

- 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

25

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

1. Deonaraine KK, *et al.* Safety of procuring research tissue during a clinically indicated kidney biopsy from patients with lupus: data from the accelerating medicines partnership RA/SLE network. *Lupus Sci Med* 2021 Aug;**8**(1):e000522.
2. Carlucci PM, *et al.* High incidence of proliferative and membranous nephritis in SLE patients with low proteinuria in the accelerating medicines partnership. *Rheumatology (Oxford)* 2022 Feb 25;keac067.
3. Arazi A, *et al.* The immune cell landscape in kidneys of patients with lupus nephritis. *Nat Immunol* 2019 Jul;**20**(7):902–914.
4. Der E. *et al.* Tubular cell and keratinocyte single-cell transcriptomics applied to lupus nephritis reveal type I IFN and fibrosis relevant pathways. *Nat Immunol* 2019 Jul;**20**(7):915–927.

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

26

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.

Learning Objectives

- Explain that shorter time to remission of LN protects against rapid progression to ESRD
- Explain that preventing flares in LN protects against rapid progression to ESRD
- Explain that longer duration of immunosuppressive therapy in LN protects against rapid progression to ESRD
- Describe the unusual features of LN that might lead to catastrophic progression to ESRD

27 INCREASED CV RISK IN WOMEN WITH SLE: STORIES FROM A PANEL OF BIOMARKERS

Piga. University of Cagliari, Italy

10.1136/lupus-2022-la.27

Cardiovascular (CV) mortality and morbidity are significant challenges in managing patients with systemic lupus erythematosus (SLE). Patients with SLE have a 2-fold higher risk of stroke and a 3-fold higher risk of myocardial infarction than in the general population. Still, the risk is much greater in young women with SLE compared to age-matched women without SLE.¹

The higher risk of CV disease in SLE patients is mainly related to accelerated atherosclerosis, leading to sub-clinical disease and clinical manifestations earlier than the general population. A complex interplay between traditional risk factors and SLE-related features is responsible for accelerated atherosclerosis, even though its pathogenesis is not fully understood.² SLE-related factors contributing to accelerated atherosclerosis include cytokines (e.g., IFN- α , BAFF) and auto-antibodies production responsible for endothelial cells dysfunction, hyperactivated T-cells directed against peptides from vascular cells, impairment in lipid profile with increased oxidized LDL and pro-inflammatory (pi)HDL, high dose or high duration of glucocorticoid therapy. Therefore, although there is an increased prevalence of Framingham traditional CV risk factors (e.g. age, hypertension, dyslipidemia, diabetes, current smoking), it is not surprising that they do not fully account for the high CV risk observed in SLE patients.³

New biomarkers have been developed to identify potentially high CV risk SLE patients, including increased circulating leptin, antibodies against apolipoprotein A1, serum cardiac troponin T, and the soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK). In addition, a combination of both traditional (age, diabetes) and SLE-related factors (piHDL, leptin, homocysteine, sTWEAK) has shown better sensitivity (89%) and specificity (79%) than any single biomarker to predict the formation or enlargement of carotid plaques.⁴ Nevertheless, a biomarker or combination of markers to predict cardiovascular risk accurately in SLE patients is still missing.

Presently, the main objectives to lower the CV risk in SLE should be to monitor and correct traditional CV risk factors while treating the disease to target and maintain remission or low disease activity, prescribing hydroxychloroquine to virtually all patients and minimising corticosteroid use as much as possible.

REFERENCES

1. Yazdany J, et al. Systemic lupus erythematosus; stroke and myocardial infarction risk: a systematic review and meta-analysis. *RMD Open* 2020;**6**:e001247.

2. Skaggs BJ, et al. Accelerated atherosclerosis in patients with SLE—mechanisms and management. *Nat Rev Rheumatol* 2012 Feb 14;**8**(4):214–223.
3. Esdaile JM, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. *Arthritis Rheum* 2001 Oct;**44**(10):2331–2337.
4. McMahon M, et al. A panel of biomarkers is associated with increased risk of the presence and progression of atherosclerosis in women with systemic lupus erythematosus. *Arthritis Rheumatol* 2014 Jan;**66**(1):130–139.

Learning Objectives

- Describe the morbidity associated with cardiovascular diseases in SLE
- Explain the interplay between traditional risk factors and SLE related features responsible for accelerated atherosclerosis
- Discuss the most promising biomarkers of CV risk in SLE patients

Plenary III: difficult-to-treat lupus

28 APS ANTIBODIES: MANAGING PATIENTS WHEN LABORATORY SCENARIOS DON'T FIT GUIDELINES

Ricard Cervera. Hospital Clinic, Barcelona, Catalonia, Spain

10.1136/lupus-2022-la.28

Some patients with positive antiphospholipid antibodies (aPL) have not been included in randomised clinical trials or observational registries and, therefore, information on their risk of thrombotic or obstetric recurrence and optimal treatment is scarce.

In this session, the existing evidence regarding the management of two laboratory scenarios not covered by the guidelines is presented: (1) patients with antiphospholipid syndrome (APS) clinical manifestations and anti-phospholipid (aPL) positivity not fulfilling APS laboratory criteria, and (2) the possibility of discontinuing anticoagulation in APS patients whose aPLs become persistently negative.

Growing evidence suggests a role for low titres and 'non-criteria' aPL, especially in obstetric APS. Treatment is not formally recommended but might be considered according to the individual's risk profile. Regarding the question of whether or not to discontinue anticoagulants after the 'spontaneous' disappearance of aPL, there is no definite answer. Retrospective studies seem to suggest that withdrawal of anticoagulation could be safe in certain patients with APS, especially in those with a first provoked venous thrombosis and whose aPL became persistently negative during follow-up.^{1 2} Still, before the withdrawal can be recommended in routine clinical practice, multicentre and prospective studies are required to validate this hypothesis.

REFERENCES

1. Tektonidou MG, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. *Ann Rheum Dis* 2019;**78**:1296–1304.
2. Pires Da Rosa G, et al. Management of patients with antiphospholipid antibodies: what to do in laboratory scenarios that do not fit the guidelines. *Expert Rev Hematol* 2021;**14**:457–466.

Learning Objectives

- Explain the main challenges in managing patients with antiphospholipid antibodies when laboratory scenarios don't fit guidelines