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# Efficacy of Atorvastatin and Antihistamines in Comparison with Antihistamines plus Placebo in the Treatment of Chronic Idiopathic Urticaria: A Controlled Clinical Trial

**Fakhrozaman Pezeshkpoor[1], Reza Farid Hosseini[2], Houshang Rafatpanah[3], Behzad Shakerian[2], Farahzad Jabbari[4], Mohammad Reza Zandkarimi[2], Hadis Yousefzadeh[5], Homa Sadri [4], Abdolazim Bahrami[2], and Mohammad Ali Zamani[3]**

*[1] Research Center for Skin Diseases and Cutaneous Leishmaniasis, Ghaem Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
*[2] Immunology Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
*[3] Inflammation Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
*[4] Allergy Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
*[5] PhD Student of Immunology, Student Research Assembly of MUMS, Mashhad, Iran*

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**ABSTRACT**

Chronic Idiopathic Urticaria is defined as recurrent hives occurring for at least 6 weeks. In the majority of cases, there is no identifiable underlying etiology despite extensive evaluation. A subset of these patients is classified as having autoimmune urticaria defined by the presence of a functional IgG antibody to the α subunit of the high-affinity IgE receptor (FceRIa) or to IgE. The aim of this study was to evaluate the effects of the drug atorvastatin in patients with chronic urticaria compared to the placebo.

In this single-blind study, 50 patients suffering from chronic urticaria (15-45 years old) were selected and divided into two groups by simple randomization method. The first group was treated with atorvastatin and antihistamines and the second group (control group) was treated with placebo and antihistamines for 3 months. Urticaria severity was measured by score index, before and after the treatment course: ASST (Autologous serum skin test) was performed for all patients and sera were collected to measure cytokines.

In cases, IL-5 decreased and IL-10 increased after treatment compared to the time point before treatment ($p<0.05$). All patients with severe utricaria according our scoring, had positive ASST.

The patients with severe urticaria identified by urticaria score and ASST positivity had chronic idiopathic urticaria. By prescribing the Atorvastatin plus antihistamines in severe and resistant forms of urticaria, the use of more toxic medications like cytotoxic drugs may be avoided.

**Keywords:** Atorvastatin; Chronic Idiopathic Urticaria; Cytokines

**Corresponding Author**: Farahzad Jabbari Azad, MD;
Allergy Research Center, Ghaem Hospital, School of Medicine,
Mashhad University of Medical Sciences, Mashhad, Iran.
Tel/ Fax: (+98 511) 845 769, E-mail: jabbarif@mums.ac.ir



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## INTRODUCTION

Chronic Idiopathic Urticaria (CIU) is a relatively common disease that may have a profound influence on patients' quality of life and yet not much is known about the causative factors or its pathophysiology, which makes it difficult to cure [1]. It is characterized by the recurrent urticarial wheals that persist for more than six weeks [2].

The frequency of auto-antibodies against the high affinity receptor for IgE in CIU has been estimated to be 30-50% [3]. The treatment of CIU patients commonly includes prescription of antihistamines and rarely corticosteroids for resistant ones [3,4,5]. Evidence suggests increasingly that such auto-antibodies are likely to be functional in vivo, but conclusive evidence is not enough supportive [6].

Statins have been prescribed extensively for their cholesterol lowering effect. However, compelling evidence now exists that statins also have extensive immunomodulatory properties that operate independent of lipid lowering effect. Consequently, much attention has been paid toward their potential as therapeutic agent for the treatment of autoimmune diseases like multiple sclerosis [7-8], chronic renal failure [9], and severe acute graft-versus-host disease after transplantation [10].

Previous studies also reported different efficacies of statins on inhibitors of the growth and activation of human basophils [11], human mast cells (MCs), human MC line HMC-1 [12] and various cytokines including IL-1, IL-2, IL-6 and IFN-γ by human peripheral blood mononuclear cells [13].

We sought to assess the effects of the drug atorvastatin compared to placebo in patients with chronic urticaria by assessing the alterations in urticaria severity and also cytokine secretion.

## PATIENTS AND METHODS

This is a single-blind randomized clinical trial which evaluates the extra effect of Atorvastatin on reducing the signs and symptoms of CIU. Fifty patients visited from January to August 2010 in the allergy and dermatology clinics took part in this clinical trial. We defined CIU as recurrent wheals occurring at least three times per week for more than six weeks without an identifiable cause. Patients were excluded if they had urticaria by known causes including physical urticaria, urticarial vasculitis, and allergic urticaria, or those with addiction, systemic or chronic diseases, pregnancy or breast feeding. The patients were randomly divided into two groups (25 cases and 25 controls).

The randomization of participants was achieved by simple random selection method. As the patients entered to study in odd days or even days, they received atorvastatin or placebo, respectively. In this single blind study, the allergist was alert about the prescription but the patients did not know about their therapies.

The first group (case group) was administered atorvastatin (Abidi Co, Tehran, Iran) 40 mg orally twice daily. The second group (control group) was treated with placebo (Samisaz Co, Mashhad, Iran) twice daily. Both groups received H1 blocker antihistamines including Apo-Cetirizine (Apo Co, Canada) 10 mg daily, or Telfast (Fexofenadine, Sanofi-aventis Co,USA) 180 mg daily beside ranitidine as H2 blocker (kimidaro, Iran) 150 mg twice daily.

A questionnaire including demographic data, history of medications prescribed, disease duration, history of angioedema, skin prick test and ASST results (if done before) were fulfilled by each patient. Urticaria severity was evaluated according to the score Index from 0-15 points. Duration of treatment was considered to be 3 months. The analysis of CBC, ESR, AST, ALT, Urinalysis and CPK were done for all patients. Also the T3, T4, TSH, Anti β thyroglobuline antibodies, anti-peroxidase antibodies and Skin Prick Test for common regional aeroallergens and food allergens were also performed.

In order to measure cytokines, the lymphocytes were initially separated by ficoll and cultured in RPMI Media (Gibco-Bio-Cult, Glasgow, Scotland) for 48 hours. The Supernatant was collected after stimulation with Phorbol Myristate Acetate (PMA). TGF-β, IL-3, IL-4, IL-5, IL-10, and INF-γ were assessed by ELISA technique (IBL, Hamburg-Germany).

Patients were visited monthly and their satisfaction from the treatment, liver function tests (AST, ALT), CPK and any probable side effects of the drugs used were assessed. After 3 months of treatment, cytokines, ASST and urticaria score were reassessed.

**Table 1. Demographic information of studied participants**

| Variables | | Case group (n=22) | Control group (n=25) |
|---|---|---|---|
| Gender | Male | 8 (36.4%) | 5 (20%) |
| | Female | 14 (63%) | 20 (80%) |
| Age (year) | | 34.22±8.6 | 31.1±8.9 |
| Duration Disease (year) (Mean±SD) | | 3.98±4.64 | 2.94±3.54 |
| Angioedema | | 13 (59) | 11 (44) |

This study protocol was approved by Ethics Committee of Mashhad University of Medical Sciences (MUMS) and written consent form was obtained from all the patients.

**Statistical Analysis**

The data were collected in a single database and statistical evaluations were performed by SPSS Software version 11.5. Data obtained about biochemical tests (AST, ALT, CPK and ESR) and age information was described by Mean±SD. Cytokines and ASST were analyzed by T independent and chi-square tests. A *p*-value less than 0.05 was considered significant.

## RESULTS

In this study, the clinical and laboratory findings of 50 patients with chronic idiopathic urticaria, before and after the treatment course with Atorvastatin and placebo (cases and controls) were recorded and compared.

During the study, 2 patients of case group were excluded due to pregnancy and 1 patient because of drug-induced myopathy. Demographic data of studied patients is summarized in Table 1.

Positive family history of allergy was identified in 36 (76.6%) and other concurrent allergies were present in 19 (40.4%) of all studied patients. Skin prick test was negative in 42 (89.4%) and 11 (23.4%) patients in the case and control groups, respectively.

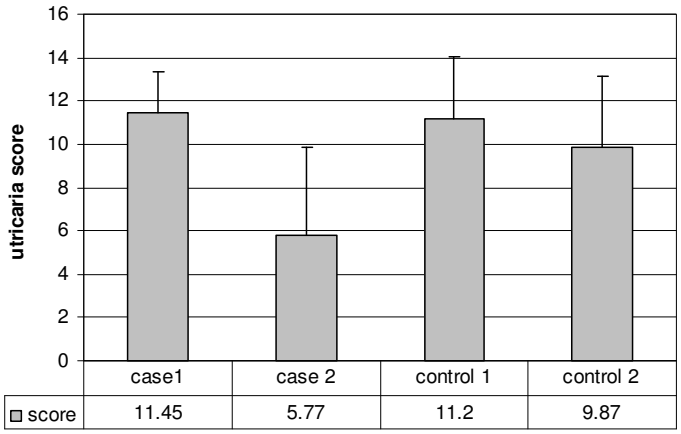
ESR, T3, T4, TSH, Antimicrosomal and Anti β-thyroglobuline antibodies were normal at the first measurement before the treatment course. Monthly analysis of AST, ALT and CPK enzymes during the treatment for three months (Table 2) showed that there were not any significant statistical differences in the serum levels of these enzymes before and after treatments ($p>0.05$).

In Table 3, the cytokine profile and ASST in case and control groups before and at the end of treatment is shown. All cytokines except IFN-γ decreased at the end of treatment in case group, while IL-3, IL-4 and IL-10 increased in control group (P>0.05). In cases, IL-5 decreased and IL-10 increased after treatment compared to the time point before treatment ($p=0.03$; $p=0.05$, respectively).

The urticaria score decreased in the two groups after the treatment (Figure 1). ASST results was decreased significantly in the case group after the treatment compared to before treatment ($p=0.001$).

**Table 2. AST, ALP and CPK test during the treatment period**

| Enzyme | First | 1th month | 2nd month | 3th month |
|---|---|---|---|---|
| AST | 30.9±4.21 | 27.72±5.7 | 28.83±6.62 | 31.89±6 |
| ALP | 28.8±7 | 28.41±6.97 | 31.27±6.57 | 30.71±4.41 |
| CPK | 119.45±16.9 | 122.33±31.74 | 113.74±18.07 | 112.9±23.55 |




Case 1 and control 1 showed before treatment and case 2 and control 2 presented after the treatment.

**Figure 1. Utricaria Severity Score before and after treatment**

**Table 3. Cytokine profile and ASST before and after treatment**

| Variable | Before | | After | | P-Value |
|---|---|---|---|---|---|
| | Case | Control | Case | Control | |
| IL-3 | 74.11±71.33 | 255.05±279.02 | 72.86±92.63 | 282.92±200.19 | 0.069 |
| IL-4 | 9.4±7.21 | 13.56±14.16 | 8.55±8.47 | 13.89±19.16 | 0.076 |
| IL-5 | 7.7±8.63 | 14.91±26.08 | 4.62±4.73 | 5.52±8.52 | 0.032 |
| IL-10 | 224.33±246.19 | 192.59±204.09 | 299.72±262.16 | 230.03±25.4 | 0.058 |
| TGF-β | 123.38±84.8 | 104.49±112.81 | 101.46±106.99 | 74.79±106.73 | 0.096 |
| IFN-γ | 174.88±139.59 | 200.236±151.24 | 188.81±167.41 | 195.34±175 | 0.077 |
| ASST | 17 (67.3%) | 11 (44%) | 5 (23.8%) | 16 (64%) | 0.001 |

ASST: Autologous serum skin test

## DISUSSION

Our study showed that atorvastatin was effective on CIU patients studied and decreased the utricaria scoring. Statins apart from their lipid-lowering activity are inhibitors of hydroxymethylglutaryl coenzymes (HMG CoA) reductase, a key enzyme in mevalonic acid (MVA) dependent signaling. Recent data suggest that statins exhibit profound anti-inflammatory effects on basophils and the major proinflammatory effector cells in diverse pathologic reactions [6]. Majlesi et al (2003) examined the in vitro effects of the five different statins on primary human basophils and concluded that cerivastatin and atorvastatin are as novel inhibitors of the growth and activation of human basophils [11]. Krauth et al (2006) examined *in vitro* effects of five different statins on primary human mast cells (MCs) and human MC line HMC-1.They found that pre-incubation of primary lung MCs with cerivastatin or atorvastatin (1-50 micro M) for 24 hours resulted in inhibition of anti-IgE induced release of histamine. The effects of both statins were dose-depended [12]. In another study, Bessler et al (2005) evaluated the *in vitro* effects of the pravastatin, atorvastatin, lovastatin and simvastatain on the production of IL-1, IL-2, IL-6 and INF-γ by human peripheral blood mononuclear cells. They found that lovastatin and simvastatin increased the production of IL-1 in a dose dependent manner and reduced secretion of IL-1 at high concentration [13]. But atorvastatin did not affect IL-1 and IL-6 while suppressed IL-2 and INF-γ production. Xiaoming et al (2007) evaluated the

relationship between autoimmune chronic urticaria and the levels of plasma prothrombin for its role in inflammatory reactions. After the treatment with loratadine and dipyridamole, the levels of prothrombin in CU patients decreased obviously in comparison to the control group [14]. Statin therapy for coronary artery disease decreased LDL and increased HDL cholesterol levels. Also, statins can reduce in vitro aspirin resistance in 65% of patients after 3 months therapy [15].

In our study, after administration of atorvastatin for 3 months, the patients' symptoms assessed by urticaria score decreased compared to the time point before treatment. By using this drug, serum level of IL-5 (a proinflammatory cytokine) decreased, while IL-10 (an inhibitory cytokine) increased in patients' serum. We concluded that Atorvastatin, could be effective in the treatment of chronic urticaria and when it was prescribed in addition to antihistamines, it could alleviate the patients' symptoms in severe and resistant forms of urticaria.

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