PO.5.98 GLOMERULAR ACTIVITY AT SECOND KIDNEY BIOPSY PREDICTS OF END-STAGE KIDNEY DISEASE IN A LARGE MULTI-CENTRIC COHORT OF PATIENTS WITH ACTIVE LUPUS NEPHRITIS

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Purpose To investigate second kidney biopsy as predictor of end-stage kidney disease (ESKD) in active lupus nephritis (LN).
Methods Patients with biopsy-proven LN (ISN/RPS 2003) who had undergone a second kidney biopsy between January 1990 and December 2018 were included. Clinical and histological findings at first and at second biopsy were analyzed with Cox proportional hazard models to predict ESKD, defined as start of kidney replacement therapy. Survival curves were calculated with Kaplan-Meier method.
Results Ninety-two LN patients were included, 87% females, mean follow-up 17.9±10.1 years. Reasons for second kidney biopsy encompassed nephritic flares (n=28, 30.4%), proteinuric flares (n=46, 50.0%) or lack of renal response (n=18, 19.5%). A distinct group of 16 patients undergoing second renal biopsy as per protocol after achievement of at least partial renal response at 6 months or complete response at 12 months (defined according to EULAR criteria) were separately investigated.

Class switch from first biopsy occurred in 50.5% of cases, mainly from non-proliferative towards proliferative classes. Class IV remained stable in over 50.0% of cases. Twenty-five patients (27.2%) developed ESKD, mostly belonging to the nephritic flare group (17/28, 60.7%). Independent predictors of ESKD at second biopsy were activity index (AI; HR 95% CI 1.20 [1.03–1.41], p=0.022), chronicity index (CI; 1.41 [1.09–1.82], p=0.008) and 24h-proteinuria (1.22 [1.04–1.42], p=0.013). AI≥2 (log-rank p=0.03), CI>4 (log-rank p=0.001), or proteinuria≥3.5 g/day (log-rank=0.009) identified thresholds for higher ESKD risk. In a subgroup analysis exploring itemized scoring for renal histology, glomerular activity and tubular chronicity mostly accounted for AI and CI association with ESKD (1.38 (1.03–1.86, p=0.032 and 1.62 (0.92–2.82), p=0.09, respectively). Within glomerular activity, presence of subendothelial deposits was independently associated with ESKD (4.8 (1.13–16.3) p=0.033). Conversely, no histological or laboratory predictors emerged at first biopsy (95%CI): AI: 0.88–1.19; CI:0.66–1.20; proteinuria 0.85–1.08.

Within the protocol biopsy group, 18.7% developed ESKD. These patients displayed persistent histological activity at the second biopsy (AI>2), confirming that clinical remission does not invariably correspond to histological remission. Due to the small sample size, no independent predictors of ESKD in this group were identified.
Conclusions We show that both high activity and chronicity at second, but not at first kidney biopsy predict ESKD in patients with LN and lack of response or flaring after standard therapy. Besides, proteinuria is confirmed as an independent damaging factor for the kidney which may benefit from additional normalizing approaches. Patients reaching a renal clinical response may harbor active histological lesions which likely impact on their long-term prognosis. Altogether, our data identify easy-to-interpret parameters at second kidney biopsy which may significantly affect patient outcome, submitting repeated biopsy as a useful tool to improve prognostic stratification and prevent long-term deterioration of renal function.

PO.5.99 DRUG REPURPOSING FOR TREATING LUPUS NEPHRITIS BASED ON TRANSCRIPTOME PROFILING AND AUTOIMMUNITY-RELATED SEROLOGICAL MARKERS

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Purpose Lupus nephritis (LN) is one of the most severe organ manifestations of systemic lupus erythematosus (SLE) and constitutes an important cause of morbidity and death among patients with SLE. The associated renal injury, and ultimately damage, is the result of an immune-mediated process which involves leukocytes, immune complexes, complement and cytokines. We investigated expression quantitative trait loci (eQTLs), the transcriptome and autoimmunity-related cytokines and autoantibodies in patients with LN to gain insights into pathogenesis and identify drug targets.
Methods We analysed differentially expressed genes (DEGs), pathways and their druggability via the Drug Gene Interaction database (DGIdb) in active LN (n=41) versus healthy controls (HC; n=497), and eQTLs in active or past LN (n=87), based on validated (identified in two independent SLE populations) DEGs in SLE (n=350) vs HC (n=497), in whole blood collected within the frame of the European PRECISESADS consortium. Genome-wide RNA-sequencing and genotyping was previously performed by Illumina assays, and serum levels of 17 cytokines and 18 autoantibodies were analysed using a Luminex assay, ELISA, IDS-iSYS and SPAPLUS analyser (Barturen et al. 2021).
Results A total of 6869 significant and validated DEGs were identified in active LN patients compared with HC. Of these, 1010 validated DEGs were tagged to 34 KEGG pathways including 24 DEGs with a fold change (FC) <0.66 or > 1.5, genes of 18 cis-eQTLs and 3 trans-eQTLs, and 1 gene from cytokines that differed significantly between active LN and HC. Moreover, 2446 validated DEGs were tagged to 216 Reactome pathways included 85 DEGs with a FC <0.66 or > 1.5, genes of 21 cis-eQTLs and 5 trans-eQTLs, and 1 gene from cytokines that differed significantly between active LN and HC. These genes could be targeted by 203 different drugs, with the proteasome inhibitor bortezomib interfering with cathepsin B (CTSB) regulation and cyclophosphamide interfering with the regulation of tumour necrosis factor receptor superfamily member 1A (TNFRSF1A) being of particular interest.
Conclusions Integrated multilevel omics analysis in LN revealed a set of enriched pathways of potential interest for future drug investigation. A prospect for proteasome inhibition was implicated.