

# The value of repeated biopsy in lupus nephritis management

Renal biopsy is essential in the initial evaluation of patients with lupus nephritis (LN). However, the role of repeated renal biopsy during the follow-up is controversial. Repeated biopsy during follow-up of patients with LN may represent a useful tool in difficult cases to evaluate the histological response to therapy, to modulate the intensity of treatment, and to predict the long-term renal outcome. Persistent or progressive proteinuria, worsening of renal function, no remission and renal flare are established indications for repeat a renal biopsy, with the main objective of guiding immunosuppressive treatment. There is growing evidence that repeated biopsies after induction or maintenance treatment can better evaluate prognosis compared to first biopsy and can detect histological activity in patients without clinical and laboratorial signs of active LN. However, there is no clear consensus on whether a biopsy should be repeated after induction or maintenance treatment.

**Keywords:** lupus nephritis • kidney biopsy • outcomes

## Introduction

Lupus nephritis (LN) is a frequent manifestation of systemic lupus erythematosus (LES), affecting approximately 60% of patients, and is a major cause of morbidity and mortality [1-3]. The initial renal biopsy is useful to distinguish histological subtypes of LN, and is the gold standard for guiding therapeutic decisions and to assess prognostic evaluation, due to the dissociation between clinical and laboratorial characteristics and histological features [4,5]. Since non-invasive biomarkers do not predict real-time events occurring in the kidney, there is a growing evidence that, despite the risks, repeated biopsy is the most feasible and reliable tool for distinguishing inflammatory activity from permanent damage, for predicting renal prognosis and relapse after treatment withdrawal [6,7]. Nonetheless, correct indications of subsequent biopsies are still under discussion. Therefore, the objective of this review is to assess the importance of repeated renal biopsy during the management of patients with LN.

## Clinical indications of repeated biopsy

The re-biopsy may be indicated in patients with worsening or refractoriness to immunosuppressive treatment (failure to decrease proteinuria by 50% or more, persistent proteinuria beyond 1 year and/or worsening of glomerular filtration rate) and at renal flare, to demonstrate change or progression in histological class, change in biopsy chronicity and activity indices, to provide prognostic information, and detect other pathologies [8].

Repeated biopsy performed for these clinical indications results in changes in immunosuppressive therapy in up to 80% of patients, since it differentiates immunological activity from scarring injury (chronicity). In addition, it can provide prognostic information [9-14]. The presence of crescents in more than 30% of glomeruli and Chronicity Index (CI) greater than 5 in repeated biopsy, for example, are associated with an increased risk of doubling serum creatinine and End Stage Renal Disease (ESRD) [14].

Histological transformations are common in biopsies repeated due to renal flare. When first biopsy has non-proliferative lesions, transition to proliferative lesion can occur in approximately 60% of patients. Interestingly, the transition from proliferative lesions to non-proliferative is less frequent (5-31%) [9,13]. Therefore, repeated biopsy in renal flare provides important information for more precise treatment choices.

## Repeated biopsy after induction treatment

Histological evaluations after 6 to 8 months of induction therapy fortify the discordance between histological and clinical response [15]. Nearly 30% of patients with clinical complete remission show significant histological activity (activity index  $\geq 5$ ). In contrast, approximately 60% of patients with complete histological remission have persistent moderate to high grade proteinuria [15,16]. Despite the discordance between clinical and histological response,

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neither the clinical nor histologic remission status immediately after induction therapy appears to correlate with long-term kidney survival. Nevertheless, the chronicity index of biopsies after induction therapy have greater association with long-term renal outcome compared with initial biopsy [15,16].

There is no sufficient evidence to support the routine use of kidney biopsy after induction treatment, since the value of persistent activity lesions on these biopsies is not known. It is possible that mild activity lesions represent remaining active lesions that disappear over time, even without increasing immunosuppression. Nevertheless, all patients with severe activity lesions had intensified immunosuppressive treatment and increased immunosuppression may have improved the long-term renal outcome in these patients [15,16].

### Repeated biopsy in maintenance treatment

The renal biopsy performed after 12 months of treatment shows the histological evaluation during maintenance treatment. It might be a better predictor of poor renal prognosis compared to clinical response assessed by proteinuria and serum creatinine. Among patients with partial and no clinical remission, 60% have no activity lesions on repeated biopsy [17]. In a prospective study by De Rosa et al. 44 patients with LN class III or IV ± V were evaluated. The patients received induction therapy with cyclophosphamide for 6 months and maintenance therapy with mycophenolate mofetil for at least 30 months. A second kidney biopsy was performed in 36 patients with complete clinical renal remission for at least 12 months, to evaluate histological status of remission. Even after 42 months of treatment and 12 months of complete clinical remission, about 45% of patients had histological activity, with the activity index greater than 2 in 20% of them. All patients with activity index greater than 2 relapsed after withdrawal of maintenance immunosuppression and it was the only predictor of renal flare [18]. Given the importance of histological activity in predicting renal flare, repeated biopsy after maintenance treatment can be an important tool in the decision of stop immunosuppression. However, despite the low risk of major complications, assessing the risks and benefits of the procedure is always required.

### Conclusion

Renal biopsy is the gold standard for diagnosis and prognosis evaluation of patients with LN, however indications for a repeat renal biopsy are not a consensus. Persistent or progressive proteinuria, worsening of renal function, no remission and renal flare are established indications for re-biopsy, with the main objective of guide immunosuppressive treatment. Nevertheless, the importance of repeated biopsies after induction or maintenance treatment needs to be better studied to investigate the importance of histological features on treatment modification and to improve long-term renal outcomes.

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### Disclosures

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