

Evaluation of combination therapy in patients with acute exacerbation of chronic obstructive pulmonary disease

Key words: *chronic obstructive pulmonary disease, immune status, fenspiride, antihomotoxic therapy.*

Chronic obstructive pulmonary disease (COPD) is one of the main causes of chronic morbidity and mortality in the world, further growth of them is prognosed according to WHO [14, 15].

The main link in the pathogenesis of COPD is an imbalance in the immune system that mediate the chronic inflammatory response in the airways and the development of systemic inflammation in response to prolonged contact with harmful particles and gases [2, 8]. In this connection, it is appropriate to use fenspiride and antihomotoxic medications (AHTM) in treatment of COPD exacerbations.

We know that fenspiride slows transformation of arachidonic acid cascade and inhibits the production of prostaglandins, leukotrienes and thromboxane, which is provide anti-inflammatory, antiplatelet effect and improves the clinical course of COPD [11]. Use of AHTM provides modulation of the immune response and activation of the drainage functions, metabolic processes and mechanisms of the body heal itself. [6]

Thereby, a comprehensive evaluation of the clinical effectiveness of therapy in patients with COPD out with respect to the state of systemic immune response was carried in this work.

The goal of the work was to establish role of immune disorders in the formation COPD stages I and II and evaluation of effectiveness of correcting it by fenspiride and AHTM.

Materials and methods

99 patients with COPD stage I-II in exacerbation males aged 38 to 65 years (the average age was $56,7 \pm 7,1$ years) were examined in dynamics to solve the problems. The average duration of disease was $(8,4 \pm 1,5)$ years.

All patients were randomized by random numbers in the comparison group and 3 clinical groups. There were 20 patients in the comparison group who underwent therapy according to standards [4]. The duration of study in all clinical groups was 3 weeks. The control group consisted of 30 healthy individuals.

Depending on the assigned treatment 3 major clinical groups were formed which were similar.

I group – 26 patients were treated by an anti-inflammatory agent fenspiride in daily dose of 160 mg (two 80 mg) on a background of standard therapy.

II group – 25 patients were treated with Lymphomyosot and Mucosa compositum on a background of standard therapy.

III group – a combination of drugs: Lymphomyosot, Echinacea compositum S, Traumeel S and Bronchalis-Heel were prescribed for 28 patients who were on a background of standard therapy without the use of anti-inflammatory drugs and mucolytics.

Populations and subpopulations of lymphocytes (Lf) in peripheral blood were defined by cytoimmunofluorescent method – CD3 + -Lf (T cells), CD4 + -Lf (T-helper), CD8 + -Lf (T-cytotoxic), CD16 + -Lf (natural killer cells), CD22 + -Lf (B cells), CD25 + -Lf (activated expressing α -chain of the IL-2). The reaction of blast transformation of lymphocytes (RBTL) performed with phytohemagglutinin (PHA). Phagocytic activity of neutrophils was assessed by the degree of absorption of latex particles calculation phagocytic index (FI) Hamburg. Concentration of middle molecular fraction (11-19S) of circulating immune complexes (CIC) studied by differential precipitation in a solution of polyethyleneglycol. Serum immunoglobulins (Ig) G, A and M were determined by Mancini

method et al. (1965). The content of interleukin-4 (IL-4) and tumor necrosis factor- α (TNF- α) quantified by ELISA in 22 patients with COPD (in 11 patients II and III clinical groups) using a set of firm ProCon (Russia).

The effectiveness of drug therapy was evaluated in points for its effect on the main clinical symptoms. The degree of dyspnea was assessed in five-point scale «Medical Research Council» (0 - no, 1 - weak, 2 - average, 3 - serious, 4 - very hard) and cough and sputum volume – for the four-point scale (0 - no 1 - light 2 - medium, 3 - severe degree).

The data were processed on a PC with usage licensed software Microsoft Excel and Statistica. Statistical analysis was performed by parametric and nonparametric methods using criteria Student's (t), signs Wilcoxon (W), χ^2 and Pearson correlation coefficient [1].

Results and discussion

In COPD patients found a significant increase in the number of IL-4, and TNF- α . Thus, patients from group II were with level were respectively ($218,2 \pm 17,8$) pg / ml and ($64,5 \pm 4,3$) pg / ml, that in 4.4 and 1.3 times higher than the value in the control group. In the third group, the level of IL-4, and TNF- α significantly increased in 6.3 and 1.7 times. On the background of activation of systemic inflammatory response, as evidence of hypercytokinemia, violations in the quantitative composition of immune cells and their functional activity were observed (Table. 1).

Analysis of the immune system in patients with COPD exacerbation identified that the most significant changes occurred with the cell link, including a significant reduction in the population of CD3 + -Lf – 20.1% and + SD16 -Lf – by 34.8%. Significant decrease of intensity of RBTL on 23.5% indicated the inhibition of functional activity of T cells, that could affect the protective capabilities of the body if their number decreases.

On the background of inhibition of T-cell immunity, an increase in the number of B-lymphocytes in 1.8 times ($p < 0,05$), which is accompanied by a decrease in their functional capacity – reduction of Ig A on 31.7% ($p < 0,05$) and Ig G – on 39.0% ($p < 0,05$).

Given that between the output levels of indicators of immune status observed-vector orientation was conducted additional analysis on conditional release three types of reactions of systemic immunity: hyperergic (5 or more indicators increased by $\geq 20\%$), hypoergic (5 or more indicators reduced by $\geq 20\%$), certain immune disorders (1 to 4 indices decreased by $\geq 20\%$), which allowed to develop a differentiated approach to the appointment of therapies (Table. 2).

Evaluating the effectiveness of drug therapy was conducted with considering of the immune system. Thus, the use of fenspiride was most effective in patients with hyperergic reaction of the immune response. Significant increase (by 55.8%), the absolute number of Lf, as well as 85.5% of CD3 + -Lf and on 45.0% CD16 + -Lf were observed in this group. At 92.3% and 96.7% level of subpopulations of CD4 + -Lf and CD8 + -Lf increased that in absolute terms amounted to ($0,75 \pm 0,12$) 10^9 / l and ($0,59 \pm 0,12$) 10^9 / l. Normalization of the immune system in patients of group I was accompanied by the most severe weakening

Table 1
The average values of indicators of systemic immunity (M m)

Index	Control group (n = 30)	Patients with COPD (n = 99)
Quantity Lf, 10^9 /l	$2,4 \pm 0,23$	$2,1 \pm 0,08$
CD3 ⁺ - Lf, 10^9 /l	$1,6 \pm 0,07$	$1,3 \pm 0,06^*$
CD4 ⁺ - Lf, 10^9 /l	$0,86 \pm 0,04$	$0,8 \pm 0,04$
CD8 ⁺ - Lf, 10^9 /l	$0,52 \pm 0,03$	$0,49 \pm 0,03$
CD4 ⁺ - Lf / CD8 ⁺ - Lf	$1,7 \pm 0,19$	$1,6 \pm 0,11$
CD16 ⁺ - Lf, 10^9 /l	$0,46 \pm 0,05$	$0,3 \pm 0,012^*$
CD25 ⁺ - Lf, 10^9 /l	$0,59 \pm 0,06$	$0,7 \pm 0,05$
RBTL with PHA, 10^9 /l	$1,7 \pm 0,18$	$1,3 \pm 0,07^*$
Phagocytic index (PI), %	$69,8 \pm 7,2$	$60,5 \pm 1,1$
CD22 ⁺ - Lf, 10^9 /l	$0,39 \pm 0,04$	$0,7 \pm 0,04^*$
IgG, g/l	$13,8 \pm 1,5$	$8,4 \pm 0,18^*$
IgA, g/l	$2,0 \pm 0,24$	$1,4 \pm 0,05^*$
IgM, g/l	$0,76 \pm 0,02$	$0,83 \pm 0,016$
CIC, con. units	$51,7 \pm 3,2$	$60,7 \pm 0,45^*$

Note. * - Statistically significant ($p < 0,05$) the difference between the control group and patients.

Table 2
Distribution of patients in groups depending on the reaction of the immune response

Groups of patients	Reaction of the immune response					
	Hyperergic		Hypoergic		Certain immune disorders	
	Abs.	%	Abs.	%	Abs.	%
Comparison	5	25,0	4	20,0	11	55
I	6	23,1	5	19,2	15	57,7
II	6	24,0	5	20,0	14	56,0
III	6	21,4	7	25	15	53,6
Total number of patients	23	23,2	21	21,2	55	55,6

of inflammatory reactions, that manifested by significant decrease in the intensity of dyspnea, cough, sputum excretion and increase on 19.5% ($p<0,05$) FVC values and on 17.1% ($p<0,05$) FEV1.

Expected decline in the absolute number of Lf on 38.0% ($p<0,05$) and CD3 + -Lf on 50.5% ($p<0,05$) in patients with hyperergic type of immune response after the combination Lymfomyosot and Mucosa compositum was observed. Also the decrease of immunoregulatory subpopulations – CD4 + -Lf to 51.7% ($p<0,05$) and CD8 + -Lf on 39.1% ($p<0,05$) was found. In group II patients significant improvement in respiratory function (FVC increased on 16.6% and FEV1 – 17.9%), was noted, that proves the efficiency AHTM.

Significant improvements of the indicators of immune status in patients of groups I and II with some immune disorders were found, only in third group of patients increase in CD4 + -Lf on 42.1% ($p<0,05$) and reducing the number of CD8 + -Lf on 15.4% ($p<0,05$) were observed. Positive immune changes in group III patients were noted, a significant regression of clinical manifestations of disease and increase FVC on 16.2% ($p<0,05$) and FEV1 – 15,5% ($p<0,05$) accompanied these changes.

Clinical efficacy of the therapy was evaluated by scoring on the basis of the main symptoms of regression (Fig. 1).

The largest clinical efficacy was observed in 84.6% of patients after using fenspiride, which was on 14.6% more effective than in the comparison group ($p<0,05$) and the achievement of complete clinical remission exceeded its value by 2.8 times ($p<0,05$). The low efficiency of fenspiride was received only if hyperergic reaction of the immune response. Prescription AHTM in the second and third groups was effective respectively in 84.0% and 82.1% of patients with COPD that exceeded the indicators of the control group on 14.0% and 12.1% (Fig. 1).

The data demonstrates the effectiveness of differentiated use of fenspiride and antihomotoxic drugs in the treatment of patients with COPD stage I-II with exacerbation considering the type of immune response.

Conclusions

1. 3 types of reactions of the immune system were identified in patients with COPD: hyperergic (5 or more indicators increased more than 20%), hypoergic (5 or more indicators decreased more than 20%), certain immune disorders (1 to indices decreased over 20%). It is allows to provide differentiated therapy by fenspiride and antihomotoxic drugs.

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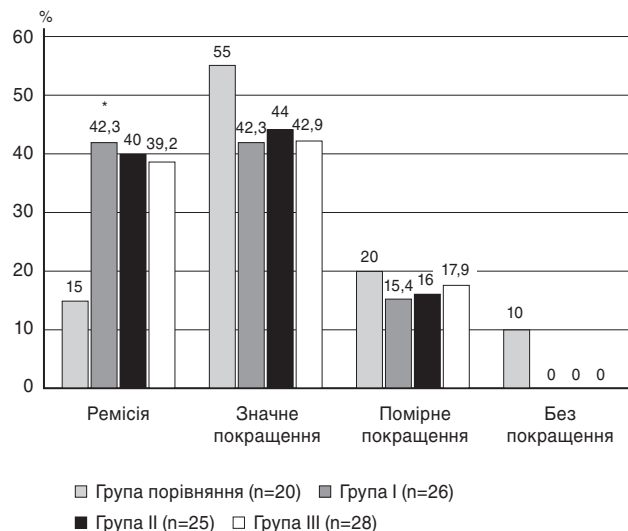


Fig.1. The effectiveness of treatment in groups of patients by clinical dynamics:

* – Statistically significant ($p<0,05$) difference between the comparison group and clinical groups by criterion χ^2 .

2. The observed increase of levels of blood cytokines such as proinflammatory (TNF- α) in 1.5 times and anti-inflammatory (IL-4) in 5,3 times is evidence of inflammatory activity in patients with COPD.

3. The most effective use of fenspiride in hypoergic type of immune response, that accompanied by positive changes in the immune status and lung function (FEV1 increases on 17.1% and FVC on 19.5%, $p<0,05$). Hyperergic type is the most optimal for assignment of Lymfomyosot and Mucosa compositum (increase of FEV1 on 18% and FVC on 17%, $p<0,05$) in the presence of certain immune disorders – combined therapy by Lymphomyosot, Traumeel S, and Echinacea compositum Bronhalis Heel (increase of FEV1 on 15.5% and FVC on 16.2%, $p<0,05$).

4. Prescription of fenspiride in patients with COPD stage II in exacerbation increases the number of patients with clinical remission and a significant improvement after treatment in 14.6%. Therapy with antihomotoxic medications such as Lymfomyosot and Mucosa compositum and combination of Lymphomyosot, Traumeel S, Echinacea compositum and Bronhalis Heel was more effective than the comparison group on 14.0% and 12.1%, respectively, due to their positive impact on immune status and inhibition of inflammatory reactions.

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