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Value of C-reactive protein and the type IV collagen measurement in patients with severe COPD

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Abstract
The burden of chronic obstructive pulmonary disease (COPD) is considerable, both socially and economically. In many countries, COPD prevalence is directly related to the prevalence of tobacco smoking. Alternate risk factors to cigarette smoke include exposure to occupational dusts and chemicals, and indoor pollution from biomass fuels. Patients with COPD have an ongoing systemic inflammation, which can be assessed by measuring serum C-reactive protein (CRP).

Keywords: Chronic obstructive pulmonary disease, CRP, roflumilast, collagen IV.

1. Introduction
Chronic obstructive pulmonary disease (COPD) is a major worldwide health problem with increasing prevalence and incidence. It is characterized by cellular inflammation and structural remodeling of small airways and progressive deterioration of lung function due to airway obstruction [1-4]. Patients with COPD have an ongoing systemic inflammation, which can be assessed by measuring CRP.

Although primarily affecting the lungs, the chronic inflammatory process of COPD does have systemic repercussions. C-reactive protein (CRP) is an ancient highly conserved molecule and a member of the pentraxin family of proteins. CRP is secreted by the liver in response to a variety of inflammatory cytokines. CRPs shows a 1000-fold or more increase in concentration during the occurrence of an injury, inflammation or tissue death [5]. In COPD patients increased CRP levels are associated with poor lung function, reduced exercise capacity and worse quality of life as well as being a significant predictor of all-cause mortality [13-16].

Type IV collagen, the predominant component of basement membranes, is the most abundant nonfibrillar collagen in the lung. Type IV collagen is a main component of the basement membrane (BM); the α3 chain is the most commonly expressed in lungs. Collagen type IV is degraded by the macrophage matrix metalloprotease MMP-12, which is elevated during inflammation leading to pathological structural changes in lungs [11-12].

Systemic inflammation is associated with, and appears to be a risk factor for, a variety of symptoms and conditions including weight loss, muscle wasting, atherosclerosis, malignancy, osteoporosis, diabetes, and anemia. One novel class of compounds that may deliver therapeutic Benefit in COPD is phosphodiesterase (PDE)-4 inhibitors. PDE is a generic term that describes a large superfamily of Enzymes that catalyze the breakdown of cyclic adenosine 3,5-monophosphate-cGMP to their respective inactive nucleotide 5-monophosphates [6]. Eleven distinct PDE families have been identified, although most of the anti-inflammatory activity is believed to result from the inhibition of PDE 4, for which there is clinical precedent. Roflumilast is synthesized in five steps from 3-cyclopropylmethoxy-4-hydroxybenzald-ehyde [7-8]. Several clinical trials evaluating roflumilast in the treatment of COPD have demonstrated that roflumilast improves lung function and reduces exacerbations. Data suggest that roflumilast reduces moderate to severe exacerbations with the benefit most well established in patients with severe disease.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has included roflumilast as a new treatment option in its COPD management guidelines. A section on the new class, phosphodiesterase 4 (PDE4) inhibitors, describes the efficacy of roflumilast in patients with COPD [9-10].

2. Materials and methods of research.

The levels of CRP and collagen IV were studied in 61 patients in bronchoalveolar fluid (BALF) in patients with severe COPD. The patients were divided into groups based on the treatment assignment.

Group I – 85 patients who received maintenance treatment without roflumilast.

Group II – 66 patients was divided into:

II-a subgroup – 31 patients who as a part of maintenance treatment used roflumilast 500 micrograms (one tablet) once daily 30 days.

II-b subgroup – 24 patients, who as a part of maintenance treatment used roflumilast 500 micrograms (one tablet) once daily 90 days,

II-c subgroup – 11 patients, who as a part of maintenance treatment used roflumilast 500 micrograms (one tablet) once daily 180 days. There were 15 healthy persons examined (PHP). Maintenance treatment included: M-long-acting anticholinergics, β-2 agonists, short-acting inhaled and systemic glucocorticosteroids.

3. Results and Discussion

Before treatment the CRP levels were increased in 4.7 times (p <0.05) compared to the PHP. This rate in GOLD group D was in 2.7 times higher (p <0.05) than in GOLD group C. After 180 days treatment without roflumilast the positive dynamics of CRP level was not achieved. The BALF concentration of CRP in II-a subgroup became (5,1 ± 0,4) g/ l. It was also reduction of CRP levels in patients of II-b subgroup observed. This measurement after treatment was (4,7 ± 0,33) mg / L and it was in 2.9 times higher than in the control group and in 1.3 times lower than in patients of I group and in 1.1 times lower than in II-a subgroup (p <0.05). However, the maximum beneficial effect we still obsereved in patients in II-c subgroup. CRP level at the end of treatment in II-c subgroup was (4, 1 ± 0, 3) mg / L and it was in 1.5 times lower compared with the I group, but still remained in 2.5 times higher compared the rate of the PHP group.

Before the treatment, the collagen level was (57.46 ± 2.16) ng / ml (p1 <0.05).

When using our traditional baseline regimens for patients on the 30th day after the start of treatment the addition of roflumilast, the concentration of collagen type IV in the bronchoalveolar content decreased by 1.11 times compared with the data before treatment (p1 <0.05) (Table. 1).

Confirmation of the positive changes is also established by a significant decrease in the level of collagen IV of the 6-month follow-up dynamics under the influence of treatment with the use of roflumilast. This indicator has decreased in the process of therapy in 3,54 times (p1 <0,05). The effect of prolonged intake of roflumilast in patients with II-in experimental subgroup outperformed the positive dynamics of the level of collagen IV in the BALF in 3,12 times, compared with II-a subgroup (p2 <0,05), in 3,82 times – in comparison with II-б subgroup (p2 <0,05) and in 3,75 times – in comparison with the I group (p2 <0,05).

Table 1

Indexes	Groups						p1	p2	p3
	PHP, n=15	Before treatment, n=61	After treatment						
			Group I, n=12	II-a subgroup, n=23	II-б subgroup, n=15	II-в subgroup, n=11			
Collagen type IV (ng/ml)	46,25±2,33	139,08±5,63	131,76±4,87	124,44±4,63	88,52±4,92	70,44±3,19	<0,05	<0,05	<0,05

P1 – the reliability of the difference between the parameters between the indicators before treatment and after the treatment;

P2 – the reliability of the difference between the study groups; P3- is the reliability of the difference between the parameters of the study and control groups.

* - p> 0.05 difference between the indicators before and after the treatment

4. Conclusions

Inclusion of roflumilast in the complex of pharmacological therapy provided positive dynamics of collagen IV and CRP level concentration. These arguments allow us to recommend the proposed therapies for intensive distribution in the clinical practice.

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