Study of the Effectiveness of Statins in Coronary Heart Disease After Stentration in Persons of the Uzbek Population

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ABSTRACT

Statins occupy the main place in the treatment of ischemic heart disease CHD), in the development of which lipid metabolism disorders and inflammation are important. The effects of atorvastatin and rosuvastatin on the lipid spectrum, inflammatory factors, transaminase activity and total bilirubin content, structural and functional state and intracardiac hemodynamics of the left ventricle of the heart in patients with CHD of the Uzbek population after stenting, taking into account the polymorphism 13 of the ApoE and CYP2C19 * 2 genes, were studied. The favorable effect of statins on the studied parameters and the course of the disease was shown, and the data of genetic studies made it possible to select the most effective and safe doses of drugs. Key words: coronary artery disease, coronary artery steni, atorvastatin, rosuvastatin, lipids,, ApoE and CYP2C19 * 2 polymorphisms.

Keywords: Lipoproteins, Coronary Artery, Lipid-Lowering, Antiatherosclerotic, Antianginal, Antithrombotic Effects, Myocardial Ischemia.

In the development of coronary heart disease (IHD), lipid metabolism disorders are important, especially the metabolism of cholesterol (CHS), cholesterol of low and high density lipoproteins (CHSLNP and CHSLVP), triglycerides (TG). In this regard, lipid-lowering therapy, the use of statins, which inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A-reductase in liver cells, is of particular importance, which leads to a decrease in the synthesis of endogenous cholesterol. Percutaneous coronary intervention (PCI) with coronary artery (CA) stenting is an effective treatment for coronary heart disease (CHD).

But until now, the problem of resuming the clinic of angina pectoris caused by the restenotic process in the stent remains. The incidence of restenosis ranges from 12 to 40% depending on the angiographic and clinical situation. Treatment of coronary artery disease and prevention of its complications involves the use of drugs with antiatherosclerotic, antianginal, antiischemic and antithrombotic effects. The variability of the pharmacological response depends on the polymorphism of the genes responsible for the processes of pharmacokinetics and pharmacodynamics of the drugs used. The aim of the work is to study the effect of statins on lipids, some inflammatory factors, echocardiographic parameters in patients with coronary artery disease of the Uzbek population who underwent coronary artery stenting, depending on the polymorphism of the ApoE and CYP2C19*2 genes. Materials and research methods. The study included 40 patients with IHD and stable exertional angina (SS) of III-IV functional class (FC) (67.5% - men

and 32.5% - women) under the age of 60 years, who underwent coronary artery stenosis after coronary angiography.

The inclusion criteria were patients with coronary artery disease (an increase in the level of total cholesterol (TC) above 5.5 mmol/l, an increase in the level of total cholesterol (TC) above 5.5 mmol/l, an increase in the level of total cholesterol (TC) above 3.0 mmol/l and/or a level of triglycerides above 2 mmol/l. Patients took antiplatelet agents (aspirin and clopidogrel), beta - blockers, and from statins - atorvastatin, 20-40 mg / day (I group, 20 patients) and rosuvastatin, 10-20 mg / day (II group, 20 patients). CHSLNP, CHSLPVP, TG, C-reactive protein (CRP), fibrinogen (F), enzyme activity of alanine and aspartate aminotransferase (ALT and AST), total bilirubin (TB).

We performed genotyping of patients' deoxyribonucleic acid samples with optimized parameters of real-time PCR polymerase chain reaction and assessment of the structural and functional state and intracardiac hemodynamics of the left ventricle (LV) using echocardiography. Results. In the majority of the examined, changes were observed in the lipid spectrum (increase in the content of total cholesterol, CHSLNP and a decrease in the concentration of HDL), characteristic of atherogenic dyslipidemia.

The study of the lipid spectrum revealed higher rates of total cholesterol -7.2±0.6; TG-2.3±0.2; CHSLNP - 3.7 ± 0.26 mmol / l in patients with IHD and stable angina FC IV compared with those in patients with FC III: 6.6 ± 0.29; 3.0±0.28; 1.2±0.11 mmol/l and lower levels of HDL-C in patients with IHD CC IV FC than in patients with FC III: 1.2±0.1 and 1.15±0.14 mmol/l, respectively. TC after three months of therapy with atorvastatin decreased by 23% ($p < 0.05$), LDL cholesterol by 26%. Rosuvastatin reduced these figures by 30% and 36%, respectively. Changes in the level of anti-atherogenic HDL-C during atorvastatin therapy were not so pronounced (an increase of about 6%), but a decrease in the content of triglycerides by 30% was found ($p < 0.05$).

Rosuvastatin increased the first indicator by 8% and reduced the TG content by 38%. In relation to inflammation factors - CRP and F, the effect of statins was comparable. In patients taking atorvastatin, CRP decreased by 28%, and P by 4% (not significant). In patients treated with rosuvastatin, these figures were 35% and 4.5%, respectively (not significant). No adverse effect of the tested preparations on the activity of ALT, AST and the content of OB was found. Under the influence of statins, a slight increase in LV ejection fraction was observed.

In patients taking rosuvastatin, this figure averaged 61.5%, LV myocardial mass - 181.5 g, LV posterior wall thickness - 1.05 cm after, interventricular septal thickness - 1.05 cm, LV end-diastolic size - 4.9 cm, LV end-systolic size - 3.15 cm, end-diastolic volume - 119 ml, end-systolic volume - 49.5 ml. The same data in patients treated with atorvastatin were, respectively: 55.5%; 210 g; 1.0 cm; 1.1 cm; 5.3 14 cm; 3.3 cm; 124 ml; 57.5 ml. Rosuvastatin reduced stroke volume to 77.5 ml and atorvastatin to 82.5 ml.

Painless myocardial ischemia in patients with LV hypertrophy was more common than in examined patients without altered LV geometry. Both statins also affected another important pathogenetic link of coronary artery disease - inflammation (CRP and F). The effect of rosuvastatin was more significant. The pleiotropic properties of the studied statins were noted already in the first month of treatment, which may explain the rapid onset of the clinical effect when using these drugs against the background of standard treatment: a significant improvement in the condition of patients, a decrease in the frequency of angina attacks, a decrease in the amount of nitrates consumed, and an increase in the quality of life.

Painless myocardial ischemia in patients with LV hypertrophy was more pronounced than in patients without altered LV geometry. The results obtained may indicate a poor prognosis regarding the risk of cardiac complications. Painless myocardial ischemia is an early manifestation of these possible complications. The appearance of painless myocardial ischemia in LV myocardial hypertrophy is most likely a consequence of an increase in the oxygen demand of the

hypertrophied myocardium and a decrease in coronary blood flow.

It was determined that 37 patients had C/C allele (normal) - 92.5% and 3 patients had C/T allele (heterozygous) - 7.5%. The variant of the rs445925 polymorphism of the APOE gene in the heterozygous state is associated with a decrease in the level of cholesterol and LDL-C in the blood. In carriers of the e2 allele, statin therapy was more effective. A study of the frequency of rs6511720 polymorphism revealed a heterozygous G/T variant (13.2% occurrence) and a homozygous G/G variant in 2.6%, with the normal and most common G/G allele in 84.2% of cases. An increased response to statin therapy causes the rs6511720 polymorphism (-2.6% per allele; P=0.005). The rs5063, rs632793, and rs198388 loci formed the best model with the highest testing accuracy.

During the genotyping of the rs445925 polymorphism of the APOE/APOC gene, it was determined that the C/C allele (normal) was more common in patients and the C/T allele (heterozygote) was much less common. The genetic polymorphism of HMG-CoA reductase had a certain impact on the process of statin treatment. The ApoE and HMGCR genes associated pharmacogenetic biomarkers represent a very similar set regardless of the drug, however, the contribution of certain genes to these processes may differ depending on the nature of the statin. The association of allele C with an insufficient decrease in LDL during statin therapy was revealed:

x2=4.79 p=0.03, OR - 2.53; 95% CI: 1.09-5.9. In the population, there is polymorphism a according to E with the presence of 3 main alleles, encoding 3 main isoforms of apoE: the predominant isoform E3 and two mutants - E4 and E2. Sensitivity to statin therapy was higher in apoE2 carriers. These patients showed a more pronounced decrease in the level of LDL-C, as well as a greater increase in the level of LDL-C. There was a tendency to a more pronounced response (decrease in cholesterol and LDL-C) to drugs in carriers of the 2 allele than in 3 homozygotes and carriers of the 4 allele. The anoE gene locus was a significant predictor of the response of LDL-C and triglycerides to treatment with atorvastatin at a dose of 10 mg/day.

In men with the 2 allele, there is a significantly (p=0.01) greater response in the level of LDL-C than in 3 and carriers of the 4 allele. Carriers of the 2 allele showed a greater decrease in TG levels (p=0.01). In carriers of the CC genotype, on the background of 3-month therapy with atorvastatin, there is no statistically significant decrease in atherogenic blood lipids, in contrast to individuals with TT and TC genotypes. The carriage of T and C alleles does not independently contribute to the effectiveness of treatment with atorvastatin. The detected mutations are associated with coronary artery disease and atherosclerosis, associated with hypercholesterolemia, including its hereditary and familial forms.

These mutations reduce the number of LDL receptors within somatic cells and impair the ability of the receptors to remove cholesterol from the blood. The presence of polymorphism of the cytochrome P450 gene (CYP2C19) with the presence of 3 genotypes was established: wild-type homozygotes, heterozygotes, homozygotes for the mutant allele. The frequency of occurrence of carriers of the mutant allele among the examined patients does not differ from the population and is no more than 20%. Among carriers of the mutant allele, overweight is significantly more common (p=0.0182). However, some patients remained at an increased risk of thrombotic complications and restenosis.

In this regard, the selection of effective and safe doses of antiplatelet agents and statins, taking into account the polymorphism of the ApoE and CYP2C19*2 genes, will prevent the development of drug resistance and, accordingly, restenoses. Conclusion. The studied statins had a favorable effect on the course of coronary artery disease after PCI, and the genetic studies performed made it possible to select the most effective and safe doses of drugs. This approach allows to achieve maximum efficiency, excluding the development of complications and side effects. When prescribing statins, it is necessary to take into account the individual genetic

characteristics of the patient, in particular, the structural organization of his genome.

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