated with their disappearance? If these autoantibodies disappear with spontaneous remission, then which immune events are responsible for this self-regulating phenomenon? Do spontaneous remissions differ mechanistically from therapeutically induced remissions? Are differing agents similar or discordant in their underlying mechanisms for induction of remissions? The answers to these and more questions are likely to be forthcoming in the not-too-distant future. Until then, the study of Polanco et al. will stand as an important reference for examining the course of membranous nephropathy unmodified by immunosuppressive drugs, with valuable caveats for managing this all-too-common disorder.

DISCLOSURES

None.

REFERENCES


Treatment of Chronic Hyponatremia: Now We Know How, but Do We Know When or If?

Arthur Greenberg and Ruediger W. Lehrich
Division of Nephrology, Duke University Medical Center, Durham, North Carolina

DOI: 10.1681/ASN.2010020157