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Evaluation of the Effectiveness of Immunomodulatory Therapy in Chronic Obstructive Pulmonary Disease

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Abstract

The purpose of our study was to evaluate the effectiveness of sodium deoxyribonucleate (Derinat, solution for intramuscular injection) in combination with standard therapy in the treatment of COPD Group C patients in outpatient settings.

Materials and Methods: The study included 80 patients (43 men and 37 women) with COPD (Group C), mean age of 51.7±1.4 years. Blood sampling for the study was carried out 3 times—before the start of therapy, and on days 5 and 15. Using monoclonal antibodies, we determined the number of lyphocytes carrying markers CD3+, CD+, CD8+, and CD72+. The quality of life (QL) indicators were evaluated using the St. George's Respiratory Questionnaire (SGRQ). For at least 15 days, patients received standard COPD therapy. All patients were divided into 2 groups: Group 1 included 41 patients who received Derinat 75 mg intramuscularly once daily for 5 days; then - 5 injections with an interval of 48 hours against the background of standard therapy. Group 2 included 39 patients who continued to receive standard COPD therapy.

Results: The inclusion of Derinat in the complex therapy of COPD contributed to the normalization of the T-cell to B-cell ratio, an increase in the number of T suppressors. Assessing the clinical effects of combination therapy with the inclusion of the studied drug, a marked decrease in shortness of breath, cough, and the amount of sputum excreted can be noted in comparison with standard therapy. The improvement of the immunological status and clinical indicators against the background of complex therapy was accompanied by an increase in QL. (**International Journal of Biomedicine. 2019;9(4):300-303.**)

Key Words: sodium deoxyribonucleate • pro-inflammatory mediators • immunomodulatory therapy

Introduction

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death in the world [(1)] but is projected to be the third leading cause of death by 2020.[(2)] It should be noted that in most cases, COPD is diagnosed only in the late stages of the disease. A competent assessment of the dynamics of the COPD course is possible only with an in-depth study of all the links in the pathogenesis of the disease, namely chronic systemic inflammation and an imbalance in the system of local and systemic immune responses.

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The trigger agent for the onset of COPD is abnormal inflammation, which occurs in the small bronchi and bronchioles under the influence of various factors. Secretion of pro-inflammatory cytokines in the mucous membrane of the bronchi leads to the activation of fibroblast structures of connective tissue and development of fibrosis. All these mechanisms trigger a cascade of important pathogenic reactions, which ultimately provoke an imbalance between the immune response of the bronchial mucosa and their reparative properties. Thus, systemic inflammation is associated with local inflammation accompanied by the production of biologically active substances.[(3-5)] Macrophages are a leading factor in the pathophysiology of COPD. It has been found that the number of them in the airways reliably correlates with the severity of the disease.[(6)]

The initiation and prolongation of local inflammation is provided by neutrophils containing a complex of pro-inflammatory mediators, in particular, IL-6, IL-1β, TNF-α and CRP.[2,7] Systemic inflammation is interconnected with local inflammation and is the result of the release of biologically active substances into the systemic circulation, activation of leukocytes in the peripheral blood, as well as stimulation of hematopoietic organs with pro-inflammatory mediators. The biomarkers of the inflammatory process in COPD are IL-8, TNF-α.[8] The number of these cytokines correlates with the number of neutrophils.[9]

The relationship between the immunosuppressive effects of COPD risk factors and the inflammatory response to an infectious agent is not currently in doubt, and a number of studies confirm this.[6,10,11] In this regard, adequate immunomodulatory therapy can help increase the effectiveness of treatment. Immunomodulators are widely represented in the pharmaceutical market; however, it is extremely difficult to assess their declared effectiveness. Many studies have shown that the maximum clinical effect of immunomodulating drugs in the complex treatment of COPD can be obtained by combining the immunotropic and reparative effects of the drugs, which together provide a pronounced clinical efficacy.[7,12]

At present, sodium deoxyribonucleate (Derinat) related to nucleic acid derivatives is of particular interest as an immunomodulator in chronic diseases. According to the literature, sodium deoxyribonucleate is an agonist for Toll-like receptor 9 (TLR-9, CD289).[13,14] The immunomodulating effect of the drug is due to the interaction of the active substance (cytosine-guanine) with TLR9 on immunocompetent cells, which leads to the subsequent activation of a number of immune mechanisms. First, the stimulation of TLR in dendritic cells increases their ability to influence the differentiation of T helper cells in the direction of the formation of Type 2 T helper cells (Th2). Under the influence of Th2, B-lymphocytes differentiate into plasma cells secreting IgG_2, IgG_4, and IgM. Stimulated by TLR9, epithelial cells enhance the secretion of sIgA, which performs both the barrier function and the function of opsonin for interaction with the cellular element of the local immune response: macrophages and NK.[7,15] Thus, stimulation of macrophage TLR9 with an increase in IFNγ production leads to the activation of three levels of antiviral macrophage response.[3]

The purpose of our study was to evaluate the effectiveness of sodium deoxyribonucleate (solution for intramuscular injection, 15 mg/ml) in combination with standard therapy in the treatment of COPD Group C patients in outpatient settings.

Materials and Methods

We conducted a randomized controlled clinical trial. The study included 80 patients (43 men and 37 women) with COPD (Group C), mean age of 51.7±1.4 years.

The investigation was approved by local ethics committees, and written informed consent was obtained from all participants.

All patients had a smoking index of more than 18 pack-years and a history of no data on the presence of atopy and bronchial asthma. The diagnosis of COPD was based on a) clinical symptoms (cough, sputum production, shortness of breath), b) a history of exposure to risk factors, and c) signs of airflow limitation on spirometry: a post-bronchodilator FEV1/FVC ratio < 70%.[16]

Blood sampling for the study was carried out 3 times—before the start of therapy, and on days 5 and 15. Using monoclonal antibodies, we determined the number of lyphocytes carrying markers CD3+, CD4+, CD8+, and CD72+. Lymphocytes were isolated by sedimentation in the density gradient of ficoll verographin, according to the Böyum method. Immediately after isolation from the blood, their viability was assessed. The lymphocyte absolute number in peripheral blood was calculated according to Friemel's criteria.[17]

The quality of life (QL) indicators were evaluated according to scores on the St. George's Respiratory Questionnaire (SGRQ)[18] before the study, and on Day 15 of therapy. Scores are based on a scale of 0 to 100, with lower scores indicating better functioning. For the SGRQ, a decrease in the score reflects an improvement. The minimum important difference in the SGRQ total score has been reported to be a change of -4 points.[19,20]

Since the development of COPD by bronchitis type makes it possible to predict the deterioration of the functional state of the patient and the increased risk of exacerbation of the disease, special attention was paid to the evaluation of coughing using the Chung scale score.[21]

For at least 15 days, patients received standard COPD therapy: salmeterol 25 μg (one inhalation twice daily) and fluticasone 500 μg twice daily. All patients were randomly divided into 2 groups: Group 1 included 41 patients who received Derinat 75 mg intramuscularly once daily (slow injection for 1.5-2 minutes) for 5 days; then - 5 injections with an interval of 48 hours against the background of standard therapy. Group 2 included 39 patients who continued to receive standard COPD therapy. Patients of Groups 1 and 2 were comparable in their age, gender, clinical performance, and duration of observation

Statistical analysis was performed using StatSoft Statistica v10.0 Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean±SEM for continuous variables. Student's unpaired and paired t-tests were used to compare two groups for data with normal distribution. Mann-Whitney U test and Wilcoxon criterion were used to compare means of variables not normally distributed. A probability value of $P<0.05$ was considered statistically significant.

Results

The study results showed that in all patients before therapy, the levels of CD3+, CD4+ and CD8+ lymphocytes were decreased relative to the physiological norm by an average of 22.4±2.7%, and the values of CD72+ lymphocytes were higher than normal values by 11.4±2.7%, which indicated a prolonged sluggish chronic course of COPD in the observed patients.

Table 1.

The changes in blood lymphocyte populations and subpopulations during treatment

Day	CD3+			CD4+			CD8+			CD72+		
	Group 1	*P*	Group 2	Group 1	*P*	Group 2	Group 1	*P*	Group 2	Group 1	*P*	Group 2
Initial data	59.7±0.61	>0.05	58.1±0.59	26.4±0.51	>0.05	26.7±0.44	29.1±0.88	>0.05	28.8±0.62	16.4±0.37	>0.05	17.1±0.59
Day 5	63.1±0.39*	<0.05	59.8±0.41	31.4±0.34*	<0.05	27.8±0.57*	33.7±1.2*	<0.05	31.1±0.37*	12.8±1.4*	<0.05	15.7±0.11
Day 15	66.4±0.27*	<o.o5	61.4±0.22*	35.7±0.49*	<0.05	31.7±0.19*	41.7±0.31*	<0.05	36.3±1.1*	9.7±0.22*	<0.05	12.4±0.37*

**P<0.05 - compared to initial data*

On Day 5 of therapy, in Group 1 there was a significant increase in the levels of CD3+, CD4+, and CD8+ lymphocytes and a decrease in the CD72+ level (Table 1). By this time, in Group 1 the severity of clinical symptoms (cough, sputum, shortness of breath) was significantly reduced, which was not observed in Group 2 (Table 2). On Day 15 of therapy, in Group 1 the marked dynamics for all cells increased significantly. In Group 2, there was also a dynamics similar to Group 1, but to a much lesser extent, which was expressed by the presence of significant differences between groups at all stages of treatment. On Day 15 of therapy, in Group 1 the severity of all clinical symptoms continued to significantly decrease, in contrast to Group 2, where only cough and shortness of breath significantly decreased.

Table 2.

The dynamics of clinical symptoms during treatment

Symptom	Before treatment		Group 1		Group 2	
	Group 1	Group 2	Day 5 after therapy	Day 15 after therapy	Day 5 after therapy	Day 15 after therapy
Cough	2.3±0.2	2.4±0.1	1.4±0.2*	0.8±0.1	2.2±0.2*	1.8±0.1*
Sputum	1.5±0.2	1.4±0.1	1.1±0.1*	0.6±0.1*	1.2±0.1	0.9±0.1
Shortness of breath	2.9±0.2	2.8±0.1	1.9±0.1*	1.1±0.1*	2.4±0.2*	1.6±0.1*

**P<0.05 - compared to initial data*

Table 3.

Mean changes in SGRQ scores on Day 15 of therapy

Group	Symptoms score (points)	Activity score (points)	Impact score (points)
Group 1	-8.1±0.4	-4.6±0.3	-0.8±0.2
Group 2	-3.8±0.2	-2.1±0.2	1.4±0.1

On Day 15 of therapy, an analysis of QL using the SGRQ questionnaire indicated that more pronounced shifts on the domains of "Symptoms," "Activity" and "Impacts" (social functioning, psychological disturbances) were recorded in Group 1. In Group 2, a low QL was maintained (Table 3).

Conclusion

The inclusion of Derinat in the complex therapy of COPD contributed to the normalization of the T-cell to B-cell ratio, an increase in the number of T suppressors, which probably can increase the expression of receptors mediating the Fas-dependent mechanism of apoptosis induction, contributing to the normalization of the protective function of the bronchial mucosa and a pronounced reparative effect. However, more accurate conclusions regarding the immunotropic effects of Derinat can be obtained during a longer study with the participation of a larger group of COPD patients. Assessing the clinical effects of combination therapy with the inclusion of the studied drug, a marked decrease in shortness of breath, cough, and the amount of sputum excreted can be noted in comparison with standard therapy. The improvement of the immunological status and clinical indicators against the background of complex therapy was accompanied by an increase in QL.

Competing Interests

The authors declare that they have no competing interests.

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