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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 auto-antibody 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^{fl/fl} Flt4-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^{fl/fl} Flt4-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

half-life, thereby allowing sCAR T cell killing only when the antiCD19 switch is present. Treatment of BXSB males with sCAR T plus continuous antiCD19 switch reduced B cell numbers, circulating immunoglobulins, autoantibodies, and nephritis. To document the efficacy of a shorter course of treatment, B6 mice were given three every other day doses of antiCD19 switch. There was depletion of virtually all CD19⁺ B cells and plasma cells from the bone marrow, spleen, and peritoneum, as well as most CD19⁺ plasma cells in the bone marrow and spleen. When BXSB males with active disease were similarly treated, there was a transient elimination of B cells and disease remission associated with about a 2-month prolonged survival. To address whether recurrence could be prevented by repeated sCAR T +antiCD19 treatment, BXSB males with active lupus were given an additional two cycles of antiCD19 switch at 60 and 138 days. Circulating B cells, IgM and IgG, and anti-chromatin levels were reduced after each switch cycle and increased in the intervening periods. Notably, proteinuria did not recur, and there were no deaths beyond day 8 after the start of treatment compared with 100% mortality in the sCAR T +PBS controls. These studies inform on the potential effectiveness and limitations of therapeutic depletion of B cells in SLE and suggest a possible strategy for employing CAR T cells to minimize immunosuppression.

1206

SPHINGOSINE 1-PHOSPHATE (S1P) REGULATION OF VASCULAR AND IMMUNE SYSTEMS: MECHANISMS AND THERAPEUTIC APPROACHES

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Metabolism of cellular membranes forms lipid mediators that activate their cognate G protein- coupled receptors (GPCR) to regulate cellular responses. Our laboratory has contributed to this area by cloning of the human cyclooxygenase-2 (COX-2) that produces prostanoids as well as cloning and deorphaning of the first S1P receptor (S1PR1). This GPCR is now the target of small molecule drugs that are approved to treat many autoimmune diseases, including multiple sclerosis and ulcerative colitis. Recent clinical trials are testing if S1PR1-targeted compounds are beneficial for systemic lupus erythematosus (SLE). Our recent studies on S1P have focused on S1P chaperones, which are defined as proteins that bind and present S1P to its GPCRs to direct specific signaling modes. Specifically, HDL-bound apolipoprotein M (ApoM) binds to S1P and regulates specific biological processes, such as maintenance of vascular endothelial cell (EC) barrier function, suppression of cytokine-induced inflammatory gene expression, EC survival and regulation of lymphopoiesis. HDL-bound S1P levels are decreased in SLE, sepsis, diabetes, aging and cardiovascular disease, and contributes to pathological processes by suppressing EC S1PR1 signaling. To develop a therapeutic strategy to enhance HDL-S1P/EC S1PR1 signaling axis that supports EC resilience, we engineered two recombinant fusion proteins – a soluble form (ApoM-Fc) and ApoA1-ApoM (A1M) that forms HDL-like nanoparticles. Recent work shows that A1M chaperones S1P as well as prostacyclin (PGI₂), enhances EC barrier function and suppress inflammatory processes *in vitro* and *in vivo*. ApoM-

bound S1P does not suppress lymphocyte egress suggesting that its large size prevents it from entering secondary lymphoid organs and acting as a functional antagonist to down-regulate lymphocyte S1PR1. Studies on chaperone bound S1P action on ECs during pathological changes will be presented. These mechanistic studies have deepened our understanding of S1P biology thus allows rational design of new therapeutic approaches to not only tame the immune system but also enhance vascular endothelial functions.

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Lupus Clinical Trials

1207

UPDATE ON PROGRESS OF THE MESENCHYMAL STROMAL CELL TRIAL IN REFRACTORY LUPUS

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Body There is a growing interest and use of cellular therapies in almost all fields of medicine. Mesenchymal stromal cells (MSCs) are pluripotent in their ability to differentiate in chondrocytes, adipocytes and osteoblasts. They more recently were reported to have significant immune activity, primarily by producing anti-inflammatory molecules. They can be derived from umbilical cords, adipose tissue and bone marrow primarily. Recent studies have tested their safety and efficacy in immune mediated diseases including graft versus host disease, inflammatory bowel disease and Type I diabetes among others. Reports of uncontrolled trials of MSCs in China suggest safety and efficacy of MSCs as treatment for refractory lupus. Based on encouraging results of a Phase I trial of 6 patients with lupus treated with MSCs, we initiated the first placebo- controlled trial of MSCs to treat lupus patients refractory to standard of care medications. There are nine participating centers across the US. The trial has two cohorts, one receiving low dose MSCs (one million cells/kg) and a high dose cohort of five million cells per kg, given as a one- time infusion. Patients then attend 10 follow-up visits over a year. Primary outcome is a decrease in the SRI of 4 at week 24. Inclusion criteria are patients with confirmed lupus refractory to 6 months of standard of care therapy defined by a SLEDAI of 6 or greater at screening. Exclusions were ongoing use of biologics, pregnancy, active infections, cancer, active CNS lupus or advanced renal disease. The first patient was screened in November of 2018. Patients are randomized with a 2/1 ratio of MSCs/placebo. Cohort 1 consisting of 41 patients was completed in May of 2021. We have infused 10 out of 40 patients in Cohort 2 to this point. Extensive studies of B cell, T cell, monocyte, dendritic cell and PMN number, function and phenotype are being performed. To this point there are no safety signals or concerns with DSMB reviews quarterly. There have been no SAEs