ORIGINAL ARTICLE

The influence of simvastatin on selected inflammatory markers in patients with chronic obstructive pulmonary disease

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KEY WORDS

chronic obstructive pulmonary disease, inflammation, simvastatin

ABSTRACT

INTRODUCTION There is growing evidence that chronic obstructive pulmonary disease (COPD) is a risk factor for coronary heart disease. Simvastatin is a hypolipemic drug with proven efficacy in the prevention of cardiovascular diseases. Observational studies showed that statins may be useful in the reduction of mortality from COPD. Experimental studies on animals showed anti-inflammatory effects of statins on the lung tissue.

OBJECTIVES The aim of this study was to evaluate the influence of simvastatin on inflammatory markers in patients with COPD.

PATIENTS AND METHODS Fifty-six patients (aged 44–80 years) with stable COPD (a mean forced expiratory volume in 1 second [FEV_1] 55%), were randomly assigned (1:1) to receive simvastatin 40 mg/day or to receive no statin treatment. Blood samples were collected before, 2 weeks, and 3 months after statin administration. The levels of fibrinogen, C-reactive protein (CRP), tumor necrosis factor-α, interleukin 6 (IL-6), and matrix metalloproteinase-9 were measured.

RESULTS The groups did not differ significantly in terms of demographic data, clinical symptoms, pharmacological treatment, spirometry, and lipid profile at baseline. Among comorbidities only arterial hypertension was more frequent in the statin group (32.1% vs. 17.9%, $P = 0.03$). After 2 weeks as well as 3 months of simvastatin treatment, no significant reduction of any measured inflammatory markers was observed. There was a nonsignificant reduction of CRP and IL-6 in the subgroup with $FEV_1 > 50\%$ during simvastatin treatment. There was a decrease in total cholesterol (from 5.7 to 4.7 mmol/l, $P = 0.0018$) and low-density lipoprotein cholesterol (from 3.46 to 2.47 mmol/l, $P = 0.000037$) in the statin group.

CONCLUSIONS In COPD patients, a 3-month treatment with simvastatin does not reduce circulating inflammatory markers.

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INTRODUCTION Chronic obstructive pulmonary disease (COPD) is a chronic and progressive inflammatory respiratory disorder with clinical manifestation of airflow limitation that is not fully reversible.[1,2] The pathogenesis of COPD lies in an abnormal, enhanced inflammatory response of the lungs invoked by noxious particles and gases, especially cigarette smoke.[3,4] Lung macrophages and epithelial cells in response to insults such as cigarette smoke produce and release proinflammatory chemokines, such as tumor necrosis factor-α (TNF-α), interleukin 8 (IL-8), leukotriene B_4, which induce activation and migration of neutrophils to the lungs.[5-8] Activated neutrophils damage the lung tissue by producing and releasing proteinases and reactive oxygen species and by inactivating protective antiproteinases.[9-11] Prolonged irritation of the respiratory tract with noxious particles in susceptible individu-

als provokes an uncontrolled inflammation and irreversibly destroys the lung tissue.

Pathological changes in COPD affect the proximal and peripheral airways as well as the lung parenchyma and vasculature causing chronic bronchitis, emphysema, and pulmonary hypertension. Extrapulmonary manifestations of COPD include cachexia, muscle wasting and weakness, depression, and an increased risk of cardiovascular diseases.

Several retrospective studies showed an association between the symptoms of COPD, airway obstruction measured by spirometry and increased morbidity and mortality from cardiovascular diseases.[12-15] Another study showed that symptoms of airway obstruction, together with elevated blood levels of C-reactive protein (CRP), increased the risk of myocardial infarction in the future.[16]

Simvastatin represents a class of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins), which decrease the blood cholesterol level by inhibiting its synthesis and increasing the expression of low-density lipoprotein (LDL) receptors in the liver. Apart from hypolipemic effect, the blocking of HMG CoA reductase inhibits the synthesis of isoprenoids, derivatives of mevalonic acid, which activate many cell signal pathways and are responsible for the so called pleiotropic properties of statins.[17-20] Anti-inflammatory and antithrombotic effects of statins reduce cardiovascular event rates and mortality.[21]

It has been observed that statin treatment has a beneficial effect in patients with COPD. Retrospective analysis of the mortality rate from various causes and the amount of statins sold in the Japanese population aged over 65 years demonstrated a correlation between statin use and reduction of mortality, not only from cardiovascular diseases, but also from COPD, pneumonia, as well as overall mortality.[22] A prospective study with a 2-year follow-up conducted in Norway on patients hospitalized due to COPD exacerbation showed better survival of patients treated with statins.[23] Retrospective analysis based on the registry of patients in Quebec, Canada, showed that statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers reduced the rate of hospitalizations due to COPD exacerbations, regardless of the treatment with inhaled corticosteroids.[24]

Apart from observational studies, there has been experimental research on animals that provided relevant data on statin use. In rats exposed to cigarette smoke simvastatin treatment inhibited lung tissue damage as well as the development of pulmonary hypertension through decreasing the migration of inflammatory cells and synthesis of matrix metalloproteinase-9 (MMP-9) in the lung tissue.[25] In another study, simvastatin-treated rats exposed to chronic hypoxia were protected from pulmonary hypertension by reducing smooth muscle cell proliferation in pulmonary vessels.[26]

Despite these data, the mechanisms of statin action in COPD are not fully understood. In our study, we aimed to evaluate whether simvastatin administration in patients with stable COPD can influence the levels of selected inflammatory markers measured in blood.

PATIENTS AND METHODS

Patients

We studied 56 patients, aged 44 to 80 years, with stable COPD (mean FEV_1: 55%, mean FEV_1/FVC: 57%), without exacerbations in the previous month. The exclusion criteria included the use of statin or oral corticosteroids within the past 3 months, unstable angina, myocardial infarction within the previous 6 months, congestive heart failure, chronic inflammatory diseases, liver dysfunction, renal failure, cancer, and inability to comply with study requirements. The study was approved by the local Ethics Committee and patients gave informed consent.

Study protocol

After obtaining informed consent, all patients were asked to fill out the questionnaire concerning their symptoms, smoking status, and medical history. Then, they underwent physical examination, spirometry tests, electrocardiography, and echocardiography. The participants were randomized on an open-label basis into 2 groups: the statin group received simvastatin (Zocor, MSD) 40 mg daily for 3 months, and the control group did not receive simvastatin treatment. Randomization was based on the list randomly generated by the computer. Fasting blood was collected 3 times: at the beginning of the study, and during follow-up at 2 weeks and 3 months. Lipid profile, glucose, creatinine, alanine aminotransferase (ALT), and creatine kinase (CK) levels were measured using standard laboratory methods on the day of each visit. Blood samples for the assessment of inflammatory markers were centrifuged and stored at –80°C until analysis. Fibrinogen was determined in plasma using the von Clauss method. High-sensitivity CRP level in serum was measured by nephelometry (Dade Behring, Germany). TNF-α, IL-6, and MMP-9 levels in serum were assessed by immunoassay, using commercial kits (R&D Systems, Great Britain).

Statistical analysis

Demographic data, clinical symptoms, comorbidities, treatment, spirometry and laboratory results were compared between groups using the t-test for independent variables and χ^2 Pearson test for qualitative variables. The results of inflammatory markers obtained during the 3 visits were analyzed, independently in each group, using the analysis of variance (ANOVA). Both groups were then divided into 2 subgroups according to the FEV_1 value and their results were analyzed (the cutoff value was 50%). The level of significance was set at $P < 0.05$. All calculations were performed with the Statistica 6.0 software.

TABLE 1 The comparison of the study groups in terms of demographic data, comorbidities, clinical symptoms, lipid profile, treatment, and spirometry at baseline

	Statin group (n = 28)	Control group (n = 28)	*P*
age, x ±SD	66.10 ±11.42	63.82 ±8.37	NS
male, n (%)	25 (89.3)	26 (92.7)	NS
current smoking, n (%)	11 (40)	9 (32)	NS
hypertension, n (%)	18 (64.3)	10 (35.7)	0.032
ischemic heart disease, n (%)	9 (32.1)	4 (14.3)	NS
prior myocardial infarction, n (%)	2 (7.1)	2 (7.1)	NS
hypercholesterolemia, n (%)	20 (71.4)	18 (64)	NS
diabetes mellitus, n (%)	0	0	NS
peripheral artery disease, n (%)	0	0	NS
signs/symptoms			
dyspnea, n (%)	25 (89.3)	23 (82.1)	NS
cough, n (%)	24 (85.7)	21 (75)	NS
sputum, n (%)	20 (71.4)	18 (64)	NS
lipid profile			
total cholesterol (mmol/l), x ±SD	5.69 ±1.39	5.60 ±1.05	NS
LDL cholesterol (mmol/l), x ±SD	3.47 ±0.99	3.56 ±0.80	NS
HDL cholesterol (mmol/l), x ±SD	1.43 ±0.31	1.32 ±0.30	NS
triglycerides (mmol/l), x ±SD	1.64 ±1.33	1.70 ±0.96	NS
drugs			
short-acting β mimetics, n (%)	3 (10.9)	1 (3.6)	NS
long-acting β mimetics, n (%)	26 (94.5)	24 (87.3)	NS
short-acting cholinolytics, n (%)	23 (83.6)	19 (69.1)	NS
long-acting cholinolytics, n (%)	0	0	NS
inhaled corticosteroids, n (%)	15 (54.5)	15 (54.5)	NS
theophyllin, n (%)	7 (25.5)	10 (36.7)	NS
ASA, n (%)	2 (7.1)	4 (14.3)	NS
ACE inhibitors, n (%)	5 (19.9)	9 (32.1)	NS
diuretic, n (%)	5 (19.9)	4 (14.3)	NS
β-blockers, n (%)	3 (10.9)	4 (14.3)	NS
spirometry			
FEV_1 (%), x ±SD	56.25 ±16.27	53.18 ±15.66	NS
FEV_1/FVC (%), x ±SD	57.60 ±11.58	57.48 ±10.23	NS
MEF25 (%), x ±SD	33.21 ±15.90	29.00 ±13.07	NS
MEF50 (%), x ±SD	30.04 ±15.37	28.73 ±14.19	NS
MEF75 (%), x ±SD	39.43 ±21.84	35.70 ±21.80	NS

Abbreviations: ACE – angiotensin-converting enzyme, ASA – acetylsalicylic acid, FEV_1 – forced expiratory volume in 1 second, FVC – forced vital capacity, HDL – high-density lipoproteins, LDL – low-density lipoproteins, MEF – maximal expiratory flow, NS – nonsignificant, SD – standard deviation

RESULTS

Patient characteristics

The groups did not differ significantly in terms of demographic data. No significant differences were observed with regard to clinical symptoms, lipid profile, pharmacological treatment, and baseline spirometry results. Among comorbidities, only arterial hypertension was more frequent in the statin group (32.14% vs. 17.86%, $P = 0.032$) (TABLE 1).

Lipid-lowering effect

The compliance in the statin group has been proven by a significant decrease in both total cholesterol (from 5.68 mmol/l to 4.71 mmol/l, $P = 0.0018$) and LDL cholesterol (from 3.46 mmol/l to 2.47 mmol/l, $P = 0.000037$) after 3 months of statin treatment. The decrease occurred after 2 weeks and was maintained to the end of the study. The safety of simvastatin treatment was monitored by measuring CK and ALT levels. No increase in these markers that would indicate serious adverse events and would result in exclusion from the study and terminating the treatment was detected in any of the participants (TABLE 2). Control spirometry at 3 months was comparable to the baseline results (TABLE 3).

TABLE 2 Compliance and safety measures measured during simvastatin administration at subsequent visits

	Statin group				Control group			
	visit 0	visit 1	visit 2	*P*	visit 0	visit 1	visit 2	*P*
CK (U/l)	145 ±25.82	114 ±81.56	145 ±106.1	NS	108 ±61.43	98 ±43.7	127 ±67.83	NS
ALT (U/l)	29 ±8.4	33 ±12.5	32 ±10.4	NS	33 ±14.3	33 ±9.4	32 ±7.1	NS
total cholesterol (mmol/l)	5.68 ±1.39	4.44 ±1.14	4.71 ±1.4	0.0018	5.6 ±1.04	5.72 ±1.05	5.52 ±0.99	NS
LDL cholesterol (mmol/l)	3.46 ±0.98	2.34 ±0.89	2.47 ±0.91	0.000037	3.55 ±0.79	3.56 ±0.88	3.434 ±0.86	NS

The results are shown as mean values with standard deviations.

Abbreviations: ALT – alanine aminotransferase, CK – creatine kinase, others – see TABLE 1

TABLE 3 The comparison of spirometry values at the beginning and at the end of the study

	Statin group			Control group		
	visit 0	visit 2	*P*	visit 0	visit 2	*P*
FEV_1 (%)	56.25 ±16.2	56.03 ±15.8	NS	53.17 ±15.6	56.18 ±15.4	NS
FEV_1/FVC (%)	57.6 ±11.6	57.07 ±11.5	NS	57.47 ±10.2	56.7 ±9.8	NS

The results are shown as mean values with standard deviations.

Abbreviations: see TABLE 1

None of the participants reported drug intolerance or exacerbation of symptoms. No acute cardiovascular events were observed. Pharmacological treatment was not modified in any of the patients throughout the study.

Inflammatory markers After 3 months of simvastatin treatment, there were no significant differences in the levels of any measured inflammatory markers (TABLE 4). Only an insignificant decrease in CRP was observed in the statin group (FIGURE 1). The statin group was divided into 2 subgroups: the subgroup of patients with FEV_1 >50% (with mild and moderate COPD, according to the Global Initiative on Obstructive Lung Diseases classification) and the subgroup of patients with FEV_1 <50% (with severe and very severe COPD). Such division was necessitated by a small number of patients with mild and very severe COPD – a division into 4 groups would make the statistical analysis unreliable. The subgroups were similar with regard to age, smoking status, hypercholesterolemia, and comorbidities (TABLE 5). Data analysis did not reveal significant between-group differences in the levels of inflammatory markers at baseline, 2 weeks, and 3 months, except for the IL-6 concentration, which was significantly lower in patients with mild and moderate COPD at the end of the study ($P = 0.016$) (FIGURE 2). The levels of the measured markers in individual groups remained stable throughout the study (there were no significant differences between subsequent measurements). An insignificant decrease of CRP and IL-6 was observed in the subgroup of patients with mild and moderate COPD (TABLE 6).

DISCUSSION The present study has been one of the first to investigate the effect of statin treatment on inflammation in COPD in a randomized study. Baseline concentrations of the inflammatory markers were comparable in both studied groups. CRP and IL-6 levels were similar to those observed by Garrod et al.,[27] and the meta-analysis of Gan et al.[28] showed similar CRP and fibrinogen levels. After 3 months of simvastatin treatment no significant changes in the levels of the measured markers were observed. There was

TABLE 4 Concentrations of inflammatory markers in both groups at subsequent visits

	Statin group				Control group			
	visit 0	visit 1	visit 2	*P*	visit 0	visit 1	visit 2	*P*
CRP (mg/l)	6.3 ±6	8.88 ±16.03	3.62 ±4.47	NS	3.58 ±5.24	5.21 ±7.2	3.52 ±5.03	NS
fibrinogen (g/l)	4.06 ±1.52	4.43 ±1.59	4.27 ±1.57	NS	3.94 ±1.83	4.31 ±1.68	4.11 ±1.55	NS
TNF-α (pg/ml)	2.01 ±1.05	1.67 ±0.41	1.8 ±0.7	NS	4.2 ±9.56	2.42 ±1.43	2.51 ±1.33	NS
IL-6 (pg/ml)	4.1 ±2.37	4.15 ±3.16	3.63 ±2.78	NS	3.94 ±3.5	3.78 ±3.24	3.38 ±3.05	NS
MMP-9 (ng/ml)	599 ±331	585 ±221	537 ±294	NS	548 ±262	604 ±243	621 ±241	NS

The results are shown as mean values with standard deviations.

Abbreviations: CRP – C-reactive protein, IL – interleukin, MMP – matrix metalloproteinase, TNF-α – tumor necrosis factor-α, others – see TABLE 1

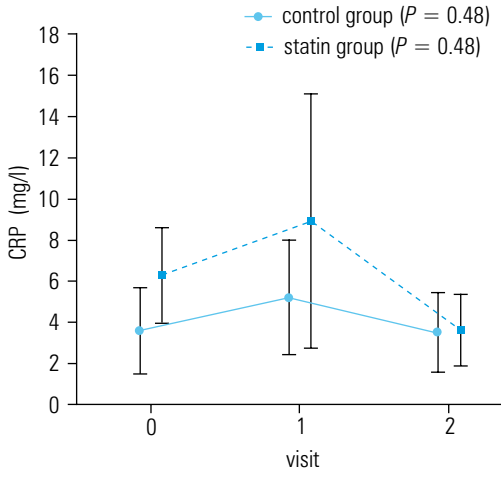

FIGURE 1
Concentrations of C-reactive protein (CRP) in the statin group and in the control group at subsequent visits. Data are shown as mean with 95% confidence intervals.

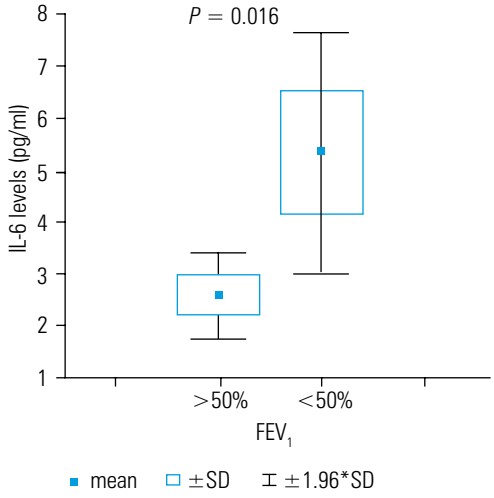

FIGURE 2 Interleukin-6 concentration in the subgroups (FEV_1 <50% and FEV_1 >50%) of the statin group at visit 2. The data are shown as mean and standard deviations.
Abbreviations: see TABLES 1 and 4

an insignificant decrease in CRP level in the statin group and in IL-6 concentration in the subgroup of patients with mild and moderate COPD. Additionally, at 3 months, a significantly lower concentration was observed in patients with FEV_1>50% when compared with the other subgroup. Our results are not consistent with the study of Lee et al.,[29] in which a significant decrease in CRP and IL-6 levels was observed. However, their study lasted 6 months, the groups were much larger, and the subjects received pravastatin. Moreover, Lee et al.,[29] observed higher IL-6 values at baseline, and reduced CRP levels were demonstrated only in patients with elevated baseline CRP. In our study, an insignificant decrease in CRP was observed mainly in patients with mild and moderate COPD.

Our results, together with the data from retrospective studies, show the complex mechanisms involved in the pathogenesis of COPD. The beneficial properties of statins, associated with a reduction of risk of cardiovascular events as well as their influence on inflammatory markers measured in blood, may be related to statin-mediated effect on unstable atherosclerotic plaques, activated endothelium, and inflammatory cells circulating in blood. The inflammatory parameters in these disorders are measured exactly at the site affected by the disease. We measured blood levels of inflammatory markers, which may not be sufficient because the major site of inflammation in COPD is the respiratory tract, even though systemic inflammation is a feature of COPD. Samples obtained directly from the respiratory tract, e.g., bronchoalveolar lavage or exhaled air condensate, might be more appropriate for the assessment of statin induced effects in COPD.

Apart from the site of inflammation, other mechanisms by which statins operate should also be considered. Numerous experimental studies showed antithrombotic and immunomodulatory properties of statins. In ischemic heart disease statins reduce the risk of acute coronary events, and thus mortality, not only by stabilizing the plaque but also by inhibiting platelet aggregation and thrombin formation.[30] Such prothrombotic and proinflammatory state occurs in exacerbated or unstable coronary heart disease. In COPD we also observe such intensification of inflammation during exacerbations. Polosa et al. revealed enhanced inflammatory state, increased activation of endothelial cells, hemostasis, and fibrinolysis during COPD exacerbations when compared with stable periods in the same patients.[31] They measured the concentration of IL-6, expression of the von Willebrand factor, and levels of D-dimer and prothrombin fragment F1+2. Blamoun et al. conducted a 1-year follow-up of patients after COPD exacerbation. They found that patients receiving statins before exacerbation were significantly less likely to have another exacerbation and were at a lower risk of intubation during follow-up.[32] Our study included only stable patients, therefore we did not observe

TABLE 5 The comparison of the subgroups with FEV_1 >50% and FEV_1 <50% of the statin group in terms of age, smoking status, comorbidities, and treatment with inhaled corticosteroids

	FEV_1 >50% (n = 18)	FEV_1 <50% (n = 10)	*P*
age, x ±SD	63.7 ±12.42	67.5 ±9.2	NS
current smoking, n (%)	7 (38.9)	4 (40)	NS
hypertension, n (%)	13 (72.2)	4 (40)	NS
ischemic heart disease, n (%)	7 (38.9)	3 (30)	NS
hypercholesterolemia, n (%)	13 (72.2)	6 (60)	NS

Abbreviations: see TABLE 1

TABLE 6 Concentrations of inflammatory markers in the subgroups with FEV_1 >50% and FEV_1 <50% of the statin group at subsequent visits

	FEV_1 >50% (n = 18)				FEV_1 <50% (n = 10)			
	visit 0	visit 1	visit 2	*P*	visit 0	visit 1	visit 2	*P*
CRP (mg/l)	6.3 ±6	5.9 ±9.62	3.18 ±4.47	NS	6.3 ±11.7	14.3 ±32.2	4.42 ±8.3	NS
fibrinogen (g/l)	4.09 ±1.52	4.36 ±1.79	4.37 ±1.27	NS	4.01 ±3.11	4.55 ±2.68	4.12 ±3.25	NS
TNF-α (pg/ml)	1.87 ±1.08	1.60 ±0.61	1.80 ±0.93	NS	2.25 ±1.94	1.79 ±0.45	1.80 ±0.63	NS
IL-6 (pg/ml)	3.82 ±2.77	3.29 ±2.65	2.60 ±1.78	NS	4.57 ±3.92	5.69 ±5.76	5.34 ±5.42	NS
MMP-9 (ng/ml)	620 ±434	587 ±192	513 ±294	NS	563 ±362	581 ±294	576 ±438	NS

The results are shown as mean values with standard deviations.

Abbreviations: see TABLES 1 and 4

differences in inflammatory markers, even in relation to disease severity. The comparison of our results with those obtained during exacerbations might provide more information about the action of statins.

It has already been mentioned that both in COPD and cardiovascular diseases enhanced inflammation is accompanied by increased activation of blood coagulation. Such observations were reported by Alessandri et al.[33] and by Ferroni et al.[34] The beneficial effect of statins may be partly associated with their antithrombotic properties. Undas et al. assessed fibrin clots obtained in vitro from COPD patients before and after simvastatin treatment. They showed that fibrin clots from COPD patients are more dense and resistant to fibrinolysis than those obtained from healthy subjects.[35] These properties were positively correlated with CRP levels. It is possible that during COPD exacerbation, when CRP level is elevated, coagulation is also activated. They also found that simvastatin administration improved the clot structure and susceptibility to fibrinolysis, so this mechanism might possibly reduce mortality in COPD patients treated with statins.

Voelkel et al. investigated the role of endothelial dysfunction in the development of pulmonary hypertension and emphysema in COPD.[36] They emphasize a key role of the vascular endothelial growth factor (VEGF) in the proper functioning of pulmonary vessels and the surrounding lung tissue. VEGF deficiency may cause dysfunction of the pulmonary endothelium by reducing prostacyclin and nitric oxide synthesis. It may also account for lung damage and development of emphysema by decreasing superoxide dismutase expression in endothelial cells and increasing pulmonary endothelial and epithelial cell apoptosis.[37] Nishimoto-Hazuku et al. discovered that simvastatin augmented VEGF synthesis in endothelial cells,[38] and this mechanism may also be in part responsible for the beneficial effect of statins in COPD, such as prevention from pulmonary hypertension in rats exposed to hypoxia as observed by Girgis et al.[39]

Limitations of the study The group of patients was relatively small and heterogeneous, and the follow-up was short. The inflammatory markers were measured only in blood and we limited the study group only to stable patients. However, the negative results obtained in our study do not exclude the potential benefits of statin use in COPD patients. Given all publications that show clinical benefits of statin use in COPD, the current results show the complexity of inflammatory processes involved in this disease as well as other potential mechanisms of action of these drugs. Thus, further prospective studies with a longer follow-up should be planned to assess the action of statins both clinically and biochemically. The inflammatory markers should also be measured in the material collected from the respiratory tract, such as exhaled air condensate or bronchoalveolar lavage, both during stable periods and exacerbations.

Conclusions In conclusion, simvastatin treatment in patients with stable COPD had no statistically significant influence on the inflammatory markers measured during the observation. A trend towards a decrease in CRP level was observed in the statin group, particularly in a subgroup with mild and moderate COPD at the end of the study, but it did not reach statistical significance. An insignificant decrease in IL-6 concentrations was observed in the subgroup of patients with mild and moderate COPD receiving simvastatin. However, there was a significant difference in IL-6 concentrations, between the subgroups with FEV_1 >50% and <50% of the statin group after 3 months of treatment.

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REFERENCES

1 Global initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2006). http://www.goldcopd.org.

2 Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J. 1977; 1: 1645-1658.

3 Burrows B, Knudson RJ, Cline MG, et al. Quantitative relationships between cigarette smoking and ventilatory function. Am Rev Respir Dis. 1977; 115: 195-205.

4 Matheson MC, Benke G, Raven J, et al. Biological dust exposure in the workplace is a risk factor for chronic obstructive pulmonary disease. Thorax. 2005; 60: 645-651.

5 Barnes PJ, Shapiro SD, Pauwels RA. Chronic obstructive pulmonary disease: molecular and cellular mechanisms. Eur Respir J. 2003; 22: 672-688.

6 Barnes PJ. Alveolar macrophages as orchestrators of COPD. COPD. 2004; 1: 59-70.

7 Chung KF. Cytokines in chronic obstructive pulmonary disease. Eur Respir J. 2001; 18: 50S-59S.

8 Barnes PJ. Mediators of chronic obstructive pulmonary disease. Pharmacol Rev. 2004; 56: 515-548.

9 Stockley RA. Neutrophils and the pathogenesis of COPD. Chest. 2002; 121: 151S-155S.

10 Noguera A, Batle S, Miralles C, et al. Enhanced neutrophil response in chronic obstructive pulmonary disease. Thorax. 2001; 56: 432-437.

11 Burnett D, Hill SL, Chamba A, Stockley RA. Neutrophils from subjects with chronic obstructive lung disease show enhanced chemotaxis and extracellular proteolysis. Lancet. 1987; 2: 1043-1046.

12 Jousilahti P, Vartiainen E, Tuomilehto J, et al. Symptoms of chronic bronchitis and the risk of coronary disease. Lancet. 1996; 348: 567-572.

13 Rosengren A, Wilhelmsen L. Respiratory symptoms and long-term risk of death from cardiovascular disease, cancer and other causes in Swedish men. Int J Epidemiol. 1998; 27: 962-969.

14 Schunemann HJ, Dorn J, Grant BJ, et al. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. Chest. 2000; 118: 656-664.

15 Engstrom G, Hedblad B, Janzon L, et al. Respiratory decline in smokers and ex-smokers - an independent risk factor for cardiovascular disease and death. J Cardiovasc Risk. 2000; 7: 267-272.

16 Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. Circulation. 2003; 107: 1514-1519.

17 Jantzen F, Könemann S, Wolff B, et al. Isoprenoid depletion by statins antagonizes cytokine-induced down-regulation of endothelial nitric oxide expression and increases NO synthase activity in human umbilical vein endothelial cells. J Physiol Pharmacol. 2007; 58: 503-514.

18 Arnaud C, Burger F, Steffens S, et al. Statins reduce interleukin-6-induced C-reactive protein in human hepatocytes: new evidence for direct antiinflammatory effects of statins. Arterioscler Thromb Vasc Biol. 2005; 25: 1231-1236.

19 Undas A, Topór-Mądry R, Tracz W. Simvastatin increases clot permeability and susceptibility to lysis in patients with LDL cholesterol below 3.4 mmol/l. Pol Arch Med Wewn. 2009; 119: 461-468.

20 Undas A, Brummel-Ziedins KE, Mann KG. Statins and blood coagulation. Arterioscler Thromb Vasc Biol. 2005; 25: 287-294.

21 Undas A, Brożek J, Musiał J. Anti-inflammatory and antithrombotic effects of statins in the management of coronary artery disease. Clin Lab. 2002; 48: 287-296.

22 Ishida W, Kajiwara T, Ishii M, et al. Decrease in mortality rate of chronic obstructive pulmonary disease (COPD) with statin use: a population-based analysis in Japan. Tohoku J Exp Med. 2007; 212: 265-273.

23 Søyseth V, Brekke PH, Smith P, et al. Statin use is associated with reduced mortality in COPD. Eur Respir J. 2007; 29: 279-283.

24 Mancini GB, Etminan M, Zhang B, et al. Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. J Am Coll Cardiol. 2006; 47: 2554-2560.

25 Lee JH, Lee DS, Kim EK, et al. Simvastatin inhibits cigarette smoking-induced emphysema and pulmonary hypertension in rat lungs. Am J Respir Crit Care Med. 2005; 172: 987-993.

26 Nishimura T, Faul JL, Berry GJ, et al. Simvastatin attenuates smooth muscle neointimal proliferation and pulmonary hypertension in rats. Am J Respir Crit Care Med. 2002; 166: 1403-1408.

27 Garrod R, Marshall J, Barley E, et al. The relationship between inflammatory markers and disability in chronic obstructive pulmonary disease (COPD). Prim Care Respir J. 2007; 16: 236-240.

28 Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax. 2004; 59: 574-580.

29 Lee TM, Lin MS, Chang NC. Usefulness of C-reactive protein and interleukin-6 as predictors of outcomes in patients with chronic obstructive pulmonary disease receiving pravastatin. Am J Cardiol. 2008; 101: 530-535.

30 Undas A, Celińska-Löwenhoff M, Kaczor M, Musiał J. New nonlipid effects of statins and their clinical relevance in cardiovascular disease. Thromb Haemost. 2004; 91: 1065-1077.

31 Polosa R, Cacciola RR, Prosperini G, et al. Endothelial-coagulative activation during chronic obstructive pulmonary disease exacerbations. Haematologica. 2008; 93: 1275-1276.

32 Blamoun AI, Batty GN, DeBari VA, et al. Statins may reduce episodes of exacerbation and the requirement for intubation in patients with COPD: evidence from a retrospective cohort study. Int J Clin Pract. 2008; 62: 1373-1378.

33 Alessandri C, Basili S, Violi F, et al. Hypercoagulability state in patients with chronic obstructive pulmonary disease. Chronic Obstructive Bronchitis and Haemostasis Group. Thromb Haemost. 1994; 72: 343-346.

34 Ferroni P, Basili S, Alessandri C, et al. Proinflammatory cytokines and hemostatic system in patients with chronic obstructive pulmonary disease. Platelets. 1997; 8: 255-259.

35 Undas A, Kaczmarek P, Sładek K, et al. Fibrin clot properties are altered in patients with chronic obstructive pulmonary disease. Beneficial effects of simvastatin treatment. Thromb Haemost. 2009; 102: 1176-1182.

36 Voelkel NF, Cool CD. Pulmonary vascular involvement in chronic obstructive pulmonary disease. Eur Respir J Suppl. 2003; 46: 28S-32S.

37 Kasahara Y, Tuder RM, Cool CD, et al. Endothelial cell death and decreased expression of vascular endothelial growth factor and vascular endothelial growth factor receptor 2 in emphysema. Am J Respir Crit Care Med. 2001; 163: 737-744.

38 Nishimoto-Hazuku A, Hirase T, Ide N, et al. Simvastatin stimulates vascular endothelial growth factor production by hypoxia-inducible factor-1-alpha upregulation in endothelial cells. J Cardiovasc Pharmacol. 2008; 51: 267-273.

39 Girgis RE, Li D, Zhan X, et al. Attenuation of chronic hypoxic pulmonary hypertension by simvastatin. Am J Physiol Heart Circ Physiol. 2003; 285: H938-H945.

ARTYKUŁ ORYGINALNY

Wpływ simwastatyny na wybrane parametry stanu zapalnego u chorych z przewlekłą obturacyjną chorobą płuc

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SŁOWA KLUCZOWE

przewlekła obturacyjna choroba płuc, simwastatyna, zapalenie

STRESZCZENIE

WSTĘP Istnieją doniesienia o związku przewlekłej obturacyjnej choroby płuc (POChP) z rozwojem chorób układu krążenia. Simwastatyna to lek hipolipemizujący o udowodnionym działaniu w prewencji chorób układu sercowo-naczyniowego. W badaniach obserwacyjnych stwierdzono, że statyny mogą zmniejszać śmiertelność z powodu POChP, a w badaniach eksperymentalnych na zwierzętach wykazano działanie przeciwzapalne statyn w tkance płucnej.

CELE Celem pracy była ocena wpływu simwastatyny na wybrane markery zapalne mierzone we krwi u chorych na POChP.

PACJENCI I METODY Do badania włączono 56 osób (w wieku 44–80 lat), ze stabilną POChP (średnia natężona objętość wydechowa pierwszosekundowa [*forced expiratory volume in 1 second* – FEV_1] wynosiła 55%). Pacjentów podzielono losowo na grupę badaną otrzymującą simwastatynę 40 mg/d oraz grupę kontrolną nieotrzymującą statyny. Próbki krwi pobierano wyjściowo, po 2 tygodniach i 3 miesiącach od rozpoczęcia terapii simwastatyną. Oceniano stężenia fibrynogenu, białka C-reaktywnego (*C-reactive protein* – CRP), czynnika martwicy guza α (TNF-α), interleukiny-6 (IL-6) i metaloproteinazy macierzy zewnątrzkomórkowej-9 (*matrix metalloproteinase-9* – MMP-9).

WYNIKI Obie grupy nie różniły się pod względem danych demograficznych, objawów klinicznych, stosowanego leczenia, parametrów spirometrycznych oraz profilu lipidowego przed leczeniem. Z chorób współistniejących jedynie nadciśnienie tętnicze występowało częściej w grupie otrzymującej simwastatynę (32,1% *vs* 17,9%, $P = 0,03$). Po 2 tygodniach oraz po 3 miesiącach stosowania simwastatyny nie zaobserwowano istotnego zmniejszenia stężeń badanych parametrów stanu zapalnego. W podgrupie chorych z $FEV_1 > 50\%$ zaobserwowano jednak nieznamienne zmniejszenie stężeń CRP i IL-6 w trakcie stosowania simwastatyny. Stwierdzono zmniejszenie stężenia całkowitego cholesterolu (z 5,68 do 4,71 mmol/l; $P = 0,0018$) oraz cholesterolu lipoprotein o małej gęstości (z 3,46 do 2,47 mmol/l; $P = 0,000037$) w grupie leczonej statyną.

WNIOSKI U chorych na POChP 3-miesięczna terapia simwastatyną nie prowadzi do zmniejszenia stężeń krążących we krwi parametrów stanu zapalnego.

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