Treatment of Membranous Lupus Nephritis: Where Are We Now?

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Approximately 60% of patients with systemic lupus erythematosus develop clinically evident kidney disease.[1] Although most have proliferative (class II, III, or IV) lupus nephritis, 10 to 15% have pure membranous lupus nephritis (MLN; class V).[2] In contrast to class III or IV lupus nephritis, MLN may present without other clinical or serologic manifestations of lupus. Thus, a clinician should not be dissuaded from the diagnosis of MLN in a young woman who has heavy proteinuria and happens to lack anti-dsDNA antibodies and have normal complement levels. Like idiopathic membranous nephropathy, MLN is manifest clinically by the nephrotic syndrome and ultrastructurally by podocyte foot process effacement and the presence of subepithelial immune deposits. Features that distinguish MLN from idiopathic membranous nephropathy include the presence of occasional mesangial or subendothelial immune deposits, the lack of an IgG4 subclass predominance in these deposits,[3] and endothelial tubuloreticular structures. The predilection of immune complexes to deposit or form in a subepithelial location, which dictates a noninflammatory course of glomerular disease, remains unexplained. Lupus autoantibodies and nucleosomal antigens have been co-localized in these subepithelial immune deposits in MLN,[4] but their relation to disease initiation is unclear.

Whereas the short-term risk for renal damage from MLN is not as great as that from proliferative forms of lupus nephritis, patients are at risk from the thrombogenic effects of nephrotic syndrome, and >10% of patients with pure MLN will progress to end-stage kidney disease.[5] Progression may be due to progressive glomerulosclerosis and interstitial damage associated with massive proteinuria or transition of pure MLN to a more proliferative form of lupus nephritis. Prognostic indicators of progression have been studied,[5,6] but there is no clear consensus on what should be considered a "danger feature." Indications for treatment of MLN include marked nephrotic syndrome, worsening renal function, and class V disease mixed with class III or IV lupus nephritis.

Treatment of MLN largely involves the same immunosuppressive agents, and schedules that prove effective in both idiopathic membranous nephropathy and proliferative lupus nephritis often include alkylating agents and calcineurin inhibitors; however, because of the varied agents and regimens and the relatively few patients with MLN who compose most clinical trials, there is no consensus as to the most effective treatment for membranous disease.[7] The long-awaited results of a randomized, controlled study begun in 1988 at the National Institute of Diabetes and Digestive and Kidney Diseases and published in this issue of *JASN* by Austin *et al.*[8] provide a welcome addition to the literature that should aid nephrologists and rheumatologists alike in their decision to implement effective treatment for patients with MLN.

Austin *et al.* present data from their prospective study of immunosuppressive therapy in 42 patients with nephrosis and pure MLN (patients with evidence of proliferative lupus nephritis were excluded).[8] The number of patients enrolled in this study is relatively small; however, this sample is larger than in many of the other retrospective and/or uncontrolled articles about treatment of MLN, recently reviewed by Waldman and Appel.[9] The patients were randomly assigned to a 1-yr treatment phase that involved high-dosage alternate-day prednisone alone (PRED) or adjunctive therapy with either six doses of alternate-month intravenous cyclophosphamide (IVCY) or 11 mo of daily cyclosporine started at approximately 5 mg/kg per d (CsA). The primary end point was time to complete or partial remission during this 1-yr treatment protocol. As a secondary measure, the patients were assessed for relapse in a follow-up phase with a median duration of 60 mo after the end of treatment.

Their data demonstrate 1-yr rates of combined complete and partial remissions of 27, 60, and 83% in the PRED, IVCY, and CsA groups, respectively. Two thirds of the remissions in both the IVCY and CsA treatment groups were complete. Consistent with previous therapeutic trials using CsA, however, the authors found a significant relapse rate in the CsA group, with proteinuria often rebounding to severely nephrotic levels within 1 yr of stopping therapy. CsA was started at a fixed dosage in this study and was adjusted in response to a rise in creatinine or the development of hypertension, which occurred in nine of 12 patients. No data are provided on the final dosage or CsA levels achieved in this study. Of note, patients who had not entered a remission by 12 mo or who had experienced relapse were eligible for entry into an uncontrolled observational trial with IVCY. Eight of these 10 patients subsequently experience remission with this further therapy.

The strengths of this study are its randomized, prospective design and that it is one of the largest studies directly comparing immunosuppressive therapies in membranous lupus nephritis. It is clear from these data that, as in idiopathic membranous nephropathy, corticosteroids are not sufficient to induce a remission in most cases and adjunctive treatment with either CsA or cyclophosphamide is required. It also con-

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firms the higher relapse rate in such patients treated with CsA. Because of problems with optimal randomization in such small treatment groups, it is difficult to assess directly whether CsA or IVCY is the preferred agent; the IVCY group had more favorable traditional baseline characteristics. Perhaps because of this, cyclophosphamide seems to have the edge in being equivalent to CsA in inducing remission but more reliable in maintaining patients in remission. The downsides of this agent are widely known, including its myelosuppressive activity and potential infertility, as well as a risk for bladder malignancy. Practitioners should take comfort in the fact that CsA is similarly effective in inducing remission; however, the optimal maintenance regimen or taper has not been defined to avoid a rapid relapse. Perhaps, as the authors suggest, a more extended course with lower dosages might be effective in sustaining remission, especially because there is now evidence that CsA reduces proteinuria by acting directly on podocytes and not exclusively as an immunosuppressive agent.[10]

Because of the duration of this study, which was necessary to obtain adequate numbers of patients with MLN and follow-up data, it was not able to incorporate and evaluate the newer immunosuppressive agents mycophenolate mofetil and rituximab, both of which have shown some promise for the treatment of MLN in uncontrolled trials or case reports.[11,12] These agents may have fewer short- and long-term adverse effects, which is important given the rate of adverse events that occurred in this trial. This analysis also does not provide a sense of how inhibitors of the renin-angiotensin system may have affected the results, because only a minority of the patients were treated with such agents that are now standard therapy (together with statins), and this was not factored into the multivariate analysis. Another important piece of datum that may be forthcoming is the long-term effect of the respective treatments on renal survival in this cohort of patients.

The authors attempted to identify baseline and treatment factors that may be predictive of remission by univariate and multivariate analyses. Although univariate analysis confirmed previous observations that race/ethnicity has an important effect on outcome in MLN, only a protein excretion rate of <5 g/d and adjunctive therapy with IVCY or CsA emerged as favorable predictors of remission on multivariate analysis. Interestingly, baseline renal function did not predict the probability of remission, perhaps because the range of baseline GFRs was quite narrow. Thus, given that this analysis involved an uneven distribution of baseline factors among small treatment groups and most studies of lupus nephritis show that black and Hispanic patients, as well as those with impaired baseline renal function, have a worse outcome, clinicians may still prefer to be guided by the available evidence on a case-by-case basis as to the optimal timing and choice of immunosuppressive treatment for this disease.

Despite the limitations noted here, the study by Austin *et al.* convincingly shows that immunosuppressive treatment is able to induce at least partial remission in membranous lupus nephritis and perhaps gives us more confidence in our ability to do more good than harm in this notoriously difficult-to-treat condition.

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See related article, "Randomized, Controlled Trial of Prednisone, Cyclophosphamide, and Cyclosporine in Lupus Membranous Nephropathy," on pages 901–911.