Commentary for Kidney Biopsy-Based Management of Maintenance Immunosuppression in a Lupus Nephritis Cohort

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Abstract:

Malvar et al report results of a study on protocolized repeat renal biopsies in 76 patients with class III or IV (+/- class V) lupus nephritis. They show that managing maintenance therapy in patients with lupus nephritis through protocolized repeat renal biopsies results in a lower flare rate. Provided that these results can be replicated in other studies, there is an argument for protocolized repeat renal biopsies to become the standard of care.

Renal relapse raises the risk of progressive renal failure, particularly for nephritic flares, and its avoidance is a central component of lupus nephritis therapy. Because urinary and serologic markers correlate poorly with histology there is always uncertainty as to when or whether remission of lupus nephritis is achieved. This provides a dilemma both for the treating physician and for the development of newer lupus nephritis therapies. With alternative immunosuppressives, such as, mycophenolate mofetil, the imperative to determine the necessary length of treatment, seen in the past with cyclophosphamide induction, has reduced, but the uncertainty as to how long to treat lupus nephritis remains, reflected in the current guidelines (1).

The histopathological classification for lupus nephritis was created out of the necessity to classify the variety of patterns with which lupus nephritis can present itself. It is the only histological classification system for renal disease that serves as a guideline for therapy and clinical management. In patients with systemic lupus erythematosus (SLE), the pattern of a single renal biopsy taken at time of presentation of disease or when the first signs of renal involvement become known, dictates whether specific treatment for nephritis should be commenced and influences the choice of drug. It is generally known that classes of lupus nephritis may vary and switch over time, based on different classes found in those patients who underwent multiple renal biopsies mostly in relation to flares (2). Few studies have examined protocolised repeat renal biopsies in lupus nephritis, and these were mostly focussed on outcome rather than on guiding treatment decisions (3).

Last year in Kidney International, a research led by the Lupus Flares and Histological Renal Activity at the end of Treatment Study reported on the clinical implications of SLE patients in complete remission who gave consent for a repeat renal biopsy, followed by tapering off maintenance immunosuppression approximately 36 months after nephritis diagnosis (4). The majority of patients who developed a flare had residual histologic activity on the second biopsy; and all patients with an Activity Index (AI) score > 2 experienced a flare. Other learning points from this study were that 30% of patients with proteinuric remission had histologic activity and over half of those without proteinuric remission had histologic remission. This study exemplified the usefulness of a repeat renal biopsy in the management of maintenance immunosuppression; it also suggested that withdrawal of therapy could be considered in patients in histologic remission. In the current issue of Kidney International, Malvar et al present results of a study that went one step further (5). Starting off with the premise that approximately one third of patients with lupus nephritis have persistent active renal lesions even after years of treatment, repeat renal biopsies were performed in a cohort of 76 patients with class III or IV (+/- class V) lupus nephritis with the aim to discontinue immunosuppression in those without histological activity, and to continue immunosuppression if ongoing histologic activity was present. The outcome of this study shows an overall reduced flare rate and good renal and patient survival; there were no deaths and no patients progressed to ESRD. However, it should be noticed from Supplemental Figure 1 that before enrolment, patients were excluded with chronic damage as a dominant feature on biopsy; also excluded were patients who did not respond to treatment and had rapid progression to ESRD and patients who relapsed during induction or maintenance therapy. Such bias away from those with a worse prognosis will have impacted on the results in terms of renal progression and possibly relapse.

For a study with a focus on renal biopsies being performed as a guideline for maintenance therapy, it is slightly disappointing how sparse the information on the actual findings of the biopsies is. In addition, there is relatively little information on how some clinical decisions were based on the combination of histologic and clinical findings. It is evident that the various biopsies in the study had different roles. Biopsy 1 established the diagnosis of lupus nephritis in combination with the patients’ clinical and serologic findings. Biopsy 2, a protocol biopsy performed 6-12 months after diagnosis, aimed to assess the response to induction therapy, but there is no information how this was established or interpreted. It seems that biopsy 2 had no role in moving onto the maintenance immunosuppression phase. The most important role has biopsy 3: if in this biopsy, the AI was 0, maintenance immunosuppression was tapered off, but if the AI was 1 or higher, maintenance immunosuppression was continued for another 24 months. Eventually, 20 patients underwent renal biopsy 4, and 4 patients underwent renal biopsy 5, after which ultimately, all histologic activity was absent. Although it seems fair, also from previous findings, to only consider tapering of maintenance immunosuppression when there is no activity at as defined by AI = 0, it would be of interest to consider whether, for instance, a small inflammatory infiltrate which would suffice to give a score of AI=1 would also suffice to continue immunosuppression for another 24 months. Furthermore, it is important to keep in mind not all active lesions are captured by the AI. Hypothetically, patients with active lesions not listed in the AI could have been tapered off immunosuppression while they were having active lesions such as tubulitis or vasculitis. Although this may seem unlikely, by not exemplifying the details of the histological evaluation, it cannot be ruled out either.

An interesting histologic finding that is not discussed in the manuscript is that patients in all groups already had a median chronicity index of 3 in biopsy 1, which never exceeded a median of 4 in all of the follow-up biopsies in all groups. Apparently, there was a background of chronicity that was barely influenced by treatment decisions and time.

In a commentary given on the previous report on repeat renal biopsies in lupus nephritis in Kidney International, Nachman (6) emphasized that a better understanding is still required on how to interpret the actual histopathological changes that are encountered in the repeat biopsy. In particular, he mentioned that because we do not know the time required for active lesions to resolve, we are not able to critically evaluate the need of subsequent treatment. Only by adding a control group, and subsequently studying outcomes on patients with similar histological activity randomly assigned to either maintenance or treatment withdrawal, would we learn more about the actual cut-off points from which future management protocols could benefit. Also in other areas of nephrology this issue plays an important role. For instance, as biopsy frequency increased in the setting of renal transplantation, unexpected findings such as tubulitis and interstitial inflammation were encountered in clinically stable patients. Most importantly, these findings created awareness of ongoing inflammatory processes that apparently were not controlled by maintenance therapy and most likely were related to the vast amount of chronic changes that appeared later on. Tubulo-interstitial lesions have consistently been shown to be of prognostic relevance in lupus nephritis and may represent a different pathogenesis, and require a different treatment, than glomerular lesions (7). Again, in the current study, it is unclear how much ‘activity’ is driven by these lesions or whether patients with such lesions were excluded.

The Malvar study challenges current concepts of remission in view of the discordance between proteinuric and histologic remission using a proteinuria threshold below 500mg/24 hours or equivalent. It is notable that lower proteinuria levels, below 500, associate with lower risk of relapse and presumably less histologic activity. The poor performance of this threshold is further compounded by arbitrary time points, e.g. 6 or 12 months from diagnosis, due to the different rates of proteinuria reduction between patients and continued reductions out to 18 months or beyond.

Where there seems to be a tendency for a decline in renal biopsies being performed during the diagnostic work-up of patients with glomerulonephritis, the study by Malvar et al attributes an important role for the renal biopsy in patient management which inevitably would entail an increase in renal biopsy procedures. In general, arguments against the performance of renal biopsies are the fear of patients and doctors to perform this invasive procedure – despite the low incidence of side effects (8). In the study by Malvar et al, there were no severe or life-threatening events related to the biopsy procedure. However, as commonly noticed, the experience with adverse events in relation to renal biopsies should of course be taken into account before implementation of this strategy.

In conclusion, the study by Malvar et al shows that managing maintenance therapy in patients with lupus nephritis with the help of protocolized repeat renal biopsies results in a lower flare rate than in usual practice with reference to previously published cohorts. In comparing results from this study to previous studies, it is stated that about 10 patients would need to be managed with the biopsy-informed protocol to prevent one LN flare per year. It is clear that it has to be considered whether the biopsy protocol presented in this paper weighs against the prevention of LN flares given the numbers. Nevertheless, the study elegantly demonstrates the merits of repeat renal biopsies in lupus nephritis for patient management. In the absence of more robust predictive non-biopsy biomarkers, there is an argument for protocolised repeat biopsy to become the standard of care if the results can be replicated in other studies.

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