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Immunosuppression Withdrawal in Patients with Lupus Nephritis

When, How, and for Whom Will It Be Safe?

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The goal of therapy in lupus nephritis is remission of disease activity to improve long-term kidney and patient outcomes. Current therapy fails to induce clinical remission in most patients, and morbidity and mortality remain significant. Even when patients achieve complete clinical responses, repeat kidney biopsies often exhibit persistent active inflammation. About 15%–20% of lupus nephritis patients eventually develop kidney failure. On the other hand, long-term immunosuppression is associated with considerable morbidity, irreversible organ damage, and malignancies. Despite a lack of consensus on the duration of therapy, the majority of patients with lupus remain on immunosuppression 10 years after induction therapy.[1] Importantly, evidence and real-world experience demonstrate that immunosuppressant withdrawal after a prolonged course of treatment is possible in more patients than would be expected, especially considering that lupus and lupus nephritis are chronic autoimmune conditions that theoretically could require life-long immunosuppression.[2] Understanding how to identify patients with lupus nephritis who are candidates for immunosuppression withdrawal is critical to balancing kidney survival and treatment morbidity.

A risk of withdrawing immunosuppression is that lupus nephritis may flare, requiring reintroduction of therapy. Besides the morbidity associated with adding back (often high-dose) immunosuppression, each nephritis flare results in kidney inflammation, cumulative chronic kidney damage, and irreversible loss of nephrons, promoting progression toward kidney failure.[3] Treatment of flares also becomes more complicated as fewer nephrons exposed to increasing hemodynamic and metabolic overload in the damaged kidney may contribute to treatment resistance.[4]

Currently, complete and partial kidney response criteria rely on improvement or stabilization of kidney function and improvement of proteinuria.[5,6] However, proteinuria is a problematic biomarker of immunological response as it is a marker of acute and chronic damage. Proteinuria due to chronic damage and consequent higher filtration pressure in remaining nephrons can be misinterpreted as immunological activity. A repeat biopsy study characterized the time course of resolution of the individual components of the activity index in patients with lupus nephritis who responded well to therapy and achieved complete and durable clinical responses.[3] As expected, inflammatory lesions declined with treatment, but the rate of resolution of individual histologic lesions was variable. For example, cellular crescents, karyorrhexis, and fibrinoid necrosis tended to resolve rapidly during initial therapy, whereas endocapillary hypercellularity, hyaline deposits, and interstitial inflammation cleared more slowly during maintenance therapy over 3 or more years. Glomerular immunoglobulins and complement persisted more than 3 years and, often, complete resolution of glomerular immunofluorescence exceeded 10 years. Furthermore, despite aggressive immunosuppression, chronic kidney damage accrued early in the disease course.[3] Therefore, the gold standard to distinguish ongoing intrarenal immunologic activity from chronic damage is the kidney biopsy. We suggest that combining clinical and histologic data when considering withdrawal of immunosuppression will better inform this decision.

In this context, consider the Weaning of Maintenance Immunosuppressive Therapy in Lupus Nephritis trial.[7] Patients (n=96) with biopsy-proven proliferative lupus nephritis were randomized to withdraw or continue immunosuppression for 2 years after 2–3 years of treatment and

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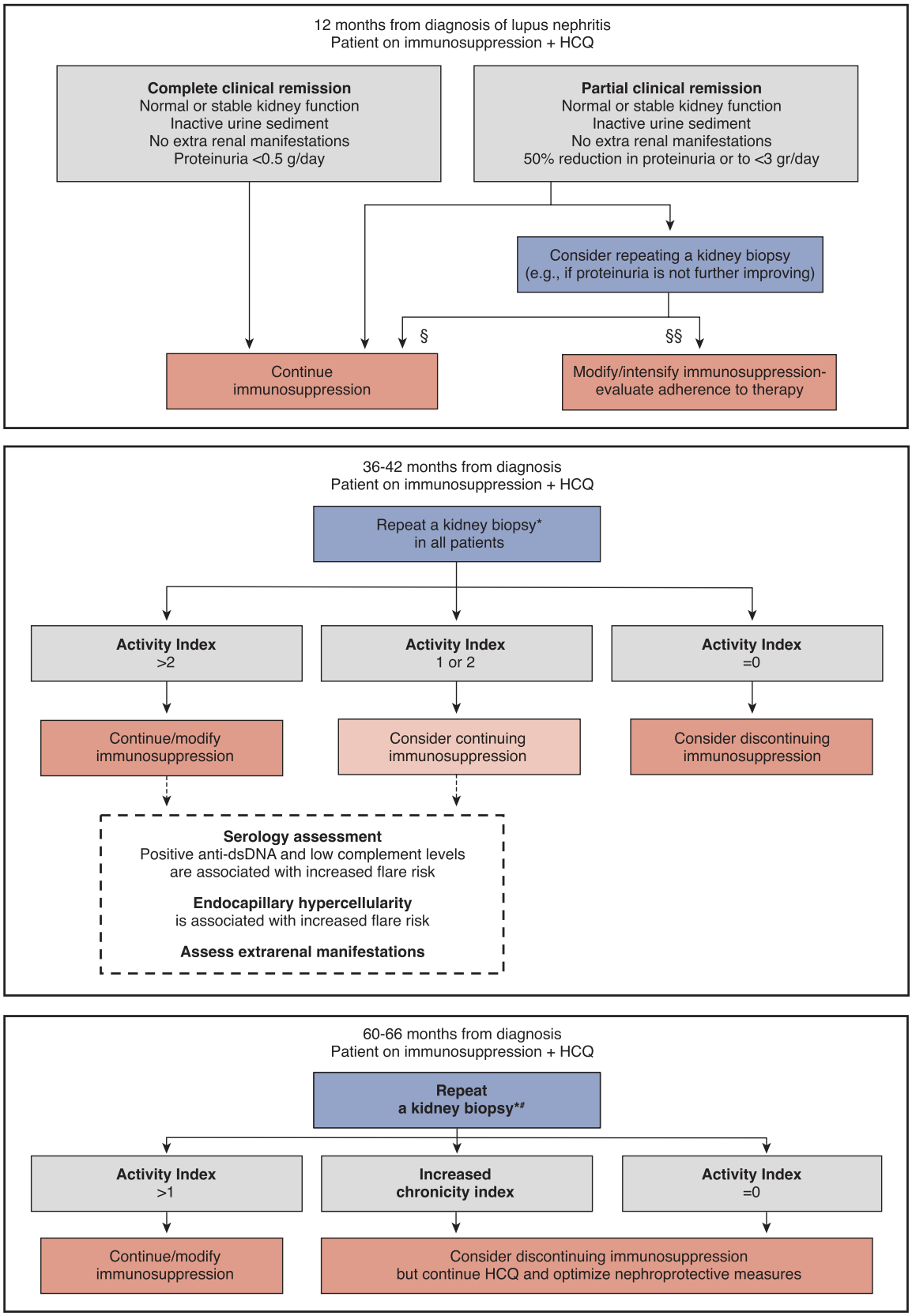

Figure 1. Proposed algorithm for immunosuppression continuation or slow and gradual withdrawal in patients with lupus nephritis in complete or partial clinical remission. At 12 months from diagnosis, patients are on maintenance immunosuppression and antimalarials to maintain control of disease activity and on renin-angiotensin system inhibition for kidney protection. At this time point, patients with complete clinical remission

Figure 1. *Continued.* should continue immunosuppression as immune memory is long lasting. In patients who have achieved partial clinical remission by 12 months and in whom proteinuria has been continuously improving, the same immunosuppression should be continued as lesions may need a longer time to completely resolve. However, in patients with partial clinical remission but in whom proteinuria has not been further improving, a repeat biopsy should be considered to evaluate whether the plateau in proteinuria is due to chronic damage or because the activity index has not improved or has increased. If the plateau in proteinuria is due to chronic damage, current immunosuppression should be continued; if activity is not improving or is worsening, treatment modification/intensification should be considered. Thirty-six to 42 months from diagnosis, when intrarenal immunological remission can be achieved even without proteinuria reaching response criteria, we propose performing a repeat biopsy in all patients (irrespective of proteinuria levels) to gain information about specific active and chronic lesions. In patients with an activity index of more than 2, immunosuppressant withdrawal should not be attempted. In patients with complete histologic remission (activity index of 0), immunosuppressant withdrawal should be attempted under close observation. The first medication to taper off and discontinue is steroids. After determining the patient is stable off steroids, mycophenolate mofetil or azathioprine should be discontinued next, slowly decreasing the dose over 6 months. Data on the outcome of patients with an activity index of 1 or 2 are lacking. In these patients, the same immunosuppression scheme should be continued. Persistently positive anti-dsDNA, low serum complement, and endocapillary hypercellularity in repeat biopsy are associated with a flare risk. Extrarenal lupus manifestations should be taken into account. For patients who have not achieved histologic remission and continue immunosuppression, a repeat biopsy should be considered every 24 months until either the activity index becomes 0 or the patient develops sufficient chronic damage that risk of immunosuppression exceeds the benefit of bringing the activity under control. At this point, immunosuppression may be withdrawn, unless extrarenal disease necessitates ongoing treatment. Hydroxychloroquine should be maintained in all patients and nephroprotective measures should be optimized in patients with chronic damage. The algorithm does not apply to patients who did not achieve complete or partial clinical remission by 12 months from diagnosis. §Continue immunosuppression if the activity index is improving. §§Modify/intensify immunosuppression and evaluate adherence to therapy if the activity index has not improved from baseline biopsy or is increasing. *In repeat kidney biopsies, more than ten nonglobally sclerosed glomeruli and immunofluorescence are required. #A repeat biopsy should be considered every 24 months until either activity index becomes 0 or sufficient chronic damage has accumulated such that the risk of continued immunosuppression exceeds the benefit of treating any remaining activity. Complete and partial clinical remission: Normal or stable serum creatinine with inactive urine sediment in the absence of extrarenal lupus activity with either proteinuria <0.5 g/d or 50% reduction in proteinuria and to <3 g/d, respectively. Serological remission: Negative anti-dsDNA antibodies and normal serum complement levels. Intrarenal immunological remission: Absence of glomerular immunoglobulins or complement by immunofluorescence microscopy. Complete histologic remission: Activity index of 0 at repeat biopsy. anti-dsDNA, anti-double stranded DNA antibodies; HCQ, hydroxychloroquine.

achieving complete or partial clinical remission (normal or stable kidney function, inactive urinary sediment, proteinuria <0.2 g/d or normal or stable kidney function; inactive urinary sediment, stable proteinuria or proteinuria <0.5 g/d, respectively). Lupus nephritis flares (biopsy confirmed) occurred in 12.5% of patients who continued immunosuppression but 27.3% of patients who stopped immunosuppression. This was not statistically significant.[7]

One of the caveats of the Weaning of Maintenance Immunosuppressive Therapy in Lupus Nephritis data is that clinical remissions were not confirmed by biopsy, so persistent histologic activity could not be excluded. The relevance of clinically undetected histologic activity for future lupus nephritis flares was shown in the LuFla study.[8] In LuFla, 44 patients on immunosuppression for at least 36 months and in clinical complete remission (proteinuria <0.5 g/d, inactive urinary sediment, normal serum creatinine) for at least 12 months underwent a second biopsy and then gradually discontinued immunosuppression. Over the next 2 years, 11 patients (25%) experienced a lupus nephritis flare yielding a flare rate of 5.5 flares per year. All but one of these 11 (91%) patients had had persistent intrarenal immunologic activity in biopsy 2. Everyone with an activity index over 2 flared. By multivariable analysis, the best model associated with a future flare included duration of lupus and the presence of residual endocapillary hypercellularity on biopsy 2.[8] This model gives an area under the receiver operating characteristic curve of 0.99 and a misclassification rate of 5.6%. Other models using the total activity index at biopsy 2 or residual subendothelial deposits on biopsy 2 also predicted flare well, but with higher misclassification rates and/or lower areas under the receiver operating characteristic curve than endocapillary hypercellularity.[8] As discussed previously, endocapillary hypercellularity is one of the slowest histologic lesions of lupus nephritis to resolve.[3]

To test whether withdrawal of immunosuppression in patients with clinical *and* histologic remission may reduce subsequent kidney flares, a cohort of 75 patients with stable complete clinical response (proteinuria <0.5 g/d, normal serum creatinine, and no extrarenal lupus activity) underwent a repeat biopsy after at least 42 months of therapy to inform the withdrawal decision.[9] Immunosuppressants were discontinued only in those with histologic remission, defined as an activity index of 0 at repeat biopsy. In patients who continued therapy, repeat biopsies were performed every 24 months until no histologic activity was observed, and therapy was discontinued accordingly. In this cohort, only seven patients (9.2%) developed a lupus nephritis flare, translating to a flare rate of 1.5 lupus nephritis flares per year.[9]

While these investigations rigorously defined histologic remission as an activity index of 0, it is conceivable that a low activity index, for example 1 or 2, may be easier to achieve therapeutically but similarly can identify patients for whom immunosuppressant withdrawal is safe. In a study of 56 patients with lupus nephritis in complete clinical remission (proteinuria <0.5 g/d, normal GFR or within 10% of previous GFR) or partial remission (≥50% reduction in proteinuria to subnephrotic level, normal or near normal

kidney function),[10] persistent histologic activity on a second kidney biopsy taken after a median of 41.1 months of treatment was defined as an activity index ≥2. Immunosuppression was withdrawn from 29 of the 42 patients with an activity index <2, and of them, eight (27.5%) patients had a kidney flare. The activity index was ≥2 in 12 patients; five stopped immunosuppression and two (40%) flared.[10] In another cohort of 42 patients, the relationship between flare and activity was assessed by a second biopsy taken a median of 24 months after starting treatment.[11] Although this was not an immunosuppression withdrawal study, the investigators found that 10% of patients with an activity index ≤2 flared, compared with 41% with an activity index >2. When an activity index of 3 was used as the cutoff, 14% flared with an index ≤3 and 50% flared with an activity index of >3.[11] These data must be viewed in the context of very small sample sizes and the lack of knowledge of what histologic lesions were making up the activity index. That said, the data do support the idea that histology combined with clinical response provides a better chance of avoiding lupus nephritis flares when deciding whether immunosuppression should be withdrawn than clinical response alone. While comparing studies cannot be done statistically, the flare rates for patients with low (activity index of 1–2) residual activity compared with no residual activity seem to be higher.

We have translated all of these data into an algorithm to help guide the decision of when it may be appropriate to withdraw immunosuppression in patients who are doing well clinically (Figure 1). It must be stressed that none of the studies was definitive or appropriately powered. Data came from very different patient populations, clinical response definitions were not uniform, activity and chronicity cutoffs were different, follow-up duration varied, and treatment was different. Nonetheless, the algorithm is testable and provides an evidence-based starting point to investigate this important management issue. Prospective studies, such as the ReBioLup (ClinicalTrials.gov NCT044449991), are underway to address the impact of ongoing histological activity after a kidney flare and the importance of clinical inactivity. Finally, because the kidney biopsy is an invasive procedure, albeit relatively safe, histology-based treatment protocols should only be implemented in centers with expertise in performing native kidney biopsies, whose adverse outcome rate is low.[3,8–10] There may also be reluctance from some patients to have a repeat biopsy, given these are not yet standard of care. Ultimately, our expectation is that noninvasive blood or urine biomarkers of kidney histology will become available to reduce the need for rebiopsy.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at http://links.lww.com/JSN/E631.

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