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Influence of the course of stabilization of chronic obstructive pulmonary disease with bronchial obstruction of the II degree in basic tiotropium bromide treatment on the dynamics of TNF α , INF γ , IL-4, IL-6 levels and lung surfactant system

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Abstract

The research work represents data on pathogenetic characteristics of immune response, tumour necrosis factor- α (TNF α), interferon- γ (INF γ), interleukin-4 (IL-4), interleukin-6 (IL-6) and lung surfactant system (LSS) in the process of treatment of chronic obstructive pulmonary disease. Administration of tiotropium bromide (Spiriva® "Boehringer Ingelheim") in comprehensive treatment of chronic obstructive pulmonary disease with bronchial obstruction of the II degree promotes faster regression of clinical and laboratory symptoms, leading to the decrease of TNF α and IL-6 levels, as compared to patients receiving traditional therapy. The use of tiotropium bromide ensures more adequate restoration of IL-4 and INF γ levels in bronchoalveolar fluid in patients suffering from COPD with bronchial obstruction of the II degree. It has been established that the restoration of surface-active fraction of LSS was much better in patients receiving tiotropium bromide as part of their comprehensive treatment, which clearly correlates with the prolongation of drug administration.

Keywords: Chronic obstructive pulmonary disease, tumour necrosis factor - α , interferon- γ , interleukin-4, interleukin-6, lung surfactant system, tiotropium bromide

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most important issues of practical pulmonology. Particularly, world investigations show that this pathology is diagnosed on the average in 4-6% of the adult population: 14.2% of cases occur among smokers, 6.9% – among those who gave up smoking and 3.3% of cases – among those who has never smoked [1]. Over the period of 2006-2007, the incidence of chronic bronchitis in Ukraine increased by 0.51% [2].

Despite the fact that the development of COPD treatment is heavily invested, this pathology still remains one of the leading causes of mortality around the world. Currently, there are several groups of medications that can control the disease, reduce the frequency of exacerbations, and therefore modify its course. UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) research findings showed that the use of tiotropium (Spiriva®) for the treatment of COPD patients has greatly improved the lung function [4]. UPLIFT is one of the largest studies in the history of COPD, which involved 5993 patients with COPD from 37 countries worldwide. Within four years, patients who were administered tiotropium reported improvement in their quality of life as compared to the study initiation. During the treatment period the risk of mortality has reduced by 16% ($p=0.016$) in the group of patients receiving tiotropium [3]. The investigation has established positive effect of tiotropium treatment on the survival rate, even when the analysis involved some deaths cases of those who stopped using the medication ($p=0.034$) [4]. The UPLIFT research testified that tiotropium prevents the disease exacerbation and significantly reduces the number of cases of exacerbation of the disease. In addition, tiotropium significantly reduces the risk of exacerbation of the disease with subsequent hospitalization (risk ratio – 0.86; ($p<0.002$)) as compared to the control group [4].

In our opinion, the effectiveness of treatment of any pathology depends on the deep knowledge of all the components of its pathogenesis. For this reason, the study of complex and multi-system processes originating in the body during chronic obstructive pulmonary disease, the

peculiarities of local regenerative-restorative potentials formation, along with the improvement of complex medical management, by the use of tiotropium bromide (Spiriva® "Boehringer Ingelheim") with its characteristic effect, is relevant and will promote the development of modern science and improve the administration of medical care to the population. The goal of this research work is to evaluate the effect of tiotropium bromide (Spiriva® "Boehringer Ingelheim"), as an element of complex therapy, on the dynamics of TNF α , INF γ , IL-4, IL-6 levels and lung surfactant system in bronchoalveolar fluid of patients suffering from COPD with bronchial obstruction of the II degree.

Materials and methods. We have examined 11 patients suffering from COPD with bronchial obstruction of the II degree. The diagnosis was verified and formulated in accordance with the order №128 of the Ministry of Health of Ukraine from March 19, 2007 – “On the approval of clinical protocols for the provision of medical care in the specialty “Pulmonology”^[5]. The investigation was performed prior to treatment and on the 180th day of therapy with the use of conventional treatment regimens combined with tiotropium bromide (Spiriva® "Boehringer Ingelheim"). The control group involved 15 apparently healthy individuals (AHI) without obvious signs of respiratory tract disorders or any other pathology of internal organs.

The study material involved bronchoalveolar lavage, obtained with account of localization of inflammatory lung damage during fiber-optic bronchoscopy (FOB) based on Clements (1967) procedure in Ramires' modification (1980). The levels of TNF α , INF γ , IL-4, IL-6 were determined by means of enzyme-linked immunoassay using “StatFax 303 Plus” analyzer and “ProKon” reagents (LLC “Protein Contour”, Russia) in bronchoalveolar fluid obtained during fiber-optic bronchoscopy based on the above-mentioned procedure. The Vilgelm-Lugmer torsion scale was used to study the lung surfactant system.

Research findings and their discussion. The findings showed that the level of TNF- α in bronchoalveolar fluid of healthy individuals was (18.26 \pm 1.74) pg/ml, IFN- γ level was (1.28 \pm 0.11) pg/ml, IL-4 – (9.29 \pm 0.23) pg/ml, IL-6 – (46.98 \pm 3.23) pg/ml.

It has been determined that the levels of TNF- α have significantly increased by 48.91% (p <0.05) in bronchoalveolar fluid in moderate COPD course with the development of exacerbation phase as compared with the indices of the control group of patients (Table 1). The identified IFN- γ deficiency is indicative of COPD with bronchial obstruction of the II degree, as its level has decreased by 46% before treatment as compared to the AHI group where this index was (1.28 \pm 0.11) pg/ml (p <0.05). As it follows from our research, the level of IL-4 in COPD patients with bronchial obstruction of the II degree before the initiation of treatment in exacerbation phase was 3.1 times (p <0.05) lower than the similar indicator in the group of apparently healthy individuals (AHI). It must be emphasized that the characteristic feature of COPD with bronchial obstruction of the II degree was the extremely sharp increase of IL-6 titers in bronchoalveolar fluid: this indicator has increased by 3.92 times at the time of hospitalization, as compared to the indices in control group of patients (p <0.05). The obtained research data indicate disorders of local immune

response and endobronchial factors of nonspecific resistance in patients suffering from chronic obstructive pulmonary disease with bronchial obstruction of the II degree. The study revealed the involvement of immune processes in both pathogenesis and destabilization mechanisms and generation of exacerbation phase of the investigated pathology. The values of immune responsiveness vary: failure of local barrier function of respiratory-ventilative tract, stable imbalance of cytokine cascade with predomination of proinflammatory and inhibition of anti-inflammatory transmitters and endogenic interferons in bronchoalveolar fluid, and correlate to the manifestations of clinical symptoms.

The analysis of obtained findings revealed alterations in the contents of surface-active fraction of lung surfactant system as compared to the data in apparently healthy individuals (p <0.05). So the fact is that the development of exacerbation phase of COPD degree II is accompanied by the decrease of the contents of surface-active fraction of LSS. In general, patients with the studied pathology showed tendency to a significant decrease by 1.84 times of the contents of surface-active fraction of the lung surfactant system as compared to the group of apparently healthy individuals (p <0.05), which is probably related to the depletion of the cellular component.

The obtained research findings show that destabilization of inflammatory processes in bronchial system, which is the development of COPD exacerbation phase, causes depletion in the amount of surfactant in lungs due to the surface-active fraction, which may be considered as the result of dysfunction of alveolar macrophages – cellular component, namely the cellular component of surfactant system. Prolonged overload of alveolar macrophages and macrophages of airways with antigenic stimuli and products of both local and systemic inflammatory processes in COPD inhibits the chain of surfactant recycling that in its turn interrupts the supply of type II pneumocytes with the substrate necessary for regeneration of its active form. These dysfunctions result in disorders of protective barrier and anti-atelectatic mechanisms of respiratory ways.

The above-mentioned aspects of the dynamics of surface-active fraction of lung surfactant system and their dependence on the development of exacerbation phase of COPD with bronchial obstruction of the II degree suggest the importance to use complex drug therapy from the early stages of disease development; as complex drug therapy will allow to not only eliminate bronchoconstriction and inflammation but minimize destabilization and exacerbations of COPD course.

The use of tiotropium bromide (Spiriva® "Boehringer Ingelheim") for 180 days as a part of complex therapy made it possible to record the following positive tendencies. Thus, the level of TNF α reached maximum positive and close-to-normal indices upon the completion of drug therapy, so its level has substantially decreased by 1.85 times (p <0.05) (Chart1). The evaluation of the obtained findings showed that the administration of tiotropium bromide for 180 days as a part of complex drug therapy was the most effective. Upon the completion of drug therapy this index, having obtained the most positive changes, has considerably increased by 2.0 times (p <0.05), that was only 7.8% (p <0.05) lower as compared to its indices in the control group of patients.

Speaking about the IL-4 dynamics in the process of tiotropium bromide administration in patients suffering from COPD with bronchial obstruction of the II degree it must be said that we have observed the following changes. Upon the completion of drug therapy the level of IL-4 in

bronchoalveolar fluid has increased by 2.96 times ($p<0.05$). The registered reliable increase of IL-4 levels with the tendency to maximally reach the control indices is a positive indicator of the effectiveness of the administered treatment. It must be emphasized that clearly expressed positive dynamics on the part of IL-6 levels in bronchoalveolar fluid of patients suffering from COPD with bronchial obstruction of the II degree is a prominent evidence of the effectiveness of prolonged administration of tiotropium bromide. The level

of IL-6 in bronchoalveolar fluid after administered treatment has maximally reached the control group indices. It has substantially decreased by 3.4 times ($p<0.05$). We have also observed the expressed compensation of the surface-active fraction of LSS. Upon the completion of therapy this index has increased by 1.63 times, as compared to its indices before treatment ($p<0.05$), and has maximally reached the control indices.

Table 1: Changes in the levels of IL-6, IL-4, IFN- γ and TNF α (pg/ml) and surface-active fraction of the lung surfactant system ($\mu\text{mol/l}$) in bronchoalveolar fluid in the process of treatment of patients with chronic obstructive pulmonary disease with bronchial obstruction of the II degree, ($M\pm m$)

Indices	Groups of examined patients			p
	AHI, n=15	Prior to treatment, n=11	After treatment n=11	
IL-6	469.8 \pm 3.23	184.28 \pm 5.75	54.18 \pm 2.96	<0.05
IL-4	9.29 \pm 0.23	2.99 \pm 0.21	8.86 \pm 0.32	<0.05
IFN- γ	1.28 \pm 0.11	0.59 \pm 0.06	1.18 \pm 0.01	<0.05
TNF α	18.26 \pm 1.74	36.29 \pm 0.14	19.67 \pm 0.41	<0.05
Content of surface-active fraction of LSS	10.78 \pm 0.55	5.84 \pm 0.13	9.54 \pm 0.55	<0.05

Note: p – significance of differences of parameters between the indices recorded prior to and after the administered treatment

Conclusions

Summing up the obtained research data, it should be noted that complex treatment with the use of tiotropium bromide had a more pronounced effect on the correction of proinflammatory and anti-inflammatory interleukins and interferon. Prolongation of the drug administration to 180 days in complex therapy of patients suffering from COPD with bronchial obstruction of the II degree promoted ultimate regeneration of physiological significance of the studied transmitters of inflammatory process and highest possible compensation of one of the key functional units of work and barrier mechanisms of lungs – surfactant system.

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