ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Effect Of Genetic Polymorphism Of Cytokine Genes On The Drug Response Of Statins In Conditions Of Respiratory Infections.

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ABSTRACT

High mortality from coronary heart disease dictates the need for further research on the subtle mechanisms of development of this pathology. In the study, the effect of gene polymorphism of proinflammatory and anti-inflammatory interleukins on the severity of the lipolipidemic effect of rosuvastatin in the starting dose in patients with coronary heart disease in combination with acute respiratory viral infection was studied. The study of phenotypic features showed the presence of associations between the genotypes –511CT of the IL-1β gene and an increase in the synthesis of IL-1β and low-density lipoprotein cholesterol; –511CC IL-1β gene - with increased levels of low-density lipoprotein cholesterol; –174GG IL-6 gene - with increased production of IL-6 and low density lipoprotein cholesterol; –1082GG of the IL-10 gene - with an increase in the synthesis of IL-10, a decrease in the level of cholesterol and C-reactive protein; –589TT of the IL-4– gene with increased formation of C-reactive protein and IL-4. Detection of genotypes –511CT, –174GG, –1082AA recommends the prescription of rosuvastatin 20 mg / day. to achieve the target level of low-density lipiprotein cholesterol.

Keywords: ischemic heart disease, acute respiratory viral infections, inflammation of statins, genotypes.

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ISSN: 0975-8585

INTRODUCTION

Despite the serious efforts of modern medicine, cardiovascular diseases remain very common in various human populations [1,2]. Genetic disorders, often in the form of point nucleotide substitutions in different regions of the genome [3,4], as well as the presence of various modifiable risk factors [5, 6] are of great importance in their widespread occurrence. One of the leading reasons for limiting the lifespan of people of working age is the continuing high mortality from coronary heart disease [7]. It is recognized as the leading among all deaths from diseases of the cardiovascular system [8]. According to the WHO, in 2017 in Russia, 53.3% of deaths were due to coronary heart disease [9]. The cause of adverse outcomes is atherosclerosis, as one of the main etiopathogenetic components.

The etiology of atherosclerosis is diverse, currently there is no one accurate theory of its development. Immuno-inflammatory theory is considered to be the most relevant [10].

Today, inflammation is considered as the effect of aggression factors on the endothelial layer of blood vessels with the development of endothelial dysfunction [11].

Stress, viruses, hypercholesterolemia, toxins, arterial hypertension, impaired hemodynamics, exposure to catecholamines, serotonin, angiotensin II act as provoking factors that violate the endothelium integrity. The role of inflammation in the development of atherosclerosis is due to the production of T-helper type 1 pro-inflammatory cytokines tumor necrosis factor-a, IL-1β, IL-6, contributing to the proliferation of smooth muscle cells of the media and the release of collagen and elastin for the future plaque. Proinflammatory interleukins activate endotheliocytes, macrophages, promote the production of free radicals and enhance coagulant activity [13, 14].

Thus, atheroma is a chronic aseptic inflammation. There are published data confirming the detection of influenza viruses, chlamydia pneumonia, and cytomegalovirus in atherosclerotic plaque [15] (Figure 1).

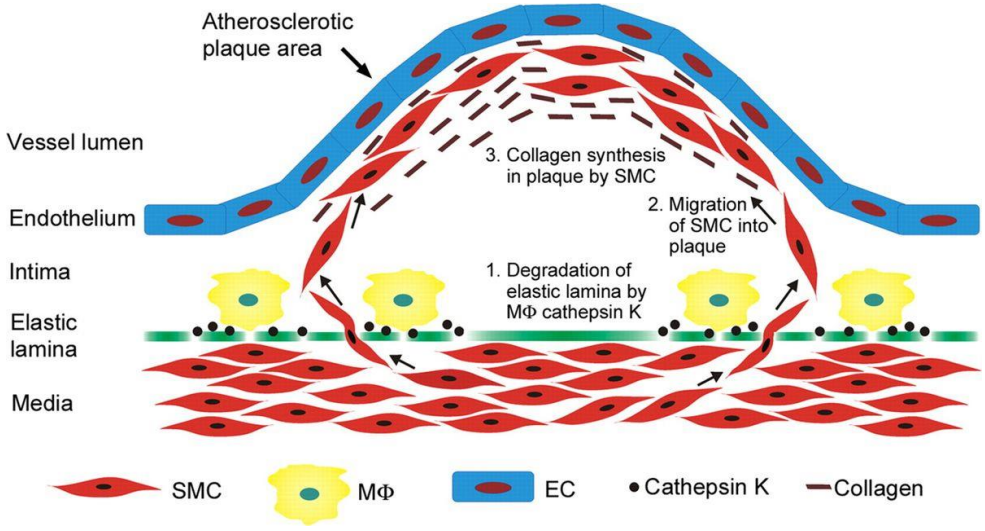

Figure 1. Pathogenesis of atherosclerosis.

The addition of any infectious disease can activate the course of chronic inflammation in an atherosclerotic plaque, with the involvement of the cytokine system [16].

Published many works confirming the existence of a relationship with a change in the status of patients with coronary heart disease with concomitant acute respiratory viral infections. Infectious disease can be considered as a trigger to destabilize the course of atherosclerosis and coronary heart disease. There are known facts of the negative impact of viral and bacterial infections on the course of atherosclerosis, confirmed laboratory and instrumentally [17]. The aggravation of the course of atherosclerosis in viral infections of the upper respiratory tract (influenza, acute respiratory viral infections), confirmed by changes on the electrocardiogram with ST depression, was noted. The accession of infectious diseases in the autumn-winter

periods of the year contributes to the growth of hospitalization of patients with coronary heart disease in cardiology departments, which is especially characteristic of Russia, where the seasonality of the season is pronounced and the cold season accounts for about 6 months [18,19].

The course of acute respiratory viral infections is characterized by an imbalance of the cytokine system against the background of herpes, cytomegalovirus and other infections, and may be irreversible with the active development of inflammation, which in turn will cause irreversible changes in the lipid transport system of patients with ischemic heart disease [20]. Thus, the role of inflammation in the processes of changing the course of coronary heart disease is indisputable, which motivates to revise the usual approaches to the pharmacological correction of hyperlipidemia in the presence of viral diseases of the respiratory system.

The aim of this work was to assess the relationship of polymorphism of pro- and anti-inflammatory interleukin genes (IL-1β, IL-6, IL-4 and IL-10) with changes in the drug response of statins in patients with ischemic heart disease with acute respiratory viral infections.

MATERIALS AND METHODS

The study included 170 patients with ischemic heart disease, stable angina, I-II functional class with atherogenic hypercholesterolemia (men and women in postmenopausal age from 41 to 60 years). The diagnosis of ischemic heart disease and functional class of angina of exertion is confirmed by the clinical picture and data of veloergometry at the prehospital stage. Verification of hypercholesterolemia was carried out on the basis of the presence of elevated lipid metabolism (cholesterol> 5.5 mmol/l, triglycerides> 1.7 mmol/l).

Patients were excluded from the study to identify individual intolerance to rosuvastatin; adverse reactions from therapy (increased levels of alanine aminotransferase and aspartate aminotransferase 3 times); refusal of therapy; associated diseases that can cause changes in the lipid system.

120 patients with coronary heart disease with acute respiratory viral infections included in the study comprised a group of patients with coronary heart disease with comorbidities.

As therapy for coronary heart disease, patients received antianginal drugs (nitrospray on demand), β-blockers (bisoprolol 5 mg / day, statins (rosuvastin 10 mg / day) [21, 22]

Pharmacological correction of infectious agents was carried out with antiviral drugs: (oseltamivir - 0.75 g 2 times a day., Umifenovir - 0.2 g 4 times a day), antibiotics (macrolides - azithromycin - 0.5 g 1 time a day. Or cephalosporins III generation - ceftriaxone - 1.0 g, 2 times per day/M) with the development of bacterial complications [23].

The content of low-density lipoprotein cholesterol was determined using Vitalab Flexor E kits and Analyticon kits. The level of interleukins in the serum was determined by the method of immunofermental analysis on the analyzer "Tecan" sets of the company "Vector Best". For the detection of influenza ribonucleic acid, a polymerase chain reaction was performed.

Genotyping of polymorphisms of proinflammatory IL-1β –511C> T IL-6 –174G> C, anti-inflammatory cytokines IL-4 –589C> T, IL-10 –1082G> A was performed by polymerase chain reaction on a CFX96 amplifier of Bio-Rad Laboratories (USA).

Statistical processing of the results was carried out in Microsoft Excel Office 2007. The nature of the distribution of quantitative traits was normal, and therefore the reliability of differences in the groups was evaluated by the Student's t-test. Significantly significant indicators took the value of the level of $P < 0.05$. Correlation analysis was carried out by calculating the correlation coefficient (r) by Pearson. The distribution of genotypes of the studied cytokine genes corresponded to the Hardy – Weinberg law. The significance of differences in the frequency distribution of alleles and genotypes between groups was assessed by $\chi 2$. The relative risk of developing a phenotype for a specific genotype was calculated as a odds ratio [24].

ISSN: 0975-8585

RESULTS AND DISCUSSION

Patients with coronary heart disease before inclusion in the study as a hypolipidemic correction of hypercholesterolemia received rosuvastatin 10 mg / day. The estimated level of the target density of low-density lipoprotein cholesterol (1.8 mmol/l) showed a decrease in the possibility of achieving it when verifying with acute respiratory viral infections, which resulted in a decrease in the number of patients who reached the target level of low-density lipoprotein cholesterol from 55.7% to 49, 7% of the studied.

In order to achieve the target level of low-density lipoprotein cholesterol, the dose of rosuvastatin was increased to 20 mg / day. 7 days after detection of signs of an infectious process. Achieving the target level of low-density lipoprotein cholesterol in both dose regimens of rosuvastatin was monitored 7, 14, 30 days and 3 months after the addition of an infectious disease.

So, by 3 months, 69% of patients with coronary heart disease were able to reach the target cholesterol level while taking rosuvastatin 20 mg / day. and 60% at 10 mg / day.

In the group of patients with ischemic heart disease with acute respiratory viral infections, the target level of low-density lipoprotein cholesterol reached 64% of patients with a dose regimen of 20 mg / day. and 62% at 10 mg / day.

To assess the contribution of acute inflammation to the destabilization of atherosclerosis, associations of interleukins with lipid spectrum parameters have been studied [25, 26] (Figure 2).

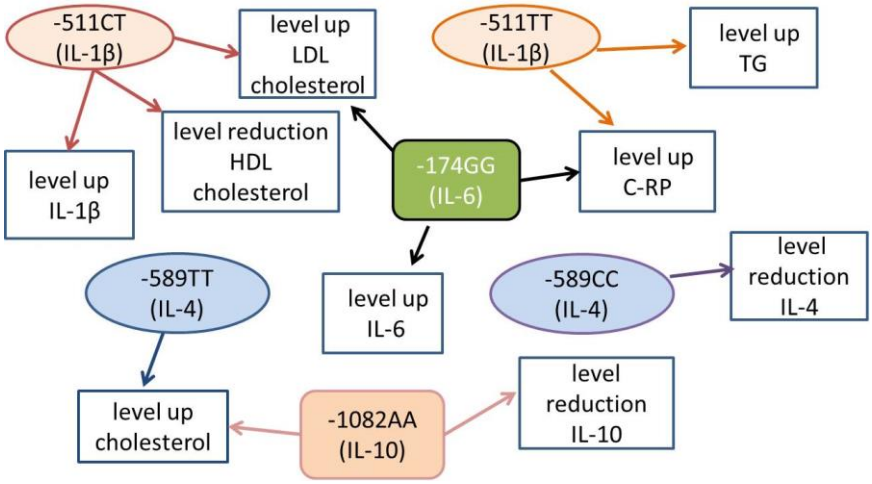

Figure 2. Phenotypic associations of pro- and anti-inflammatory cytokine genotypes in patients with ischemic heart disease and acute respiratory viral infections.

In patients with ischemic heart disease under conditions of concomitant pathology with the carriage of the genotype -511CT, an increase in the level of low-density lipoprotein cholesterol, an increase in the level of IL-1, and a decrease in the level of high-density lipoprotein cholesterol were observed. For patients with the genotype -511TT, there is a connection with an increase in C-reactive protein and triglycerides [27]. The -174GG genotype is also associated with the growth of C-reactive protein, low-density lipoprotein cholesterol and IL-6 [28]. Genotypes -1082AA and -589TT anti-inflammatory cytokines are associated with increased cholesterol levels. In patients with the detection of the genotype -1082AA, there was a decrease in the production of IL-10 itself, and in the presence of the genotype -58CSS - a decrease in the production of IL-4 [29].

In the group of patients with ischemic heart disease without an infectious process, the genotype -511TT was associated with increased levels of high-density lipoprotein cholesterol, C-reactive protein and lower levels of low-density lipoprotein cholesterol (Figure 3). This genotype had anti-inflammatory properties [30, 31].

ISSN: 0975-8585

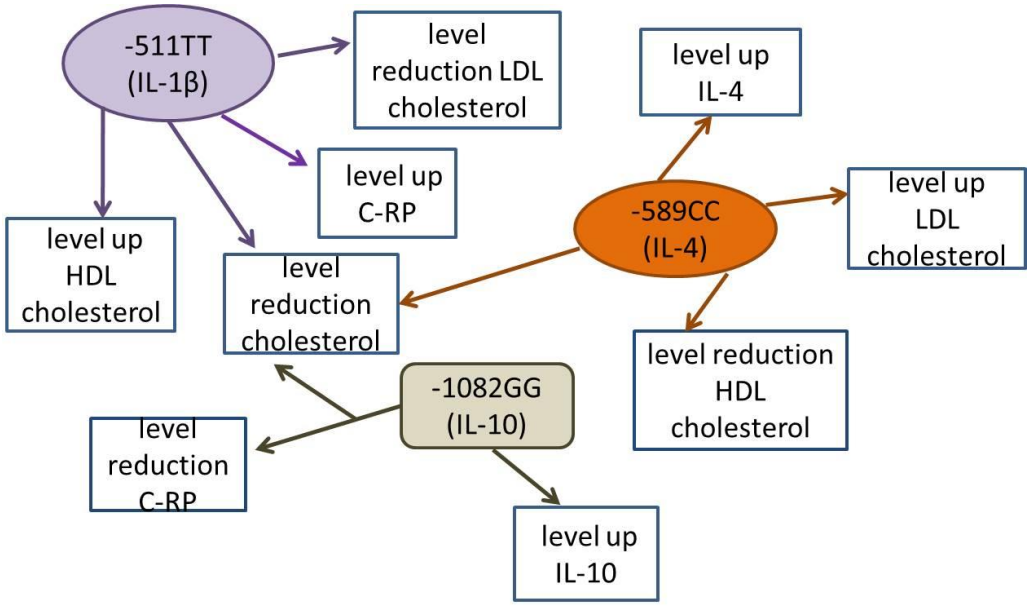

Figure 3. Phenotypic associations of genotypes of pro- and anti-inflammatory cytokines in patients with ischemic heart disease without acute respiratory viral infections.

At the same time, the anti-inflammatory genotypes -1082GG and -589CC were characterized by an increase in the production of these cytokines, low-density lipoprotein cholesterol, and a decrease in high-density lipoprotein cholesterol [32,33].

Genetic analysis to personalize the pharmacological correction of lipid metabolism disorders in patients with ischemic heart disease during acute respiratory viral infections contributed to the isolation of genotypic models when low-density lipoprotein cholesterol was reached or not achieved (Figure 4).

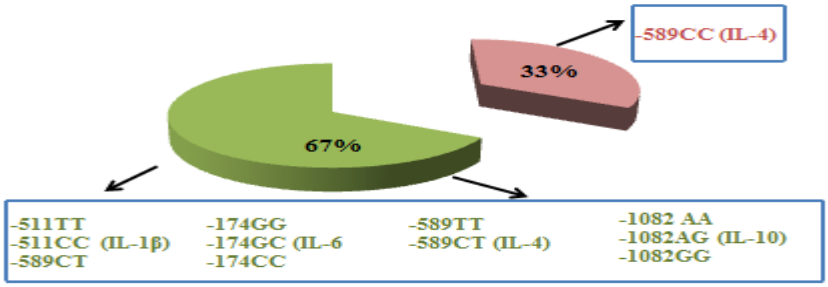

Figure 4. The number of patients who have reached the target level of low-density lipoprotein cholesterol.

By the end of the observation, 67% of the studied patients had reached the target level of low-density lipoprotein cholesterol. They identified genotypes of the pro and anti-inflammatory cytokine genes, in which the lipid-lowering effect of rosuvastatin 10 mg / day was realized. and 20 mg / day [34]. Patients who did not achieve the target level of low-density lipoprotein cholesterol in the course of pharmacological correction were carriers of the IL5 genotype -589CC, and therefore needed to be given higher doses of statin therapy.

CONCLUSION

The study studied the effect of polymorphism of proinflammatory and anti-inflammatory interleukin genes on the severity of the lipid-lowering effect of rosuvastatin in the starting dose in patients with ischemic heart disease in combination with acute respiratory viral infection. The study of phenotypic features showed the presence of associations between the genotypes –511CT of the IL-1β gene and an increase in the synthesis of IL-1β and low-density lipoprotein cholesterol; –511CC IL-1β gene - with increased levels of low-density

lipoprotein cholesterol; –174GG IL-6 gene - with increased production of IL-6 and low density lipoprotein cholesterol; –1082GG of the IL-10 gene - with an increase in the synthesis of IL-10, a decrease in the level of cholesterol and C-reactive protein; –589TT of the IL-4– gene with increased formation of C-reactive protein and IL-4. Detection of genotypes –511CT, –174GG, –1082AA recommends the prescription of rosuvastatin 20 mg / day. to achieve the target level of low-density lipiprotein cholesterol.

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