Therapy of Membranous Nephropathy in Systemic Lupus Erythematosus

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Historic changes in the criteria for pathologic diagnosis and classification of lupus membranous nephropathy (LMN) have precluded definitive descriptions of the natural history, prognosis, and treatment of this disorder. The interim practice, based on the 1982 World Health Organization classification system, of admixing membranous and proliferative lupus nephropathies under the rubric of LMN has confounded the medical literature. Cases with mixed histology should be treated according to recommendations for proliferative lupus nephritis. Patients with LMN should be treated early with angiotensin antagonists to minimize proteinuria, as well as lifestyle changes and appropriate drugs to reduce attendant cardiovascular risk factors. In patients with protracted nephrotic syndrome, consideration should be given to immunosuppressive therapies including corticosteroids, cyclosporine, mycophenolate, and cyclophosphamide. Prospective controlled trials clearly are needed to establish solid clinical practice guidelines for use of these drugs and other experimental therapies currently under study in LMN.
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MORE THAN ONE HALF of patients with systemic lupus erythematosus (SLE) develop clinically significant nephropathy during the course of their disease. Approximately 20% of those with SLE renal involvement are found on renal biopsy examination to have lupus membranous nephropathy (LMN). Unfortunately, LMN has not been defined in a uniform fashion over the past several decades. This makes it difficult to ascertain consistent information about the frequency, natural history, prognosis, and treatment of LMN from published literature.[1-3]

CLASSIFICATION OF LUPUS NEPHRITIS

Table 1 summarizes selected milestones and various approaches used in the classification of LMN.[4-9] Given that the pathology of lupus nephritis is characteristically extremely pleomorphic and irregularly distributed among glomeruli, it is not surprising that there would have been a diversity of approaches to classification. When attempting to understand the natural history and prognosis of LMN, one must be cognizant of the different definitions of this entity over time. In the early years of renal biopsy examination in SLE practice, membranous nephropathy was considered to have a benign prognosis and, therefore, to not require

specific intervention to reduce the risk for renal failure. Typical recommendations were to tailor immunosuppressive drugs according to the requirements for control of extrarenal SLE disease activity.

The original perspective on renal prognosis was altered dramatically by the 1982 World Health Organization classification system to subsume certain proliferative lesions within the rubric of LMN.[4] This practice substantively altered descriptions of the prognosis of and recommendations for the treatment of LMN. Indeed, in some published series, LMN had the worst prognosis of all the classes of lupus nephritis.[10]

Most clinicians have welcomed the 1995 revision of the World Health Organization classification, which restored the previous, more limited definition of LMN by the exclusion of subsets manifesting anything more than mesangial expansion and deposits.[5] Indeed, some pathologists and clinicians have proposed that the remaining distinction of pure membranous from membranous superimposed on mesangial nephropathy should be eliminated in future updates, given evidence that mesangial deposits nearly always are present and constitute the lowest common denominator of lupus nephritis (unpublished observations, Working Group on the Classification of Lupus Nephritis, the International Society of Nephrology and Renal Pathology Society).

PROGNOSIS OF LMN

Beyond the conundrum resulting from the different approaches to classification, there appear to be additional, but poorly defined, variables that further confound a clear understanding of the prognosis of LMN. Table 2 depicts the renal

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Table 1. Selected Milestones in the Classification of Lupus Nephritis, Emphasizing Changes in Approach to Diagnosis of LMN

Study	Milestone
Muehrcke et al,[4] 1957	One of the earliest renal biopsy examination series of lupus nephritis (limited to light microscopy findings); initial biopsy findings classified as normal glomerulitis (mild lupus nephritis) and glomerulonephritis (severe lupus nephritis), irregular capillary loop thickenings termed *membranous changes* were considered to be the precursor of proliferative and fibrinoid reactions within the glomeruli; membranous nephropathy was not recognized as a separate entity, although it was recognized that membranous changes may predominate
Pollak et al,[5] 1964	Larger light microscopy series, 10% of initial biopsy examinations had predominant capillary wall thickening without concomitant proliferative or fibrinoid lesions; separate histologic diagnosis of membranous lupus glomerulonephritis was proposed
McCluskey,[6] 1975 Baldwin et al,[7] 1970	Standard light, immunofluorescence, and electron microscopy criteria for classification of lupus nephritis (so called original World Health Organization classification): I, normal; II, mesangial; III, focal proliferative; IV, diffuse proliferative; and V, membranous lupus nephritis
Churg and Sobin,[8] 1982	Revision of World Health Organization classification based on recommendations of the International Study of Kidney Diseases in Children. Subdivisions proposed for classes II, III, IV, and V, as well as a new class VI, advanced sclerosing disease. Classes III and IV, proliferative lupus nephritis, were divided according to the predominance of active or sclerosing lesions. Class V membranous nephropathy was divided into 4 subsets: Va, pure membranous; Vb, membranous with mesangial changes; Vc, membranous with concomitant class III; and Vd, membranous with concomitant class IV.
Churg et al,[9] 1995	Latest revision of World Health Organization classification system; recision of classes Vc and Vd with the proposal that these entities be classified as mixed membranous and proliferative for diagnostic purposes and managed according to guidelines for proliferative lupus nephritis

survival of patients with LMN from different centers around the world.[10-21] As shown, the 10-year renal survival averages 80%, but survival estimates range widely from 47% to 90%. Among patients with LMN participating in stud-

ies at the National Institutes of Health during the 1970s and 1980s, 10-year renal survival was 65%, whereas 10-year patient survival was 74%. Interestingly, patients with LMN that have entered our clinical trials during the 1990s have

Table 2. Representative Studies of LMN That Include 10-Year Patient and/or Renal Actuarial Survival Data

Study	Location	No. Patients	Actuarial Survival Estimates at 10 Years		
			Renal	Patient	Composite
Donadio et al,[10] 1995	Rochester	67	63%		
Pasquali et al,[11] 1993	Italy	42			92%
GISNEL,[12] 1992	Italy	91	90%		
Bakir et al,[13] 1994	Chicago	22			90%
Mercadal et al,[14] 2002	France	66	88%		
Tateno et al,[15] 1982	Japan	14			85%
Leaker et al,[16] 1987	Australia	20		84%	
Wang and Looi[17] 1984	Malaysia	13		75%	
Sloan et al,[18] 1996	Chicago	36			72%
Huong al,[19] 1999	France	32	77%	90%	
Bono et al,[20] 1999	England	21		55%	
Appel et al,[21] 1987	New York	10	47%	45%	
Weighted average (range)			80% (47% to 90%)	79% (45% to 100%)	84% (72% to 92%)

shown substantially more favorable trends in renal and patient survival rates.

Most,[3,17-19] but not all,[11] studies show that patients with LMN and more than mesangial disease (ie, subclasses Vc or Vd, or what we prefer to call *mixed membranous* and *proliferative lupus nephritis*) have a worse 10-year patient and renal survival. Among the other potential explanations of the variability in reported patient and renal survivals are differences in racial and ethnic backgrounds, severity of proteinuria, and treatments used at the various centers, all of which warrant further study and analysis.

Given the diversity in rates of renal outcomes from different centers, it is apparent that ascertaining the effects of various treatments must be based on randomized design and concurrent control groups. As with proliferative lupus nephritis, use of historic controls is unreliable and simply fosters contention and controversy about the effects of treatment of LMN.

APPROACHES TO TREATMENT OF LMN

Solid, evidence-based recommendations for treatment of LMN are lacking. The relatively low risk for renal failure attributable to LMN has long been the chief argument against the use of immunosuppressive drugs. More recently, recognizing that there are substantial morbidity and mortality risks associated with protracted nephrotic syndrome,[22-24] some have begun to argue that every effort must be made to reduce proteinuria in LMN as the primary approach to reducing the thrombotic diathesis and dyslipidemia that confer substantial cardiovascular risks. Although there is general appreciation of these risks in patients with membranous nephropathy, there is a paucity of data delineating the magnitude of these risks over time in patients with LMN.[25-27]

SUPPORTIVE THERAPIES

Because of the considerable uncertainty about the definitive choice and effectiveness of immunosuppressive treatment of LMN, we recommend early treatment with angiotensin system antagonists to minimize proteinuria and optimize general renoprotective effects.[28] If hyperlipidemia persists after the maximal reduction of proteinuria that can be achieved with angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockers, lipid-lowering therapies also should be started to offset cardiovascular risk factors associated with glomerular disease.[29] There have been provocative suggestions (albeit short of definitive proof) that these agents also may have some effect on the pathogenetic processes causing glomerular disease.

IMMUNOSUPPRESSIVE THERAPIES

Most reports on the clinical course of LMN have included a variable mix of patients that have been left untreated or treated in accordance with the physicians' individual preferences. Given this diversity of practice, it is not surprising that few investigators have attempted to analyze the effects of particular treatments on the course of this disease. Many of the therapeutic approaches espoused for LMN are based on extrapolations from results of clinical trials in idiopathic membranous nephropathy. Table 3 contains a synopsis of the small number of reports that have attempted to analyze the effects of immunosuppressive drugs in patients with classic LMN.

Corticosteroids

No prospective controlled trials have been performed to evaluate the effects of corticosteroids on LMN. The studies cited are retrospective comparisons of renal outcomes among patients treated with high-dose, low-dose, or no corticosteroids.[30-32] Although the small numbers of patients and outcomes precluded statistical analysis, most authors considered that there were no objective trends in the data to support the benefits of corticosteroids. Against the general inclination of physicians to doubt the efficacy of corticosteroids, many patients with LMN experiencing high-grade proteinuria and/or progressive renal dysfunction receive an empiric trial of corticosteroids. In particular, high-dose alternate-day regimens of prednisone are used widely for 2 to 4 months.

Alkylating Agents

Again, many of the natural history studies represented in Table 2 included patients that, at some phase during the course of LMN, were treated with cytotoxic drugs. The lack of consensus on indications for treatment or preferred regimen precludes an analysis of the impact of the various treatments used in LMN. Table 3 includes 3 studies of alkylating drugs that were administered in a generally systematic fashion. The study by Moroni et al[33] applied the immunosuppressive drug regimen that

Table 3. Systematic Studies of Immunosuppressive Drug Treatments in Patients With Classic (Va and Vb) LMN

Corticosteroids

    Donadio et al,[30] 1977: 28 patients, no differences in renal outcomes among patients treated with high-dose, low-dose, or no steroids the conclusion that corticosteroids have no consistent benefit in LMN was affirmed in a subsequent review by the same investigator[31]

    Gonzales-Dettoni and Tron,[32] 1984: 12 patients with proteinuria treated with high dose steroids; outcomes comparable with those occurring in small control group

Alkylating agents

    Moroni et al,[33] 1998: 19 patients with nephrotic syndrome; 11 patients treated with alternate-month cycles of intravenous pulse methylprednisolone and chlorambucil; all patients had remission of nephrotic syndrome (compared with only 4 of 8 patients treated with corticosteroids alone)

Chan et al,[34] 1999: 20 patients with nephrotic syndrome-induction therapy; prednisone and oral cyclophosphamide for 6 months; maintenance therapy low-dose prednisone and azathioprine; at 1 year, 55% complete and 35% partial remission of proteinuria

    Austin (unpublished experience): 12 patients with heavy proteinuria (mean 7.4 g/d); treated with alternate-day prednisone and alternate-month intravenous pulse cyclophosphamide for 1–3 years; proteinuria reduced to <2 g/d in 9 of 12 patients

Cyclosporine

    Radhakrishnan et al,[35] 1994: 10 patients with nephrotic syndrome, treated with low-dose prednisone and cyclosporine (4–6 mg/kg/d) for up to 43 months, proteinuria reduced to <1 g/d in 6 patients

    Hallegua et al,[36] 2000: 10 patients with proteinuria; treated with cyclosporine (2–6 mg/kg/d) for an average of 2 years; proteinuria decreased from mean of 5.6 g/d at baseline to mean of 1.4 g/d

Controlled trial and pilot study of sirolimus (rapamycin) therapy

    Austin et al,[37] 2000: 41 patients with heavy proteinuria (mean 5.8 g/d), all treated with alternate-day prednisone (tapering) and randomized to alternate-month intravenous pulse cyclophosphamide, low-dose cyclosporine, or no additional treatment; at the end of the 1-year treatment period, a significantly larger proportion of patients receiving adjunctive cyclophosphamide or cyclosporine had complete or partial remission of proteinuria than did controls; after an additional year of follow-up, a significantly greater proportion of patients previously treated with cyclosporine relapsed than did those previously treated with cyclophosphamide

    Austin (pilot study): Sirolimus is an immunosuppressant that has the capacity to suppress proliferation of B and T lymphocytes and mesangial cells; it inhibits the differentiation of B lymphocytes into antibody-producing cells; it also has antifibrotic properties[38, 39]; preliminary studies have shown benefit in lupus-prone mice[38]; a phase 2 clinical trial is underway to examine the effect of sirolimus in patients with LMN, patients with persistent nephrotic syndrome on angiotensin antagonists will be treated with a 12-month course of sirolimus; tolerability of sirolimus will be assessed carefully and efficacy will be judged by reduction of proteinuria

their group from Milan had shown previously in prospective controlled trials to be effective in idiopathic membranous nephropathy. In this small retrospective analysis, patients treated with alternate-month cycles of pulse methylprednisolone and chlorambucil had more favorable rates of remission of nephrotic syndrome than patients treated with corticosteroids alone.

As in idiopathic membranous nephropathy, there is general reluctance to use daily oral cyclophosphamide in LMN. This is based in large part on concerns about toxicity and less on doubts about prospects of efficacy. The study by Chan et al[34] presents a favorable experience with combined prednisone and cyclophosphamide for 6 months, followed by azathioprine maintenance. At 1 year, the investigators reported a 90% response rate (55% complete and 35% partial remission of proteinuria) with low rates of drug side effects.

Cyclosporine

Two studies have provided pilot observations on the potential benefits of cyclosporine in LMN.[35,36] Each study involved 10 patients and extended courses of treatment with low-dose cyclosporine of 6 mg/kg/d or less. Major improvements in proteinuria were seen in both studies. Although there was no evidence of severe cyclosporine nephrotoxicity, Hallegua et al[36] noted that treatment led to mildly reduced renal function and worsened hypertension.

Controlled Trial of Cyclophosphamide and Cyclosporine

For the past several years, we have been conducting a prospective, randomized, controlled trial to evaluate the effects of adding alternate-month pulse cyclophosphamide or low-dose cyclosporine to alternate-day prednisone in patients with LMN. Preliminary results in 41 patients have shown that

Table 4. Treatment Recommendations and Options for LMN

Mixed membranous and proliferative nephropathies treat as proliferative lupus nephritis
Membranous nephropathy with nephrotic-range proteinuria
   First-line treatment usually is high-dose alternate-day prednisone (eg, 1–2 mg/kg) for 2 months; taper to ~.25 mg/kg
   alternate days within 3–4 months
   Optional adjuncts to prednisone therapy
     Cyclosporine ≤5 mg/kg/d
     Pulse cyclophosphamide ≤1 g/m^2 every 1–3 mo
     Pulse methylprednisolone, alternating with cyclophosphamide (or chlorambucil): pulse methylprednisolone; 1 g/d
     for 3 days followed by 27 days of prednisone (0.5 mg/kg/d) alternating with 30 days of cyclophosphamide 2 mg/
     kg/d (or chlorambucil 3–6 mg/m^2/d); 3 cycles of each therapy over a 6-month period
     Oral cyclophosphamide, 2 mg/kg/d
Membranous nephropathy with nonnephrotic proteinuria treat according to extrarenal disease activity; consider
angiotensin antagonists to minimize proteinuria and statins for hyperlipidemia; monitor patients carefully for evidence
of progression to nephrotic syndrome or to mixed membranous and proliferative nephropathy

Adapted with permission from Balow et al.[40]

both pulse cyclophosphamide and cyclosporine are more effective in achieving remissions of proteinuria than prednisone alone.[37] Extended follow-up has shown that remissions tend to be more enduring with cyclophosphamide than with cyclosporine.

Subsequently, we have analyzed results of 1 to 4 years of treatment with alternate-month intravenous pulse cyclophosphamide in 12 patients with LMN who had refractory or relapsed severe proteinuria. Preliminary analyses have indicated greater than anticipated rates of improvement in nephrotic range proteinuria. These results underscore the fact that optimal duration of treatment with any of the therapeutic options for LMN remains uncertain.

Experimental Pilot Study of Sirolimus (Rapamycin)

There is widespread support for studies to define new therapeutic options for patients with LMN. Based on extensive experience in organ transplantation, sirolimus has been considered to have excellent immunosuppressive potential. In vitro data indicate that sirolimus has several properties that offer salutary effects in glomerular diseases, both in controlling active disease and retarding the accrual of chronic injury (Table 3). Sirolimus suppresses proliferation of both T and B lymphocytes; it inhibits the differentiation of B lymphocytes into antibody-producing cells; it also has antifibrogenic properties by suppression of fibroblast activity and matrix production, as well as inhibition of mesangial proliferative responses to growth factors.[38,39] Preclinical testing in murine lupus nephritis indicate a favorable effect of sirolimus on lupus serologies, glomerular disease, and survival.[39] If favorable preliminary data on tolerance and efficacy are obtained, we intend to conduct a subsequent controlled trial comparing sirolimus with other therapeutic options for LMN.

INTERIM GUIDELINES, CURRENT TREATMENT RECOMMENDATIONS, AND THERAPEUTIC OPTIONS

Table 4 contains our current recommendations for patients with LMN according to the presence of concomitant proliferative lupus nephritis and the degrees of proteinuria. In all cases, patients should be treated with adjunctive agents for renoprotection, minimization of proteinuria, optimization of blood pressure, and control of cardiovascular risk factors arising from the pathophysiology of nephrotic syndrome. The optimal duration of treatment is undefined, but the relatively high rate of relapse, particularly with calcineurin inhibitors, indicates that studies of maintenance therapy also are needed. The clinician caring for the patient with LMN must be vigilant in detecting evidence of transformation to more aggressive proliferative forms of lupus nephritis and the need to intensify immunosuppressive drug treatment.[40] Finally, it is clear that there are abundant challenges and much to learn about LMN.[41]

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