eGFR remained stable throughout the study period and the significant and meaningful reductions in proteinuria achieved in AURORA 1 were maintained. These data provide evidence of a long-term treatment benefit of VCS in patients with LN.

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Abstract 1202 Figure 1 LS Mean eGFR over Time. Analysis of AURORA 2 patients includes data from pre-treatment baseline of AURORA 1, 12 months in AURORA 1 and up to 25 months in AURORA 2 (including 4-week post-treatment visit). Renal function assessed with corrected eGFR (Chronic Kidney Disease Epidemiology Collaboration equation) using a prespecified ceiling of 90 mL/min/1.73 m². CI, confidence interval; eGFR, estimated glomerular filtration rate; FUP, follow-up visit (4-week post-treatment visit); LS Mean, least squares mean.

Abstract 1202 Table 1 Overall Summary of Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Control (n=100)</th>
<th>Voclosporin (n=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Any AE</td>
<td>80 (80.0)</td>
<td>100 (86.2)</td>
</tr>
<tr>
<td>Treatment-related AE</td>
<td>21 (21.0)</td>
<td>28 (24.1)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>23 (23.0)</td>
<td>21 (18.1)</td>
</tr>
<tr>
<td>Serious Treatment-related AE</td>
<td>2 (2.0)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>AE Leading to Study Drug Discontinuation</td>
<td>17 (17.0)</td>
<td>11 (9.5)</td>
</tr>
<tr>
<td>Death*</td>
<td>4 (4.0)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related Death</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*The four deaths in the control arm were due to pulmonary embolism (n=1) and coronavirus infection (n=3). Includes adverse events starting on or after the first dose of study drug in AURORA 2 up to 30 days after the last dose and all events of death reported during study follow-up. Adverse events were aggregated by System Organ Class and Preferred Term and coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0. AE, adverse event.

BLOCKADE OF THE MECHANISTIC TARGET OF RAPAMYCIN ELICITS RAPID AND LASTING IMPROVEMENT OF DISEASE ACTIVITY THROUGH RESTRAINING PRO-INFLAMMATORY T CELL LINEAGE SPECIFICATION IN PATIENTS WITH ACTIVE SLE


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Background Systemic lupus erythematosus (SLE) patients exhibit proinflammatory lineage development in the immune system that has been attributed to mechanistic target of rapamycin (mTOR) activation. Moreover, mTOR activation has also been shown in resident cells of tissues affected by end-organ damage. Therefore, safety, tolerance, and efficacy of rapamycin were examined in prospective 1 and retrospective biomarker-driven clinical trials 2,3.

Methods 40 patients having active disease and unresponsive or intolerant to conventional medications were enrolled in a prospective study 1. Sirolimus was started at 2 mg/day with dosage adjusted to tolerability and 6-15 mg/mL trough levels. Disease activity was evaluated by BILAG, SLEDAI, and prednisone use over 12 months. Blood samples of 56 matched healthy subjects were obtained as controls for...
immunometabolic outcomes monitored at each visit. The effects of sirolimus was also investigated retrospectively in 73 patients with or without nephritis and 187 patients with lupus nephritis.

**Results**

As primary clinical efficacy endpoint, SLEDAI disease activity scores were reduced over 12 months in 16/29 patients (55%). 19/29 patients (65.5%) met criteria for SLE Responder Index (SRI). Arthritis, rash, pyuria, and hypocomplementemia improved among SLEDAI components, while cardiopulmonary, musculoskeletal, mucocutaneous, and vasculitis BILAG organ-domain scores also declined. Prednisone use diminished from 24.3±4.7 mg/day to 7.2±2.3 mg/day (p<0.0009). Sirolimus expanded CD4+CD25+FoxP3+ Tregs and CD8+ memory T cells and inhibited IL-4 and IL-17 production by CD4+ and CD4-CD8- double-negative T cells after 12 months. CD8+ memory T cells were selectively expanded in SRI- responders.

In 12 patients of 73 patients who had lupus nephritis, proteinuria (p=0.0287), hematuria (p=0.0232), anti- DNA antibody levels (p=0.0028) and steroid use were reduced (p=0.0200). In the non-renal cohort of 61 patients, anti-DNA antibody levels (p=0.0332) and steroid use were reduced (p=0.0163). Both in the renal and non-renal cohorts, C3 (renal p=0.0070; non-renal p=0.0021) and C4 complement levels were increased (renal p=0.0063; non-renal p=0.0042)

Adverse effects of mouth sores (2/73), headaches (1/73), and gastrointestinal discomfort were noted in a minority of patients (6/73). Sirolimus was only discontinued in two of 73 patients due to headache and recurrent infections.

The retrospective study of 187 LN patients evaluated mTOR activation in renal tissue of 187 LN patients in comparison to 20 diabetic nephropathy (DN) patients, 10 minimal change disease (MCD) patients, and 10 normal controls (NCs). mTOR complexes 1 and 2 (mTORC1/2) were activated in podocytes, mesangial cells, endothelial cells and tubular epithelial cells of LN patients as compared with those with MCD or NC. The glomerular mTORC1 activation was higher in LN patients compared with DN patients. mTORC1, but not mTORC2, activation strongly correlated with crescent formation, interstitial inflammation and fibrosis and serum albumin, complement C3, and proteinuria. mTORC1 activation was identified as a prognostic marker in LN patients.

**Conclusions**

These studies suggest that sirolimus is well tolerated and exerts long-term therapeutic efficacy in controlling renal and non-renal manifestations of SLE. Renal mTORC1 activation may predict clinical prognosis and therapeutic response to sirolimus in patients with LN.

**Acknowledgements**

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Improving lymphatic function to reduce B cell responses in lupus

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Abstract

Background In SLE, that ultraviolet radiation exposure can induce both photosensitive skin responses and increased autoantibody titers suggests a critical and targetable role for the communication from skin to draining lymph nodes in regulating lymph node B cell responses. Lymphatic vessels bring cells and signals from skin to draining lymph nodes to regulate immunity and dysfunction of lymphatic flow has the potential to alter immunity. Here we examine lymphatic flow function in SLE humans and models, showing that lymphatic flow from skin to lymph nodes is compromised. That improving lymphatic flow by manual lymphatic drainage (MLD) or in a transgenic model reduces lymph node B cell responses, and delineate the mechanistic underpinnings of how lymphatic flow modulates draining lymph node function.

Methods We examined lymphatic vessel luminal area considered to be reflective of lymphatic flow function in healthy controls, SLE, and control disease (anti-phospholipid antibody + non-SLE patients) by immunohistochemistry and image analysis. We examined lymphatic function and performed manual lymphatic drainage in both MRL/lpr and imiquimod-induced lupus models. Lymphatic function was assessed by Evans blue tissue clearance assays and lymph node function was assessed by mainly by flow cytometry. Lymphatic flow was improved by either manual lymphatic drainage, adapted to mice based on techniques used in humans, or in a transgenic PTEN+/ Flt4-CreKR model with increased lymphatic numbers and function.

Results SLE patient skin showed increased lymphatic vessel lumen size in skin and multiple SLE mouse models showed reduced clearance of intradermally-injected Evans blue, both suggesting reduced lymphatic flow in SLE. Improving lymphatic flow by manual lymphatic drainage (MLD) or in imiquimod-treated PTEN+/ Flt4-CreKR mice reduced both cutaneous photosensitivity and lymph node germinal center and plasma cells.

Mechanistically, improved flow restrains B cell responses by upregulating lymph node fibroblastic reticular cell CCL2, which modulates monocye phenotype to limit germinal center and plasma cell numbers.

Conclusions Our results suggest a scenario whereby dysfunctional communication between the skin and the immune system alters lymph node function to modulate disease, point to a lymphatic flow-lymph node stromal axis as a therapeutic target, and suggest the possibility of manual lymphatic drainage, an existing treatment modality used in breast adjunctive treatment in SLE.