Lupus Nephritis: When to Re-Biopsy After Induction Therapy

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> Managing lupus nephritis (LN) demands precise assessment of treatment efficacy, particularly after induction therapy. The question of when and whether to perform a repeat renal biopsy to guide subsequent management has long been a point of contention among nephrologists and rheumatologists. A recent study published in Lupus Science & Medicine offers new data on the utility of re-biopsy and the correlation of clinical and histological responses.1

KEY TAKEAWAYS

- The Pivot: Histopathological renal response on re-biopsy after induction therapy correlates with clinical Target Renal Response (TRR).
- The Data: Among patients achieving TRR, 70.6% showed complete or partial histological response on re-biopsy.
- The Action: Consider re-biopsy in patients with persistent proteinuria despite clinical improvement, as it may reveal ongoing histological activity not captured by routine labs.

Lupus nephritis, a severe manifestation of systemic lupus erythematosus (SLE), affects up to 60% of adult patients and is a leading cause of morbidity and mortality. The disease is characterized by immune complex deposition in the glomeruli, leading to inflammation and progressive kidney damage. Initial diagnosis relies on renal biopsy, which classifies the nephritis according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) criteria and guides induction therapy. But the optimal timing and necessity of a repeat biopsy to assess treatment response, particularly in patients who show an incomplete clinical response, has been debated. Clinicians often rely on surrogate markers like proteinuria and serum creatinine, but these do not always reflect the underlying histological activity.1

Egypto and colleagues conducted a prospective observational study involving 34 adult patients with biopsy-proven lupus nephritis (ISN/RPS Class III, IV, or V) who had completed at least six months of induction therapy. The patients, predominantly female (88.2%) with a mean age of 32.5 years, received either cyclophosphamide or mycophenolate mofetil as induction. All patients underwent a repeat renal biopsy after induction, typically around six months, to evaluate histopathological changes. The investigators aimed to correlate these histological findings with clinical response, defined by the Target Renal Response (TRR) criteria, and to assess the utility of various serum and urinary biomarkers.1

The Clinical and Histological Disconnect

The study found a significant correlation between clinical response and histological improvement on re-biopsy. Among the 34 patients, 17 (50%) achieved a Target Renal Response (TRR), defined as a 50% reduction in proteinuria to less

than 0.8 g/day, or a reduction to less than 0.2 g/day if baseline was below 0.8 g/day, along with stable or improved renal function. Of these 17 TRR responders, 12 (70.6%) demonstrated either a complete or partial histological response on re-biopsy. Complete histological response meant a reduction in both activity and chronicity indices, or a stable chronicity index with reduced activity. Partial response indicated a reduction in the activity index without a significant increase in chronicity.1

But the picture was not entirely straightforward. Five patients (29.4%) who achieved TRR still showed persistent histological activity on re-biopsy, indicating ongoing inflammation despite clinical improvement. This finding highlights the potential for a disconnect between clinical markers and actual renal pathology. Conversely, among the 17 patients who did not achieve TRR, 10 (58.8%) showed persistent histological activity, while 7 (41.2%) surprisingly exhibited histological improvement. This group, despite not meeting clinical TRR, had some degree of histological healing, suggesting that clinical criteria alone might understate therapeutic effect in some cases.1

The mean activity index (AI) on initial biopsy was 5.4 ± 2.2, decreasing to 3.1 ± 1.9 on re-biopsy (P=.001). The mean chronicity index (CI) also decreased, from 2.1 ± 1.2 to 1.8 ± 1.1, though this change did not reach statistical significance (P=.12). This suggests that while inflammation (activity) responds to induction therapy, established scarring (chronicity) is less reversible, even with effective treatment. The persistence of chronicity highlights the importance of early diagnosis and aggressive induction to prevent irreversible damage.1

Biomarkers and Their Limited Utility

The investigators also explored the correlation of various serum and urinary biomarkers with clinical and histological responses. They assessed serum creatinine, 24-hour proteinuria, C3 and C4 complement levels, anti-dsDNA antibodies, and urinary biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), monocyte chemoattractant protein-1 (MCP-1), and transforming growth factor-beta (TGF-β). The goal was to identify non-invasive markers that could potentially obviate the need for repeat biopsies.1

Serum creatinine, a standard measure of renal function, did not significantly correlate with histological activity or chronicity indices on re-biopsy. This is not entirely unexpected, as creatinine levels often remain stable until significant renal damage has occurred. 24-hour proteinuria, however, showed a moderate correlation with the activity index (r=0.45, P=.008) and a weaker correlation with the chronicity index (r=0.31, P=.07). This suggests that proteinuria, while a key clinical endpoint, is an imperfect surrogate for the full spectrum of histological changes.1

Complement levels (C3, C4) and anti-dsDNA antibodies, traditional markers of SLE disease activity, also showed limited utility in predicting histological response. C3 levels correlated weakly with the activity index (r=0.28, P=.11), and C4 and anti-dsDNA showed no significant correlation. This finding aligns with previous research suggesting that systemic markers of lupus activity do not always mirror renal-specific inflammation, especially after targeted induction therapy. For a deeper dive into the broader management of lupus, including novel therapies, clinicians might consult resources like the Lupus Management: Progress and Persistent Challenges at EULAR 2026 coverage.1

The urinary biomarkers, NGAL, KIM-1, MCP-1, and TGF-β, were also evaluated. NGAL and KIM-1 are markers of tubular injury, while MCP-1 is a chemokine involved in inflammation, and TGF-β is a pro-fibrotic cytokine. None of these urinary biomarkers demonstrated a strong or consistent correlation with either the activity or chronicity indices on re-biopsy. For instance, NGAL showed a weak correlation with the activity index (r=0.22, P=.21), and KIM-1 was similarly unconvincing. This lack of strong correlation suggests that while these biomarkers reflect aspects of renal

injury, they do not provide a comprehensive picture of the complex inflammatory and fibrotic processes captured by histology.1

Implications for Clinical Practice

The study's findings reinforce the notion that a repeat renal biopsy can provide critical information not always evident from clinical parameters alone. The 29.4% of TRR responders who still had active histological lesions on re-biopsy represent a subgroup of patients who might benefit from continued or intensified immunosuppression, even if their proteinuria has improved. Conversely, the 41.2% of non-TRR patients with histological improvement might have their therapy de-escalated or adjusted differently if a re-biopsy reveals less severe underlying disease than suggested by their clinical markers. This highlights the value of the Oxford Handbook of Rheumatology as a quick reference for complex autoimmune conditions.

The decision to re-biopsy remains a clinical judgment, balancing the risks of the procedure against the potential benefits of more precise treatment guidance. The Egypto study suggests that in cases of incomplete clinical response, or even in some cases of apparent clinical response where there is suspicion of ongoing subclinical activity, a re-biopsy provides actionable data. This is particularly relevant for patients with persistent proteinuria despite achieving other clinical endpoints, as proteinuria showed the strongest, albeit still moderate, correlation with histological activity.1

The study's relatively small sample size of 34 patients is an obvious caveat. While the prospective design and consistent re-biopsy protocol are strengths, the limited number of participants restricts the generalizability of the findings and the power to detect subtle correlations, especially with biomarkers. The study also included a heterogeneous mix of ISN/RPS classes (III, IV, V), which might obscure class-specific responses to therapy. Different histological classes often respond differently to induction regimens, and a larger, stratified study would provide more granular insights.1

Another limitation is the lack of a control group that did not undergo re-biopsy, making it difficult to definitively assess the impact of re-biopsy-guided therapy on long-term renal outcomes. The study also did not standardize the induction therapy beyond cyclophosphamide or mycophenolate mofetil, and variations in dosing or duration could influence histological response. The absence of a standardized protocol for biomarker collection and analysis across all patients could also introduce variability.1

Still, the study's contribution lies in its direct comparison of clinical and histological responses, offering a clearer picture of their concordance and discordance. It reinforces the idea that clinical markers, while useful, are not perfect surrogates for the complex pathological changes occurring in the kidney. The lack of strong correlation with novel urinary biomarkers suggests that while these are not yet ready to replace biopsy in guiding treatment decisions for lupus nephritis, they do show potential for future development. The field continues to search for reliable non-invasive markers, but for now, histology remains the gold standard for assessing renal pathology in LN.1

The findings also prompt consideration of the optimal timing for re-biopsy. Six months post-induction is a common interval, allowing sufficient time for treatment effects to manifest. But whether earlier or later re-biopsies might offer different insights, particularly in rapidly progressive cases or those with very slow clinical response, remains an open question. The data does not address the long-term impact of re-biopsy-guided therapy on patient outcomes, which would require a much larger, randomized controlled trial.1

Where it falls short

The study's reliance on a single center in Egypt, while ensuring consistent biopsy interpretation, limits the diversity of the patient population and potential genetic or environmental factors that could influence disease progression and treatment response. The relatively short follow-up period post-re-biopsy also means that the long-term clinical consequences of histological findings, particularly in those with persistent activity despite clinical TRR, are not fully elucidated. Future research should focus on larger, multicenter studies with longer follow-up periods and standardized treatment protocols to validate these findings and explore the prognostic value of re-biopsy.1

The utility of re-biopsy in lupus nephritis is not universally accepted, with some clinicians arguing against routine repeat procedures due to invasiveness and cost. But this study provides evidence that re-biopsy can offer unique, clinically relevant information that may alter management, particularly in patients with discordant clinical and histological findings. The challenge remains to identify which patients will benefit most from this invasive procedure, moving beyond a blanket recommendation to a more personalized approach.1

CLINICAL IMPLICATIONS

The Egypto study provides a stark reminder that clinical metrics alone are insufficient for fully understanding disease activity in lupus nephritis. Relying solely on proteinuria and creatinine after induction therapy risks undertreating patients with ongoing histological inflammation or overtreating those whose pathology has improved despite lagging clinical markers. The 29.4% of clinical responders with persistent histological activity are precisely the patients who need a re-biopsy to guide appropriate escalation of immunosuppression, preventing irreversible damage.

For nephrologists, this means embracing re-biopsy as a valuable, albeit invasive, diagnostic tool, particularly when clinical response is ambiguous or incomplete. The current suite of urinary biomarkers, while promising in theory, simply does not offer the granular detail provided by tissue histology. Until non-invasive markers prove their mettle, the needle remains essential for truly understanding the kidney's status.

The industry, meanwhile, should take note: the search for reliable non-invasive biomarkers for lupus nephritis remains an unmet need. Current offerings fall short of replacing biopsy, leaving a significant gap for diagnostics that can accurately reflect renal inflammation and fibrosis. This is an area ripe for innovation, as clinicians would readily adopt a less invasive, equally informative alternative.

The decision to re-biopsy should be a shared one, weighing the procedural risks against the potential for more precise, pathology-driven treatment. It is not a routine procedure, but a targeted one for when the clinical picture is muddy. The data here suggests that in a substantial minority of patients, a re-biopsy will change management, and that alone justifies its consideration.

REFERENCES

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