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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