patients with distinct classes of lupus nephritis and their association with clinical and histopathological features.

**Methods** Quantification of IFN-I and defensin-α3 transcripts was performed in kidney biopsies from 24 patients with various classes of lupus nephritis (6 class III, 14 class IV, 4 class V) and 3 control samples by real-time PCR. Demographic characteristics, creatinine levels, and histopathological characteristics, including activity and chronicity indices, presence of active glomerular lesions, and tubulointerstitial or vascular involvement were analyzed.

**Results** IFNα2 and β transcripts were overexpressed in renal tissues from patients with proliferative forms of lupus nephritis (III/IV) compared to patients with membranous nephritis and control kidneys. Such difference was not detected between membranous nephritis and control biopsies. Defensin-α3 transcripts, overexpressed in lupus nephritis biopsies – particularly those with segmental necrotizing lesions - were correlated with higher activity index (r=0.61, p=0.02). Patients with proliferative lupus nephritis with impaired renal function, as attested by elevated creatinine levels, displayed higher relative expression of IFNα2 transcripts in renal tissues compared to those with normal renal function (26.6 ±18.0 vs. 7.1 ±6.2, p=0.013).

**Conclusion** IFN-I transcripts are produced locally in kidneys from patients with the proliferative, but not membranous, forms of lupus nephritis in association with impaired renal function. Neutrophil transcript defensin-α3 is a potential biomarker for increased renal pathologic activity. These findings provide insight into mechanisms of proliferative lupus nephritis and could impact therapeutic decisions in clinical practice.

### Lupus Nephritis

**1111 TYPE I INTERFERON AND NEUTROPHIL TRANSCRIPTS IN LUPUS NEPHRITIS RENAL BIOPSIES: CLINICAL AND HISTOPATHOLOGICAL ASSOCIATIONS**

1-3 Clio P Mavragani, 1 Kyrkiakos A Kirou, 5 Surya V Seshan, 1 Mary K Crow, 1 Mary Kirkland Center for Lupus Research, Hospital for Special Surgery and Weill Cornell Medical College, NY, NY, 10021, USA; 2 Department of Physiology, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

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**Objectives** To investigate the expression of type I interferon (IFN-I) and neutrophil transcripts in kidney tissue from patients with lupus nephritis.

**Methods** AURA-LV and AURA 1 enrolled patients with biopsy-proven active lupus nephritis (Class III, IV, or V ± III/IV) and proteinuria ≥1.5 mg/mg (≥2 mg/mg for Class V). Pooled data included 268 patients in the voclosporin arm and 266 patients in the control arm; all patients received MMF (target dose 2 g/day) and low-dose steroids (target dose 2.5 mg/day by week 16 according to protocol-defined steroid taper). We assessed the following EULAR/ERA treatment targets: ≥25% reduction in urine protein creatinine ratio (UPCR) at 3 months, ≥50% reduction in UPCR at 6 months, UPCR ≤0.7 mg/mg at 12 months, and steroid dose ≤7.5 mg/day at 12 months.

**Results** After 3 months of treatment, 78.4% of patients in the voclosporin arm and 62.4% of patients in the control group achieved ≥25% reduction in UPCR (odds ratio [OR] 2.25; 95% confidence interval [CI] 1.52, 3.33; p< 0.0001). The percentage of patients achieving a reduction of ≥50% in UPCR at 6 months was significantly greater in the voclosporin arm (66.0% vs 47.0%, respectively; OR 2.24; CI 1.57, 3.21; p< 0.0001). At 12 months, 52.6% and 33.1% of the voclosporin and control arm, respectively, achieved a UPCR ≤0.7 mg/mg (OR 2.52; CI 1.75, 3.63; p< 0.0001). A total of 89.6% and 82.8% of patients in the voclosporin and control arm, respectively, had reached the recommended steroid dose of ≤7.5 mg/day at 12 months. The proportion of patients achieving a UPCR ≤0.7 mg/mg and having a steroid dose ≤7.5 mg/day at 12 months was 44.4% in the voclosporin arm and 27.1% in the control arm (OR 2.42; CI 1.66, 3.53; p< 0.0001).

**Conclusions** The addition of voclosporin to a background regimen of MMF and low-dose steroids resulted in significantly higher complete renal response rates at 24 weeks in AURORA-LV (32.6% vs 19.3%; odds ratio [OR] 2.03; p=0.045) and 52 weeks in AURA 1 (40.8% vs 22.5%; OR 2.65; p< 0.0001). The complete renal response rates at 24 weeks in AURORA 1 (40.8% vs 22.5%; OR 2.65; p< 0.0001) in patients with lupus nephritis.

**Intro/Background** A decline of urine protein-to-creatinine ratio (UPCR) to < 0.5 is associated with better long-term preservation of kidney function in lupus nephritis (LN). UPCR < 0.5 defines complete response in guidelines and clinical trials when achieved after 1 or 2 years. Biomarkers of early response are needed to guide early treatment changes. We studied longitudinal urine proteomic profiles in LN to identify early predictors of proteinuric response.

**Methods** We quantified 1200 biomarkers (Kiloplex, RayBiotech) in urine samples collected on the day of (73%) or within 3 weeks (27%) of kidney biopsy and week 12, 24, or 52 in LN patients (ISN class III, IV, V, or mixed) with proteinuria > 1 g/d. Response was defined at one year from renal biopsy: Complete = UPCR <0.5, serum creatinine (sCr) <125% of baseline, prednisone ≤ 10mg/d; Partial = UPCR < 50% from baseline but >0.5, sCr <125% of baseline, but
Abstract 1112 Figure 1 Proteins linked to intrarenal activity (NIH activity index) decrease in treatment responders. Volcano plot of the changes of the urinary proteomic profile of treatment responders at 3 months (A) after kidney biopsy/treatment compared to baseline at time of biopsy. (B) Volcano plot displaying the Spearman’s correlation coefficients of urinary biomarkers at time of biopsy with histological activity defined as the NIH activity index. Blue arrows indicate 4 examples of shared urinary biomarkers that indicate both intrarenal activity and response to treatment. FDR, false discovery rate; q, adjusted p value.

Abstract 1112 Figure 2 Changes in specific urinary biomarkers at 3 months predict 1-year response better than proteinuria (urine protein-to-creatinine ratio, UPCR). Analyses for all patients and for proliferative LN only are summarized and A-B and C-D, respectively. (A, C) Volcano plots displaying the area under the curve (AUC) indicating the performance of a change of a biomarker at 3 months compared to the urine sample collected at time of kidney biopsy. For reference, UPCR (the current clinically used biomarker) is indicated in red. (B, D) ROC curves comparing the performance of a decline at 3 months of UPCR and urinary biomarkers. FDR, false discovery rate. q, adjusted p value.
Lupus Nephritis

THE TRANSCRIPTOMIC LANDSCAPE OF NEPHRITIC KIDNEYS REVEALS MECHANISMS FOR END ORGAN RESISTANCE TO DAMAGE IN LUPUS-PRONE MICE

Andrea R Daamen, Hongyang Wang, Prathyusha Bachali, Nan Shen, Kathleen M Kingsmore, Robert D Robl, Amrie C Grammer, Shu Man Fu, Peter E Lipsky.

1AMPEL BioSolutions LLC, Charlottesville, Virginia, USA; 3Division of Rheumatology; Department of Medicine, University of Virginia School of Medicine; Charlottesville, VA 22908; USA; 2Center for Immunity, Inflammation, and Regenerative Medicine; Department of Medicine, University of Virginia School of Medicine, Charlottesville, VA 22908; USA; 4Division of Rheumatology; Department of Medicine, University of Virginia School of Medicine, Charlottesville, VA 22908; USA; 5Shanghai Institute of Rheumatology, Renji Hospital, Shanghai, China. 10.1136/lupus-2022-lupus21century.78

Background Pathologic inflammation is a major driver of kidney damage in lupus nephritis (LN), but the immune mechanisms of disease progression and risk factors for end organ damage are poorly understood. Previous studies established the NZM2328 lupus-prone mouse strain as a model for human proliferative glomerulonephritis (GN). These studies determined that disease in female NZM2328 mice presents in acute (AGN) and chronic (CGN) stages, each of which was associated with genetic loci (Agnz1 and Cgnz1). In addition, male mice and the congenic NZM2328.R27 strain were found to be resistant to the development of chronic nephritis. To characterize molecular profiles through the development of LN, we carried out gene expression analysis of micro-dissected kidneys from lupus-prone NZM2328 mice at different stages of disease severity and examined male and R27 mice as a means to define pathogenic processes associated with disease progression. Gene expression analysis of human LN patients was carried out to determine whether similar molecular profiles could be identified in human LN kidneys.

Methods Kidneys from NZM2328 and R27 mice were harvested and the stage of GN was confirmed by histological classification at regular intervals of disease progression. Tissues from young mice, before disease development, were used as a control for diseased mice. Laser capture microdissection was used to isolate glomeruli and tubulointerstitial tissue from control and diseased mice. Total RNA was extracted and hybridized to Affymetrix Mouse Clariom D (NZM2328 and R27 female) or Mouse 430 v2.0 (NZM2328 male) arrays. Differential expression (DE) analysis, gene set variation analysis (GSVA), and linear regression were utilized to define the stages of GN in NZM2328 mice and identify immune populations and processes associated with disease progression. Human orthologs of selected murine gene signatures were utilized for GSVA of two gene expression datasets from kidneys of human LN patients.

Results Gene expression profiling identified a continuum of inflammatory processes associated with progression from acute inflammatory to chronic destructive disease initiated in the glomeruli and progressing to the tubules. AGN mice exhibited evidence of immune cell infiltration including enrichment of inflammatory M1-like macrophages and activated lymphocytes (figure 1). We also uncovered a newly recognized transitional (TGN) stage in which we observed the greatest level of immune activity and that served as a critical checkpoint driving progression to the CGN stage and de-enrichment of kidney tissue cells. Male mice exhibited minimal immune infiltration in the glomeruli resulting in non-progressive renal pathology. Immune infiltrates in the glomeruli of R27 mice expressed a regulatory gene signature and especially a dominance of M2-like macrophages. Moreover, R27 mice manifested an enhanced kidney tubule signature, with evidence of increased mitochondrial and metabolic activity consistent with a functional resistance to cellular damage. The robust tubule signature was associated with the absence of an immune/inflammatory gene signature. Numerous genes in the R27 genetic region were upregulated in NZM2328 nephritic kidneys and could contribute to the protective effect of this interval on the evolution of LN. The gene expression profiles of human LN were similar to those noted in the NZM2328 mouse suggesting comparable stages of LN progression.

Conclusion Transcriptome analysis revealed distinct immune profiles for AGN, after initial IC deposition in the kidney glomerulus, TGN in which inflammatory cell and pathway enrichment is at its peak, and CGN in which the accumulated insults result in irreversible damage to the kidney tissue. In addition, we identified distinct mechanisms of resistance to chronic disease based on differences in gender and genetics. Using a gene expression-based clustering approach, we identified a core set of gene signatures able to classify disease stage.