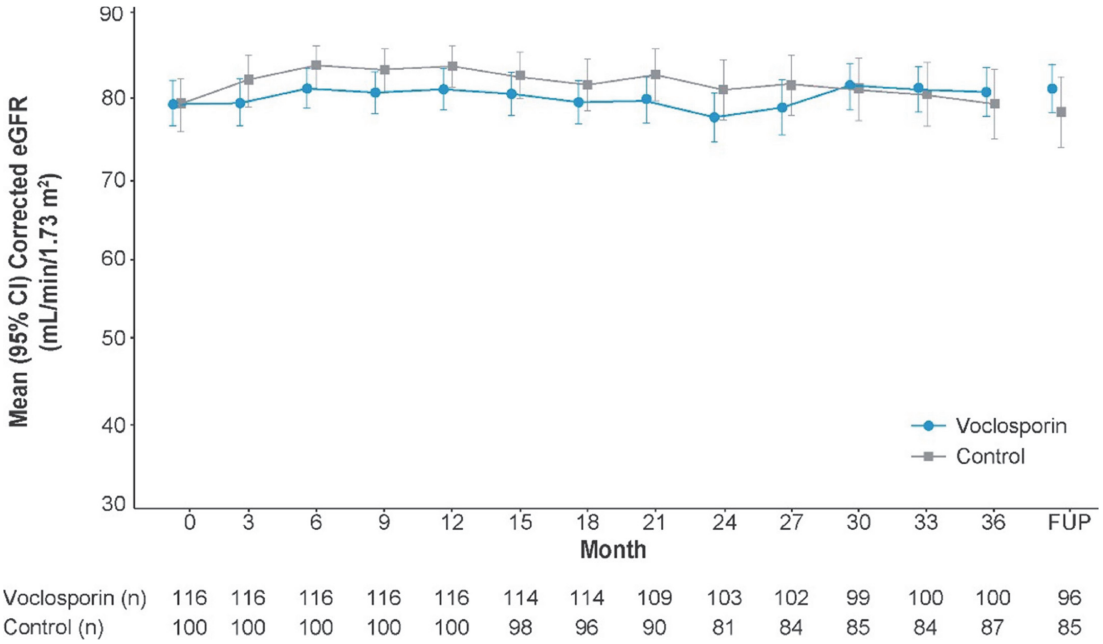

Abstract 1202 Figure 1 LS Mean eGFR over Time. Analysis of AURORA 2 patients includes data from pre-treatment baseline of AURORA 1, 12 months in AURORA 1 and up to 25 months in AURORA 2 (including 4- week post-treatment visit). Renal function assessed with corrected eGFR (Chronic Kidney Disease Epidemiology 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

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

*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.

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.

Disclosures AS reports payments for Aurinia Pharmaceuticals Inc. speaker bureaus; primary investigator for Aurinia Pharmaceuticals Inc. clinical trials; advisory fees from Eli Lilly, AstraZeneca, GlaxoSmithKline and Kezar Life Sciences. YKOT reports research grants from commercial organizations including an unrestricted research grant from GlaxoSmithKline and Aurinia Pharmaceuticals Inc.; primary investigator for Aurinia Pharmaceuticals Inc. clinical trials; consultancy fees paid to institution from Aurinia Pharmaceuticals Inc., Novartis, GlaxoSmithKline, KezarBio, Vifor Pharma and Otsuka Pharmaceuticals. CC, NE, and HL are employees and shareholders of Aurinia Pharmaceuticals, Inc. HL is an employee and shareholder of Aurinia Pharmaceuticals, Inc. Data first presented by Saxena A et al. at the EULAR Congress June 1-4, 2022. Editorial support provided by MediComm Partners Ltd. Aurinia Pharmaceuticals Inc. provided funding for the study and presentation.

1203 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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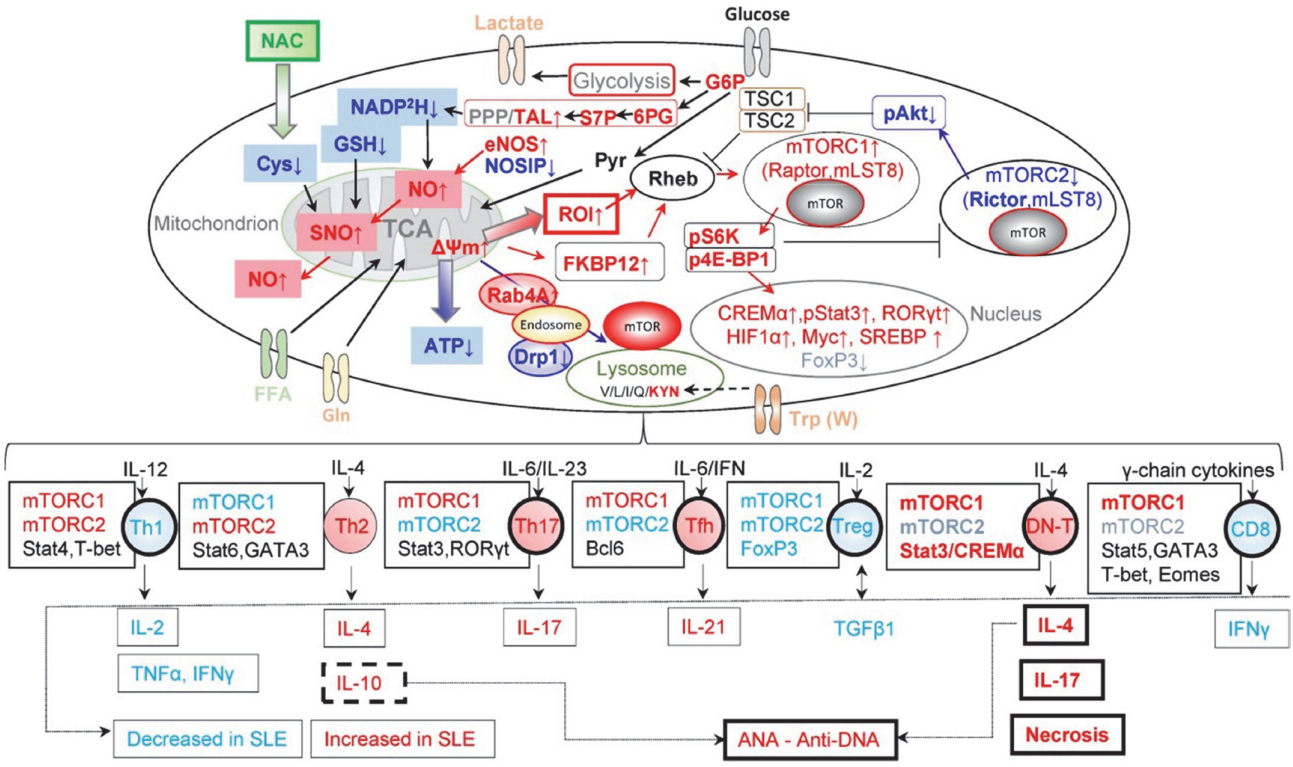
Background Systemic lupus erythematosus (SLE) patients exhibit proinflammatory lineage development in the immune system that has been attributed to mechanistic target of rapamycin (mTOR) activation. Moreover, mTOR activation has also been shown in resident cells of tissues affected by end-organ damage. 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 tolerance and 6-15 ng/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



Abstract 1203 Figure 1 Metabolic control of pro-inflammatory T-cell lineage specification in SLE. Schematic molecular order of pathways upstream and downstream of activation of the mechanistic target of rapamycin (mTOR) in SLE. mTOR is activated on the surface of lysosomes in a state of amino acid sufficiency (V/L/I/Q/Kyn)[4]. Oxidative stress, in particular cysteine oxidation, also activates mTORC1 through association with Rheb[5]. Given the results of our randomized double-blind placebo-controlled clinical trial showing that therapeutically effective reversal of GSH depletion by NAC blocks mTORC1 *in vivo*[6], GSH depletion will be considered the primary metabolic checkpoint of pro-inflammatory T-cell lineage specification in SLE. The depletion of GSH will be mechanistically connected to the depletion of cysteine (Cys) and NADPH and to the accumulation of kynurenine (Kyn) which have been uncovered by comprehensive metabolome studies of PBL from SLE and healthy subjects matched for age, gender, and ethnicity and processed in parallel [7]. Blockade of mTOR with rapamycin reverses the depletion of effector-memory CD8 T cells and Tregs and the expansion of pro- inflammatory CD4-CD8- double-negative T cells in patients with active SLE in vivo [1]. Red and blue arrows reflect direction of changes in SLE.

immunometabolic outcomes monitored at each visit. The effects of sirolimus was also investigated retrospectively in 73 patients with or without nephritis [2] and 187 patients with lupus nephritis [3].

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 [1].

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, respectively [2].

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) [3]. 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 suggests 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.

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WS1234172 from Pfizer and grants AI 048079, AI 072648, and AI 122176 from the National Institutes of Health and the Central New York Community Foundation.
Trial Registration Prospective Study of Rapamycin for the Treatment of SLE; ClinicalTrials.gov Identifier: NCT00779194. Treatment trial of SLE with N-acetylcysteine; ClinicalTrials.gov identifier: NCT00775476.
Lay summary Rapamycin, also called as sirolimus, has been newly identified as a new treatment with promising clinical effectiveness and well-defined mechanism of active in patients with moderate to severe SLE.

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Lupus-Targeted Therapeutics

1204 IMPROVING LYMPHATIC FUNCTION TO REDUCE B CELL RESPONSES IN LUPUS

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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 $PTEN^{f/f}$ $Flt4\text{-}Cre^{ER}$ 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 $PTEN^{f/f}$ $Flt4\text{-}Cre^{ER}$ 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 monocyte 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.

Lupus 21st Century 2022 Abstract

1205 TREATMENT OF LUPUS-PRONE BXSB MICE WITH A MODULATABLE CAR T CELL SYSTEM TARGETING CD19

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Chimeric antigen receptor (CAR) T cells directed against CD19 have demonstrated efficacy in treating active lupus in both human and mouse lupus. However, a significant limitation of this approach is immunodeficiency due to the long-term depletion of B cells. To address this issue, we studied the potential of a switchable CAR (sCAR) T cell system targeting CD19 to transiently eliminate B cells and provide therapeutic benefit with less immunosuppression. This approach consists of a CAR that, instead of targeting CD19 directly, binds to a soluble antiCD19 Fab switch with a short