



Sirolimus in patients with clinically active systemic lupus erythematosus resistant to, or intolerant of, conventional medications: a single-arm, open-label, phase 1/2 trial

Zhi-Wei Lai, Ryan Kelly, Thomas Winans, Ivan Marchena, Ashwini Shadakshari, Julie Yu, Maha Dawood, Ricardo Garcia, Hajra Tily, Lisa Francis, Stephen V Faraone, Paul E Phillips, Andras Perl

Summary

Background Patients with systemic lupus erythematosus have T-cell dysfunction that has been attributed to the activation of the mammalian target of rapamycin (mTOR). Rapamycin inhibits antigen-induced T-cell proliferation and has been developed as a medication under the generic designation of sirolimus. We assessed safety, tolerance, and efficacy of sirolimus in a prospective, biomarker-driven, open-label clinical trial.

Methods We did a single-arm, open-label, phase 1/2 trial of sirolimus in patients with active systemic lupus erythematosus disease unresponsive to, or intolerant of, conventional medications at the State University of New York Upstate Medical University (Syracuse, NY, USA). Eligible participants (aged ≥ 18 years) had active systemic lupus erythematosus fulfilling four or more of 11 diagnostic criteria defined by the American College of Rheumatology. We excluded patients with allergy or intolerance to sirolimus, patients with life-threatening manifestations of systemic lupus erythematosus, proteinuria, a urine protein to creatinine ratio higher than 0.5, anaemia, leucopenia, or thrombocytopenia. Patients received oral sirolimus at a starting dose of 2 mg per day, with dose adjusted according to tolerance and to maintain a therapeutic range of 6–15 ng/mL. Patients were treated with sirolimus for 12 months. Safety outcomes included tolerance as assessed by the occurrence of common side-effects. The primary efficacy endpoint was decrease in disease activity, assessed using the British Isles Lupus Assessment Group (BILAG) index and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Blood samples of 56 matched healthy individuals were obtained as controls for immunobiological outcomes monitored at each visit. The primary efficacy endpoint was assessed in all patients who completed 12 months of treatment, and all patients who received at least one dose of treatment were included in the safety analyses. This trial is registered with ClinicalTrials.gov, number NCT00779194.

Findings Between March 9, 2009, and Dec 8, 2014, 43 patients were enrolled, three of whom did not meet eligibility criteria. 11 of the 40 eligible patients discontinued study treatment because of intolerance (n=2) or non-compliance (n=9). SLEDAI and BILAG disease activity scores were reduced during 12 months of treatment in 16 (55%) of 29 patients who completed treatment. Mean SLEDAI score decreased from 10.2 (SD 5.6) at enrolment to 4.8 (4.5) after 12 months of treatment ($p < 0.001$) and the mean total BILAG index score decreased from 28.4 (12.4) at enrolment to 17.4 (10.7) after 12 months of treatment ($p < 0.001$). The mean daily dose of prednisone required to control disease activity decreased from 23.7 mg (SD 9.6) to 7.2 mg (2.3; $p < 0.001$) after 12 months of treatment. Sirolimus expanded CD4⁺CD25⁺FoxP3⁺ regulatory T cells and CD8⁺ memory T-cell populations and inhibited interleukin-4 and interleukin-17 production by CD4⁺ and CD4⁺CD8⁻ double-negative T cells after 12 months. CD8⁺ memory T cells were selectively expanded in SRI-responders. Patient liver function and lymphocyte counts were unchanged. Although HDL-cholesterol ($Z = -2.50$, $p = 0.012$), neutrophil counts ($Z = -1.92$, $p = 0.054$), and haemoglobin ($Z = -2.83$, $p = 0.005$) were moderately reduced during treatment, all changes occurred within a range that was considered safe. Platelet counts were slightly elevated during treatment ($Z = 2.06$, $p = 0.0400$).

Interpretation These data show that a progressive improvement in disease activity is associated with correction of pro-inflammatory T-cell lineage specification in patients with active systemic lupus erythematosus during 12 months of sirolimus treatment. Follow-up placebo-controlled clinical trials in diverse patient populations are warranted to further define the role of mTOR blockade in treatment of systemic lupus erythematosus.

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Introduction

Systemic lupus erythematosus is a chronic inflammatory disease that primarily affects women of child-bearing age, with debilitating and potentially life-threatening consequences.¹ The disease represents an unmet medical need because the drugs that are

available are only partly effective and have considerable side-effects.² Consequently, 10% of patients with systemic lupus erythematosus die within 5 years of diagnosis.³ Although the cause of systemic lupus erythematosus is incompletely understood, it is thought to involve cellular dysfunction of the immune system

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Division of Rheumatology (Prof A Perl MD, Z-W Lai MD, R Kelly PhD, T Winans BSc, I Marchena MD, A Shadakshari MD, J Yu MD, M Dawood MD, R Garcia MD, H Tily MD, L Francis MD, Prof P E Phillips MD), Department of Psychiatry (Prof S V Faraone PhD), Department of Medicine (Prof A Perl, Z-W Lai, R Kelly, T Winans, I Marchena, A Shadakshari, J Yu, M Dawood, R Garcia, H Tily, L Francis, Prof P E Phillips), Department of Microbiology and Immunology (Prof A Perl), and Department of Biochemistry and Molecular Biology (Prof A Perl), State University of New York Upstate Medical University, Syracuse, NY, USA

Correspondence to:
Prof Andras Perl, Department of Medicine, State University of Upstate Medical University New York, Syracuse, NY 13210, USA
perla@upstate.edu

Research in context

Evidence before this study

An unmet need exists for treatment in systemic lupus erythematosus. Mammalian target of rapamycin (mTOR) activation has been identified as a driver of pro-inflammatory lineage skewing in the immune system. We searched PubMed for English language articles published between Jan 1, 2000, and Oct 13, 2017, using the search terms “sirolimus,” “rapamycin,” or “mTOR” and “lupus”. We found that research investigating the blockade of mTOR by sirolimus has been limited to a single retrospective study and two confirmatory case reports, which suggest that sirolimus has clinical efficacy in patients with systemic lupus erythematosus.

Added value of this study

This is the first prospective study of sirolimus in patients with systemic lupus erythematosus. This open-label study shows that

treatment with sirolimus is safe, with rapid and lasting improvement of disease activity after 12 months of treatment resulting from the blockade of pro-inflammatory T-cell lineage specification in patients with active systemic lupus erythematosus. The depletion of CD8 effector-memory T cells predicts therapeutic response, and the progressive restoration of this cell population occurs with clinical improvement.

Implications of all the available evidence

The results of this study show that sirolimus is potentially a safe and efficacious treatment in patients with active systemic lupus erythematosus who are unresponsive to, or intolerant of, conventional medications. The results warrant double-blind placebo-controlled follow-up studies with sirolimus alone or in combination with potentially synergistic interventions, such as acetylcysteine, in larger and more diverse patient populations.

For the **study protocol** see <https://clinicaltrials.gov/ct2/show/NCT00779194>

See **Online** for appendix

and the production of autoantibodies.¹ Activation of the mechanistic target of rapamycin (mTOR) has emerged as a key driver of abnormal lineage specification within the immune system,⁴ which has been attributed to metabolic stress in people with systemic lupus erythematosus.^{5–8} Although mTOR activation⁹ and its therapeutic reversal were originally identified in the T cells of patients with systemic lupus erythematosus,¹⁰ studies have also reported mTOR activation in parenchymal organs such as the liver in mice¹¹ and the kidneys in patients with antiphospholipid syndrome.¹²

mTOR is a serine-threonine kinase that takes its name after rapamycin, an antifungal antibiotic produced by *Streptomyces hygroscopicus*, a soil bacterium from Easter Island, known by its inhabitants as Rapa Nui.¹³ Rapamycin effectively inhibits antigen-induced T-cell proliferation,¹⁴ and has been developed as a medication to prevent organ transplant rejection under the generic designation of sirolimus.¹⁵ Sirolimus forms a high-affinity complex with its cellular receptor, FKBP12, a 12 kD protein that is overexpressed in lupus T cells.⁹ This complex of sirolimus and FKBP12 blocks mTOR activation.¹⁶ In vivo, sirolimus completely abrogated autoimmunity in lupus-prone mice,^{17,18} and blocked disease activity in a retrospective study of patients with systemic lupus erythematosus.¹⁰ We initiated this prospective study to assess tolerance, safety, and the metabolic, immunological, and therapeutic effect of sirolimus in patients with severe systemic lupus erythematosus who are intolerant of, or do not respond to, other conventional medications.

Methods

Study design and participants

We did a prospective, single-arm, open-label, phase 1/2 trial at the Division of Rheumatology, State University of New York Upstate Medical University (Syracuse, NY, USA) with approval from the institutional review board

and the US Food and Drug Administration (IND 101566). The study protocol is available online.

We assessed the safety and efficacy of sirolimus for patients with active systemic lupus erythematosus. We also obtained blood from a healthy control group matched with patients for age, sex, and ethnicity, and freshly isolated cells from healthy control participants were used in parallel as controls for immunological studies (appendix pp 3–9).

We enrolled patients aged 18 years or older with systemic lupus erythematosus that fulfilled four or more of 11 diagnostic criteria defined by the American College of Rheumatology.^{19,20} We anticipated that most patients enrolled in the study would have active disease (Systemic Lupus Erythematosus Disease Activity Index [SLEDAI] score ≥ 4)²¹ and were receiving prednisone 10 mg or more per day, but these were not formal inclusion criteria. Patients with allergy or intolerance to sirolimus, and patients with life-threatening manifestations of systemic lupus erythematosus (eg, cerebritis substantiated by inflammatory MRI lesions, catastrophic antiphospholipid antibody syndrome, rapid progressive glomerulonephritis requiring intravenous cyclophosphamide, or a glomerular filtration rate of < 40 mL/min) were excluded. Patients with proteinuria exceeding 500 mg/24 h, a urine protein to creatinine ratio higher than 0.5, anaemia (haemoglobin < 10 g/dL), leucopenia (white blood cell [WBC] count < 3000 cells per μ L), or thrombocytopenia (platelet count $< 100\,000$ cells per μ L) were excluded. Patients with a WBC count of 3000–3500 per μ L, haemoglobin concentration of 10–12 g/dL, or platelet counts of 100 000–150 000 per μ L were monitored every week for 1 month. If WBC and platelet counts were sustained or improved, patients were followed up according to standard protocol. Patients with total cholesterol concentrations of more than 300 mg/dL or triglyceride concentrations of more than 400 mg/dL were

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