OPTIMIZATION OF PHARMACOTHERAPY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE COMPLICATED BY BRONCHIECTASIS IN PATIENTS WITH CARDIOVASCULAR PATHOLOGY

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Summary. Chronic obstructive pulmonary disease is a weighty social health and economic problem, and remains one of the major causes of morbidity and mortality worldwide. Presently, special attention is paid to comorbid conditions, when the patient has a combination of respiratory and cardiovascular pathologies. This research has been devoted to establishing ways optimizing the treatment of moderate to acute exacerbations of chronic obstructive pulmonary disease complicated by bronchiectasis of coronary origin.

Key words: obstructive bronchitis, bronchiectasis, coronary heart disease, glutoxim, L-arginine.

INTRODUCTION

In the 20th-21st century there were accounts of sudden increase in the number of patients with chronic obstructive pulmonary disease (COPD). This pathology has now become of significant medical, social and economic problem, and remains one of the major causes of morbidity and mortality worldwide [7, 20]. Currently, according to WHO, COPD affects 0.8% of the world population, in different countries from 8 to 22% of the adult population aged 40 years and older are affected [9]. The prevalence of COPD in Europe is from 3.7 to 6.7% of the population and the number of relapses in patients with this disease varies from 1 to 4 times per year [5, 9, 20]. Morbidity and mortality rates are constantly rising. In Europe COPD is the cause of death of 200-300 thousand of people annually [9, 16]. In Ukraine, the death rate from COPD is 41.2 per 100 000 population, which is higher than the death rate from pneumonia and asthma [7, 8]. High morbidity of COPD accounts for a significant economic burden on the economies of all countries. Thus, according to GOLD in EU annual direct costs of treating COPD patients amount to 38,600,000,000 euros, in the US, the figure is 21,800,000,000 dollars, and indirect costs exceed 17 billion dollars [6, 7]. In recent decades, there has been a constant increase in the incidence of COPD. This is due to environmental pollution, especially air, smoking and aging population worldwide [7, 9].

Underdiagnosis of COPD and inadequate antimicrobial therapy have led to an increase in cases of COPD complicated by bronhiectasis. Among disadvantageous factors, attention should also be given to tobacco smoking, which is a common risk factor in the development of both cardiovascular and respiratory disease [2, 7]. Significant relevance acquires polymorbidity, which is typical of older age groups. It was in this group of patients, older than 40 years, where rapid progression of coronary heart disease (CHD) was observed. CHD occupies one of top positions in the structure of morbidity and mortality in Ukraine. The country has about 6.8 million of patients with CHD. Over the past 10 years, the incidence and mortality from CHD have been increasing continuously [1]. Considering high prevalence of CHD and high probability of serious complications that cause disability and death rate this problem has acquired not only medical but also a significant social character.

Therefore managing COPD exacerbations complicated by bronchiecstasis in patients with cardiovascular diseases require more attention and discussion as there are few reports in the literature of the subject.

The pathogenesis is due to the activity of oxidant aggression on the mucosa of the respiratory tract by reactive oxygen species and other free radicals, resulting in lipid peroxidation and damage to biological membranes [19, 23], including immune cells. Today, more and more attention is paid to the immunological reactivity in patients with COPD [3]. It has been found that the development and exacerbation of COPD is accompanied by inhibition of a local immune defense against respiratory viruses and bacteria including systemic damage to cellular and humoral immunity [12]. Systemic violations of cellular and humoral immunity was noted in patients with acute exacerbation of COPD [13]. Violations of cellular immunity, e.g. inhibition of alveolar macrophage suppressor systems, reducing the number of T-helper cells, effector cytotoxic lymphocytes with the most pronounced inhibition of T-suppressor lymphocytes are common in patients receiving long-term antibiotic therapy [24]. Many infectious agents lead to an exacerbation of COPD, disturb mucous clearance, increase production of mucus thick bronchial secretions, locally disintegrate immunoglobulins, inhibit phagocytic activity of neutrophils and alveolar macrophages, and enhance the release of histamine and other inflammatory mediators [3, 4]. Among the endogenous risk factors are the most important features of immune reactivity due to genetic factors. It is known that higher propensity of man to infection with respiratory viruses and damage to ciliated epithelium determines selective IgA deficiency, and is associated with a deficit of IgG [3].

Therefore, it is necessary for the patients with acute exacerbations of COPD to receive medications which will activate the mechanisms of self-regulation, the adequacy of the immune response and improve the barrier function of the bronchial mucosa. The medication Glutoxim is an immunorehabilitator that has immunomodulatory, bronchodilatory, desensitizing, anti-inflammatory and antimicrobial effect. [18]. Glutoxim (registration number 98 \ 279 \ 3) is a chemically synthesized biologically active compound, a hexapeptide with the stabilized disulfide bond. Glutoxim is a representative of a new class of drugs, i.e. thiopentone that has a modulating effect on intracellular processes, plays an important role in the regulation of metabolic processes in the tissues and organs, as well as in endogenous production of cytokines: interferons and interleukins. [10].

According to modern concepts, hypertension plays one of the leading roles in the onset and progression of cardiovascular diseases, (including coronary heart disease) and vascular endothelial dysfunction [25]. The vascular endothelium is the only body that regulates hemodynamics and perfusion according to the needs of each organ or tissue. The main role of the endothelium is the allocation of a number of biologically active substances. The proper functioning of the endothelium depends on the vascular tone (total vascular resistance, blood pressure), athrombogenic vascular wall, platelet activity, blood coagulation, inflammation, antioxidant resistance, as well as the preservation of the structural layers of the vascular wall and the manifestation of atherogenesis. It is likely that a violation of these regulatory mechanisms leads to changes in the organs and systems that serve as the basis for the pathogenesis of many pathological processes, such as cardiovascular disease. Therefore, reducing damage, correction and maintenance of adequate functioning of the endothelium is one of the most urgent problems of modern therapy of vascular disease. Other drugs used in cardiology normalize the effects against endothelial dysfunction to a different degree. One of such group of drugs is NO donator, in particular L-arginine aspartate, which positively effects endothelial dysfunction. [14]. In addition, L-arginine aspartate has detoxifying, membrane stabilizing, anti-hypoxic, cytoprotective, antioxidant and antiradical activity. It also manifests itself as an active process controller of power supply and intermediary metabolism. L-arginine aspartate stimulates the activity of thymus which plays a leading role in differentiation and maturation of T-lymphocytes. Moreover, L-arginine aspartate promotes correction of acid-base balance which is even more important. The accumulation of new data about cardiovascular and respiratory pathology has changed the paradigms of patients' treatment.

The purpose of this study was to establish ways to optimize the treatment of moderate COPD complicated by bronhiectasis of CHD origin.

MATERIALS AND METHODS

The study included 63 patients with COPD complicated by bronhiectasis of CHD origin, aged 40-65 years (52.5 ± 4.5yrs) who were hospitalized at the pulmonary ward of TH №1 for aggravation of their disease. COPD diagnosis was established on the basis of clinical, radiological, laboratory and functional examinations in accordance with

the guidelines of the Ministry of Health of Ukraine of 27.06.2013, №555. COPD complicated by bronchiectasis was confirmed by X-rays and computed tomography in all patients. Specialist tests included pulmonary ventilation with the registration "flow-volume" curve, forced expiratory and conduct standard bronchodilation by inhalation of salbutamol. The diagnosis of CHD was verified according to the guidelines of the Ministry of Health of Ukraine, №54 of 14.02.2002. The diagnosis of ischemic heart disease was confirmed on the basis of WHO standard cardiac profile (Rose questionnaire), the nature of electrocardiographic changes at rest according to the recommendations of the VI National Congress of Cardiologists of Ukraine.

All patients were divided into 3 groups. Clinical group 1 and 2 were patients of similar age and clinical course of the disease. The control group consisted of 10 patients who received standard therapy with antibiotics, mucolytics over 10 days. Clinical group 1 (26 patients) received 3% Glutoxim, 1ml (30 mg) once a day, i.m., for 10 days in addition to standard therapy. Clinical group 2 (27 patients) was given Glutoxim in combination with 4.2% L-arginine aspartate, i.v. 100 ml once a day for 10 days in addition to standard therapy. The volume of the standard therapy for patients in the clinical groups was the same as in the control group. In cases when the patients received β2-agonists (salmeterol, formoterol) or anticholinergics (ipratropium, tiotropium) prior to the study, such treatment was continued for the entire period of observation in doses corresponding to the severity. The observation period was 14 days.

Immunological examination of patients was carried out during the first 3 days after admission and after 10 days of treatment. It included: quantitative evaluation of T and B components of immunity by immunofluorescence method, counting the cell phenotype CD3+, CD4+, CD8+, CD16 +, CD22+ and immunoregulatory index (IRI – the ratio of CD4+/CD8+) [21]; the reaction of blast transformation of lymphocytes (RBTL) [15]; performance study of serum IgG, IgA, IgM [17]; concentration of circulating immune complexes (CIC) in the average size serum [11]; study of phagocytic activity of neutrophils with the calculation of phagocytic index (PI), Hamburg and phagocytic number (FF) Wright [21].

In addition, this study evaluated the dynamics of indicators of quality of life in COPD basic therapy and therapy with glutoxim. To evaluate the quality of life in patients at different periods of COPD exacerbation, treatment, rehabilitation, a version of general MOS SF-36 questionnaire was used (MOS SF Item Short Form Health Survey). In order to evaluate the effects of treatment on quality of life of patients with COPD a global assessment of the quality of the patient's care and the doctor's management was additionally performed. The test results were evaluated by the point score system. Patients were asked to answer the SF-36 questionnaire:

1. at the beginning of the treatment on admission (acute phase of the disease);
2. at the stationary completion of treatment (days 12-14);
3. 2 months later.

Statistical processing of the results was carried out on a personal computer using a standard package of functions «MS Excell» and «Statistica for Windous. Release 6.0».

RESULTS AND DISCUSSION

The analysis of initial results of immunological studies showed that the patients had significant disorders of the immune functions at cellular and humoral level. The common features of immunological disorders in patients with COPD included violation of humoral immunity – a significant decrease in the levels of IgG and IgA along with the increase in the number of B-lymphocytes (CD22+ lymphocyte population), as well as increased serum concentration of the medium size CEC. Common signs of cellular immune disorders included a significant decrease in the total number of subpopulations of lymphocytes and CD3+, CD4+, CD16+ lymphocytes. The analysis of baseline T-cell immunity in patients with COPD showed heterogeneity and multi-vector violations. Similar results were obtained by other researchers, and coincide with the literature data [13].

Most often multi-vector violations of cellular immunity were observed in patients with COPD. Some patients had mainly T-helper immune deficiency with low immunoregulatory index, others predominantly T-suppressor immunodeficiency high immunoregulatory index. That can explain different orientation of the immune response depending on the adaptive-adaptive capabilities of a particular organism, the progression of bronchial obstruction and persistence of infectious and inflammatory process in the bronchial tree. Depending on these results all examined patients

in the clinical groups were divided into two subgroups. The criteria for inclusion were the importance of the immunoregulatory index and type of immunodeficiency. Each clinical group was divided into subgroups: In subgroup A were patients with T-helper immune deficiency and low immunoregulatory index (in 95% of patients with IRI was within 0.8-1.3); A.1 – 13 patients, A.2 – 12 in the subgroup were patients with T-suppressor immunodeficiency and high immunoregulatory index (in 96% of the patients IRI ranged from 2.1-2.6); B.1 – 13 patients B.2 – 15 respectively.

After a 10-day treatment of patients positive dynamics of clinical symptoms with a decrease in the intensity of dyspnea and cough, reduced volume and purulence of sputum, normalization of the body temperature, improvement in general well-being were achieved in both clinical groups. Patients recovered, regained the state of health from before their disease. Positive clinical dynamics was accompanied by improvement in pulmonary ventilation.

The analysis of immunological parameters in the patients in the control group showed that despite the advent of standard treatment, improvement in the immune status was observed. The total number of lymphocytes increased from 1.70 ± 0.14 to 1.98 ± 0.76, CD4+ - lymphocyte from 0.48 ± 0.11 to 0.46 ± 0.21, performance values were irrelevant. There was a significant decrease in spontaneous RBTL from 0.055 ± 0.006 to 0.034 ± 0.008 ($p \geq 0.05$), although the change RBTL with PHA was not significant from 1.37 ± 0.11 to 1.49 ± 0.2. There was a trend to reduce the number of populations: from CD3+ 0.95 ± 0.18 to 0.84 ± 0.42, and CD8+ lymphocyte subpopulations from 0.41 ± 0.17 to 0.36 ± 0.22, immunoregulatory index of decreased tendency was noted from 1.76±0.15 to 0.51 ±0.85, amid tendency to increase the population of lymphocytes from CD16+ 0.26± 0.10 to 0.31±0.12. In humoral immunity reduction of CD22+ - lymphocytes from 0.69 ± 0.08 to 0.66 ± 0.38 was observed as well as in the content of IgG, from 8.40±0.19 to 7.97±0.74, IgA from 1.31±0.15 to 1.26 ± 0.22, IgM from 0.91± 0.06 to 0.83±0.11, the number of CEC from 61.1±2.71 to 62.47±4.75. However none of the paremeters was significantly changed. Phagocytic activity of neutrophiles remained at the same level, FI from 51.0±3.6 to 50.32± 8.31, from the FF 4.4± 0.47 to 6.2±3.51.

Clinical improvement of immune parameters was observed in both groups. Patients from subgroups A.1 after treatment had a statistically significant increase in the total number of lymphocytes from 1.69±0.15 to 2.12±0.12 ($p \geq 0.05$) populations: CD3+ lymphocytes from 1.02±0.21 to 1.50±0.09 ($p \geq 0.05$), CD4+ - cells to 0.44±0.13 0.78 ± 0.09 ($p \geq 0.05$), CD16+ lymphocytes from 0.26±0.05 to 0.41±0.02 ($p \geq 0.05$), proliferative activity of lymphocytes with PHA RBTL from 1.45±0.08 to 1.69±0.04 ($p \geq 0.05$). Changes in spontaneous RBTL from 0.055± 0.005 to 0.046±0.004, the number of CD8+ - lymphocytes from 0.49±0.08 to 0.50 ±0.15; those values were insignificant though. These prove positive effects of prescribed treatment on the immune response of the body. As a result, there was a decrease in the manifestations of T-cell immunodeficiency, which was accompanied by a statistically significant normalization of the immunoregulatory index from 1.13±0.16 to 1.83±0.22 ($p \geq 0.05$). Similar rates of immune status were obtained in the subgroup A2 so there was an increase in the total number of lymphocytes up to 2.19±0.09 ($p \geq 0.05$), populations: CD3+ lymphocytes up to 1.51±0.08 ($p \geq 0.05$), CD4+ - cells up to 0.81±0.10 ($p \geq 0.05$), CD16+ lymphocytes up to 0.40±0.04 ($p \geq 0.05$), proliferative lymphocyte activity with RBTL PHA to 1.67±0.06 ($p \geq 0.05$). Changes in spontaneous RBTL to 0.049±0.006, the number of CD8+ - lymphocytes to 0.52± 0.11 were not significant. This was accompanied by a statistically significant normalization of the immunoregulatory index to 1.83± 0.19 ($p \geq 0.05$).

Patients in the clinical group B showed improvement in quantitative and functional characteristics of the most affected T-suppressor/ cytotoxic lymphocyte subpopulations. After treatment the following changes were noted in subgroup B.1: a statistically significant increase in the number of CD3+ lymphocyte populations from 0.87±0.15 to 1.27±0.11 ($p \geq 0.05$) and a subset of CD8+ lymphocytes from 0.32±0.05 to 0.47±0.03 ($p \geq 0.05$), CD16+ lymphocytes from 0.25±0.06 to 0.40±0.02 ($p \geq 0.05$); a statistically significant normalization of the immunoregulatory index from 2.39±0.14 to 1.85±0.13 ($p \geq 0.05$). Functional activity of lymphocytes activated with PHA RBTL tended to improve as it increased from 1.28±0.14 to 1.48±0.11, spontaneous changes in RBTL from 0.054 ± 0.006 to 0.038±0.009, total number of lymphocytes from 1.71±0.12 to 2.04± 0.17, the number of CD4+ - lymphocyte 0.51±0.15 to 0.73±0.07. Those values were insignificant. A similar pattern was also observed in subgroup B.2. There was a statistically significant increase in the number of CD3+ lymphocyte population up to 1.26±0.10 ($p \geq 0.05$) and a subset of CD8+

lymphocytes to 0.49± 0.06 (p≥0.05), CD16+ lymphocytes to 0.41±0.04 (p≥0.05), which was accompanied by a statistically significant normalization of the immunoregulatory index to 1.87±0.16 (p≥0,05). Functional activity of lymphocytes with PHA RBTL tended to improve as it increased to 1.47±0.10, spontaneous changes in RBTL to 0.039±0.007, changes in the total number of lymphocytes to 2.06±0.15, the number of CD4+ - lymphocytes to 0.76±0.09, however the changes were not significant. Phagocytic activity of neutrophils improved in both clinical groups - a statistically significant increase in FI and FF was observed. So in class A.1: FI from 52.1±2.7 to 64.3±3.3 (p≥0.05), FF from 4.6±0.37 to 6.8±0.9 (p≥0.05), and the corresponding figures in the subgroup A2: PHI to 65.1±3.1 (p≥0.05), the FF to 6.7 ±0.7 (p≥0. 05) in the subgroup B.1: FI from 49.9±4.54 to 62.9±4.1 (p≥0.05), FF from 4.2±0.56 to 5.5±0.25 (p ≥0.05), a similar pattern was also observed in the subgroup B.2: PHI to 61.8±3.22 (p≥0.05), the FF to 5.6±0.31 (p ≥0.05).

Significantly less pronounced changes were observed in the humoral immunity of the patients in both clinical groups. In subgroup A.1 a reduced tendency was noted in the number of B cells: CD22+ lymphocyte population from 0.62±0.06 to 0.53±0.06, in the subgroup A2 to 0.54±0.08, although in a subset of these results were statistically significant with 0.76±0.09. In subgroup B.1 to 0.48 ±0.07 (p≥0.05) in the subgroup B.2 to 0.47±0.05 (p≥0.05). Both clinical groups showed a statistically significant increase in serum IgA: A.1 in subgroup from 1.29 ±0.14 to 1.76±0.11 (p≥0.05); A.2 to 1.75±0.09 (p≥0.05); in subgroup B.1 from 1.33±0.15 to 1.69±0.08 (p≥0.05); B.2 to 1.71±0.09 (p≥0.05). Reduction of circulating immune complexes in subgroup A.1 from 62.8±2.72 to 56.3±1.49 (p≥0.05); A.2 - to 55.4±1.45 (p≥0.05); B.1 from 59.4±2.69 to 53.2±1.22 (p≥0.05); B.2 - to 52.5±1.20 (p≥0.05). This was accompanied by a decreasing tendency in the number of IgM and IgG. In subgroup A.1 IgG content increased from 7.83± 0.21 to 8.10±0.29, A.2 –to 8.32±0.28, in subgroup B.1 from 8.96±0.18 to 9.56± 0.15; B.2 - to 9.57±0.14. In group A, the content of IgM decreased from 0.88± 0.05; A.1 - to 0.77±0.03; A.2 –to 0.76±0.05, in group B from 0.93±0.06; B.1 –to 0.86±0.04; B.2 –to 0.87±0.03, these figures were irrelevant, though. Considering short period of observation such changes could have been expected.

The analysis of quality of life of patients in both clinical groups found significant improvement in all parameters. In the control group, significant changes were observed only in the index of vitality (VT). In subgroups A.1 and B.1 on glutoxim therapy improved vitality (VT), role functioning (RP), and physical functioning (PF) were significant parameters. In the control group, the parameters were changed insignificantly. In the clinical groups slight positive changes related to indicators of general health (GH) were significant. In subgroups A.2 and B.2 on glutoxim combined with L-arginine aspartate significant improvement in general health (GH), vitality (VT), role functioning (RP), physical functioning (PF) and the restoration of mental health (MH), emotional functioning (RE) were observed which eventually led to an increase in patients' viability (VT). It should be noted that the improvement in these indicators is beneficial not only to the quality of life of patients, but also to compliance with medical regimen. Long-term observation showed reduction in the number of exacerbations in subgroups A.2 and B.2, which was possible due to the improvement of stress resistance in patients.

CONCLUSION

Major disorders of T-cell immunity in COPD patients with complication of bronhiectasis of CHD origin include T cell immunodeficiency, predominantly T-helper or T-suppressor of immune deficiency. Identified types of immunological disorders are the basis for immunological correction using glutoxim. The administration of glutoxim was effective and showed improved immunological parameters in patients with impaired cellular immunity.

In addition to standard therapy, treatment with glutoxim in combination with L-arginine aspartate not only improved body's immunological defense, but also significantly improved all parameters of the quality of life. Long-term follow-up in these patients showed a decrease in the number of exacerbation episodes.

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