Lupus Nephritis: The Case for Repeat Kidney Biopsy in the Management of Maintenance Therapy

By Brad H. Rovin and Samir V. Parikh

The therapy of proliferative lupus nephritis (LN) is generally divided into an initial phase of high-intensity immunosuppression to induce prompt clinical improvement, followed by a maintenance phase of lower-intensity immunosuppression to consolidate improvement into remission. Induction most often lasts 3 to 6 months, but maintenance lasts years and often indefinitely. The average duration of maintenance therapy in several recent randomized clinical trials was 3.5 years but ranged beyond 5 years. In fact, one of the most difficult management decisions in the care of LN patients is how long to continue maintenance immunosuppression. The most recent Kidney Disease Improving Global Outcomes (KDIGO) glomerulonephritis guidelines suggest continuing maintenance immunosuppression for at least 1 year beyond a complete renal response (1). However, this recommendation is not supported by randomized, prospective data, and no recommendations for withdrawal are given for a partial renal response. The 2012 LN guidelines sponsored by the American College of Rheumatology make no recommendations about the duration of maintenance immunosuppression (2), and the European League Against Rheumatism/European Renal Association-European Dialysis and Transplant Association guidelines suggest continuing maintenance therapy for at least 3 years (3).

Some insights into the duration of maintenance therapy can be derived from studies of repeat kidney biopsy in LN patients who have been treated with standard-of-care therapies. After 1.5 to 4.7 years of treatment, 30 to 77 percent of patients who underwent a repeated biopsy showed ongoing active proliferative LN or had undergone conversion to membranous LN, which also represents continued disease activity. Importantly, many of these patients had persistent substantial proteinuria, abnormal serum creatinine levels, or both. More worrisome are data showing that about one third of patients who had achieved complete clinical remission, and were clinically inactive for 2 years, still had histologic disease activity on repeat biopsy (4). These findings demonstrate that there can be discordance between the clinical metrics of renal response and histology. This discordance can also go in the other direction. A small study described several LN patients who had been aggressively treated but had persistent proteinuria (5). On repeat biopsy, these patients had no residual histologic activity and, barring sampling error, were complete responders histologically but not clinically (5).

We suggest that a repeat kidney biopsy could be a useful tool in guiding withdrawal of maintenance immunosuppression. For patients who have had a complete renal response, a biopsy before making the decision whether to taper off immunosuppression would identify patients who still have histologic activity and in whom it may be desirable to continue or even intensify immunosuppression. In the spirit of full disclosure, there have been no trials to test whether a patient who has achieved a complete clinical response, but still has some histologic activity on biopsy, will benefit from continuing or intensifying immunosuppression. For patients who have reached a partial remission and are in a stable condition for more than a year, a repeat biopsy could identify those who have achieved histologic remission and for whom tapering of immunosuppression may be considered.

Even if a kidney biopsy is used to inform a decision to taper off maintenance therapy, the question of when to perform the biopsy remains. This is difficult to answer on the basis of the available literature. At one extreme, some patients show no active lesions on biopsy specimens taken after induction therapy. It is conceivable that such patients could taper therapy at this point and avoid long-term maintenance immunosuppression. This rationale supports a role for repeat biopsy after the induction phase. However, tapering therapy after induction is not likely to become the prevailing consensus in the lupus community unless it is prospectively demonstrated to be safe. Most studies of repeat biopsy after LN induction therapy show improving histologic activity but not resolution of inflammation. An estimate of the minimal amount of time therapy is needed can be derived from existing studies of repeat biopsy. Several studies showed proliferative LN lesions in patients re-biopsied after 2 years of immunosuppressive therapy. One study found that 60 percent of patients who had achieved a complete renal response after 18 to 24 months of total treatment still had evidence of histologic activity in the kidneys (6). By contrast, after an average of 45 months of total therapy (minimal duration 42 months), only 30 percent of patients still had persistent activity on repeat biopsy (4). When these data are put together, a repeat kidney biopsy to inform the decision of whether to withdraw maintenance therapy could be considered after 3 to 3.5 years of total therapy (induction + maintenance) in clinically quiescent patients.

In summary, Figure 1 offers an algorithm for performing kidney biopsies in patients with LN to guide therapeutic choices. This algorithm has limitations because it is based on currently available data, most of which are neither prospective nor randomized. A study comparing renal outcomes in patients treated only on the basis of clinical data, or treated after consideration of clinical and repeat biopsy data, is needed to guide practice.

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Figure 1. Algorithm for using the kidney biopsy to manage maintenance therapy of lupus nephritis. After the initial diagnostic biopsy, a repeated biopsy can be considered upon finishing induction therapy in patients who have completely responded. Some of these patients may be able to avoid prolonged treatment with immunosuppression, but this is not currently recommended. Most patients will be given maintenance immunosuppression after induction. Patients who achieve a complete renal response and have received more than 3 years of therapy are candidates for withdrawal of immunosuppression. This decision may be facilitated by a repeated biopsy to confirm histologic remission. Patients who do not achieve a complete clinical response, but have responded partially, may be considered for a repeat biopsy to determine whether they have attained a histologic remission. If so, and after a similar duration of total immunosuppressive therapy, such patients may be considered for withdrawal of maintenance therapy.