Editorial

Prognostic Stratification of Lupus Nephritis: The Importance of Renal Histology

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Advancement in immunosuppressive and nonimmunosuppressive therapies for lupus nephritis (LN) has led to a substantial reduction in the incidence of endstage renal disease (ESRD) and mortality.¹ However, pooled data from different ethnic groups in both developed and developing countries revealed plateauing of the rates of patient and renal survival of LN after the mid-1990s.¹,² There are unmet needs for further improving the treatment outcomes of LN. This aim could be achieved by several possible strategies: (1) developing novel modalities with enhanced efficacy:toxicity ratio; (2) an early combination/cocktail strategy to increase the clinical response rate and dampen kidney inflammation within the “window of opportunity,” particularly in patients at higher risk of renal function decline; (3) a treat-to-target (T2T) approach to minimize residual inflammation and subsequent kidney damage; and (4) better stratification of patients to receive personalized therapies to enhance cost-effectiveness.³,⁴

A number of genetic, serological, urine, and tissue biomarkers have been explored in the past 2 to 3 decades for their prediction of severity, histological classes, ESRD, and disease flare before a change in conventional clinical variables such as serum creatinine and proteinuria in LN. These include markers for LN activity, such as urinary monocyte chemoattractant protein 1 (MCP-1), neutrophil gelatinase–associated lipocalin (NGAL), tumor necrosis factor–like weak inducer of apoptosis (TWEAK), vascular cell adhesion molecule 1 (VCAM-1), soluble CD163, and matrix metalloproteinase 7 (MMP-7); and chronicity, such as epidermal growth factor (EGF) and uromodulin.⁴ However, none of these markers have been thoroughly validated in longitudinal cohorts of different ethnicities to allow for routine clinical use. This is partly because of the lack of certainty about data reproducibility, reference ranges of the biomarkers, and the optimal cut-off values for predicting useful clinical outcomes.⁵ As a result, the gold standard for assessing activity and prognosis of LN remains a kidney biopsy, although this is an invasive procedure that many patients are reluctant to undergo.

Renal biopsy is important for establishing the diagnosis of LN and assessing the severity of active and chronic lesions. In addition to the histological classes, individual histopathological features, such as cellular crescents, fibrinoid necrosis, thrombotic microangiopathy, interstitial inflammation, tubular fibrosis, and podocytopathy, exhibit prognostic significance that would influence therapeutic approaches. It is well recognized that clinical metrics, such as the urine protein-to-creatinine ratio (UPCR) and sediments, correlate poorly with histological features of LN.⁶ For instance, class I/II and class III/IV LN could be detected in 72% and 17%, respectively, of renal biopsy samples in patients with systemic lupus erythematosus (SLE) who did not have urinary abnormalities or impaired renal function (“silent LN”).⁷ In a cohort of proliferative LN (III/IV) comprising predominantly White and Hispanic individuals, 29% of patients had an activity index of ≥ 5 on repeat renal biopsy 6 months after induction therapy, which would qualify as a complete renal response.⁸ Conversely, 62% of patients with histological remission (activity index = 0) had UPCR > 0.5. A previous study found a substantial proportion of patients with LN who are relatively asymptomatic but have persistent proteinuria, with or without active SLE serology, developed slow and progressive renal function decline.⁹ These observations underscore the importance of having a renal histology assessment on making decisions regarding induction regimens and therapy switching, as well as on the feasibility of treatment deintensification.

In this issue of The Journal of Rheumatology, Liao et al¹⁰ retrospectively reported the histopathological features of 526 Taiwan Chinese patients with LN and their correlation with ESRD (estimated glomerular filtration rate [eGFR] < 15 mL/min/1.73 m²) and mortality. The most common histological class of LN was class IV ± V (n = 310), followed by class III ± V (n = 111) and pure class V (n = 85). Over a median of 7.5 years, ESRD and mortality occurred in 58 (11%) and 64 (12%) patients.

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respectively. A stepwise Cox regression analysis revealed a significant association between tubulointerstitial inflammation and tubular atrophy with ESRD at 10 years. Cellular crescents were associated with mortality in male subjects, but fibrous crescents were associated with reduced survival in female patients. The strength of this study is the large sample size and the minimization of interrater variability by having the histological review by a single and experienced renal pathologist. However, there are several caveats. First, the number of events is still inadequate for analyses of all factors associated with ESRD or mortality, such that adjustment for confounding covariates could be performed only in a stepwise regression model. As a consequence, the confounding effects of clinically important determinants of LN prognosis, such as age, sex, and immunosuppressive regimens, were not considered. Second, the severity of histological lesions was not weighted quantitatively. Third, other poor prognostic factors for LN, such as delay in referral and treatment adherence, were not evaluated. Finally, only the initial renal biopsy was used to correlate with the long-term outcome. The absence of data on serial biopsies for residual activity and scarring, and histological class switching, which is more predictive of the outcomes of LN, does not enhance the knowledge about the importance of a repeat renal biopsy on the ultimate prognosis of LN.

A recent multicenter randomized controlled trial conducted in France (WIN-Lupus) involving 96 patients with stable LN receiving maintenance immunosuppressive therapy (MIT; mycophenolate mofetil or azathioprine) for 2 to 3 years did not demonstrate noninferiority of MIT discontinuation compared to MIT continuation regarding relapse of proliferative LN at month 24. In fact, there were more severe SLE flares in the MIT discontinuation group. Although the results from this study echo the old literature reporting high rates of flares of LN after discontinuation of immunosuppression and support the prolonged use of MIT, interpretation is confounded by the absence of data on glucocorticoid use and residual LN activity on renal histology. This again highlights the importance of renal biopsy in selecting patients with LN who require treatment augmentation or tapering until a blockbuster biomarker or biomarker panel becomes readily available. Molecular profiling of renal tissue samples by transcriptomic analyses could further identify histological chronicity and predict clinical nonresponsiveness to guide treatment decisions.

Despite its limitations, the study by Liao et al reiterates the importance of renal histology in the assessment of LN. The ongoing multinational project in Europe, Repeat Kidney Biopsy in Incident Cases of Lupus Nephritis (REBIOLUP; ClinicalTrials.gov: NCT04449991), will shed light into the effectiveness of an additional posttreatment renal biopsy on treatment decisions and ultimate clinical outcomes of LN.

REFERENCES