A double-blind, placebo-controlled, phase-II clinical trial to evaluate oral simvastatin as a treatment for vitiligo

To the Editor: Vitiligo is an autoimmune disease caused by autoreactive $CD8^+$ T lymphocytes that target melanocytes, and interferon-γ-induced CXCL10 plays an important role.[1] Simvastatin inhibits interferon-γ signaling by blocking activation of STAT1[2] and prevented and reversed disease in our mouse model.[3] A case report described a patient with vitiligo who repigmented with simvastatin.[4] We conducted a small, randomized, double-blind, placebo-controlled, phase II clinical trial to test simvastatin as a treatment for vitiligo. After obtaining informed consent, we enrolled men ages 18 to 64 years with vitiligo affecting 3% to 50% of their body surface area (BSA). We excluded patients with a segmental presentation; those already taking a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor; those with existing thyroid disease; and women, based on their increased risk of simvastatin-induced myopathy. This study was approved by our institutional review board (Clinicaltrials.gov identifier number: NCT01517893).

Fifteen patients were randomized to either 40 mg of simvastatin daily for the first month and 80 mg for the remaining 5 months of the study period, or placebo. Topicals were discontinued for at least 2 weeks, oral immunomodulators for 4 weeks, and phototherapy for 8 weeks before enrollment. We measured treatment response using 4 outcome measures: (1) Vitiligo Area Scoring Index (VASI) score (Supplemental Fig 1; available at http://www.jaad.org), (2) change in size of a "sentinel" patch, (3) investigator global assessment, and (4) subject global assessment. We also measured serum CXCL10, a target of interferon-γ that promotes depigmentation in vitiligo.[1] Seven participants were randomized to receive placebo and 8 to simvastatin, and 3 withdrew from the simvastatin group. Supplemental Table I (available at http://www.jaad.org) summarizes baseline patient characteristics.

The treatment group experienced an average worsening of disease (Fig 1), with a 26% increase in the mean VASI (95% confidence interval −45:97%), whereas the placebo group had a 0% change in the mean VASI (95% confidence interval −5:5%), and the difference between groups was not significant (*P* value = .094). Inclusion of withdrawn participants did not change the result. The average worsening in the treatment group was a result of patient 9 who experienced an episode of inflammatory vitiligo, more than doubling his involved BSA, but he regained partial repigmentation by his final visit (Supplemental Table I). Neither the change in the sentinel patch nor mean investigator global assessment or subject global assessment was significantly different between groups. Simvastatin

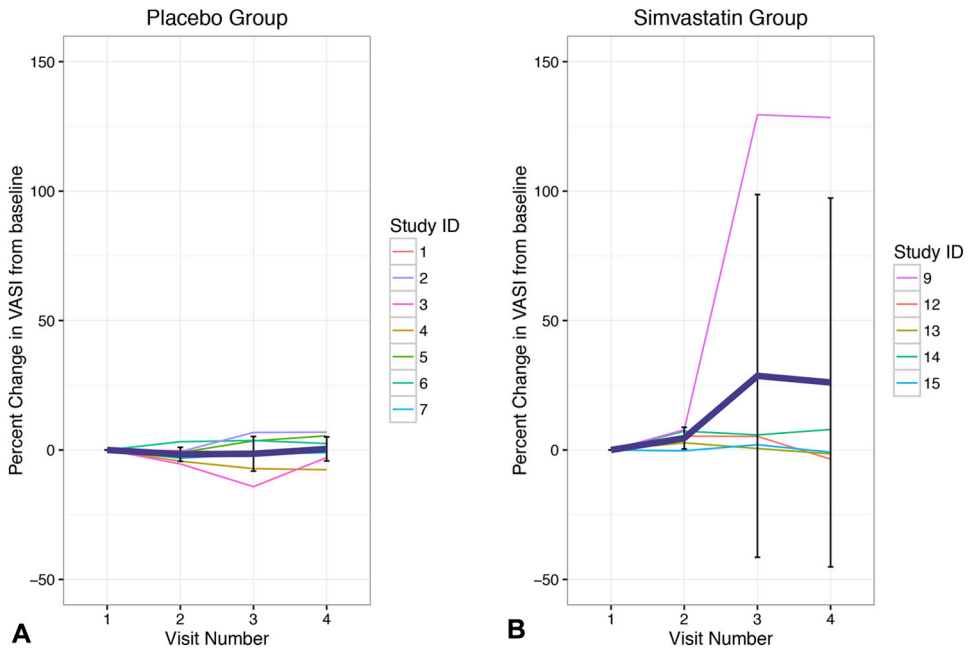

Fig 1. Relative change in Vitiligo Area Scoring Index (*VASI*) score between visits 1 and 4 in placebo (**A**) and simvastatin (**B**) groups. *Thick purple line* represents the mean change of each group. Visit 1, 0 months; Visit 2, 1 month; Visit 3, 3 months; Visit 4, 6 months.

did not affect serum CXCL10 levels, consistent with observations in our mouse model[3] (Supplemental Fig 2; available at http://www.jaad.org). The most common side effects of simvastatin were self-limited myalgia in 4 participants and diarrhea in 2 participants. Three participants had mild, transient transaminitis and 4 had mild creatine phosphokinase elevations, none requiring dose modifications. Only 1 withdrawal, because of vertigo, was thought to be treatment-related.

Our study does not support the use of oral simvastatin for the treatment of vitiligo. Disparate findings in this study compared with our mouse model may be a result of dosing limitations in humans because of potential toxicity, which is not a concern in mice. Our failure to show efficacy may also have been influenced by long-standing disease in our participants (responses are best in those with recent onset), small sample size, or lack of sensitive measures of treatment response. The VASI relies on an estimation of affected BSA, with limited sensitivity to change (>4.7% BSA).[5] Newer outcome measures may provide more sensitive options for monitoring responses. Simvastatin may induce myopathy at higher doses; however, topical treatment may allow the delivery of sufficiently high local concentrations without systemic toxicity and could be tested in larger studies.

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Conflicts of interest: None declared.

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Increased blood levels of NKG2D$^+$CD4$^+$ T cells in patients with alopecia areata

To the Editor: Natural killer group 2D (NKG2D) is a key target of not only alopecia areata (AA) but other autoimmune diseases. AA is a T_H1-mediated disease driven by interferon-γ (IFN-γ) and IFN-γ–induced cytokines.[1] NKG2D$^+$ cells, including NK, NKT, and CD8$^+$ T cells, and NKG2D-activating ligands have a key role in AA pathogenesis. Excessive IFN-γ secretion by activated NKG2D$^+$ cells can lead to collapse of hair follicle immune privilege.[2] It is well known that CD4$^+$ T cells highly infiltrate the tissue of the "bee swarm" in AA.[3] However, the functional role and expression patterns of NKG2D$^+$CD4$^+$ T cell in AA remain largely unknown. In this study, we investigated the changes in blood levels of NKG2D$^+$CD4$^+$ T cells in patients with AA.

Forty-three patients with AA (18 men and 25 women) and 26 healthy controls (10 men and 16 women) with no scalp lesions in their personal history or on clinical examination were enrolled. The cell surface expression of NKG2D on peripheral blood mononuclear cells was studied by flow cytometry analysis (FACS Aria; BD Biosciences, Franklin Lakes, NJ). Results in each group were expressed as a percentage of CD4$^+$ T cells, CD8$^+$