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Frequency Of Cyp3a5 (A6986g) Gene Polymorphism In Patients With BA, COPD, And ACO

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Relevance: Asthma and COPD are the most common chronic respiratory diseases, each with a specific pathophysiology. Usually, asthma is characterized by chronic inflammation of the airways with reversible symptoms, while COPD is characterized by persistent respiratory changes in the bronchopulmonary system. However, patients can sometimes have clinical features of both diseases, and this condition is called the asthma-COPD overlap (ACO) recommended by the joint guidelines of GINA (Global Strategy for the Management and Prevention of Asthma) and GOLD (Global Initiative on Chronic Obstructive Pulmonary Disease). According to this guide, ACOis characterized by "permanent airflow limitation with some features of asthma and COPD."

The clinical picture of ACO includes symptoms of both asthma and COPD. Many studies have confirmed that these pathologies have a different inflammatory response, more precisely, asthma is an eosinophil-dominated inflammation driven by Th2 cytokines, while COPD is an inflammatory process with a predominance of neutrophils and macrophages, driven by Th1 cytokines. GINA 2021 marked new key positions on the problem of the combination of asthma and COPD. The point is that distinguishing between asthma and COPD can be problematic, especially in smokers and the elderly, and some patients may have clinical features of both asthma and COPD. The term "combination of asthma and COPD" does not describe a single disease, but rather includes patients with several different forms of respiratory disease (phenotypes), caused by a number of different underlying mechanisms. To avoid the impression that it is a single disease, it is no longer recommended to use the term "ACOS" (Asthma and COPD Overlapping Syndrome), which was used in the previous GINA study. According to Hardin et al. Patients with asthma with COPD features are characterized by more frequent exacerbations, poor quality of life, rapid decline in lung function and higher mortality, and more severe symptoms in the morning and at night. According to the results of the Swedish study RHINE and GALEN (Stephanie Mindus et al., 2017), asthma in combination with COPD is associated with a high severity of sleep disturbance and the severity of nocturnal respiratory symptoms. Asthma was the initial disease in every second patient with a combination of asthma and COPD, according to the analysis, based on data from Adelphi Real-Life respiratory programs conducted in Spain, Italy, France, Germany, the UK and other countries. depression, diabetes, osteoporosis, and obesity was higher in cross-over patients compared with patients with COPD. Researchers from Japan Toshio Suzuki in their experience after analyzing a group of 140 patients with asthma found that the proportion of overlapping syndrome was 28%.

Inhaled corticosteroids (ICS) in combination with long-acting beta-agonists (LABA) and/or long-acting muscarinic antagonists are recommended for ACO, while LABA alone is not. In contrast, pharmacotherapy with inhaled bronchodilators, LABA and LAMA, alone or in combination, is the mainstay of COPD treatment. Inhaled corticosteroids are

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recommended in patients with a high and frequent risk of exacerbations in history. However, it is interesting that, despite the lack of randomized controlled trials to assess the relative benefits and risks of different treatment options, a recent observational study from Taiwan involving more than 250,000 patients with PAH and more than 500,000 patients with COPD found that the same drugs (LAMA or ICS/LABA combination), which were effective in reducing the risk of acute exacerbations in patients with COPD alone, also proved to be effective in patients with a combination of asthma and COPD. The inclusion of these types of patients is critical to understanding the optimal therapeutic strategy for patients with ACO.

The intersection of bronchial asthma and COPD is a serious medical and social health problem. The progression of allergic diseases, the deterioration of environmental conditions and the growth of bad habits (smoking, alcohol abuse) cause an increase in the incidence rate, and a more severe course of the disease of ACO than isolated BA and COPD leads to an increase in mortality rates worldwide. The presence of a wide variety of phenotypes of this pathology is associated with various etiological risk factors, one of which is a genetic predisposition, which is represented by a wide variety of candidate genes. Monitoring the course of the disease and improving the quality of life of patients is carried out by choosing an adequate anti-inflammatory (basic, maintenance, ICS, antihistamine, LABA) therapy. Metabolism of ICS is carried out with the participation of isoenzymes of cytochrome P450 (CYP) family 3A. Changes in the structure of genes lead to a shift in the sensitivity of the bronchial tree to ICS and, as a result, a more severe course of bronchial asthma. Although an early study was conducted among children, we did not find data on CYP3A5 polymorphism in patients with ACO.

Purpose of the study: To study the effect of the CYP3A5 gene polymorphism G6986A in patients with asthma, COPD and ACO.

Materials and methods of research: We have studied the CYP3A5 gene polymorphism G6986A in 110 patients with BA, COPD, PBAH. 72 practically healthy people made up the control group. DNA extraction from whole blood was carried out using the DNA-EXPRESS-BLOOD reagent kit (manufactured by LLC NPF Litekh, Moscow, RF). Real-time PCR amplification was performed using a complement of reagents for AS-PCR detection of CYP3A5 gene polymorphism (A6986G) (manufactured by OOO NPF Litekh, Moscow, RF). Statistical processing of the obtained data was carried out by the method of variation statistics according to Fisher-Student andused Pearson's χ^2 test.

Research results: We examined 42 patients diagnosed with bronchial asthma. In this group of patients, the AA genotype was found in 2.38% (n = 1), the GA genotype was found in 23.81% (n = 10), GG in 73.81% (n = 31) of the examined patients, the frequency of occurrence of the A allele was 14 .29% (n = 12), G allele frequency – 85.71% (n = 72).

When analyzing the results obtained, it was found that in this sample of patients, allele A was a significantly significant marker of predisposition with a high index (OR=0.400, $\chi2$=4.097). In turn, marker G was less common in the group of patients compared to practically healthy individuals (OR=0.400, $\chi2$=4.097). The GG genotype was characterized by a distribution similar to the allelic distribution in this sample of the studied individuals. The GG genotype was more common in the healthy group than in the BA group (OR=0.352, $\chi2$=4.343), while the GA genotype was found with the highest relative risk and significance in this group, indicating its predisposing significance (OR =2.902, $\chi2$ =4.149). The AA genotype was more common in the BA group than in the healthy group, but it was not significant (OR=1.732, $\chi2$=0.151).

Next, we examined 38 patients diagnosed with chronic obstructive pulmonary

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disease. In this group of patients, the AA genotype was not detected, the GA genotype was found in 13.16% (n = 5), GG in 86.84% (n = 33) of the examined patients, the frequency of occurrence of the A allele was 6.58% (n = 79), the frequency of the G allele was 93.42% (n = 71).

When analyzing the results obtained, it was found that in this sample of patients, allele A was a significantly significant marker of predisposition with a high index (OR=2.153, $\chi2$=9.132). In turn, the G genotype marker was characterized by a distribution similar to the allelic distribution in a healthy sample of the studied individuals (OR=0.947, $\chi2$=0.009). The GG genotype was more common in the healthy group than in the COPD group (OR=0.825, $\chi2$=0.1), while the GA genotype was found with the highest relative risk and significance in this group, indicating its predisposing significance (OR=1.407, $\chi2$=0.302, Wald 95% CI: 0.415 >1.407> 4.774).

We examined 30 patients diagnosed with ACO. In this group of patients, the AA genotype was found in 6.67% (n = 2), the GA genotype was found in 30.00% (n = 9), GG in 63.33% (n = 19) of the examined patients, the frequency of occurrence of the A allele was 21 .67% (n = 13), G allele frequency – 78.33% (n = 47).

When analyzing the results obtained, it was found that in this sample of patients, allele A was a significantly significant marker of predisposition with a high index (OR=2.253, $\chi2$=9.279). In turn, marker G was less common in the group of patients compared to practically healthy individuals (OR=0.241, $\chi2$=9.478). The GG genotype was more common in the group of healthy people compared to the group of patients with ACO (OR=0.216, $\chi2$=9.124), while the GA genotype was more common in terms of relative risk and significance in this group (OR=3.980, $\chi2$ =6.584). The AA genotype has the highest relative risk and significance, indicating its predisposing significance. Met more frequently in the ACO group compared to the healthy group (OR=5.071, $\chi2$=2.066)

Findings: Thus, based on the data obtained, it can be concluded that the AA genotype of the CYP3A5 polymorphic marker (A6986G) is a significantly significant marker of predisposition to the development of ACO in the Uzbek nationality. Considering that the severity of chronic bronchopulmonary process is diagnosed depending on the volume of control therapy, it can be concluded that the AG genotype and the presence of the A allele (CYP3A5 gene (G6986A)) are associated with the need for patients to use large doses of ICS and a combination of ICS with long-acting β2 agonists.

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