

Abstract 1107 Figure 2 PCA was used to characterize the variability in cell subset frequencies across LN patients. (A) The first PC, representing the balance between lymphoid cells and monocytes/macrophages, was found to be significantly correlated with the Chronicity index. (B) The fourth PC, representing the degree of macrophage differentiation, was found to be significantly correlated with the Activity index. Shown in each case are the Spearman correlation and its associated p-value.

Methods Droplet-based single-cell RNA-sequencing was applied to the analysis of dissociated kidney samples, collected from 155 LN patients with active kidney disease and 30 living donor controls as part of the Accelerating Medicines Partnership (AMP) in SLE consortium - a large-scale, multi-center study. 73,440 immune cells passing quality control were identified, spanning 134 cell subsets, representing various populations of tissue-resident and infiltrating leukocytes, as well as the activation states these cells assume as part of their disease-related activation and differentiation (figure 1). Principal component analysis (PCA) was used to characterize the variability in cell subset frequencies across the LN patients. Relationships between the resulting principal components (PCs) and the demographic, clinical and histopathological features of the patients were then assessed.

Results The main source of variability in immune cell subset frequencies, as represented by the first PC (PC1), reflected the balance between lymphocytes and monocytes/macrophages. Subsequent PCs represented the balance between B cells and T cells (PC2); the levels of cytotoxic T lymphocytes and NK cells, as compared to plasma cells (PC3); and the degree of macrophage differentiation to an alternatively activated phagocytic profile (PC4). PC1 was significantly correlated with the Chronicity index, such that patients with a higher percentage of lymphocytes compared to monocytes/macrophages had a higher Chronicity score (rho = -0.422, p-value < 0.001; figure 2A). A high degree of macrophage differentiation, as represented by PC4, was associated with a high Activity score (rho = 0.387, p-value < 0.001; figure 2B), and, in addition, with proliferative or mixed histology class, compared to pure membranous nephritis (p-value = 0.001, Kruskal-Wallis test). The ratio of B cells to T cells, as represented by PC2, demonstrated a positive correlation with the Activity index (rho = 0.311, p-value < 0.001). We further identified a significant correlation of PC1 with age; specifically, older patients had a higher relative frequency of lymphocytes compared to

monocytes/macrophages (rho = -0.239, p-value = 0.003). Our analysis indicated that these relations are not driven by demographic, clinical and technical sources of variation in our data, including race, ethnicity, the mixture of different nephritic classes, and the inclusion of both first and later biopsies.

Conclusion Our work identifies distinct leukocyte populations active in different LN patients and, possibly, different stages of disease, and points to potential therapeutic targets, that must be validated in mechanistic studies. This approach may pave the way to personalized treatment of LN.

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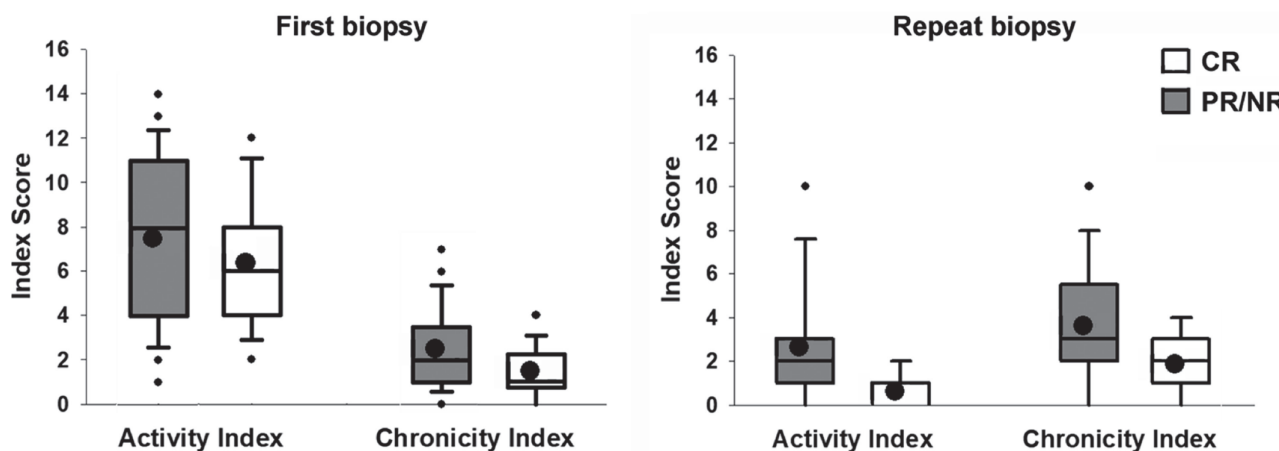
REPEAT KIDNEY BIOPSY FOR LUPUS NEPHRITIS AFTER INDUCTION: HISTOLOGIC AND CLINICAL RESPONSES IN CHILDHOOD-ONSET SLE

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Background In children with proliferative lupus nephritis, response to induction treatment is based on clinical parameters. The added benefit of repeat kidney biopsy in defining therapy response remains unclear. Emerging adult data suggests a discordancy between clinical and histological outcomes. In children, we hypothesize that histologic reassessment after induction therapy correlates better with clinical remission.

Methods A single-center retrospective observational cohort study was conducted in childhood-onset proliferative lupus nephritis with a repeat biopsy after 5-9 months of induction therapy from 2007 to 2019. LN response was determined



Abstract 1108 Figure 1 Findings at first biopsy (baseline, at time of nephritis diagnosis) and repeat biopsy (5-7 months into therapy) stratified by clinical response at time of repeat biopsy (CR, complete response; PR, partial response; NR, no response). Shown are medians (lines), means (large circles), and ranges (activity index scored 0 to 24 and chronicity index scored 0 to 12 based on ISN/RPS schema).

clinically. Histologic activity and damage were calculated using National Institutes of Health activity and chronicity indices. Lupus nephritis class transformation and changes in the degree of immune complex deposition were determined. Descriptive statistics and comparison tests were used before and after induction treatment.

Results A total of 44 patients were identified. Complete clinical response was achieved in 43% (19/44) after induction and 69% (29/42) at one year. None of the complete responders after induction had histologic activity index of > 2 on repeat biopsy (figure 1). Activity index after induction in complete responders (median 1, range 0-2) was lower than in partial or non-responders (median 2, range 0-10) (p -value < 0.005). Complete clinical response was associated with transformation to a non-proliferative class in 79% (15/19) and a reduction in immune complex deposition in 68% (13/19) on repeat biopsy.

Conclusions Unlike adult-onset lupus nephritis, clinical and histologic remission are more congruent after induction therapy in childhood-onset disease. There was good correlation between clinical response and activity index.

Lay Summary Lupus nephritis can cause kidney failure. The need to balance risks and benefits of immunosuppression requires stringent monitoring. In adults with lupus, available diagnostics are insufficient to gauge response to initial "induction" therapy and repeat biopsy studies are necessary to rigorously test novel biomarkers. Here we show that repeat biopsy in children performed 1/2 year into therapy correlates well with clinical response, but there is a subset of children with sub-clinical scarring that would be missed without repeat biopsy - this subset may be at risk long-term for kidney failure.

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VISUALIZING *IN SITU* IMMUNE PATHOGENIC MECHANISMS IN HUMAN LUPUS NEPHRITIS

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For over 50 years, systemic lupus erythematosus (SLE) has been thought to result from a break in systemic tolerance and production of pathogenic autoreactive antibodies. In the kidney, the manifestation of systemic autoimmunity is glomerulonephritis (GN). However, tubulointerstitial inflammation (TII)—and not GN—predicts progression to end stage renal disease (ESRD). Lupus TII is associated with a local immune response very different than the inflammation observed in glomeruli. These observations indicate that *in situ* immunity is a central pathogenic mechanism of lupus nephritis. Recently, we developed computational pipelines by training and implementing several deep learning models to identify cells and cellular spatial relationships in biopsies from lupus nephritis patients. When applied to confocal micrographs of renal tissue, this analytic approach revealed discrete *in situ* inflammatory states in lupus nephritis which differed in cellular constituency, spatial architecture and prognosis. These observations demonstrate the utility of studying *in situ* immunity to both identify prognostic groups and therapeutic targets. In follow up studies, we are using high dimensional confocal microscopy to capture the full complexity of lupus nephritis *in situ* immunity innate and adaptive immunity in order to identify those immunological pathways that lead to fibrosis and renal failure.

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Lupus Nephritis

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VOCLOSPORIN IS EFFECTIVE IN ACHIEVING PROTEINURIA TREATMENT TARGETS IN LUPUS NEPHRITIS DEFINED BY EULAR/ERA RECOMMENDATIONS

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Background Pooled data from the Phase 2 AURA-LV and Phase 3 AURORA 1 studies demonstrated that adding voclosporin, a novel calcineurin inhibitor, to mycophenolate mofetil