# A prospective observational cohort study highlights kidney biopsy findings of lupus nephritis patients in remission who flare following withdrawal of maintenance therapy

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**One of the most difficult management issues in lupus nephritis (LN) is the optimal duration of maintenance immunosuppression after patients are in clinical remission. Most patients receive immunosuppression for years, based mainly on expert opinion. Prospective data are unavailable. Complicating this issue are data that patients in clinical remission can still have histologically active LN; however, the implications of this are unknown. To study this, the Lupus Flares and Histological Renal Activity at the end of Treatment study (ClinicalTrial.gov, NCT02313974) was designed to examine whether residual histologic activity predisposes to LN flares in class III and IV LN. Patients in complete clinical remission for at least 12 months who had received at least 36 months of immunosuppression were eligible. Patients consented to a second kidney biopsy, were tapered off maintenance immunosuppression and were then followed prospectively for LN flares over 24 months. Forty-four patients were enrolled, and 36 completed the study. LN flares occurred in 11 patients, and ten of these had residual histologic activity on the second biopsy. All patients with an NIH activity index over two flared. The activity index and duration of systemic lupus erythematosus at the second biopsy were independent predictors of flare. A predictive equation based on these variables discriminated between flare and no flare with a sensitivity of 100%, specificity of 88%, and a misclassification rate of 8.3%. Thus, a repeat kidney biopsy may be useful in managing maintenance immunosuppression in LN, and patients in histologic remission may be candidates for withdrawal of therapy.**

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Systemic lupus erythematosus (SLE) has a relapsing and remitting course, with patients experiencing episodic disease activity (flares) over time. Kidney biopsy plays an important role in the initial diagnosis and staging of lupus nephritis (LN). It also guides the appropriate selection of treatment, especially for high-risk patients.[1,2]

The duration of maintenance treatment for International Society of Nephrology/Renal Pathology Society (ISN/RPS) class III and IV LN is currently based on the clinical evolution of the LN flare. Many guidelines recommend at least 3 years of total treatment and 1 year of complete remission before withdrawing treatment. These recommendations are based mainly on expert opinion, as there are few data to develop an evidence-based guideline. Protocol repeat biopsy studies after complete remission show continuing histologic activity in a significant number of patients.[3–7] Stopping maintenance immunosuppression in such patients may theoretically put them at risk of renal flare. Management of maintenance therapy is even more uncertain in patients with stable partial renal remission and no extrarenal lupus activity. Such patients often have ongoing proteinuria, and thus continue to receive immunosuppression indefinitely. Repeat biopsies in such patients[3,4,8] have shown that many have no histologic activity and are in histologic remission. Persistent proteinuria may be from past injury and scarring, so continuing treatment may put such patients at risk for infectious morbidity with little benefit for the LN.[2,9]

We suggest that a repeat biopsy in LN patients on long-term maintenance therapy who have been in complete renal remission for at least 1 year may help guide the withdrawal of maintenance immunosuppression. We postulated that patients with remaining histologic activity will have a greater tendency toward LN flares than those with no remaining activity, and tested this hypothesis prospectively in the Lupus Flares and Histological Renal Activity at the End of the Treatment (LuFla) study (ClinicalTrial.gov identifier: NCT02313974).

## RESULTS

The overall study design and patient flow of LuFla is shown in Figure 1. LuFla recruited 44 patients, and 36 completed the study. All patients were Hispanic and white, 25 (83%) were female, and the average age of the cohort at biopsy 1 was 31.6 ± 11.3 years. Table 1 presents the demographic, clinical, and histologic characteristics of the patients at biopsy 1 segregated by renal flare status after stopping immunosuppression.[10] Patients who experienced flare were comparable to patients who did not in all respects except for having a longer overall duration of SLE. There were fewer males in the flare group, but this did not reach significance. LN histologic classes were distributed as follows: IV A ($n = 7$), IV A/C ($n = 16$), III A ($n = 7$), III A/C ($n = 6$), and 4 of the class III A patients had concomitant class V LN.

After a minimum of 36 months of immunosuppression and at least 12 months of clinical renal remission, a repeat kidney biopsy (biopsy 2) was performed. The clinical and histologic findings at biopsy 2 are summarized in Table 2. Overall, 20 patients (55.6%) achieved complete histologic remission with an activity index (AI) of 0. Nine patients (25%) had an AI of 1 or 2. The remaining 7 patients (19.4%) had an AI between 3 and 5. Despite complete clinical renal remission, persistent histologic activity was present in 16 patients (44.4%). The histologic components of the AI that were found in these patients were endocapillary proliferation in 13 (81%), subendothelial deposits in 14 (88%), and interstitial inflammation in 4 (25%). No patient had persistent glomerular crescents or necrosis.

After maintenance therapy was tapered and discontinued, LN flared in 11 patients (30.5%). The clinical findings at flare for these patients are shown in Table 3. All but 1 flare (91%) occurred in patients who had active histology at biopsy 2, and everyone with an AI $> 2$ experienced flare (Figure 2). Among the no-flare group, 6 patients (24%) had an AI of 1 to 2 on biopsy 2. In the entire cohort, the incidence of renal flare in patients who had an AI $\leq 2$ at biopsy 2 was 13.8%.

Clinical, serologic, and histologic findings at biopsy 2 are provided in Table 2. Although proteinuria decreased below 500 mg/d in all patients, the flare patients showed a trend ($P = 0.06$) toward more proteinuria than the no-flare patients in remission. Additionally, while not statistically significant, more patients who experienced flare were positive for anti–double-stranded DNA antibodies, had low C3 and C4 levels at biopsy 2, and showed a decline in C3 in the 6 months preceding biopsy 2 ($P = 0.06$). Proteinuria, change in C4, and anti–double-stranded DNA antibody status at biopsy 2 did not correlate with the presence or absence of persistent histologic activity in biopsy 2 (AI $= 0$ vs. AI $> 0$). The decline in C3 in the 6 months preceding biopsy 2 showed a tendency to associate with the AI ($P = 0.073$ by logistic regression), but its correlation was not strong (Spearman $r = –0.20$; $P = 0.23$).

Chronicity at biopsy 2, measured by the chronicity index (CI), did not correlate with proteinuria at biopsy 2 (Spearman

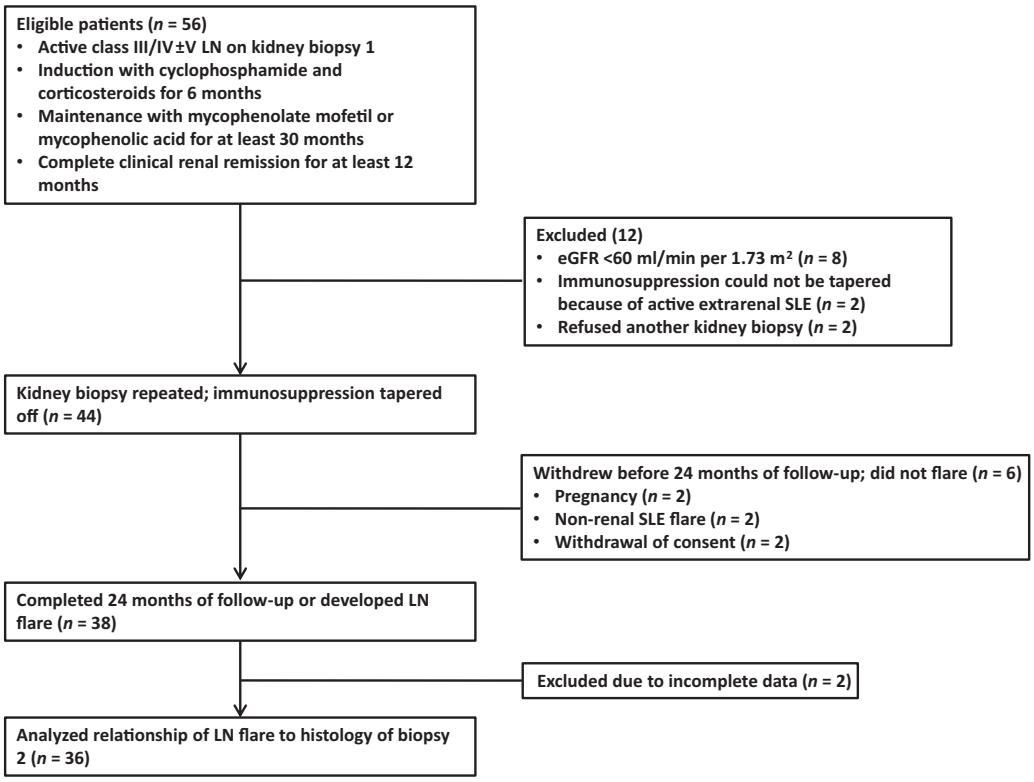


**Figure 1 | Lupus Flares and Histological Renal Activity at the End of the Treatment (LuFla) study design and patient flow.** eGFR, estimated glomerular filtration rate; LN, lupus nephritis; SLE, systemic lupus erythematosus.