Background: 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 [1]. The associated renal injury, and ultimately damage, is the result of an immune-mediated process which involves leukocytes, immune complexes, complement, and cytokines [2].

Objectives: 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 [1]. The associated renal injury, and ultimately damage, is the result of an immune-mediated process which involves leukocytes, immune complexes, complement, and cytokines [2].

Methods: We analysed differentially expressed genes (DEGs), pathways and their drugability via the Drug Gene Interaction database (DGIdb) [3] 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 [4]. Genome-wide RNA-sequencing and genotyping was previously performed by Illumina assays, and serum levels of 17 cytokines and 17 autoantibodies were analysed using a LumineX assay, ELISA, IDS-lys and SAPAPLUS analyser [4].

Results: A total of 6 869 significant and validated DEGs were identified in active LN patients compared with HC. Of these, 1010 validated DEGs were tagged to 216 Reactome pathways including 24 DEGs with an |fold change (FC)| > 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 (CTS B) regulation and cyclophosphamide interfering with the regulation of tumour necrosis factor receptor superfamily member 1A (TNFRSF1A) being of particular interest.

Conclusion: 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.

REFERENCES:

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Disclosure of Interests: None declared

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TRANSSCRIPTOME PROFILING AND AUTOIMMUNITY-RELATED SEROLOGICAL MARKERS IDENTIFY TPS5 AND C3AR AS DRUG TARGETS IN NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

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Results: The primary results of the APRIL-SLE study – the effect of atacicept compared to placebo in preventing new flares in patients with moderate-to-severe SLE – have been reported (Isenberg et al., 2013). We performed a post hoc analysis to describe the effect of atacicept compared to placebo on measures of renal function in patients with SLE; this effect has not been reported previously.

Methods: The APRIL-SLE study excluded patients with moderate to severe glomerulonephritis, as defined by either of the following: urinary protein/creatinine ratio (UPCR) >1 mg/mg and/or hematuria or a significant renal impairment as defined by estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m². Patients with proteinuria and mild to moderate chronic kidney disease, as assessed by KDIGO criteria were eligible. UPCR and eGFR were measured at baseline, week 2, and then every 4 weeks until week 52. The median change from baseline to each of these timepoints was calculated for eGFR and UPCR using the Safety Analysis Set, comprised of all randomized patients who received at least 1 dose of study medication. Enrollment in the atacicept 150 mg group was discontinued prematurely due to 2 deaths from pneumonias. When treatment was discontinued, 62 of 144 patients in this group had completed 52 weeks of treatment; 27 other patients had already been withdrawn for various reasons; and, in the remaining 55 patients, treatment was stopped early as a safety precaution. Patients in the other two groups completed the protocol.

Results: In total, 111 patients in the placebo group, 112 patients in the atacicept 75 mg group, and 62 patients in the atacicept 150 mg group completed 52 weeks of treatment. The eGFR time course was stable for the atacicept groups compared to a 4.4% decline in the placebo group from baseline at week 52 (Figure 1 and Table 1). UPCR from baseline at week 52 declined in the atacicept groups and increased in the placebo group.

Table 1. Median Percent Change from Baseline of Estimated Glomerular Filtration Rate (eGFR) and Proteinuria at Week 52 – Safety Analysis Set

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Atacicept 75 mg</th>
<th>Atacicept 150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (mL/min)</td>
<td>n=110</td>
<td>n=111</td>
<td>n=62 *</td>
</tr>
<tr>
<td>median</td>
<td>-4.35</td>
<td>-1.49</td>
<td>0.57</td>
</tr>
<tr>
<td>UPCR (mg/mg)</td>
<td>n=108</td>
<td>n=108</td>
<td>n=63</td>
</tr>
<tr>
<td>median</td>
<td>6.29</td>
<td>-6.27</td>
<td>-12.72</td>
</tr>
<tr>
<td>UPCR (mg/mg) *</td>
<td>n=12</td>
<td>n=15</td>
<td>n=8</td>
</tr>
<tr>
<td>median</td>
<td>26.11</td>
<td>-54.42</td>
<td>-12.15</td>
</tr>
</tbody>
</table>

*Among patients with screening UPCR ≥0.2 mg/mg. *Enrollment in the atacicept 150 mg arm was discontinued prematurely (described in Isenberg et al., 2015).

Conclusion: Results from this double-blind, placebo-controlled, Phase 2 study suggest a potential for improved renal function with atacicept treatment of patients with moderate-to-severe SLE.

REFERENCES:

Disclosure of Interests: David Isenberg Consultant of: Professor Isenberg has consulted for Verax, Servier, Asta-Zeneca, Idorsia, Merck Serono, and Amgen. His honoraria are passed onto a local arthritis charity. Celia J. Fin Shareholder of: Dr. Fin is an employee of Vera Therapeutics, Inc., Employee of: Dr. Fin is an employee of Vera Therapeutics, Inc., Amy Kao Shareholder of: Dr. Kao own stocks of Merck KGaA, Darmstadt, Germany, Employee of: Dr. Kao is an employee of EMD Serono Research & Development Institute, Inc (a business of Merck KGaA), Aida Arsalan Aydemir Employee of: Ms. Aydemir is an employee of EMD Serono Research & Development Institute, Inc (a business of Merck KGaA), Caroline Gordon Speakers bureau: Dr. Gordon reports personal fees for speakers bureau from UCB, Consultant of: Dr. Gordon reports personal fees for honoraria from consultancy work from the Center for Disease Control and Prevention, Amgen, Astra-Zeneca, AbbVie, EMD Serono, MGP, Sanofi, and UCB, Grant/research support from: Dr. Gordon reports an educational grant from UCB to Sandwell and West Birmingham Hospitals NHS Trust that supported previous research work unrelated to any specific drug (last payment July 2019).