

The Effect of Atorvastatin on Flare Rates in Patients with Systemic Lupus Erythematosus

IRB protocol

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A. Study Purpose and Rationale

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease affecting well over 250,000 Americans. (1) This disease is characterized by a chronic remitting and relapsing course that imposes a significant burden on both quality of life and healthcare expenditure. Flares are an important outcome in SLE because during those periods of uncontrolled disease activity, end organ damage ensues, which is a major determinant of long term prognosis. (2) Although the life expectancy of SLE patients has improved from an approximate 4-year survival rate of 50% in the 1950s to a 15-year survival rate of 80% today, flares still continue at relatively high rates. (1-2) Therapies traditionally used to both minimize the incidence and severity of flares also carry their own high risks; thus there is a need for a therapy to prevent flares that carries a lower side effect profile.

Statins are primarily used for the treatment of hyperlipidemia for the prevention of cardiovascular outcomes; however, they are known to have wider pharmacologic effect. Ex-vivo activities of statins include suppression of adhesion molecule expression, leukocyte cytokine release, MHC class II expression, lymphocyte and macrophage interactions, and effects on reactive oxygen and nitrogen intermediate production. (3) Statins also modify apoptosis in smooth muscle and endothelial cells leading to altered vascular function and neovascularization. (4) These properties offer the potential to modify chronic inflammatory disease states such as SLE with drugs that show minimal toxic effects in both the short and long term.

A review of the literature shows inconclusive evidence for the role of statins as immunomodulators in SLE. A small case series showed that in patients with active, refractory, severe disease statins may have some effect in reducing the severity of the flare. (5) In a randomized placebo controlled trial, atorvastatin was shown to improve disease activity in patients with active rheumatoid arthritis. (6) Two other randomized controlled trials showed no difference in CRP levels in SLE patients on a statin vs. placebo. These trials also showed no difference in lupus disease activity; however, neither study was powered to detect a difference disease activity. (7-8)

Given this inconclusive data, we propose a randomized, placebo controlled trial to test whether atorvastatin can reduce the rate of lupus flares in SLE patients with active disease.

B. Study Design and Statistical Analysis

1. The proposed study will be a randomized, placebo-controlled, double-blind, trial. Safety of the investigational treatments will be monitored by The Data Safety Monitoring Board throughout the trial

- 2. Study Arms:** patient will be randomly assigned to 1 of 2 arms
- 40 mg atorvastatin orally daily
 - placebo

3. Randomization: Because African American ethnicity and low C4 levels have been associated with higher flare rates, patients will be randomly selected from each of the four following strata:

- African American, $c4 < 10$ mg/dl
- African American, $c4 \geq 10$
- non African American, $c4 < 10$
- non African American, $c4 \geq 10$

4. Primary Outcome: Rate of lupus flare at 12 months with flare defined as a new A (severe flare) or B (moderate flare) score in at least one system that previously scored a C, D, or E on the British Isles Lupus Activity Group Index (BILAG) (9)

5. Secondary Outcome: Rate of lupus flare at 3 and 6 months using BILAG index and difference in SLE Disease Activity Index (SLEDAI) at 3, 6, and 12 months

6. Statistical Analysis

a. Sample size: In order to achieve 80% power with a P value of 0.05 a sample size of 103 patients in each arm was calculated using the Chi-square test, assuming a treatment effect of 50% and a placebo response of 70%. 115 patients will be recruited for each arm to account for attrition.

b. The primary outcome will be analyzed using chi square test and multiple logistic regression. The secondary outcomes will be analyzed using the t-test and multiple linear regression.

C. Study Procedure

Informed consent will be obtained from each patient. Patients will then be randomized as described above to placebo group or treatment group. Hematology, chemistry, hepatic function panel, urinalysis, spot urine protein, complement levels, anti-double stranded DNA, CPK, and SLE disease activity scales (Systemic Lupus Erythematosus Disease Activity Index [SLEDAI] and the British Isles Lupus Assessment Group [BILAG] index), were evaluated every 3 months which is congruent with standard for clinical care. Changes to immunosuppressive agents and corticosteroid therapy were permitted as clinically indicated. The study will run for a full year.

D. Study Drugs

Atorvastatin- FDA-approved; will be given in standard dosing of 40 mg orally daily

1. Mechanism of action: lowers cholesterol by inhibiting hydroxymethylglutaryl-CoA reductase, the rate-determining enzyme located in hepatic tissue that produces

mevalonate, a small molecule used in the synthesis of cholesterol and other mevalonate derivatives

2. Adverse side effects: Myopathy with elevation of creatinine kinase (CK) and rhabdomyolysis is the most serious, although rare <1%. Headache is the most common side effect, occurring in more than 10% of patients. Side effects that occur in 1-10% of patients taking atorvastatin include: weakness, insomnia and dizziness, chest pain and peripheral edema, rash, abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea, urinary tract infection, arthralgia, myalgia, back pain, arthritis, sinusitis, pharyngitis, bronchitis, rhinitis, infection, flu-like syndrome, allergic reaction, elevation of alanine transaminase (ALT) and aspartate transaminase (AST). Other very rare side effects occurring in less than 1% of patients are: alopecia, anaphylaxis, angina, angioneurotic edema, arrhythmia, bullous rashes, cholestatic jaundice,^[32] deafness, dyspnea, erythema multiforme, esophagitis, facial paralysis, glaucoma, gout, hepatitis, hyperkinesia, impotence, migraine, myasthenia, myositis, nephritis, pancreatitis, paresthesia, peripheral neuropathy, petechiae, photosensitivity, postural hypotension, pruritus, rectal hemorrhage, rhabdomyolysis, somnolence, Stevens-Johnson syndrome, syncope, tendinous contracture, thrombocytopenia, tinnitus, torticollis, toxic epidermal necrolysis, urticaria, vaginal hemorrhage, and vomiting^[7].

E. Medical Device

N/A

F. Study Questionnaires

N/A

G. Study Subjects

1. Inclusion criteria : Adult patients (age ≥ 18 years) fulfilling the American College of Rheumatology (ACR) criteria for SLE who had active disease as defined by a SELENA-SLEDAI score of ≥ 4 at screening were eligible for enrollment. In addition, adult patients were required to be receiving a stable regimen of prednisone (5-40 mg/day), antimalarials, or immunosuppressive agents for at least 60 days prior to day 0 (first dose).

2. Exclusion criteria: Patients with severe SLE at baseline defined by SLEDAI >30 . Patients with known atherosclerotic event or hyperlipidemia such that statin therapy is clinically indicated. Patients with serum creatinine >2.0 mg/dl, a history of hepatitis or abnormal liver function tests (alanine amino transferase >2 times upper limit of normal), a history of myositis or serum creatinine kinase (CPK) >500 U/l, currently taking cyclosporine, and those with an allergy to statins, pregnant or considering pregnancy, were excluded. Women of childbearing age will be required to have a negative urine pregnancy test at the start of the study and to use reliable birth control during the study.

H. Recruitment of Subjects

We will obtain the treating rheumatologist's approval to contact potential subjects meeting study eligibility criteria, and will mail letters and telephone to recruit.

I. Confidentiality of Study Data

All study data will be coded and data will be stored in a secure location that is only accessible to the study investigators.

J. Potential Conflict of Interest

There are no potential conflicts of interest to disclose.

K. Location of Study

This study will be conducted at Columbia University Medical Center.

L. Potential Risks

The potential risks include that the treatment has no effect and possible side effects of the study medication as outlined above.

M. Potential Benefits

The potential benefits include reduction in lupus flares, disease activity, and cholesterol levels.

N. Alternative Therapies

N/A

O. Compensation to Subjects

The study drug will be provided free of cost during the study. All medical visits and laboratory test will also be provided free of charge. No other compensation will be provided.

P. Costs to Subjects

Subjects will not incur any additional costs as a result of participating in the study.

Q. Minors as Research Subjects

Minors will be excluded from the study

R. Radiation or Radioactive Substances

N/A

S. References

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