ORIGINAL ARTICLE

The Remarkable Beneficial Effect of Adding Oral Simvastatin to Topical Betamethasone for Treatment of Psoriasis: A Double-blind, Randomized, Placebo-controlled Study

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Abstract

Background: *Psoriasis is a common chronic inflammatory disease with unpredictable prognosis. Given the immunomodulatory effects of statins, the present study was conducted to determine whether the addition of orally administered simvastatin to the topical betamethasone, a standard antipsoriatic treatment, can produce a more powerful therapeutic response against this clinical conundrum.*

Method: *In a double-blind study, 30 patients with plaque type psoriasis were randomly divided into two equal treatment groups. Group 1 received oral simvastatin (40 mg/d) plus topical steroid (50% betamethasone in petrolatum) for 8 weeks and group 2 received oral placebo plus the same topical steroid for the same time period. Psoriasis Area and Severity Index (PASI) score was checked before and at the end of the treatment period.*

Results: *PASI score decreased significantly in both groups, but the decline of PASI score was more significant in patients who received simvastatin (Mann-Whitney test; P-value=0.001). No side effect or any laboratory abnormality was detected in patients.*

Conclusion: *Our work, which is the first double-blind, randomized, placebo-controlled study on this subject, shows that oral simvastatin enhances the therapeutic effect of topical steroids against psoriasis. The increased risk of cardiovascular accidents in psoriatic patients and the protective effect of statins against cardiovascular disease further encourages their use in the treatment of this clinical conundrum.*

Keywords: *Simvastatin – Psoriasis – Treatment – Topical Steroids*

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Introduction

Psoriasis is a common chronic skin disease with worldwide distribution. The prognosis is unpredictable and recurrence is a rule regardless of the type of treatment[1]. Treatment modalities are divided into local and systemic treatments, including topical steroids, tar, anthralin, topical retinoids, phototherapy, retinoids, methotrexate and many other modalities, each associated with many side effects[1].

Statins are well-known, safe and cheap antihyperlipidemic drugs which inhibit 3-Hydroxy-3-methyl glutaryl CoA (HMG-CoA) reductase enzyme. In addition, they have proven anti-inflammatory and immunomodulatory effects via several mechanisms[2]. Simvastatin reverses the effects of TNF-α-2 4 decreases the expression of adhesion molecules on monocytes and macrophages[5], and inhibits leukocyte function associated antigen-1 (LFA-1)[6].

The immunomodulatory effects of statins and their potential use in the treatment of diverse dermatological disorders were first introduced to the dermatology literature in 2004[3]. Recently, a non-randomized, non-controlled, open pilot study on a small number of psoriatic patients (7 patients) revealed the reduction of PASI score with orally administered simvastatin 40 mg/d plus emollients or weak topical steroids for 8 weeks, suggesting the efficacy of statins against psoriasis[2]. Herein, we report the results of our double-blind, randomized, placebo-controlled study on this subject.

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Patients and Methods

This study was conducted from November 2006 to November 2007 at the Dermatology Department of Shiraz University of Medical Sciences, the most prestigious academic dermatology department of the southern Iran. This study was approved by the ethical committee of Shiraz University of Medical Sciences.

Thirty otherwise-healthy patients with typical psoriasis vulgaris who gave informed consent were randomly divided into two equal groups.

The patients below 10 and above 80 years of age, pregnant and lactating women, patients with erythrodermic or pustular psoriasis, patients with lesions on face and flexural areas, patients treated with any topical or systemic medication in the past 1 month, and the patients with any hepatic or muscular disorders were excluded from the study.

Patients in group 1 received simvastatin at the dose of 20 mg two times daily plus topical steroid (50% betamethasone in petrolatum) for 8 weeks. Patients in group 2 received completely identical oral placebo tablets twice daily plus the same topical steroid for 8 weeks.

The severity of psoriasis was evaluated by a physician blinded to treatment identifications before the initiation of the treatment and after 8 weeks using Psoriasis Area and Severity Index (PASI) score.

Serum levels of lactate dehydrogenase (LDH), creatine phosphokinase (CPK) and also liver function tests (LFT) were checked in all patients at the beginning and at the end of the treatment.

The data were analyzed using Wilcoxon and Mann-Whitney tests.

Results

All 30 psoriatic patients (15 patients in each group) completed the study. Group 1 (oral simvastatin plus topical steroid) included 6 female and 9 male patients. Group 2 (oral placebo plus topical steroid) included 4 female and 11 male patients. There was no significant difference between sex ratios in the two groups (P=0.44).

The ages of the patients in group 1 were between 16 and 64 years (average: 38.5 years old) and in group 2 were between 16 and 70 years (average: 45.4 years old). The difference in mean ages of the two groups was not statistically significant (P= 0.27).

In group 1, average baseline PASI score was 9.51, which decreased to 3.38 after 8 weeks of treatment (P-value = 0.001). In group 2, the average baseline PASI seore was 5.64, which decreased to 3.98 after 8 weeks of treatment (P-value = 0.006). Mann-Whitney test revealed the significantly more reduction of PASI score in group 1 compared to group 2 (P-value=0.001) (Table I).

No side effect or any laboratory abnormalities were detected in any patient.

Table I: Average PASI score of psoriatic patients treated with oral simvastatin plus topical steroid vs. oral placebo plus topical steroid

	Before treatment	After treatment	P Value
Group 1*	9.51	3.83	0.001
Group 2 **	5.64	3.98	0.006

PASI score reduction is more significant in group 1 than group 2 (Mann-Whitney test; P-value=0.001).

* Oral simvastatin plus topical betamethasone** Oral placebo plus topical betamethasone

Discussion

Psoriasis is a relatively common recurrent Th1-mediated chronic troublesome disease[7].

Recently, the anti-inflammatory and immunomodulatory effects of statins have been recognized and the results of treatment of some autoimmune diseases, e.g. rheumatoid arthritis, with these drugs have been encouraging[2].

The ability of statins to scavenge free radicals and to modulate immune functions, as well as their low cost and safety make them favorable candidates in the treatment of immunologically-mediated dermatologic diseases like psoriasis[3].

In the present study, oral simvastatin plus topical steroid and oral placebo plus topical steroid were both effective in the treatment of plaque type psoriasis but the former treatment plan was more effective than the latter.

Statins inhibit the expression of intercellular adhesion molecule (ICAM-1), lymphocyte function-associated antigen (LFA-1), and monocyte chemotactic protein-1 (MAC-1) on leukocytes and endothelial cells and interfere with LFA-1–ICAM-1 interaction through binding to LFA-1, thereby suppressing leukocyte infiltration into the inflammation site which is a hallmark of psoriasis [(3,6)]. Interference with LFA-1–ICAM-1 interaction and inhibition of expression of major histocompatability complex (MHC) class II results in suppression of antigen presentation and lymphocyte activation. Moreover, statins prevent leukocyte entry to the inflammation sites by significant downregulation of Th1-type chemokine receptors, CCR5 and CXCR3, on T-cells and inhibition of chemokine release by endothelial cells [3].

Statins block the induction of inducible nitric oxide synthase (iNOS) and production of the proinflammatory cytokines, tumor necrosis factor-α, interferon-γ, interleukin-8 (IL-8), IL-1β, and IL-6 in macrophages and induce a bias toward Th2 cytokines ex vivo[2,3,11].

Statins decrease C-reactive protein (CRP) serum levels[2]. CRP amplifies complement activation, induces secretion of tissue factors from monocytes, and enhances the expression of adhesion molecules[8].

In the present study, simvastatin caused no xerosis or eczema. Reiter et al[9] have also shown that simvastatin had no significant effect on the skin cholesterol levels.

Activated inflammatory cells and pro-inflammatory cytokines, which contribute to the development of psoriatic lesions, play an important role in the atherogenesis and the breakdown of atherosclerotic plaques. Psoriasis is associated with an increased cardiovascular risk profile compared with the general population and cardiovascular disease is an important cause of morbidity and mortality in these patients. So, statins can possess a double benefit for psoriatic patients: improving their illness plus protecting them against cardiovascular disease[10]. Given the different antipsoriatic mechanisms of retinoids and statins, their co-administrations could prove to exert a synergistic anti-psoriatic effect plus the additional benefit of normalization of retinoid-induced lipid abnormalities. There is some evidence that statins exert anti-cancer effect[11,12], so administration of statins and phototherapy can expedite the therapeutic response to phototherapy while mitigating the carcinogenicity of the latter.

Noteworthy, a recent interesting paper by Wolkenstein et al[13] has shown the decreased risk of psoriasis associated with statin intake.

Our work, which is the first double-blind, randomized, placebo-controlled study on this subject, reveals the marked beneficial effect of adding statins (simvastatin 40 mg/d) to the topical steroids in the treatment of psoriasis.

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