Lupus Nephritis: Keeping the Wolf at Bay

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From the beginning part of this century, we have witnessed a dramatic improvement in the prognosis of patients with SLE. Several factors have contributed to this improvement, such as a better understanding of the pathophysiology, recognizing the essential role of the kidney biopsy in defining and prognosticating lupus nephritis (LN), and the development of relatively effective treatment for severe lupus. As a consequence, mortality has sharply declined in these patients, from 10-year survival rates of around 50% in the 1950s to up to 90% in the late 1990s (1). With the introduction of alkylating agents in the 1970s, the long-term prognosis of LN had significantly improved compared with corticosteroid-only regimens, albeit at the cost of major side effects in many patients (2). So where do we stand in the new millennium with respect to the management of LN? In this Moving Points feature, some of the key management issues faced by nephrologists and rheumatologists when taking care of these complicated patients are highlighted.

The first paper will examine the role of the kidney biopsy in management of lupus patients. Previously, in the era of cyclophosphamide (CYC)–containing regimens, it was critical to biopsy patients with suspected LN to provide an estimate on the activity (i.e., potential reversibility) and chronicity (irreversible disease) before treating with a toxic drug regimen. With the advent of the less toxic and (probably) equally effective mycophenolate mofetil (MMF)–containing regimens, is the kidney biopsy as critical as it used to be in helping us guide therapy? Has the International Society of Nephrology/Renal Pathology Society classification that replaced the earlier World Health Organization classification made a real difference in our understanding of the disease and clinical management of these patients? The following is probably the most difficult question: What are the indications for a kidney biopsy? Giannico and Fogo attempt to tackle these issues in the article “Lupus Nephritis: Is the Kidney Biopsy Currently Necessary in the Management of Lupus Nephritis?”

Once a diagnosis of LN is made, it should be fairly easy to prescribe a “standard” induction therapy protocol. Unfortunately, there is no such standard therapy despite fairly robust clinical trial evidence. With the advent of MMF, the hope was that the more toxic CYC-containing regimens would be phased out, but unfortunately, that was not to be the case. Despite smaller studies showing superiority of MMF over CYC, the largest study, the Aspreva Lupus Management Study, did not show any difference between the two protocols (3). Furthermore, there are no long-term studies showing whether MMF can provide lasting protection similar to, or better than, CYC. Lastly, how do we treat patients with severe or relapsing disease? In their article titled “Lupus Nephritis: Induction Therapy in Severe Lupus Nephritis—should MMF Be Considered the Drug of Choice?,” Rovin et al. address all of these and other issues surrounding induction therapy in these difficult patients.

A significant proportion of patients do not respond well (or not at all) to induction therapy with either MMF– or CYC-containing regimens. For example, in the Aspreva Lupus Management Study, remissions (mainly partial remissions) were seen in only half of patients (3). The remaining patients had significantly active nephritis after 6 months of therapy. The implication of uncontrolled disease is obvious—a significant proportion of these patients will have progressive renal failure. It is critical to define what “refractory” means and unfortunately there is no consensus on this point. Being labeled refractory implies failure of current therapy and the consideration that immunosuppression will be increased (with the potential for more side effects). My colleagues and I will discuss these issues and touch upon the potential role for targeted therapy against B cells and experience with other treatment options available for treating the patient with resistant disease.

Finally, there is the issue of maintenance therapy. The very definition of “maintenance” therapy is a little blurry because MMF is currently used both as induction and maintenance; furthermore, only a minority of patients is in complete remission when they switch to maintenance. There are several issues related to optimizing maintenance therapy. When does one make the switch to a maintenance regimen? Which drug regimen is preferred? Do calcineurin inhibitors provide protection as well as azathioprine and MMF? Contreras et al. will discuss the pros and cons of different drug regimens and address the issue of “how long” in their article on maintenance therapy.

My hope is that these articles will provide a sharper focus on some of the controversial issues that exist in the treatment of LN. Some of the best clinical trials in glomerular disease have been done in patients with LN and the treatment choices for this previously fatal and morbid disease have dramatically improved. However, the cup is still half empty. Current treatments are not uniformly effective with significant rates...
of nonresponse and relapse and side effects; much more needs to be done to address these issues. We urgently need more effective and less toxic regimens and this compendium of articles will hopefully provide the basis to design future studies to improve the outcomes of these patients.

Disclosures
J.R. served on an advisory board to Genentech.

References

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