

- Describe the properties of main instruments for measuring SLE disease activity and identifying treatment targets
- Demonstrate the ability to assess and interpret the SLE-DAS

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MOLECULAR SIGNATURES IN KIDNEY BIOPSIES AND THEIR RELATIONSHIP TO CLINICAL ACTIVITY

Jill Buyon. *New York University Grossman School of Medicine, Division of Rheumatology, New York, NY, USA*

10.1136/lupus-2022-la.25

Initiated to molecularly deconstruct lupus nephritis (LN), the Accelerating Medicines Partnership (AMP) is a public-private consortium involving the National Institutes of Health, pharmaceutical companies, and lupus investigators across fifteen clinical sites collecting urine, blood, skin biopsies, and kidney biopsies from patients with LN.

Almost 500 lupus patients have been enrolled in the AMP and their phenotypic data and specimens have been collected and applied to various technologies to provide insights into disease pathogenesis with the aim of facilitating more personalized medicine. Through several phases of AMP (technical preparation, pilot enrollment, and large-scale enrollment), 475 patients undergoing a clinically indicated percutaneous kidney biopsy consented to provide tissue for research. Overall, the rate of serious adverse events was 3.8%, consistent with that reported for standard procedures, supporting the safety of the procedure.¹ The cohort is largely female and minority dominant. For nearly two thirds of the patients, this was a repeat biopsy. It was noted that the level of proteinuria did not predict histology class and most patients with a urine protein/creatinine ratio (UPCR) <1 had histology showing Class III, IV, V or mixed LN with accompanying activity and chronicity, despite an inactive sediment or normal serologies.² These AMP data reinforced the consideration of renal biopsy at thresholds UPCR <1. For patients with UPCR >1, overall complete response rates were only 25%. Lower chronicity, but not activity, associated with complete response with proliferative histology being more responsive than membranous.

The earlier phases of AMP have yielded informative results based on single cell RNA sequencing. In brief, 21 subsets of leukocytes in LN were identified including multiple populations of myeloid cells, T cells, natural killer cells, and B cells.³ Cells expressed both pro-inflammatory and inflammation-resolving responses. Local activation of B cells correlated with an age-associated B-cell signature. Progressive stages of monocyte differentiation were evident. The majority of cells expressed a Type I interferon (IFN) response. Two chemokine receptors, CXCR4 and CX3CR1, were broadly expressed, which implicates a potential central role in cell trafficking. Kidney epithelial cells and M2-like macrophages may be coordinating traffic of immune cells infiltrating the kidney. A high Type I IFN response signature and fibrotic signature in tubular cells were each associated with non-responsiveness to therapy.⁴ Analysis of tubular cells from patients with proliferative, membranous, and mixed LN indicated pathways relevant to inflammation and fibrosis, which offer insight into their histological differences. Complete transcriptomic analysis of a larger dataset from 156 patients is underway.

REFERENCES

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3. Arazi A, *et al.* The immune cell landscape in kidneys of patients with lupus nephritis. *Nat Immunol* 2019 Jul;**20**(7):902–914.
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Learning Objectives

- Explain how AMP data confirm need for consideration of renal biopsy in patients with thresholds UPCR <1
- Discuss AMP RNA sequencing results based on the analysis of immune cells and resident kidney cells such as the tubules, endothelium and fibroblasts
- Describe the importance of collecting such data in the development of personalized medicine for patients with LN

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WHAT DRIVES RAPID PROGRESSION TO ESRD IN PATIENTS WITH LUPUS NEPHRITIS?

Murray Urowitz. *University of Toronto, Canada*

10.1136/lupus-2022-la.26

Lupus nephritis (LN) affects up to 40% of patients with systemic lupus erythematosus (SLE) and leads to end stage kidney disease (ESRD) in 17–33% after 10 years.¹ We have investigated a number of factors that have been shown to predispose to a more rapid progression to ESRD, including time to initial response to conventional therapy, number of flares during follow-up, duration of immunosuppressive therapy, unusual histologic patterns and patient compliance.

In the Toronto Lupus Cohort of 418 patients with LN, 209 (50%) achieved remission within the first year from LN diagnosis, 102 (24.4%) within the 2nd and 3rd years, 70 (16.7%) after 3 years and 37 (8.9%) never achieved remission. Sixty-six patients (15.8%) developed advanced chronic kidney disease after 9.5 years on average. The 66 patients who progressed to ESRD had a longer time to complete remission (3.0 ± 3.4 vs 1.6 ± 2.1 yrs), more often had two or more flares (40 (60.6%) vs 117 (33.2%)) and had a shorter median time on immunosuppressants from complete remission to outcome (2 yrs (0–7) versus 4 yrs (0–8)). These factors remained independently significant in a multivariable analysis accounting for multiple other relevant factors.

Catastrophic progression to ESRD was also associated with unusual histologic patterns. Examples of these included thrombotic microangiopathy, interstitial inflammation added to the classic ISN classes, collapsing glomerulopathy, concomitant anti-GBM nephropathy and poor patient compliance.

These findings emphasize the importance of achieving early remission as well as flare prevention with prolonged immunosuppressive use and attention to patient compliance to maximize renal survival in LN.

REFERENCE

1. Tektonidou MG, *et al.* Risk of end-stage renal disease in patients with lupus nephritis, 1971–2015: a systematic review and bayesian meta-analysis. *Arthritis Rheumatol* 2016 Jun;**68**(6):1432–1441.