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Use of rosuvastatin in patients with chronic obstructive pulmonary disease

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Summary

Objective

To investigate the effects of rosuvastatin on systemic inflammation, endothelial dysfunction, and clinical course of chronic obstructive pulmonary disease (COPD).

Materials and methods

This study included 110 patients with COPD and without history of cardiovascular events. These patients had high or very high cardiovascular (CV) risk (10.0 [8.0; 18.0]) according with the SCORE (Systematic Coronary Risk Estimation) scale. In order to correct CV risk, 90 patients with COPD were prescribed with rosuvastatin (10 mg) and dose titration up to reaching target levels of low density lipoprotein cholesterol according to CV risk calculated within 1 year. Control group consisted of 20 patients with COPD. We estimated the levels of high sensitive C-reactive protein (hs-CRP), inflammatory (Tumor Necrosis Factor α (TNF-α), interleukin-8 (IL-8)) and anti-inflammatory cytokines (IL-4, IL-10) in blood serum, and Vascular Cell Adhesion Molecule type 1 (VCAM-1).
Clinical course of COPD was estimated according to the number of COPD exacerbations and St.George's Respiratory questionnaire. Tolerance to physical exercise was determined using 6 minute walk test.

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Results

Therapy of rosuvastatin led to significant reduction of hs-CRP levels (21.5%, p=0.001), TNF-α (26.7%; p=0.001), IL-8 (32.6%; p=0.001), IL-4 (15.4%; p=0.001), IL-10 (16.5%; p=0.001), VCAM-1 (28.9%, p=0.003); number of COPD exacerbations (25%, p<0.001), severity of COPD symptoms according to St.George's Respiratory questionnaire (19.9%, p<0.001). The tolerance to physical exercise increased (13.2%, p<0.001). The main group demonstrated increased tolerance to physical exercise (13.2%, p<0.001). Plasma levels of TNF-α (19.3%; p=0.001) and IL-4 (30%; p=0.001) were increased in the control group together with 5% reduction of distance in 6 minute walk test (19 meters; p=0.001).

Conclusion

Rosuvastatin has anti-inflammatory, endothelium-protective, and immune-modulatory effects, influences the key systemic processes of COPD and CV diseases formation, and it can also modify the clinical course of COPD (reducing the number of exacerbations and severity of symptoms, improving tolerance to physical exercise), in patients with COPD. It is recommended to calculate CV risk and perform its correction according with the common guidelines in all patients with COPD.

Key words

Rosuvastatin, statins, chronic obstructive pulmonary disease (COPD), systemic inflammation, COPD exacerbation, COPD symptoms.

Introduction

Chronic obstructive pulmonary disease (COPD) is a global problem of modern medicine [1]. Nowadays the number of patients suffering from this disease is increasing [2]. Also the mortality caused by COPD is increasing. COPD became the 3rd leading cause of death in the world after cardiovascular diseases (CVD) [3].

CVD are the most frequent and severe comorbid diseases influencing the life quality and lifespan of patients with COPD [4–6]. Different authors indicate COPD as the cause of death in 25.0–48.8% of all death cases, 23.3% and 20.9% of them are caused by respiratory insufficiency and lung cancer, respectively [6, 7].

CVD prevalence in COPD patients is 50.0–56.5%, whereas CVD frequency in patients without COPD is 25.6% [8].

It has been found that COPD progression, increase of respiratory insufficiency worsens the prognosis of patients with COPD. Scientists agree that decrease of forced expiratory volume expired in the first second (FEV1) is one of the factors of cardiovascular lethality [9–12].

COPD patients have high cardiovascular risk, and COPD by itself is an independent factor of cardiovascular complications and mortality [13].

According with the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2017), COPD is a common disease that can be prevented and treated and that is characterized with persisting respiratory symptoms and restricted airflow related to bronchial and/or alveolar abnormalities normally caused by severe impact of damaging particles or gases [1].

At the same time, COPD is a systemic disease with extrapulmonary (systemic) manifestations that include cardiovascular system lesions, cachexia, skeletal muscle dysfunction, and osteoporosis [4, 14, 15]. Numerous observation, epidemiologic, and retrospective studies demonstrated that high levels of the markers of systemic inflammation correlated with higher frequency of admission to hospital, rapid COPD progression, and higher general and cardiovascular lethality in patients with COPD [10, 16–19].

Lungs are the epicenter of inflammation in COPD patients, and the distribution of inflammatory cytokines and oxidants into systemic circulation (so-called «spill over» effect) starts from there and leads to development of systemic inflammatory reaction [16, 20, 21].

Pulmonary inflammation in COPD patients is a pathologically enhanced inflammatory response of the airways on long-term exposure to various irritants, and cigarette smoke is the most important one of them. Inflammation plays the key role in bronchopulmonary and cardiovascular systems remodeling in COPD patients.

Modern inhalation therapy of COPD considers using M-cholinolytics, β2-agonists, glucocorticoids and reduces the severity of COPD symptoms, frequency and severity of COPD exacerbations, improves physical exercise tolerability and life quality in COPD patients, but unfortunately it fails to influence the mor-

tality of these patients and prevent progression of pulmonary function loss [1].

The active search of anti-inflammatory medications for COPD patients is going on. Potential role of various drugs like N-acetylcysteine, phosphodiesterase-4 inhibitors, cytokine antagonists, macrolides, statins, rennin-angiotensin-aldosterone system blockers has been already investigated [22, 23, 24]. At the same time, neither one of compounds with anti-inflammatory and antioxidant mechanism of action has not been included into COPD treatment guidelines by now.

Several observation retrospective studies demonstrating the following clinical effects of statin administration in COPD patients have been published, and these studies reported the reduction of total mortality, mortality caused by COPD exacerbation, decreased need of intubation during COPD exacerbation, COPD-related mortality, and reduced number of COPD exacerbations, decreased risk of admission to hospital and lung function impairment, improved tolerance to physical exercise and smaller risk of lung cancer [20, 21, 25–29].

Statins are inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA) reductase that inhibit cholesterol synthesis in liver thus mediating their lipid-lowering effect.

Pleiotropic effects of statins are caused by the fact that they abrupt formation of cholesterol synthesis pathway products like farnesyl pyrophosphate and geranyl-geranyl pyrophosphate which in their turn activate intracellular signaling regulatory molecules from the family of GTP-binding proteins (Ras, Rho, Roc) via isoprenylation. Statins reduce activation of these molecules, inhibit nuclear factor NF-kB, and activate peroxisome proliferator-activated receptors (PPAR-α and PPAR-γ) that decreases expression of adhesion molecules and chemokines (CCL2 and CXCL8), reduces synthesis of cytokines, proteinases, and down-modulates inflammation (Figure 1) [16, 17, 21, 30].

The objective of this study was to investigate the effects of rosuvastatin on systemic inflammation, endothelial dysfunction, and clinical course of COPD.

Materials and methods

This study included 110 patients with COPD (males) with 2–3 stages of the disease estimated with airflow restriction, of stable course or at least one month after successful management of COPD exacerbation who did not receive systemic glucocorticoids during at least the last 6 months. The average age of patients was 63.0 [61.0; 70.6] years. The smoking index was 49.0 [40.0; 70.0] pack-years. All patients signed informed consent for participation in this study.

Exclusion criteria were the following: history of bronchial asthma, cardiovascular events, diabetes mellitus, chronic decompensated pulmonary heart, refractory arterial hypertension (BP>140/90 mm Hg) and other diseases that could have interfered with results estimation.

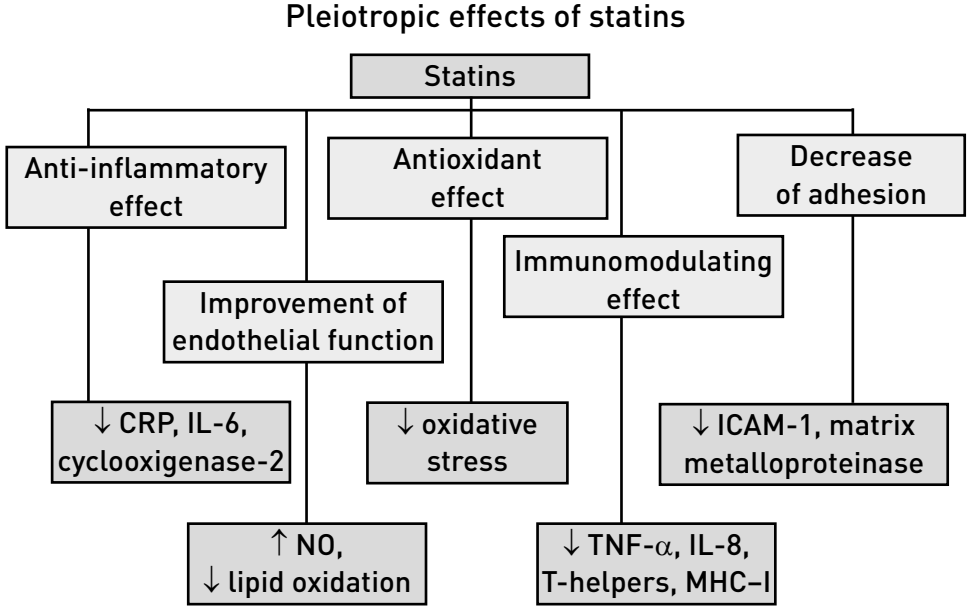

Figure 1. Pleiotropic effects of statins
CRP — C-reactive protein, IL-6 — interleukin– 6, IL-8 — interleukin 8, NO — nitric oxide, TNF-α — tumor necrosis factor — α, ICAM—Inter-Cellular Adhesion Molecule 1, MHC II — major histocompatibility complex

Table 1. **Lipid profile dynamics in COPD patients during therapy with rosuvastatin**

	Rosuvastatin group n=90				Control group n=20		
Parameters	Before treatment	After treatment	Δ (%)	p_1	Initially	After 12 months of observation	p_2
Total cholesterol (mmol/L)	5.7 [4.9; 7.1]	3.3 [2.9; 4.4]	–31.0 [–42.1; –27.6]	<0.001	5.6 [4.9; 6.9]	5.7 [4.9; 7.0]	Ns
Triglycerides (mmol/L)	1.0 [0.8; 2.1]	0.8 [0.7; 1.4]	–25.0 [–31.3; –12.5]	<0.001	1.1 [0.8; 2.0]	1.2 [0.8; 2.1]	Ns
HDL cholesterol (mmol/L)	1.5 [1.3; 1.8]	1.6 [1.4; 1.7]	6.7 [–5.6; 7.7]	Ns	1.5 [1.2; 1.7]	1.5 [1.2; 1.6]	ns
LDL cholesterol (mmol/L)	3.3 [2.9; 3.8]	1.6 [1.2; 1.8]	–50.2 [–63.2; –39.5]	<0.001	3.2 [2.7; 3.9]	3.4 [2.6; 4.0]	ns

Comment: data are present as median, the first and the third quartile (Me [Q25%, Q75%].
Δ (%) — the difference between «before» and «after» values measured in % and present as Me [Q25%, Q75%]. We used two-sided Wilkoxon t-test for estimation of differences before and after therapy with rosuvastatin. Ns — non-significant.
p_1 –significance of differences before and after therapy with rosuvastatin
p_2 — significance of differences in the control group before the study and after one year of observation

All patients underwent cardiovascular risk (CVR) estimation according with the SCORE (Systematic Coronary Risk Estimation) score that was either high or very high 10.0 [8.0; 18.0]. Patients were divided into two groups.

Rosuvastatin group included patients with COPD and it consisted of 90 individuals who received rosuvastatin for CVR correction (10 mg per day for 1 year with dose titration until reaching target levels of low density lipoprotein (LDL) cholesterol according with quantified SCORE risk: very high SCORE risk — LDL cholesterol ⩽1.8 mmol/L, high SCORE risk — LDLD cholesterol ⩽2.5 mmol/L).

20 patients with COPD were included in the control group. Members of both groups had comparable age, smoking history, COPD duration and severity, number of exacerbations, and COPD inhalation therapy. Basis COPD therapy remained unchanged during all study duration. Patients received inhalation anticholinergic drugs (ipratropium bromide, tiotropium bromide), β2-adrenomimetics (fenoterol), inhalation glucocorticoids according with the GOLD guidelines.

Concentration of cholesterol, triglycerides, LDL cholesterol, high density lipoproteins (HDL) cholesterol was performed before therapy initiation and 1, 3, 6, and 12 months after the start of treatment with rosuvastatin.

We estimated the levels of high sensitive C-reactive protein (hs-CRP), inflammatory (Tumor Necrosis Factor α (TNF-α), interleukin-8 (IL-8)) and anti-inflammatory cytokines (IL-4, IL-10) in blood serum, and Vascular Cell Adhesion Molecule type 1 (VCAM-1) in order to evaluate endothelial dysfunction using enzyme-linked immunosorbent assay.

Clinical course of COPD was estimated according to the number of COPD exacerbations and St.George's Respiratory questionnaire. Respiratory function was controlled in the beginning of the study, 6 months after the start of the treatment and one year after it. Tolerance to physical exercise was determined using 6 minute walk test.

Statistical analysis was performed using the SPSS version 22 software. Since the data were not distributed normally, data are present as median value, the first and the third quartile. Two independent samples were compared using Mann-Whitney test, whereas two-sided Wilkoxon t-test was used for comparison of two dependent samples. Comparison of dichotomous variables was performed using two-sided Fisher's exact test (for independent samples), whereas for paired nominal data we used McNemar's test. Differences were considered significant in case of $p<0.05$.

Results and discussion

All patients have reached target LDL-cholesterol levels after dose titration. There was no statistically significant dynamics of HDL cholesterol concentration (Table 1). The control group demonstrated no statistically significant dynamics of blood lipid concentration.

There were no significant changes of concentration of liver transaminases, blood glucose, and glomerular filtration rate.

Hs-CRP levels were decreased by 21.5% (p=0.001) during therapy with rosuvastatin, whereas no statistically significant dynamics was observed in the control group (Table 2).

Patients receiving rosuvastatin demonstrated significant decrease of VCAM-1 concentration by 28.9% (p=0.003), and control group patients had no significant dynamics of this parameter (Table 2).

Rosuvastatin group was characterized with statistically significant decrease of serum levels of inflammatory markers (TNF-α, IL-8) and anti-inflammatory cytokines (IL-4, IL-10) that indicated reduction

Table 2. ***Dynamics of markers of systemic inflammation and endothelial dysfunction in COPD patients during therapy with rosuvastatin***

	Rosuvastatin group n=90				Control group n=20			
Parameters	Before treatment	After treatment	Parameters	Before treatment	After treatment	Parameters	Before treatment	After treatment
Hs-CRP,mg/L	3.3 [2.2; 4.7]	2.8 [1.7; 3.8]	–21.5 [–23.5; –19.1]	0.001	3.4 [2.3; 4.6]	3.6 [2.5; 4.4]	Ns	ns
VCAM-1, ng/mL	1176 [846; 1380]	795 [740; 875]	– 28.9 [–35.3; – 4.8]	0.003	1160 [850; 1390]	1190 [960, 1400]	Ns	Ns
Blood TNF-α, pg/mL	7.02 [5.68; 7.8]	5.2 [3.8; 6.3]	– 26.7 [–32.5; –18.6]	0.001	7.3 [5.50; 7.9]	8.76 [6.27; 8.37]	19.33 [13.6; 6.18]	0.001
Blood IL-8, pg/mL	2.71 [1.5; 3.48]	1.8 [0.93; 2.85]	– 32.6 [–38.1; –17.3]	0.001	2.61 [1.71; 3.60]	3.9 [1.93; 3.66]	Ns	Ns
Blood IL-4, pg/mL	1.4 [0.8; 2.21]	1.18 [0.64; 1.99]	–15.4 [–20.4; –10.6]	0.001	1.40 [0.9; 2.22]	1.82 [1.2; 2.93]	30.0 [23.2; 63.54]	0.001
Blood IL-10, pg/mL	26.4 [15.2; 39.45]	22.0 [7.6; 39.1]	–16.5 [–50.5; –0.33]	0.001	25.2 [17.5; 39.4]	26.6 [18.0; 39.3]	Ns	Ns

Comment: see Table 1.

of systemic inflammation (Table 2). Lower levels of anti-inflammatory cytokines could be explained with smaller necessity of their involvement into systemic inflammatory reaction and suppression of macrophage activity. Control group patients demonstrated increased concentrations of TNF-α (19.33 %, p=0.001) and corresponding increase of IL-4 levels (30 %, p=0.001) that may be caused by progression of systemic inflammation (Table 2).

Decreased levels of markers of systemic inflammation and endothelial dysfunction during rosuvastatin therapy indicate their anti-inflammatory, immunomodulating, and endothelium-correcting action in patients with COPD.

Evaluation of COPD clinical course during therapy with rosuvastatin

Rosuvastatin therapy resulted in significant 25 % decrease of the number of COPD exacerbations during one year (Table 3).

The frequency of COPD respiratory symptoms (the «Symptoms» scale), physical exercise restriction (the «Activity» scale), the number of psychological and social problems related to COPD (the «Impact» scale) determined using Saint George's Questionnaire significantly decreased that demonstrated the positive impact of rosuvastatin on COPD clinical course. There was no statistically significant dynamics in the control group (Table 3).

According to the results of 6-minute walk test, patients with COPD who received rosuvastatin demonstrated statistically significant increase of physical exercise tolerance as the distance passed in this test increased by 50m (13.2 %) (p<0.001). Control group patients were characterized with decrease (p=0.001) of this test results by 19 m (5 %) and may be explained by COPD progression (Table 3).

There was no statistically significant dynamics of spirometry results during rosuvastatin therapy,

Table 3. **Dynamics of COPD clinical course during therapy with rosuvastatin**

	Rosuvastatin group n=90				Control group n=20		
Parameters	Before treatment	After treatment	Parameters	Before treatment	After treatment	Parameters	Before treatment
Number of COPD exacerbations	2.0 [1.0; 4.0]	1.5 [0.5; 3.5]	–25.0 [–50.0; –12.5]	<0.001	2.0 [1.0; 3.9]	2.0 [1.2; 3.8]	ns
Number of meters passed at 6-minute walk test	378.0 [270.0; 450.0]	428.0 [280.0; 531.0]	13.2 [3.7; 18.0]	<0.001	379.0 [271.0; 448.3]	360 [260.0; 420.0]	0.001
St.George's Respiratory questionnaire							
Symptoms, points	70.2 [56.0; 85.6]	56.2 [37.7; 74.9]	–19.9 [–32.7; –12.5]	<0.001	70.2 [56.0; 85.6]	76.9 [62.1;86.5]	ns
Activity, points	45.5 [36.6; 51.2]	38.0 [29.6; 47.2]	–16.4 [–19.1; –7.8]	<0.001	46.3 [33.6; 50.2]	45.4 [34.1; 88.2]	ns
Impact, points	36.0 [32.7; 38.1]	35.6 [33.9; 38.0]	–1.1 [–0.26; +3.7]	Ns	36.2 [32.5; 37.1]	35.6 [33.1; 38.4]	ns
Total score, points	47.8 [41.0; 54.4]	39.3 [31.4; 46.6]	–17.8 [–23.4; –14.33]	<0.001	48.1 [40.5; 55.9]	49.2 [42.8; 56.8]	ns
Comment: see Table 1							

whereas the control group demonstrated statistically significant reduction of FEV_1 ($p<0.001$).

Thus, rosuvastatin has anti-inflammatory, endothelium-protective, and immunomodulating effects in COPD patients, influences the key systemic processes of COPD and CVD development, and is able to modify the clinical course of COPD (reducing the frequency of exacerbations and severity of symptoms and improving physical exercise tolerability).

Our results correspond to previous studies that have been conducted in different countries and assessed statin use in COPD patients [20, 21, 25, 27–29].

In order to perform optimal CVD prevention in COPD patients, it is necessary to include COPD in cardiovascular risk stratification scales.

It is also necessary to conduct major randomized studies on statin use in COPD patients with/without CVD.

It is also reasonable to compare effects of various statin therapeutic regimens in COPD patients (drugs, dose, and duration of treatment) in order to reduce the risk of cardiovascular complications and to slow down COPD progression.

The problem of individual LDL-cholesterol target levels for slowing down the disease progression in COPD patients remains unsolved, and additional criteria of statin efficacy in COPD patients have not been elaborated yet.

Conclusion

In all COPD patients cardiovascular risk should be estimated according with common methods and indications for statin administration as well as individual target LDL-cholesterol levels should be identified. It is reasonable to include rosuvastatin to therapeutic regimens of COPD patients, since rosuvastatin affects the key systemic mechanisms of COPD progressing and cardiovascular damage and it also has anti-inflammatory, antioxidant, and endothelium-protective effects being able to modify COPD course and to improve the prognosis of COPD patients.

Conflict of interest: None declared

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