Lupus Nephritis in 2017: An Update

By Wai Lang Lau, MD, and Gerald B. Appel, MD, FASN

In light of recent progress in the genomics of complex traits, where do we stand with glomerular disease?

Renal involvement is clinically apparent in approximately 50% of systemic lupus erythematosus (SLE) patients and a frequent cause of significant morbidity and mortality (1). On renal biopsy, virtually all lupus patients have some findings indicative of kidney pathology. The clinical presentation of lupus nephritis is highly varied, ranging from asymptomatic hematuria and/or proteinuria to the full nephrotic syndrome or even rapidly progressive glomerulonephritis. In the kidney, the cornerstone mechanism of damage is the formation and deposition of immune complexes (including DNA nucleosome complexes and anti-DNA antibodies), which may occur by nonspecific trapping of circulating immune complexes, in situ formation, or interaction with negatively charged components of the glomerular capillary wall. In general, immune deposits in the mesangium and subendothelial location incite an active inflammatory response, whereas those in a subepithelial location do not as they are separated from the circulation by the glomerular basement membrane. Immune complex formation is followed by the binding and activation of complement and ensuing inflammatory cascades. However, a variety of other mechanisms may be at play, including activation of the coagulation system causing a thrombotic microangiopathy, podocytopathy associated with heavy proteinuria but no active inflammatory lesions, and interstitial or vascular renal disease.

The role of renal biopsy and clinical pathologic correlations

In lupus nephritis, the kidney biopsy provides diagnostic and prognostic information and can serve as a guide to therapy. Current classification describes six classes of pathology (Table 1).

Multiple studies have shown the prognostic value of this classification. In general, classes I and II have a mild presentation and benign clinical course. Treatment is targeted at blood control with antiproteinuric agents and angiotensin-converting enzyme-I (ACE-I) or angiotensin receptor blockers (ARBs). Classes III and IV are associated with active urinary sediment, substantial proteinuria, and progressive renal damage and thus, deserve vigorous therapy. Class V, membranous lupus nephropathy, is associated with heavy proteinuria (often the nephrotic syndrome) and requires special therapeutic considerations. Patients with class VI, sclerosing lesions, do not respond to immunosuppressive therapy and should be prepared for dialysis and/or transplantation.

Treatment of classes III and IV is divided into two phases: induction and maintenance

Early National Institutes of Health (NIH)-sponsored trials showed that intravenous steroids and six monthly intravenous high doses of cyclophosphamide (0.5 to 1.0 g/m²) followed by quarterly maintenance doses resulted in more clinical remissions than treatment with either steroid or cyclophosphamide alone (2). With concerns about cyclophosphamide toxicity, including infection, infertility, and malignancy development, the Euro Lupus Group studied 90 proliferative lupus nephritis patients randomized to receive either a low-dose cyclophosphamide regimen (six pulses of 500-mg doses every 2 weeks) or a high-dose regimen (six monthly pulses) similar to the NIH regimen. Both groups were then maintained on azathioprine, 2 mg/kg per day. At short- and long-term follow-up, there was no significant difference in efficacy or adverse effects. However, the number of patients with severe infection was twice as high in the high-dose cyclophosphamide group, providing support for the low-dose treatment course (3). This new regimen has been validated in other populations, including African Americans, and is now considered one of two standard induction therapies for lupus nephritis.

The alternative standard induction regimen uses mycophenolate mofetil. The Aspreva Lupus Management Study (ALMS) (4), a multicenter, multicultural trial of 370 patients with class III, IV, or V lupus nephritis, randomized induction to either mycophenolate mofetil or six monthly intravenous cyclophosphamide pulses. Both arms initially received high-dose corticosteroids, which were tapered. The trial showed similar efficacy and toxicity with both regimens in a broad range of racial and geographic groups.

Thus, the recommendations by most nephrology and rheumatology organizations are to use either cyclophosphamide or mycophenolate combined with corticosteroids as induction treatment for severe active lupus nephritis. Individual preference, compliance, tolerability, and specific clinical scenarios all influence selection. However, if patients fail therapy with one agent, they are most often switched to rescue with the second therapeutic regimen.

Maintenance therapy of proliferative lupus nephritis

After remission through induction has been achieved, a number of studies have defined optimal maintenance treatment. An early trial randomized 59 patients with class III or IV lupus nephritis postinduction with 6 months of monthly pulse cyclophosphamide to receive either quarterly intravenous cyclophosphamide pulses (0.5 to 1.0 g/m²) or daily oral azathioprine or mycophenolate (5). At follow-up, the study showed that maintenance with either mycophenolate or azathioprine was more efficacious and significantly safer than continuing long-term therapy with intravenous cyclophosphamide. A study by the Euro Lupus group that randomized patients to azathioprine or mycophenolate after induction showed no significant difference in the very good outcome seen in the largely Caucasian European population studied (6). More recently, 227 patients from the ALMS who had a good clinical response to either cyclophosphamide or mycophenolate induction were randomized to receive either mycophenolate (1 g twice a day) or azathioprine (2 mg/kg per day) double blind for another 3 years. At follow-up, mycophenolate was superior to azathioprine in maintaining renal response and preventing relapse (7). This was true in different geographic areas, among different racial groups, and regardless of which induction regimen was used.

At present, both mycophenolate and azathioprine seem effective agents for maintenance therapy. Mycophenolate may have advantages in non-Caucasian populations. Azathioprine should be used in women contemplating pregnancy. Cost may be a factor for some patients, and mycophenolate is generally more expensive. Mycophenolate can be used with allopurinol or febuxostat for patients with gout, whereas azathioprine should not be used with xanthine oxidase inhibitors.

Table 1

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<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Maintenance Options</th>
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<tbody>
<tr>
<td>I</td>
<td>Minimal mesangial lupus nephritis</td>
<td>Normal light microscopy or mesangial immune deposition on IF and/or EM</td>
</tr>
<tr>
<td>II</td>
<td>Proliferative lupus nephritis</td>
<td>Mesangial hypercellularity on light microscopy with mesangial immune deposition</td>
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<tr>
<td>III</td>
<td>Focal lupus nephritis</td>
<td>Inflammatory injury affecting less than 50% of the glomeruli by light microscopy with crescents, fibrinoid necrosis, and/or subendothelial immune deposition. Both classes III and IV are classified as A with active lesions of proliferation and necrosis, C with chronic lesions of sclerosis and fibrosis, or A/C with a combination of these lesions</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse lupus nephritis</td>
<td>Inflammatory injury affecting greater than 50% of the glomeruli, again classified as A, C, or A/C. This class is further divided into segmental or global depending on the extent of injury to the individual glomerular tuft, greater than 50% in the latter category</td>
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<tr>
<td>V</td>
<td>Membranous lupus nephritis</td>
<td>Glomerular capillary thickening on light microscopy with subepithelial immune deposition on EM/IF</td>
</tr>
<tr>
<td>VI</td>
<td>Advanced sclerosing lupus nephritis</td>
<td>Over 90% glomerulosclerosis</td>
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IF = immunofluorescence; EM = electron microscopy.

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Future Therapies

Future treatments of lupus nephritis rest on a better understanding of the immune pathogenesis of the disease. Key players include T and B cells, plasma cells, the costimulatory factors that nurture these cells, and the cytokines that upregulate the inflammatory cascade. Trials of some available agents are ongoing. Rituximab with mycophenolate is being studied as a steroid-sparing regimen in the RITUXILUP Trial as mentioned above. There is interest in multitargeted therapy for severe lupus nephritis, because a positive randomized multicenter Chinese study looked at induction therapy with monthly intravenous cyclophosphamide versus treatment with mycophenolate and tacrolimus, with both groups receiving corticosteroids. Results revealed significantly more complete and partial remission in the mycophenolate/tacrolimus arm (13).

Anifrolumab, a mAb against the IFN-α receptor 1, blocks the effects of IFN-α, a major regulatory cytokine in approximately 50% of SLE patients (14, 15). In a randomized, controlled study of over 300 patients, anifrolumab provided added efficacy in induction when added to mycophenolate and corticosteroids (16). Belimumab, a humanized anti-BllyS mAb, is being evaluated for active lupus nephritis as an add-on drug (versus placebo) to standard care induction therapy (NCT 01693393). Another trial, the CALIBRATE Study, will test cyclophosphamide, rituximab, and oral prednisone followed by belimumab (NCT 02260934). Obinutuzumab, a novel anti-CD20 mAb, causes more complete peripheral and lymphoid tissue B cell depletion than rituximab (17). A phase 2 study is currently underway for patients with active lupus nephritis (NCT 02550652). Voclosporin, a novel calcineurin inhibitor with enhanced stability and activity relative to cyclosporin, is currently being studied as add-on therapy as well (NCT02141672). Finally, AC-THER gel is being studied in both proliferative and membranous lupus.

This is an exciting time for those treating patients with lupus nephritis. We already have good therapies for induction and maintenance that have been studied in large controlled, randomized trials. It is clear that treatments will evolve further as we learn more about the complex immunologic pathways involved in the disease. The quest for more effective and safer therapeutic options for lupus nephritis is paramount.

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References

1. Danila. Renal damage is the most important predictor of mortality: Data from a multiethnic US cohort. Rheumatology 2009; 48:542–545.