Spectrum Journal of Innovation, Reforms and Development
Volume 38, April 2025 | ISSN (E): 2751-1731
WEBSITE: WWW.SJIRD.JOURNALSPARK.ORG

EFFECTIVE TREATMENT METHOD IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE DEPENDING ON THE STATUS OF CITOKIN

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Abstract
This article presents an analysis of the results of anti-inflammatory treatment of chronic obstructive pulmonary disease (COPD) based on changes in the dynamics of indicators of systemic inflammation depending on the type of risk and duration of treatment. Short-term administration of the anti-inflammatory drug roflumilast into the complex therapy of low-risk COPD patients provides a significant decrease in systemic inflammatory activity, which is accompanied by a decrease in the level of anti-inflammatory cytokines (IL-6, IL-8, TNF-α), CRP, fibrinogen.

Keywords: Chronic obstructive pulmonary disease, IL-6, IL-8, TNF-α, CRP, fibrinogen, treatment, roflumilast.

Introduction

In the inflammatory pathogenesis of the respiratory tract in the COPD, the state of the body's immune reactivity is of great importance. Immune changes are primarily associated with increased levels of neutrophils, macrophages, CD8+T-lymphocytes [9]. Chronic inflammatory – significant mediators of the respiratory tract in COPD include interleukin (IL)-6, tumor necrosis factor (TNF)-α, IL-8, among others. Cytokines are considered protein mediators secreted by various immune-related cells (lymphocytes, monocytes, granulocytes, endotheliocytes, etc.) in response to the entry of pathogens such as viruses, bacteria, toxins into the body. Cytokines have a wide range of biological activity, providing intercellular interactions in the immune and inflammatory response response-they perform the function of mediators of the immune system, control the strength, duration of the immune response, determine the type and strength of the inflammatory process [2, 7].

Phosphodiesterase-4 (PDE-4) chokers have long been characterized by high anti-inflammatory efficiency [1, 3, 8]. FDE-4 sufferers were included as new class drugs in COPD treatment in GOLD's updated recommendations in a case based on the principles of proving medicine. This is the first representative of the new class of drugs – roflumilast [6, 10].

PDE-4 is a non-steroidal anti-inflammatory drug, being the enzyme inhibitors responsible for specific inflammation in COPD. Roflumilast effects are based on the PDE-4 subtype 3 (A, B, and D). Each of them is involved in the regulation of cyclic adenosinmonophosphate (sAMP) metabolism and the transition to its inactive form – AMP inflammatory calling and immune cells, which calls for a decrease in the activity of proteinkinase cells, which perform phosphorylation of effector proteins [5].

This results in the release of inflammatory calling mediators and decreased inflammatory calling activity of neutrophils, T-lymphocytes (CD8+). The specific effect of PDE-4 on s-AMP and the increase in the amount of these same isoforms in inflammatory-calling cells and structures are considered enzymes in the COPD as the main target healing effect on chronic inflammation.

The use of roflumilast leads to the cessation of a special inflammatory process in the lungs due to a decrease in the function of leukocytes, endotheliocytes, fibroblasts. Roflumilast has a positive effect on the mucociliary apparatus, prevents fibrosis and the development of emphysema in lung tissue, prevents the reconstruction of pulmonary vessels.

The improvement in external respiratory function when roflumilast is used is due to its effect on the amount of neutrophils. Based on studies, the decrease in the indicators of external respiratory activity is exactly proportional to the amount of neutrophils in sputum. Increased neutrophil levels have been observed in patients with respiratory obstruction and chronic sputum separation.

For this reason, PDE-4 sufferers belong to the group of drugs that have proven clinical efficacy, are well absorbed and have extremely low side effects. But there are no studies in the modern literature that indicate the effect of these drugs on systemic inflammatory activity, depending on the categories of oesophagus. Therefore, on the basis of the analysis of the literature, it can be said that patients with COPD were born with the need to study the consequences of the disease in the long term after the intake of these drugs [4].

The purpose of the study is to increase the effectiveness of treatment in patients with chronic obstructive pulmonary disease through the use of PDE - 4 drugs.

Material and Methods

The study was conducted in the pulmonology department of the Fergana regional Multidisciplinary Medical Center 2021-2023. The review protocol was approved by the local ethics committee. All patients included in the study were explained the examination plan and received their written consent to conduct the study.

The diagnosis of COPD was made on the basis of MKB-10, clinical protocol and clinical recommendations.

Participants in the total study were 130, including 110 patients with COPD, 20 individuals with practical health. Patients with COPD were divided into 2 Groups: 1 group (53 individuals) who were in Category A and B, and 2 groups (57 individuals) who were in Category C and D.

Depending on the type of treatment carried out, the following subgroups were allocated:

Subgroup a-group 1 and 2 patients (subgroups 1A and 2 A) who are given 500 mcg of PDE-4 sufferers (roflumilast)daily in addition to broncholytic therapy;

Subgroup B-patients receiving broncholytic drugs (subgroups 1B and 2 b) under the GOLD treatment scheme.

Enzyme immunoassay was carried out in order to identify inflammatory markers. Based on serological analysis, IL-6, IL-8 ("Vector-Best", Russia), CRP, O'NO-α ("Biochemmack", Austria). Samples examined at enzyme immunoassay had a significance range of around 2-50 mkmol/L.

After patients were admitted to the inpatient, according to treatment standards, short-acting bronchodilators in addition to broncholithics of long-exposure duration were administered in an ingalation combination form (including "Berodual N" 2 doses, 1 ingalation dose of the drug stores 21 mcg of ipratropium bromide monohydrate and 50 mcg of phenoterol hydrobromide). In the

presence of indications, GCS was applied to patients of 2 groups for 5-7 days (drinking 30-40 mg per day of prednisolone). N.R. When there are 2 criteria for Anthonisen (increased hansira, increased sputum content and pus ingress), antibiotic therapy was carried out on the basis of the sensitivity results. Based on the general analysis of sputum (but), antibiotic sensitivity (as), allergic reactions and the presence of a risk factor of unpleasant consequences, the following antibiotics were used: moxifloxacin 400 mg per day, amoxicillin/clavulanate 625 mg 2 times a day or cefixime 200 mg 2 times a day for 5 days.

If the patient's oxygen saturation level is less than 88%, oxygenotherapy is carried out through the Venturi mask for 1-2 L/minute and stopped when it reaches 88-92%.

For the purpose of daily treatment, depending on the risk category of patients GOLD, the following drugs were used: long-acting m – cholinolytic-thiotropium bromide 18 mcg per day, long-acting β2-agonist (formoterol 4.5-12 mkg) 1 time per day, or the listed drugs were used together. In addition to patients in subgroups 1A and 2A, the PDE-4 inhibitor (roflumilast) is explained to be taken in the morning for 12 months from 500 mcg.

Statistical analysis of the results obtained during the study was carried out using the Statistica 10,0 software in the method of variational series.

Results

Systemic inflammatory activity, which lies on the basis of COPD, affects the progression of the disease and the development of complications. IL-6, 8, TNF-α were selected from CRP, fibrinogen, inflammatory-calling cytokines in order to assess inflammatory activity and treatment effect.

When the pre-treatment results were analyzed, it was found that systemic inflammation rates were high.

Group 1 patients had reliably higher leukocyte counts and levels of inflammatory-calling cytokines prior to treatment than Group 2 patients ($p<0.05$). In the case of Group 2 patients, however, the CRP was found to be 2 times higher than in Group 1, while the remaining rates were barely distinguishable.

Representatives of both groups were found to have a correlation between CRP, ventilation disorders, and number of lambs (YDQS) throughout the year, i.e. a negative correlation between CRP and VFE_1 in Group 1 patients ($r=-0.48$, $p<0.01$) and a strong positive correlation between heart rate (HR) ($r=-0.39$, $p<0.05$), and a strong correlation with HR in Group 2 ($r=-0.33$, $p<0.05$) and VFE_1 ($r=-0.44$, $p<0.01$).

After 1 month of combined pathogenetic treatment, the number of leukocytes in both groups of patients decreased.

In the 1A subgroup, the leukocyte count decreased by 13.5% compared to 1B. In both subgroups of Group 2, almost no reliable differentiation was observed in the decrease in leukocyte counts ($p<0.05$). CRP, on the other hand, decreased by 13% and 6% in subgroups 1A and 1B respectively ($p<0.05$), while fibrinogen decreased by 11.5% ($p<0.05$) and 6% ($p>0.05$) respectively. In subgroups 2A and 2b of Group 2, CRP decreased by 24% ($p<0.05$) and 19% ($p<0.05$) respectively, fibrinogen by 17% and 11.5% respectively.

When inflammatory cytokines were analyzed 1 month after treatment, it was found that their amount decreased in representatives of both groups.

In subgroup 1A, IL-6 decreased by 35.9% from pre-treatment rates to 14.5 pg/mL, which was reliably lower compared to subgroup 1B ($p<0.05$), while in subgroup 2A it decreased by 11.9% to make no reliable difference from subgroup 2B. A more or less similar pattern was observed in IL-8, with a greater reduction in subgroup 1A, less variation in IL-8 in subgroups 2a and 2B, and almost indistinguishable compared to subgroups 1 (15.2% and 16.6%, $p>0.05$, respectively).
TNF-α levels decreased in both groups of patients and decreased more closely in the 1A and 2A subgroups (8.1 and 8.4 pg/ml, $p>0.05$, respectively).
But despite 1 month of treatment, the indicators examined in their patients in the study did not approach the results in healthy individuals.
Results after 6 and 12 months of treatment with roflumilast we observed a decrease in the likelihood of an inflammatory response in the body of patients with COPD (Table 1).

Table 1 Changes in dynamics of inflammatory markers after 6, 12 months of treatment in patients of Group 1

Indicators	Duration of treatment	1A (n=25)	1B (n=28)
IL-6, pg/ml	After 1 month	13,9	17,6
	After 6 month	9,3*	17,9#
	After 12 month	9,1	20,2#
IL-8, pg/ml	After 1 month	19,8	25,4
	After 6 month	17,7	23,1#
	After 12 month	17,9	24,8#
TNF-α, pg / ml	After 1 month	6,9	7,4
	After 6 month	6,1	7,2#
	After 12 month	6,3	7,8#
Leukocytes, 10^9/l	After 1 month	7,5	8,9
	After 6 month	7,3	8,8
	After 12 month	6,9	7,9#
CRP, mg/l	After 1 month	4,1	4,2
	After 6 month	3,8*	4,1#
	After 12 month	3,7	4,2#
fibrinogen, g/l	After 1 month	3,3	3,3
	After 6 month	3,2	3,5#
	After 12 month	3,3	3,6

Note: * - <0.05 difference reliability compared to previous treatment time, # - relative difference reliability between subgroups A and B

In subgroup 1A patients, when the results after 6.12 months of treatment were analyzed, IL-6 decreased vividly after 6 months compared to the result after 1 month of treatment (9.3 pg/mL), and for up to 12 months this result was kept almost the same, but in subgroup 1B patients, it was practically indistinguishable from the results after 1 month of treatment, IL-8, on the other hand, was maintained in the 1B subgroup with higher post-treatment outcomes (23.1 and 24.8 pg/mL) and differed dramatically from the 1A subgroup. In contrast, TNF-α was observed to increase almost 1.2 times (7.2 and 7.8 pg/mL) after 6 and 12 months of treatment in patients with subgroups 2A as opposed to subgroups 1A. The decrease in leukocyte levels in subgroup 1A was kept almost

uniform throughout treatment, but remained elevated in subgroup 1B even 6 months after treatment, only decreasing slightly after 12 months ($7.9*10^9$/L). CRP and fibrinogen decreased vividly after 6 months of treatment in subgroup 1A and remained the same for up to 12 months, while subgroup 1B maintained the same increased amounts until the end of treatment.
Changes in inflammatory markers in Group 2 patients 6.12 months after treatment are detailed in Table 2.

Table 2 Changes in dynamics of inflammatory markers after 6, 12 months of treatment in patients of Group 2

Indicators	Duration of treatment	1A (n=25)	1B (n=28)
IL-6, pg/ml	After 1 month	15,8	16,2
	After 6 month	14,1	14,8
	After 12 month	12,8	16,7#
IL-8, pg/ml	After 1 month	21,9	21,6
	After 6 month	20,8	21,8
	After 12 month	18,7*	22,6#
TNF-α, pg / ml	After 1 month	7,2	7,9
	After 6 month	7,1	8
	After 12 month	7	8,2#
Leukocytes, 10^9/l	After 1 month	7	7,2
	After 6 month	6,2*	7,2#
	After 12 month	6,2	7,3#
CRP, mg/l	After 1 month	8	8,3
	After 6 month	6,5*	7,7#
	After 12 month	6,1	7,4#
fibrinogen, g/l	After 1 month	3,2	3,3
	After 6 month	3,1	3,5
	After 12 month	3,1	4#

Note: * - <0.05 difference reliability compared to previous treatment time, # - relative difference reliability between subgroups A and B

In subgroup 2A patients, it was observed that the result after 6 and 12 months of IL-6 treatment decreased by almost 2 pg/ml each time from the result after 1st month, i.e. 14.1 and 12.8 pg/mL, respectively. But in subgroup 2B, IL-6 levels dropped slightly after 6 months of treatment and increased again after 12 months of treatment (16.7 pg/ml). IL-8 levels decreased vividly after 12 months of treatment in the 2A subgroup (18.7 pg/mL), but were maintained in the 2B subgroup in amounts that increased almost uniformly between 6 and 12 months after treatment (21.8 and 22.6 pg/ml). The amount of TNF-α was kept almost the same in subgroup 2A until the end of treatment, but in subgroup 2b it was slightly increased (8.2 mg/ml) compared to 2A until the end of treatment. The CRP subgroup 2A decreased vividly until the end of treatment, while the subgroup 2b experienced a smaller reduction. Fibrinogen, on the other hand, was kept in the 2A subgroup at the same reduced rate until the end of treatment, but increased after 12 months of treatment in the 2B subgroup (4 g/l).
In Group 2 patients with COPD, when after 12-month outcomes from treatment were analyzed, it was observed that in a subgroup with roflumilast administration, systemic inflammatory markers

were much reduced from pre-treatment outcomes. Of the changes to the eye, IL-6 levels showed 12.8 and 16.7 pg/mL respectively in subgroups with roflumilast administration and in subgroups with basis therapy administration ($p<0.05$).

It is noteworthy that in Groups 1 and 2, the results in the periods after 6 and 12 months from treatment recorded an even higher result than the results of healthy individuals, indicating the presence of latent persisting inflammation at the same time.

Based on the results obtained, it can be said that patients with low risk of COPD showed the effect of roflumilast 1 month after treatment and stored for 12 months. During 12 months of treatment with roflumilast, pronounced changes were observed in subgroups 1A and 1B.

The effect of treatment in patients with high risk of COPD began after 6 months, after 12 months the results of systemic inflammatory markers differed sharply between subgroups A and B.

Conclusion

1. The introduction of the anti-inflammatory drug roflumilast into the complex therapy of patients with low-risk COPD in the short term provides a significant decrease in systemic inflammatory activity, which is accompanied by a decrease in the level of anti-inflammatory cytokines (IL-6, IL-8, TNF-α), CRP, fibrinogen.
2. The greatest positive dynamics of systemic inflammatory signs (IL-6, IL-8, TNF-α, CRP) in patients with high-risk COPD was achieved during long-term treatment (6 months or more) with the help of anti-inflammatory roflumilast therapy.

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