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Role of Pathogenetic Therapy and Non-Pharmacological Methods in Treatment of Patients with Chronic Obstructive Pulmonary Disease and Concomitant Type 2 Diabetes Mellitus.

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ABSTRACT

Chronic obstructive pulmonary disease and type 2 diabetes mellitus represent one of the most common comorbidities. The study included 90 patients with the diagnosis of chronic obstructive pulmonary disease and diabetes mellitus. All patients were divided into 2 groups. The 1st group included 45 patients with the comorbidity who took part in the pulmonary rehabilitation program developed with regard to concomitant diabetes mellitus and were prescribed a phosphodiesterase type 4 inhibitor roflumilastas well as standard pharmacological therapy. The 2nd group consisted of 45 patients with chronic obstructive pulmonary disease and diabetes mellitus who received standard medical treatment only. 12 months later there was a significant positive dynamics of a number of parameters in questionin the 1st group on the background of the use of roflumilast and participation in the rehabilitation programin comparison with the patients who received only standard therapy. The use of roflumilast and pulmonary rehabilitation can improve the clinical and laboratory parameters of the patients with chronic obstructive pulmonary disease and diabetes mellitus, increase the effectiveness of preventive measures and therapy and improve the quality of life of the patients.

Keywords: chronic obstructive pulmonary disease, diabetes mellitus, roflumilast, rehabilitation, cytokines.

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INTRODUCTION

At present chronic obstructive pulmonary disease (COPD) is one of the most widespread pathologies. According to various sources, it affects 4,0-25,0% of the adult population [1]. The prevalence of type 2 diabetes mellitus (T2DM) ranges 6,0-10,0% among the working age population and 8,9-16,0% among the elderly. Due to the aging of the population, an increase in the prevalence of hypodynamia, obesity and the use of refined food products more than 300 million people are expected to suffer from T2DMall around the world by 2025 [2].

The role of concomitant diseases in the course of COPD is emphasized in the definition of the disease according to the *Global Strategy for the Diagnosis,* Management, and *Prevention of Chronic Obstructive Pulmonary Disease*(GOLD 2017) [1]. COPD and T2DM represent one of the most common comorbidities in the outpatient clinical practice and occur in 2,0-16,0% of cases [3,4].

Recurrent acute exacerbations can be considered one of the main reasons for the progression of COPD which leads to an increase in the frequency of hospital admissions, a decrease in the spirometry values, a deterioration of the quality of life of the patients and, as a result, to the increased costs of treatment and disability and mortality rates [5].

According to GOLD 2017, the reduction of the frequency and severity of COPD exacerbations can be achieved by various means: quitting smoking, vaccination, patients' awareness about ongoing medical therapy, proper inhalation technique, adequate pharmacological therapy by individually selected doses of long-acting inhaled bronchodilators in combination with or without inhaled glucocorticosteroids as well as pathogenetic therapy –the use of phosphodiesterase type 4 (PDE-4) inhibitors[1,6]. For the prevention of acute exacerbations and progression of COPD special attention should be paid to non-pharmacological methods of treatment - pulmonary rehabilitation, including patients' education sessions (individual or in groups), tips on how to quit smoking, physical training, and dietary recommendations [1,7,8].

Soit seems relevant to develop and evaluate the effectiveness of the pulmonary rehabilitation program (PRP) including group education sessions, physical activity, dietary recommendations for patients with COPD and T2DM developed with regard to concomitant somatic pathology.

MATERIALS AND METHODS

The study included 90 patients (47 men and 43 women, their average age 47,83±0,43 years) with the diagnosis of GOLD stage 3 COPD and type 2 diabetes mellitus. They were randomly divided into two groups. The 1st group included 45 patients with COPD and T2DM (22 women and 23 men, the average age 47,09 ± 0,75 years) who took part in the PRP and were prescribed a phosphodiesterase type 4 inhibitor roflumilast as well as standard pharmacological therapy. The 2nd group consisted of 45 patients with COPD and T2DM (21 women and 24 men, the average age 48,58 ± 0,87 years) who received standard medical treatment only. Roflumilast (Daxas, Takeda GmbH, Germany) was prescribed according to the scheme: 500 mcg once a day irrespective of food intake with a sufficient amount of water for 2 months twice a year - in the fall and spring. The PRP was developed for patients with COPD with regard to concomitant T2DM. The PRP included group education sessions for the patients - within 10 weeks 10 workshops were held in groups of 4-5 people each lasting 1 hour 30 minutes with a 10 minutes' break. The sequence of topics was always the same. The first week was devoted to the issues of etiopathogenesis, symptoms, treatment and prevention of COPD; the second week - the issues of etiopathogenesis, symptoms, treatment and prevention of T2DM. All patients were given educational brochures, leaflets, information booklets. The PRP also included physical activity - medical gymnastics - which took place for 8 weeks after the workshops, and the patients were recommended to keep up physical training on their own later.

The study of somatic, laboratory and instrumental state of the patients was conducted at the stage of enrollment and after 12 months of follow-up. The complex clinical and laboratory examination of the patients included: assessment of the severity of the course of COPD based on the number of acute exacerbations, emergency calls to the ambulance, and hospital admissions in the last 12 months; the quantitative assessment of the severity of symptoms of COPD (dyspnea, cough, sputum) based on a 10-point visual analogue scale (VAS); the qualitative assessment of the severity of clinical symptoms of COPD using the modified British Medical Research Council (mMRC) questionnaire; the assessment of the extent the COPD symptoms affected

patients' wellbeing by using the Clinical Chronic Obstructive Pulmonary Disease Questionnaire (CCQ); spirometry according to the standard method; the biochemical analysis of venous blood samples including evaluation of the glycated hemoglobin (HbA1c) level; the evaluation of the activity of the systemic inflammatory response - proinflammatory (interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)) and anti-inflammatory (IL-4, IL-10) cytokines with the help of special test systems for EIA-BEST (Russia); evaluation of the adipocytokine profile – an orexigenic hormone (leptin) and anorexigenic hormone (adiponectin) with the help of special test systems for ELISA (Germany); assessment of exercise tolerance using the 6-minute walking test; evaluation of the impact of COPD on the quality of life (QOL) of the patients using the COPD Assessment Test (CAT); assessment of the QOL of the patients with the help of The Short Form Medical Outcomes Study 36 (SF-36) questionnaire and St. George Respiratory Questionnaire hospital (SGRQ). Statistical analysis of the data was performed on a personal computer using Statgraphics Plus 5.1 Plus for Windows.

RESULTS AND DISCUSSION

After 12 months of follow-up in the group of patients who took part in the PRP and received roflumilast as well as standard therapy there was a statistically significant positive dynamics of a number of clinical, laboratory and instrumental values. On the contrary, there were no statistically significant changes of the values in question in the group of patients that only received standard pharmacological treatment (p>0,05).

For instance, in the 1st group 12 months later there was a statistically significant decrease in the number of acute exacerbations, emergency calls and hospital admissions by 1,8; 1,6; and 1,3 times respectively (F=92,83; p=0,0000), (F=67,82; p=0,0000), (F=10,65; p=0,0016) (Table 1).

Table 1: COPD exacerbations, emergency calls and hospital admissions

Parameters, times a year	Patients with COPD and T2DM, n=45		Patients with COPD and T2DM, n=45	
	before	Roflumilast PRP	before	12 months later
Exacerbations	2,51±0,11	1,40±0,07*	2,53±0,12	2,86±0,09
Emergency calls	3,17±0,12	1,91±0,06*	2,91±0,08	2,95±0,11
Hospital admissions	2,04±0,09	1,60±0,09*	2,07±0,11	2,16±0,10

* p<0,05 - the differences between the groups are statistically significant

The data displayed in the Table 2 shows that in the 1st group of the patients there was a significant positive dynamics of the main symptoms of COPD: the number of points on the VAS scale decreased by 1,5 times for dyspnea;1,5 times for cough; and 1,7 times for sputum respectively (F=77,52; p=0,0000), (F=153,80; p=0,0000), (F=90,58; p=0,0000) (Table 2).On the mMRC scale the level of dyspnea of this category of patients dropped from 2,96 ± 0,10 to 1,98 ± 0,09 points(i.e. by 1,5 times) (F=54,26; p=0,0000) (Table 2). Theirtotal CCQ score decreased by 1,36 points (F=45,78; p=0,0000), the 'Symptom' subscale score decreased by 1,13 points (F=110,21; p=0,0020), the 'Functional state' subscale score - by 1,17 points (F=37,23; p=0,0000), the 'Mental state' scale score - by 1,33 points (F=33,19; p=0,0001).

Table 2: The severity of the COPD symptoms

Parameters, points	Patients with COPD and T2DM, n=45		Patients with COPD and T2DM, n=45	
	before	Roflumilast PRP	before	12 months later
Dyspnea (VAS)	5,77±0,16	3,97±0,12*	5,86±0,16	6,11±0,14
Cough (VAS)	5,93±0,11	3,82±0,13*	5,96±0,18	5,60±0,13
Sputum (VAS)	3,84±0,15	2,20±0,08*	3,64±0,12	3,71±0,15
Dyspnea (mMRC)	2,96±0,10	1,98±0,09*	2,93±0,42	2,84±0,08

* p<0,05 - the differences between the groups are statistically significant

According to spirometry results there were no significant differences in the parameters under study between the patients who received roflumilast and took part in the PRP and those who didn't (p>0,05).

There was no statistically significant dynamics of the HbA1c levels in both groups of patients as well, although in the 1st group of patients the HbA1c concentration decreased from 7,51±0,08 to 7,36±0,05 %, i.e. by 0,15% (F=3,70; p=0,0575) trending to significance. In the 2nd group, there were no significant changes of the HbA1c levels (7,48±0,07% before and 7,58±0,06% after 12 months of follow up).

12 months later the patients of the 1st group had a statistically significant decrease in the levels of proinflammatory cytokines: IL-6 decreased by 1,3 times; IL-8 - by 1,2 times; TNF – by 1,2 times (F=100,04; p=0,0000), (F=54,21; p=0,0000), (F=281,43; p=0,0000). As for the anti-inflammatory cytokines, the IL-4 and IL-10 concentrations increased by 1,5 times and 2,0 times respectively in this group of patients (F=107,14; p=0,0000), (F=125,29; p=0,0000) (Table 3).

Table 3: Cytokine profile

Parameters	Patients with COPD and T2DM, n=45		Patients with COPD and T2DM, n=45	
	before	Roflumilast PRP	before	12 months later
IL-6, pg/ml	12,84±0,20	10,07±0,19*	12,75±0,21	12,93±0,19
IL-8, pg/ml	13,84±0,17	11,26±0,30*	13,97±0,17	13,68±0,18
TNF, pg/ml	28,60±0,22	23,76±0,19*	28,31±0,23	28,86±0,25
IL-4, pg/ml	4,06±0,14	6,11±0,13*	3,95±0,13	3,82±0,14
IL-10, pg/ml	1,51±0,08	3,04±0,11*	1,58±0,09	1,48±0,09
Leptin, ng/dl	35,64±1,23	28,73±1,21*	35,57±1,24	35,68±1,21
Adiponectin, mg/ml	1,68±0,09	2,91±0,09*	1,64±0,08	1,58±0,07

* p<0,05 - the differences between the groups are statistically significant

The analysis of the 6-minute walking test results showed no statistically significant differences between the patients of the 1st and 2nd groups after 12 months.

There was a statistically significant positive dynamics of the CAT score for the patients that took part in the PRP and received roflumilast: the score dropped from 27,11±0,35 to 21,22±0,30 points, i.e. by 5,89 points (F=55,26; p=0,0000). The CAT score stayed the same for the patients who only received standard therapy: 27,20±0,42 points before and 27,67±0,45 points after 12 months of follow up.

The analysis of the QOL of the patients based on the results of the SF-36 questionnaire also showed some statistically significant differences between the patients of the 1st and the 2nd groups after 12 months. In the 1st group, the physical functioning score increased by 15,38 points (F=34,77; p=0,0000); the role-physical functioning score rose by 12,06 points (F=28,21; p=0,0001); the bodily pain score rose by 16,58 points (F=101,34; p=0,0000); the general health score - by 18,40 points (F=95,67; p=0,0020); the vitality score - by 18,48 points (F=26,11; p=0,0004); the social functioning score -by 13,11 points (F=88,32; p=0,0003); the role-emotional score - by 14,70 points (F=65,91; p=0,0000); and the mental health score increased by 12,57 points (F=65,72; p=0,0000), higher score meaning better QOL. There were no statistically significant changes for the patients of the 2nd group 12 months later (p>0,05).

The SGRQ score decreased significantly for the patients of the 1st group, lower score indicating better QOL. The number of points on the symptoms scale dropped by 14,50 points (F=67,23; p=0,0001); on the activity scale – by 10,90 points (F=23,14; p=0,0001); on the impacts score – by 13,41 points (F=122,71; p=0,0004); and the total score decreased by 14,19 points (F=47,01; p=0,0000). In the second group, there were no significant changes for the parameters under study (p>0,05).

The data obtained from the study demonstrated a high clinical efficiency of the pathogenetic therapy – the use of the PDE-4 inhibitor roflumilast – and the pulmonary rehabilitation program developed with regard to concomitant T2DM. The use of roflumilast and the PRP made a positive impact on the clinical and laboratory

states of the patients reducing the number of COPD exacerbations, emergency calls and hospital admissions; lowering the severity of clinical symptoms of COPD and their effects on the physical and emotional well-being of an individual; leading to a decrease in the activity of systemic inflammation; helping achieve individual goals of the treatment of type 2 diabetes mellitus and, as a result, leading to the overall improvement in the quality of life of the patients and their psychosocial adaptation.

CONCLUSIONS

Pathogenetic therapy – the use of the PDE-4 inhibitor roflumilast – and the pulmonary rehabilitation program for COPD patients developed with regard to concomitant T2DM contribute to significantly positive changes in the clinical and laboratory states of the patients leading to a decrease in the number of COPD exacerbations, emergency calls and hospital admissions (by 1,8, 1,6 and 1,3 times respectively). The pathogenetic therapy and pulmonary rehabilitation reduced the severity of clinical symptoms of COPD (dyspnea, cough, and sputum), their effects on the physical and emotional well-being of patients and the influence of dyspnea on the general health; reducing the activity of systemic inflammation leading to positive changes of the adipocytokine profile; improving quality of life of the patients.

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