



Do Statins Improve Lung Function in Asthmatic Patients? A Randomized and Double-Blind Trial

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Abstract

There are evidences that statins have anti-inflammatory effects beyond their cholesterol lowering properties. The study was conducted to assess the effects of atorvastatin on asthma as an inflammatory disease. Patients with moderate to severe asthma were entered this randomized, double blind, crossover clinical trial. The impact of oral atorvastatin (10 mg/day) on the lung function of normolipidemic patients was studied. The study was conducted in the National Research Institute of Tuberculosis and Lung Disease. Patients were randomized to receive either atorvastatin or placebo for 4 weeks separated by a 2-week washout period in a crossover fashion. Patients continued on their usual asthma drug treatment throughout the study. Spirometric parameters were determined at baseline and at completion of drug or placebo administration. Seventeen patients with the age of 37.12 ± 12.41 years completed the trial. Data analysis revealed no significant differences in peak expiratory flow rate (PEF), forced expiratory volume in the first second (FEV1), forced vital capacity (FVC) and FEV1/FVC between placebo and atorvastatin therapy. The results showed no significant improvement in the pulmonary function tests in asthmatic patients receiving atorvastatin. Further studies using higher doses of statins and/or higher period of statin use are recommended.

Keywords: Asthma; Atorvastatin; Clinical trials; Lung Function; Statin.

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1. Introduction

It is widely known that treatment with 3-hydroxy-3-methylglutaryl coenzyme-A

reductase inhibitors (HMG CoA reductase inhibitors) reduces plasma cholesterol levels. Statins have been advocated as anti-hyperlipidemic agents for years, however the cholesterol-independent also called "pleiotropic" effects of statins are being studied as a treatment for a variety of other conditions

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[1]. Clinical trials have demonstrated that statins reduce cardiovascular morbidity and mortality in patients with or without coronary artery disease and/or elevated cholesterol levels [2 - 4]. Both *in vitro* studies and clinical trials have shown that statins have anti-inflammatory and immunomodulatory effects in addition to their cholesterol lowering action. Among these effects, statins can reduce the production of C-reactive protein (CRP) as a consequence of reduced interleukine-6 (IL-6) [5]. They may also reduce interferon- γ (IFN- γ) activity which in turn represses major histocompatibility complex class II (MHC II) mediated T cell activation [6]. Statin administration can result in reduction of tumor necrosis factor- α (TNF- α) [7]. Statins have the potential to modify T lymphocyte driven diseases through blockade of the interaction between the cellular adhesion molecules e.g. lymphocyte function-associated antigen-1 (LFA-1) and intracellular adhesion molecule-1 (ICAM-1) [8, 9].

Recently, it has been hypothesized that statins may be effective in inflammatory lung disease such as asthma. The potential benefits of statin therapy on inflammatory airway diseases were demonstrated in experimental models of allergic airway diseases [10, 11]. Statins suppress T helper 1 (Th1) cell activation which could restrain the IFN- γ dependent pathology of chronic asthma [6].

Furthermore, statins suppress natural killer cells (NKC) [12] and inhibit apoptotic process [13], which may be a potential target for asthma treatment [13]. Treatment targeted at inhibition of the function of LFA-1, has been effective in airway eosinophilia after allergen challenge in asthmatic subjects [6]. Statins have been shown to enhance the bioavailability of nitric oxide (NO) [14], a potent vasodilator which is predominantly produced in airway epithelial cells [15] and has relaxing activity in peripheral airways [16]. Together, these raise the likelihood of the therapeutic role of statins in asthma characterized by inflammatory markers.

The intergroup differences in the anti-inflammatory potency of statins should be noted. It has been postulated that statins such as simvastatin [17] and atorvastatin with less hydrophilicity could have a greater ability to suppress inflammation and TNF- α production [18]. Atorvastatin is a stronger inhibitor of the inflammatory response compared to simvastatin, as measured by NF-kappaB block activation [19]. Atorvastatin has been associated with marked down-regulation of HLA-DR and the CD38 activation on peripheral T cells. On the contrary, superantigen-mediated T cell activation was restrained by simvastatin [20].

Based on these potential benefits both drugs seem to be reasonable choices for

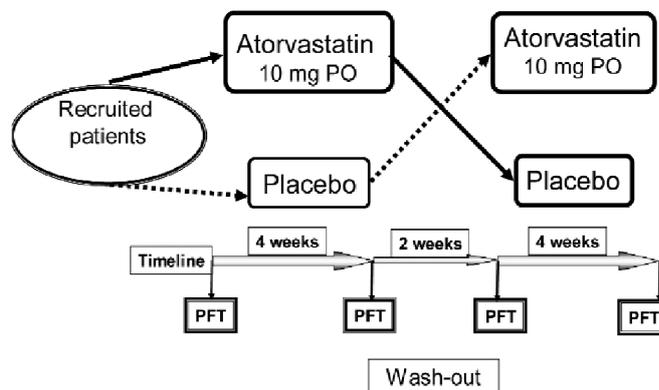


Figure 1. Illustration of the crossover study design. PO: Per Oral, by mouth; and PFT: Pulmonary Function Test.

investigation of statins' therapeutic role in asthmatic patients.

Our investigation is the first to assess the effect of atorvastatin on the clinical outcomes of asthma control including spirometric parameters.

2. Materials and methods

2.1. Study design, setting and subjects

The investigation was designed as a randomized, crossover, double-blinded, placebo-controlled study comparing the impact of oral atorvastatin 10 mg/day (Sobhan Pharmaceuticals, Rasht, Iran) versus placebo on the lung function of normolipidemic patients with moderate to severe asthma. The study was conducted in the pulmonary clinic of the National Research Institute of Tuberculosis and Lung Disease (NRITLD) during October 2006 to March 2007. The ethics committee of the NRITLD approved the study in September 2006.

Written informed consent was obtained

from all the patients. Eligibility assessment was mainly performed by two of the investigators (FF and SS). The data collecting investigator (SS), the outcome assessors (HRJ and AF), the clinical trial consultant and study statistician (JS) as well as the patients were blinded to treatment assignment for the duration of the study. Only the data monitoring investigator (FF) were aware of the un-blinded data.

Adult subjects (age 16 to 65 years) with moderate to severe asthma were entered into the study. Asthma diagnosis was confirmed by 2 pulmonologists (HRJ and AF) based on the spirometry and clinical symptoms. The following exclusion criteria were applied: LDL>130 mg/dl, TG>150 mg/dl, Cholesterol>200 mg/dl, concurrent comorbid diseases, use of any lipid lowering drugs during the past six months, use of concurrent drugs affecting atorvastatin metabolism, pregnancy or lactation, clinically significant rise in creatinine phosphokinase (CPK),

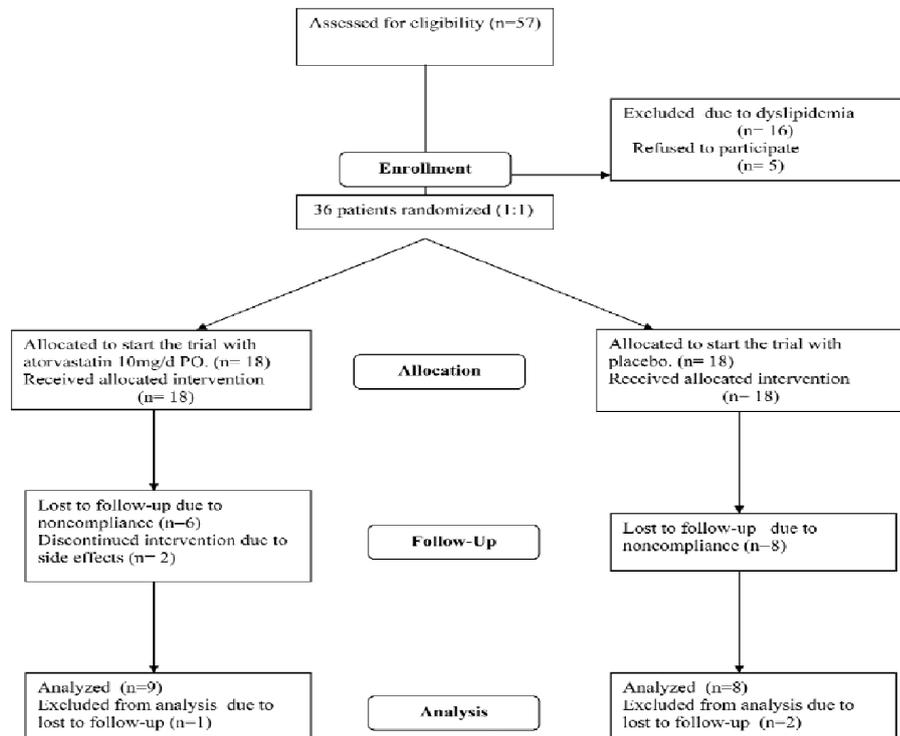


Figure 2. Study flowchart and patient drop-out

alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels during the study. Patients were also excluded if any severe adverse effect occurred during the study period or if the anti-asthma regimen was changed during the study. All patients received at least one inhaled corticosteroid and a long acting beta-2 agonist.

Patients were advised to fast for 12 h before blood samples were drawn for lipid profile. Serum cholesterol (total), LDL-cholesterol, HDL-cholesterol, triglyceride, liver function tests and CPK were measured using auto analyzer (Model Lyasis Italy) and Pars Azmoon kits (Pars Azmoon, Tehran, Iran). All the laboratory tests were confirmed by the pathologist (ZM).

After confirmation of normal lipid profile, participants were randomized to receive either placebo or atorvastatin orally 10 mg once daily, for 4 weeks. Allocation concealed by sealed opaque envelopes. The clinical pharmacist (FF) dispensed either active drug or placebo according to randomization table from a statistic book. After a 2-week washout period, patients were switched to the other group in a crossover fashion. The total duration of the study was 10 weeks (Figure 1).

Patients continued on their usual asthma treatment throughout the study. Study outcomes were spirometric parameters i.e.

peak expiratory flow rate (PEFR), forced vital capacity (FVC), forced expiratory volume in the 1st second (FEV1) and the FEV1/FVC. Parameters were measured using a portable spirometer (Spirolab II, Italy) at baseline and 4 weeks post drug or placebo administration.

2.2. Sample size determination

We used the standard deviations ($s_1=s_2=10$) obtained from a small pilot study ($n=10$) as estimates of the variances. With a maximum acceptable error (difference in the effects of the drug and placebo on spirometric parameters) equal to 10, power of 80% and the type I error equal to 0.05. Sample size of 15.68 ~16 was obtained.

2.3. Data analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS 11.0.1, SPSS Inc., Chicago, IL, USA). We used the paired 't' test for spirometric parameters comparison. The results are expressed as mean±SD, and $p<0.05$ were regarded as significance level.

3. Results

Forty seven patients were eligible for enrollment in the study. Five patients refused to participate and 16 patients were excluded

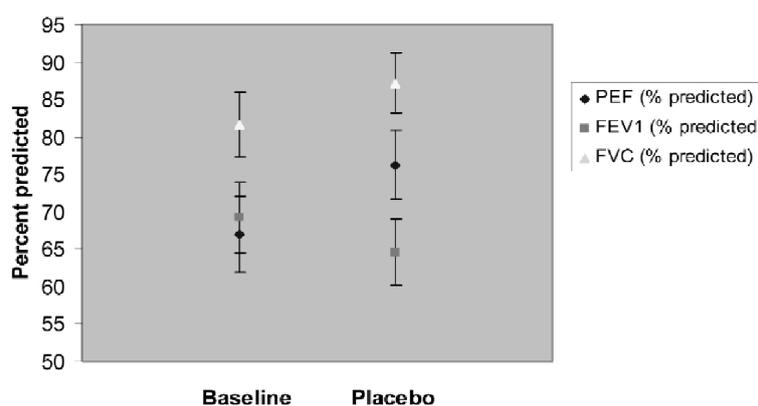


Figure 3. Spirometry at baseline and after placebo administration. PEF: peak expiratory flow rate; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity.

Table 1. Spirometric and morbidity index of the study groups at baseline and post drug/placebo therapy.

Variables	Before atorvastatin	After atorvastatin	Before placebo	After placebo	Difference*(%95 CI)	p value
PEF	65.41±21.64	72.41±20.10	66.91±25.40	76.24±21.44	2.32 (-8.27-12.91)	0.65
FEV ₁	64.59±19.82	73.94±19.51	69.19±21.75	64.56±19.82	-3.07 (-12.61-6.47)	0.51
FVC	74.71±18.02	84.35±13.49	81.64±18.87	87.18±16.67	-4.11 (-11.82-3.59)	0.28
FEV ₁ /FVC	0.85±0.11	0.86±0.13	0.83±0.12	0.86±0.13	0.04 (-6.20-6.11)	0.79
Morbidity	1.56±0.94	0.71±0.77	1.76±1.09	1.06±0.66	NA**	0.42

*Difference in means of the variation from baseline values after placebo and atorvastatin therapy; **Not applicable. PEFR: Peak expiratory flow rate; FVC: Forced vital capacity; FEV₁: Forced expiratory volume in the 1st second; CI: Confidence interval.

due to dyslipidemia. Four patients did not continue due to the lack of compliance and 2 developed headache and gastrointestinal discomfort. Data related to 3 patients were not analyzed due to loss of follow up. One patient developed a mild skin rash in the first week of therapy but continued the study. Seventeen patients (9 men, 8 women) with mean±SD age of 37.12±12.41 years completed the entire 10 weeks fully blinded study protocol (Figure 2.)

Mean±SD of the spirometric parameters, before and after atorvastatin and placebo therapy, are given in Table 1. Spirometry results at baseline and after treatment with both placebo and atorvastatin are also shown in Figures 2 and 3. No improvement effect was observed.

Data analysis revealed no significant difference between the alterations of PEF ($p=0.65$) FEV₁ ($p=0.51$), FVC ($p=0.28$) and FEV₁/FVC ($p=0.79$) in placebo and atorvastatin therapy. This is despite the significant increase in the FVC ($p=0.01$) and non-significant increasing trend in the PEF

($p=0.10$) and FEV₁ ($p=0.07$) after treatment with atorvastatin (Figure 4; Table 1).

4. Discussion

The current study is amongst the few recent reports studying the anti-inflammatory effect of 3-hydroxyl-3-methylglutaryl CoA reductase inhibitors in patients with asthma. The effects of statins on asthma have mainly been studied in animals [10, 11]. Atorvastatin's effects on human asthma are unexplored to our knowledge. However, we found one pilot study on the effect of atorvastatin on asthma control in smokers with asthma which is not yet recruiting patients [21] and an ongoing study on the effect of atorvastatin in patients with asthma [22].

Results obtained showed no significant improvement in the spirometry parameters of patients receiving atorvastatin 10 mg/day for 4 weeks compared to placebo administered for the same period of time. This could be in concordance with a recent published article by Menzies who evaluated the *in vivo* anti-inflammatory activity of simvastatin in 16

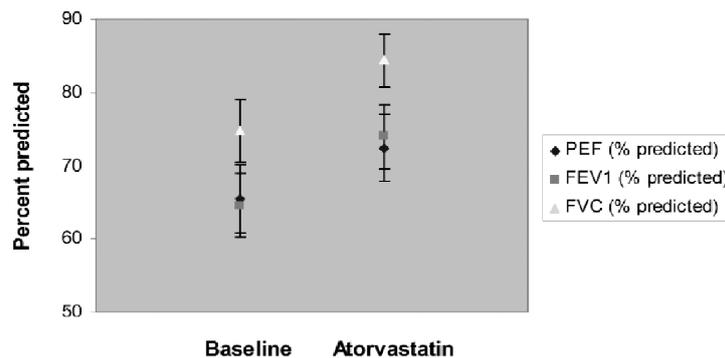


Figure 4. Spirometry at baseline and after treatment with atorvastatin. PEF: peak expiratory flow rate; FEV₁: forced expiratory volume in the first second; FVC: forced vital capacity.

patients with asthma and could not prove therapeutic usefulness [18].

Present knowledge on the anti-inflammatory effect of statins in various inflammatory conditions is not fully understood. Evidence is lacking as to whether these drugs might have a role in modulation of inflammatory conditions in which Th2 is involved. The anti-inflammatory properties of statins observed in animal models of allergic asthma [10] allergic airway inflammation [23] and smoking induced lung disease [24], suggest that statins could improve lung function. Statins have been used to treat autoimmune diseases in experimental models that are mainly T cell driven and are characterized by a pathogenic Th1 response [25]. These publications mainly suggest immunomodulatory effects for statins [17]. There are reports of effectiveness of atorvastatin in murine model of collagen-induced arthritis [26]. These autoimmune diseases have a more multifaceted etiology which results in systemic inflammation. Although it is difficult to compare the effects of statins on diseases that have a different pathogenesis, the effect of atorvastatin has been more impressive on induced models of diseases that are Th1 driven.

Although short term clinical trials confirm that statins can reduce inflammatory markers, a recent study have reported no significant effect of simvastatin on inflammatory status of induced systemic low grade inflammation in healthy volunteers evidenced by no changes in IL-6, TNF- α , and CRP levels [27].

Asthma is obviously an inflammatory disease and it is not clear whether the in vivo anti-inflammatory effects of statins may also occur with atorvastatin levels achieved after a 10 mg oral dose. It has been shown that suppression of inflammatory markers occurs in a dose dependent manner [10, 28]. Perhaps higher doses may have yielded different results.

As we have assessed only the effects on

clinical symptoms and spirometric parameters, we can not exclude that statins might possess anti-inflammatory properties at tissue, endothelial or cellular levels. For more accurate conclusion on the anti-inflammatory effect of HMG CoA reductase inhibitors, study of the systemic inflammatory biomarkers and inflammatory changes at tissue, endothelial or cellular levels of the respiratory system is recommended.

In conclusion, administration of oral atorvastatin 10 mg/day for 4 weeks did not illustrate a significant impact on spirometric parameters and asthma relief in normolipidemic moderate to severe asthma. Statins have shown more effects on biomarkers *in vivo* and *in vitro* than on clinical outcomes. Further studies using higher doses of statins are still required to find the evidence of statins' clinical value in asthma. If clinical improvements are seen, then larger trials would be appropriate.

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