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ORIGINAL ARTICLE

Influence of Statin Therapy on Exacerbation Frequency in Patients with Chronic Obstructive Pulmonary Disease

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Abstract

OBJECTIVES: Chronic obstructive pulmonary disease (COPD) is an inflammatory disease, in which chronic and systemic inflammation plays an important role. By decreasing neutrophil infiltration and cytokine production, statins have anti-inflammatory mechanisms.

MATERIALS AND METHODS: Fifty-seven patients who had diagnosis of chronic obstructive pulmonary disease according to GOLD guideline were included in the study; 20 of them were statin users. Statin users group were patients being under medication with regular simvastatin, atorvastatin or rosuvastatin 20 mg per day for at least the past 1 year.

RESULTS: There was statistically no significant difference between patients with or without statin treatment with respect to; age, female-male ratio, COPD severity level, medication used for COPD, pulmonary function tests results and smoking habits. COPD exacerbation frequency in patients using statins was significantly less than patients not using statins ($p<0.05$). Patient number with COPD exacerbation, antibiotic treatment and outpatient clinic administration and outpatient clinic administration frequency was significantly lower in statin using patients ($p<0.05$).

CONCLUSION: COPD patients receiving statins have a lower frequency of COPD exacarbations, hospital administration and antibiotic treatment compared to patients not receiving statins.

KEYWORDS: Statin, COPD, exacerbations

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease of the lungs characterized by progressive airway obstruction [1]. Some studies have proposed a significant association between smoking and pulmonary inflammation [2,3]. However, recent studies have shown an increase in systemic inflammatory markers in non-smokers, suggesting a possible association with systemic inflammation rather than solitary pulmonary inflammation [4]. Deterioration in pulmonary functions may result in decreased functional capacity, frequent hospitalization, increase in hospitalization rates, and early mortality [5]. Currently, COPD is the fourth leading cause of mortality worldwide and is projected to be the third by 2020 [6]. The economic burden of the disease is high due to close follow-up requirements, hospitalization due to exacerbations, and long-term treatments of the disease. However, the only available options that increase survival rate are oxygen treatment and smoking cessation [7,8].

Chronic and systemic inflammation plays an important role in the pathogenesis of COPD. Statins are a class of drugs that inhibit cholesterol production in the liver by blocking the mevalonate pathway. Currently, these drugs are used in the prevention of cardiovascular diseases. In addition to their cholesterol-lowering effects, recent studies have shown that they also possess immune modulatory and pleiotropic effects [9,10]. Decrease in neutrophil infiltration and cytokine production, blockage of matrix remodelling, and slow-down in endothelial and epithelial integrity and apoptosis are the antiinflammatory mechanisms of statins in COPD patients [11]. Recently, studies have reported significant reduction in mortality [12,13] and hospitalization rates in patients receiving statins [14].

This study aimed to evaluate the possible effect of statins on the annual exacerbation frequency of COPD patients.

MATERIALS AND METHODS

Patient Selection

The study was conducted between January 2009 and September 2011 on patients with COPD visiting our outpatient clinic for routine clinical follow-up. All patients had a history of at least 20 packets per year smoking habit with some of them

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being ex-smokers. Spirometric tests performed in all patients, immediately prior to inclusion in this study, were in accordance with the GOLD guideline [15]. All patients' medical treatment included long acting beta-2 agonists, tiotropium bromur, and inhaled corticosteroids. Patients with asthma, bronchiectasis, pulmonary fibrosis, pulmonary embolism, congestive heart failure, or any organ malignancy and patients being treated with oral steroids, angiotensin-converting enzyme inhibitors (ACEi), and angiotensin receptor blockers (ARB) were excluded from the study.

Study Design

Patients without the mentioned exclusion criteria were included in the study. The possible effects of statin use on clinical COPD exacerbation was assessed with questionnaires. All research procedures were designed according to declaration of Helsinki, and all participants provided written consent for the study. Patients who had exacerbations in past one year period were included in the study. Demographic data such as height, age, sex, and body weight of these patients were recorded. Disease severity was assessed with pulmonary function tests (PFT) undertaken during the stable period of the disease prior to inclusion in the study. All spirometric assessments were performed according to the American Thoracic Society's suggestions and the same device was used in all patients [16]. Forced expiratory volume (FEV_1), forced expiratory capacity (FVC), FEV_1/FVC ratio, and forced expiratory mid-flow (FEF_{25-75}) were recorded during the first second. Disease severity was classified as FEV_1>80% (low), 50%>FEV_1<80% (moderate), 30%>FEV_1<50% (severe), and FEV_1<30% or respiratory insufficiency with FEV_1<50%, according to the GOLD guideline [15].

Patients eligible for the study were asked about statin use. Statin users included patients under medication with regular simvastatin, atorvastatin, or rosuvastatin 20 mg per day for at least the past 1 year. Patients with irregular statin use or alterations made in dosage or type were not included in the study. COPD patients treated according to GOLD criteria were grouped as statin users or non-users.

Subsequent to spirometric assessment and inclusion in the study, patients were asked to fill in a questionnaire to evaluate COPD exacerbations during the past 1year. The questionnaire included an evaluation of worsening of breathing difficulty, coughing, sputum, or change in sputum nature during the past 1 year. Beside routine clinical follow-ups, outpatient and emergency clinic administration, antibiotic treatment due to exacerbations, and hospitalization episodes during the past 1 year were also assessed. Anthonisen criteria were used to define COPD exacerbations. The presence of any two of worsening of breathing difficulty, coughing, sputum, or change in sputum nature was accepted as COPD exacerbations.

Data were filled into a chart and grouped as statin users versus non-statin users. Group-wise comparisons were made to detect whether or not statin use is associated with COPD exacerbation and hospitalization.

RESULTS

Sixty-five patients filled in questionnaires, and eight of them were excluded from the study due to missing data. The final number of patients included in the study was 57 [statin users, n=20 (35%); non-statin users, n=37 (65%)]. The mean age of patients was 67.3 (range, 37-92) and male:female ratio was 0.5. There were statistically no significant differences between statin users and non-statin users with respect to age, male:female ratio, COPD severity, medication used for COPD, PFT results, and smoking habits (Table 1). Both groups were comparable. Outpatient clinic administration out of scheduled controls was reported seven times in statin users. However, in only two cases, COPD exacerbation criteria were fulfilled. The number of non-statin users applying to the outpatient clinic out of schedule and emergency was 18 (48%) and 6 (16%), respectively. COPD exacerbation criteria were fulfilled in 24 patients from this group. COPD exacerbation frequency in statin users (0.8 exacerbations per year) was significantly less than that in non-statin users (1.2 exacerbations per year) (p<0.05). The number of patients with COPD exacerbation, antibiotic treatment, and outpatient clinic administration and outpatient clinic administration frequency were significantly lower in statin users (p<0.05). Clinical results of patients are explained in detail in Table 2.

Table 1. Patient characteristics from both groups

	Statin (+)	Statin (–)	p
Patient number	20	37	>0.05
Male/female	0.53	0.4	>0.05
Mean age	67.3 (52–90)	64.3 (37–92)	>0.05
Mean packets per year smoking	33.2	34.9	>0.05
Active smokers	16 (80%)	34 (91%)	>0.05
Mean FEV_1/FVC	68.75	64.7	>0.05
Mean FEV_1	76.95	75.8	>0.05
Mean FVC	85.95	90.1	>0.05
Mean MMEF	53.75	46.4	>0.05

FEV: forced expiratory volume, FVC: Forced vital capacity, MMEF: Maximum mid-expiratory flow

Table 2. Clinical results of statin users vs. non-statin users

	Statin users	Statin non-users	
Patients with COPD exacerbation:	2 (10%)	24 (64%)	<0.05*
Patients requiring steroid treatment	0	5 (13%)	>0.05
Patients requiring antibiotic treatment	2 (10%)	20 (%54)	<0.05*
Patient number of out of schedule outpatient clinic administration	2 (10%)	18(48%)	<0.05*
Total outpatient clinic administration	4 (20%)	32 (94%)	<0.05
Hospitalized patients	0	4 (10%)	>0.05
Emergency clinic administration	0	6 (16%)	>0.05

COPD: chronic obstructive pulmonary disease, *statistically significant

DISCUSSION

Our study showed that COPD patients may benefit from statins. The 1-year retrospective evaluation of COPD patients showed that frequency of exacerbations, out of schedule hospital administration, and antibiotic treatment due to exacerbations were significantly lower in statin users than in non-statin users.

Similar to our study results, in the study of Mancini et al.[14] a lower frequency of hospitalization and mortality were reported in COPD patients receiving statins. Furthermore, Mancini et al.[14] proposed that ACEi and ARB have similar outcomes. Recently, Wang et al.[17] showed that statin use was associated with a 30% decreased risk of COPD exacerbation, and this correlated with drug dose but was independent of the duration of therapy. In our study, patients using ACEi and ARB were not included in order to have a homogenous group and focus on the assessment of statins. In a recent study, statin use in patients hospitalized for COPD exacerbation was associated with a lower risk of subsequent and severe COPD exacerbation [18]. These results are consistent with our study results that less frequent exacerbations are seen in patients receiving statins. In addition to a lower frequency of exacerbations, a lower rate of exacerbation episodes and requirement of intubations have been reported in COPD patients receiving statins [17]. In a retrospective and population-based study, a decrease in the rate of COPD-related mortality was reported [19]. Furthermore, the study has reported a decrease in pulmonary disease- and pneumonia-related mortality. In correspondence with the literature, the non-statin users in our study had a significantly higher frequency of exacerbations. In particular, emergency ward admission in non-statin users were seen in nearly half of the patients, whereas in statin users, this ratio remained as low as 10%. A further evidence of the clinically relevant information showing a more serious clinical picture in non-statin users was the significantly higher rate of medical treatment (antibiotics, steroids) required due to the secondary effects of COPD.

Studies have assessed the effect of statins on COPD severity and progression by evaluating PFTs. Independent of smoking status, some studies have reported a reduced decline in FEV_1 for statin users compared with non-users [20,21]. However, a reduced decline in FEV_1 was not observed by the Heart Protection Study Collaborative Group while assessing the effect of simvastatin on mortality due to various diseases [22]. The lowered COPD mortality rates in simvastatin users were also seen in the study group's results. As we did not perform control PFTs in our study, the possible outcomes could not be evaluated.

The current literature supports the idea of inflammation playing an important role in the pathogenesis of COPD [4,23]. Particularly, disease severity has been shown to be related with the underlying inflammation [24]. Neutrophil accumulation in the airway results in the expression of pro-inflammatory cytokines (especially TNF-alpha and interleukins), which are a fundamental part of the pathogenesis. In a recent experimental animal study evaluating the effect of simvastatin on airway inflammation in COPD, decreases in inflammatory markers such as leukocytes, macrophages, eosinophils, TNF-alpha, IL-4, and IL-13 were reported [25]. In another study evaluating the cardiovascular risk of COPD patients, an increase in C-reactive protein (CRP) was found to be related to COPD severity [26]. Although inhaled corticosteroids are beneficial in decreasing inflammation occurring in the airways, it was found to be associated with an increased risk of pneumonia [27]. The discovery of the anti-inflammatory effects of statins independent of their cardioprotective effect [28] has led to the investigations on their possible benefits in inflammatory diseases [29,30]. Although we did not evaluate the inflammatory markers of COPD patients in this study, the decrease in the frequency of exacerbations may be due to the anti-inflammatory effect of statins; similar observations have been made by Blamoun et al.[31]. Recent literature reviews have suggested that the anti-inflammatory effect of statins on the airways is independent of inhaled corticosteroid treatments [11,19,32,33]. In our study, to overcome the possible bias that would arise from different medical treatment regimens, all patients received inhaled corticosteroid treatment.

The main limitations of our study were the small sample size and no follow-up of the FEV_1 and CRP values due to the retrospective nature of the study. However, our study has objected to evaluate only one topic without causing any confusion. The study mainly aimed to assess the possible effect of statins on exacerbation frequency and its medical management.

In conclusion, this study shows that COPD patients receiving statins have a lower frequency of COPD exacerbations, hospitalization, and antibiotic treatment compared with patients not receiving statins. Further randomized prospective studies with larger sample size need to be conducted to confirm the results of this study.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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