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The state of the lipid profile in patients with hyperlipidemia during statin and combination therapy

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Abstract

Objective. *To assess the dynamics of lipid parameters in patients with hyperlipidemia during statin and combination therapy with rosuvastatin and ezetimibe.*

Materials and methods. *The lipid profiles of 120 patients aged from 45 to 65 years with primary isolated and combined dyslipidemia with very high cardiovascular risk who admitted to Kursk City Clinical Emergency Hospital. Primary hyperlipidemia and diagnosed with laboratory and morphometric parameters were analyzed. Patients with secondary hyperlipidemia according to their history were excluded from the study. All the patients from study group were diagnosed with I–II functional class of angina pectoris. Each patient was advised to follow hypolipidemic diet and prescribed with rosuvastatin for 8 weeks; in case when target parameters were not achieved, the ezetimibe was added to therapy.*

Results. *During the 8-week treatment with 10 rosuvastatin of patients with coronary heart disease (CHD) and isolated or combined hyperlipidemia the following statistically significant changes of lipid profile were detected: the decrease of total cholesterol from 30.8 % to 28 %, low-density lipoproteins (LDL) from 40 % to 31 %, atherogenic index from 42 % to 43 % and the increase of high-density lipoproteins (HDL) from 9.9 % to 11 %, respectively. At the 8th week of statin monotherapy, 35 % of patients did not achieve target levels of LDL cholesterol and were prescribed with combined therapy with the addition of 10 ezetimibe in order to decrease the level of lipids.*

Conclusion. *The combination of rosuvastatin+ezetimibe showed high effectiveness and can be recommended for the correction of lipid disturbances in patients with high or very high cardiovascular risk.*

Keywords: *hyperlipidemia, statins, ezetimibe, coronary heart disease, hypolipidemic therapy.*

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Introduction

Cardiovascular diseases (CVDs) are the main cause of death and disability among adults in the world. There is a tendency to increase of CVD morbidity due to high prevalence of modified risk factors: smoking, alcohol, obesity, arterial hypertension (AH), type 2 diabetes mellitus (T2DM), low physical activity, etc. [5]. One of the main elements in the pathogenesis and progression of CVD, especially coronary artery disease (CAD) is coronary arteries atherosclerosis caused by lipid metabolism disturbances [2, 4].

It is widely known that hypolipidemic therapy can significantly decrease the risk of cardiovascular mortality, myocardial infarction, sudden cardiac death, cerebrovascular accident. Statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, which is the main enzyme in cholesterol biosynthesis, are actively used at this stage of the disease. Thus, cholesterol anabolism decreases and the number of low-density lipoproteins (LDL) receptors compensatory increases, thereby their metabolism accelerates, and the amount of antiatherogenic high density lipoproteins (HDL) rises. Thus, statins reduce the level of atherogenic and increase the level of antiatherogenic lipoproteins. Statin IV from the group of MMC–CoA reductase inhibitors that has the highest biological activity is rosuvastatin [4].

In case of insufficient effectiveness of high doses of statins, clinical guidelines for the diagnosis and management of dyslipidemias recommend to add ezetimibe to therapy scheme.

Objective

To assess the dynamics of lipid profile in patients with CAD and primary atherogenic dyslipidemia during rosuvastatin and combination therapy with rosuvastatin and ezetimibe.

Materials and methods

The study included 120 patients aged from 45 to 65 years with CAD: stable angina with verified primary atherogenic hyperlipidemia (HLP) (combined or isolated) and very high cardiovascular risk (CVR). The control group included 29 patients. Laboratory and instrumental parameters were assessed before the treatment and after 4, 8, 24, 48 weeks of pharmacotherapy and included: cardiovascular history assessment using CVD questionnaire developed by Kursk State Medical University of the Ministry of Healthcare of Russian Federation; anthropometry; biochemical profile assessment (lipid profile: total cholesterol (TC), LDL cholesterol, HDL cholesterol, triglycerides (TG), non-HDL-cholesterol, atherogenic index (AI), creatinine, urea, transaminases: alanine aminotransferase (ALT), aspartate aminotransferase (AST), 24-hour electrocardiogram (ECG) monitoring, bicycle ergometry to determine the functional class (FC) of CAD and exercise tolerance).

The main group included male patients aged from 45 to 65 years old with CAD: I–II FC of stable exertional angina with very high cardiovascular risk (TC level >5.5 mmol/l) without contraindications for ezetimibe or rosuvastatin prescription. Patients were not prescribed with statins earlier or discontinued this treatment. Written informed consent was waived from all the participants prior to the study.

Exclusion criteria were: adverse effects of the therapy: ALT or AST levels greater than two times the upper limit of normal, creatinine over 300 μmol/l, myopathies, creatine phosphokinase greater than five times the upper limit of normal, patient's refusal to participate in the research, severe comorbidities.

The study was performed in Kursk City Clinical Emergency Hospital from 2019 to 2020 years (before the COVID-19 pandemic). All the study participants were prescribed with hypolipidemic diet with the re-

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duction of calorie intake. The hypolipidemic diet was the only method of treatment in the control group and in other groups was prescribed together with pharmacotherapy, a survey was conducted to monitor diet compliance at all subsequent stages of the study.

Initially all the patients from the study group were prescribed with rosuvastatin 10, according to the medication guidelines [6]. In case when target level of LDL cholesterol (1.8 mmol/l) was not achieved by the 8 week of the study, 10 of ezetimibe was added to rosuvastatin.

Results

According to the results of the instrumental investigation all patients were diagnosed with CAD and I–II FC of stable angina. We have found concomitant diseases in clinical remission in 70.3 % of study participants (64 patients) in the study group and in 72.4 % (21 patients) in the control group. These diseases did not induce secondary HLP and did not need additional pharmacological treatment. During the assessment of risk factors, it was found that 65.8 % (79 patients) had smoked, and 58.3 % (70 patients) had low psychical activity.

Lipid profile parameters changed significantly during 8-week treatment with 10 of rosuvastatin monotherapy in patients with CAD complicated by isolated HLP: TC level decreased by 30.8 %, LDL cholesterol decreased by 40 %, non-HDL-cholesterol — by 36 %, AI — by 42 %, the level of HDL cholesterol increased by 9.9 %, that shows the effectiveness of IV generation statin in the management of isolated HLP in patients with CAD: stable angina pectoris of I–II FC (figure 1). The dynamics of TG was not statistically significant.

The following changes of lipid profile were established in patients with combined dyslipidemia during 8-week rosuvastatin therapy: TC level decreased by 28 %, LDL cholesterol decreased by 31 %, TG — by 8 %, AI — by 43 %, the level of HDL cholesterol increased by 11 %. These changes were statistically significant and are presented in table 1.

Despite high effectiveness of 8-week treatment with rosuvastatin (10), 35 % of patients did not reach target level of LDL cholesterol that was used as the cut-off point for the assessment of lipid-lowering treatment effectiveness. These patients were prescribed with combined therapy of the ezetimibe (10) and rosuvastatin.

By 48 week of treatment patients with isolated HLP who were prescribed with rosuvastatin+ezetimibe showed additional decrease of TC by 20 %, LDL cholesterol — by 24 %, HDL cholesterol by 27 %, AI by 30 % and the increase of HDL cholesterol by 4.6 % that can be seen from table 2.

The level of TC decreased by 14.5 %, TG by 11.2 %, LDL cholesterol by 21.5 % and the change of HDL cholesterol was not statistically significant — 4.5 % in patients with CAD complicated by combined HLP after 48 weeks of lipid-lowering treatment with two various mechanisms of action. Due to changes in the lipid transport system, the level of AI decreased by 35.3 % and non-HDL cholesterol — by 22.7 %.

One of the study objectives was to evaluate the change in the level of TC by the end of the study compared with baseline after the treatment with rosuvastatin + ezetimibe in patients with combined and isolated primary dyslipidemia. The effectiveness of combination therapy was 5.6 % higher in terms of TC levels in patients with isolated dyslipidemia that can be seen from Fig. 2.

Discussion

Ezetimibe is hypolipidemic medication that inhibit intestinal absorption of cholesterol, which has shown its safety, efficacy, and good tolerability in domestic and foreign studies [3]. Ezetimibe interacts with the NPC1L1 protein, transmembrane cholesterol transporter, that inhibits the absorption of cholesterol in the intestine and from bile acids, and does not affect the absorption of other fat-soluble substances. In response to the decrease of cholesterol that enters the liver, LDL hepatocytes cholesterol receptors activate and their blood clearance increase [5]. For decades, ezetimibe has been considered as an alternative to statins in case of intolerance. Later it was approved as adjunctive treatment to statin therapy when target levels of lipids haven't been achieved [1].

Literature data allow to assess the effectiveness of treatment with statin (primary simvastatin) and NPC1L1 inhibitor (ENHANCE, SEAS, SHARP, IMPROVE-IT) [3]. This therapy involves two mechanisms that determine cholesterol blood level- its synthesis in the liver and absorption in the intestine, therefore, an additional decrease of LDL cholesterol that plays key role in the development and progression of atherosclerosis, varies between 18–25 % [1, 3].

However, studies that performed long-term monitoring (within a year) of the lipid profile in patients with combination therapy with rosuvastatin + ezetimibe

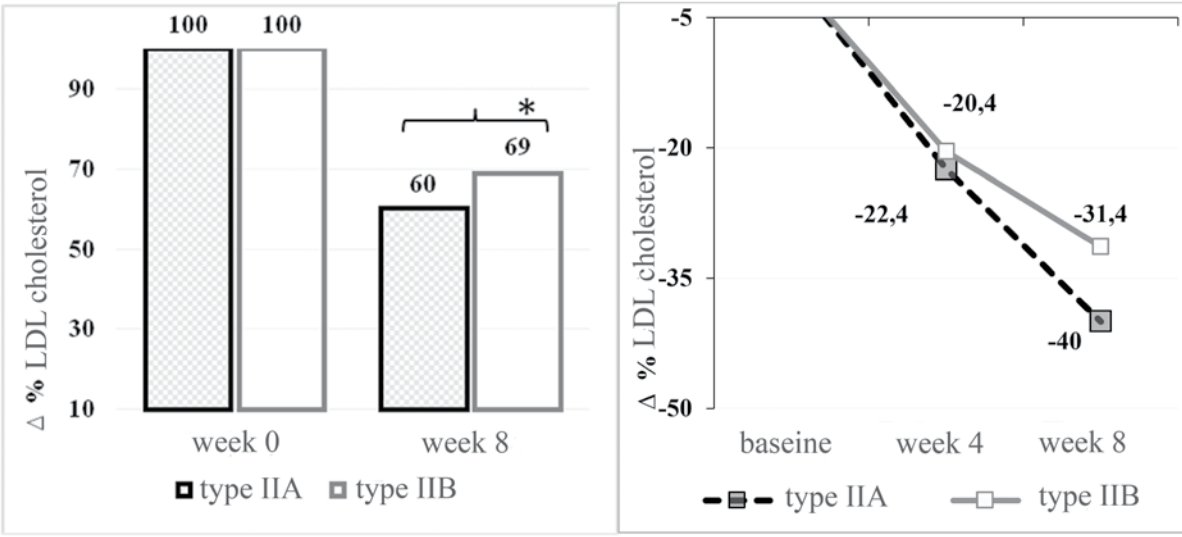

Figure 1. The dynamics of LDL cholesterol at the 8th week of rosuvastatin monotherapy (10 mg/day) in patients with CAD and HLP. Comment. *Changes are statistically significant (p<0.05).

Table 1. **The dynamics of lipid profile in patients with CAD and combined dyslipidemia during 8-week rosuvastatin monotherapy (10)**

Therapy time points	N	Lipid profile parameters, mmol/l		The change of lipid parameters compared with baseline (%)	p-value (Wilcoxon test)
		Median	Interquartile range		
Total cholesterol					<0.001*
Week 0	46	6.10	5.90–6.45		
Week 4	46	5.33	4.36–5.57	−11.62	<0.001
Week 8	46	4.38	3.75–4.60	−28.19	<0.001
LDL cholesterol					<0.001*
Week 0	46	4.27	3.95–4.60		
Week 4	46	3.40	2.41–3.59	−20.37	<0.001
Week 8	46	2.93	1.99–3.49	−31.38	<0.001
HDL cholesterol					0.037
Week 0	46	1.01	0.93–1.10		
Week 4	46	1.06	1.00–1.17	4.95	0.063
Week 8	46	1.12	1.10–1.20	10.89	0.026
Triglycerides					0.05
Week 0	46	1.84	1.78–1.91		
Week 4	46	1.77	1.71–1.82	−3.80	0.063
Week 8	46	1.70	1.60–1.77	−7.61	0.042
Non-HDL-cholesterol					<0.001*
Week 0	46	5.10	4.70–5.44		
Week 4	46	4.17	3.21–4.24	−18.24	0.025
Week 8	46	3.21	2.45–3.39	−37.06	0.022
Atherogenic index					<0.001*
Week 0	46	5.09	4.54 — 5.76		
Week 4	46	3.96	2.63–3.81	−21.11	0.040
Week 8	46	2.91	1.85–3.54	−42.83	0.031

Note. * – differences are significant at p<0.05.

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Table 2. **The dynamics of lipid profile in patients with CAD and isolated dyslipidemia during 48-week combination therapy**

Therapy time points	N	Lipid profile parameters, mmol/l		The change of lipid parameters compared with baseline (%)	p-value (Wilcoxon test)
		Median	Interquartile range		
Total cholesterol					0.019*
Week 8	10	5.76	5.33–6.10		
Week 24	10	5.1	4.89–5.34	–11.45	0.005
Week 48	10	4.60	3.90–4.86	–20.13	0.003
LDL cholesterol					0.022*
Week 8	10	3.96	3.22–4.10		
Week 24	10	3.57	3.06–3.85	–9.85	0.004
Week 48	10	3.01	2.93–3.45	–23.98	0.004
HDL cholesterol					0.449*
Week 8	10	1.09	1.06–1.20		
Week 24	10	1.12	1.10–1.22	2.75	0.241
Week 48	10	1.14	1.10–1.24	4.58	0.018
Triglycerides					0.549*
Week 8	10	1.53	1.30–1.59		
Week 24	10	1.43	1.21–1.60	–6.54	0.100
Week 48	10	1.42	1.17–1.59	–6.58	0.647
Non-HDL-cholesterol					0.022*
Week 8	10	4.51	4.05–4.89		
Week 24	10	3.90	3.75–4.10	–13.52	0.002
Week 48	10	3.29	2.98–3.49	–27.05	0.003
Atherogenic index					0.009*
Week 8	10	4.18	3.85–4.50		
Week 24	10	3.41	3.18–3.76	–18.42	0.031
Week 48	10	2.92	1.48–2.21	–30.14	0.012

Note. * — differences are significant at p<0.05.

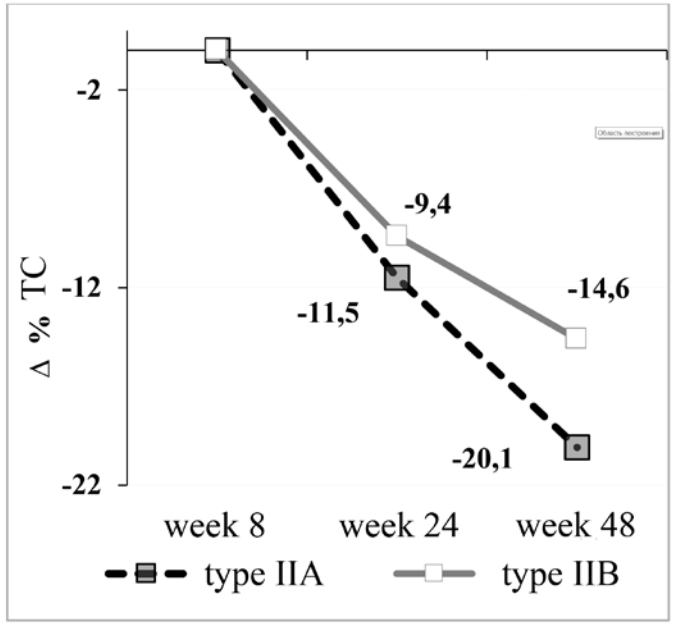

Figure 2. The dynamics of non-HDL-cholesterol by 48 week of combination therapy in patients with CAD and atherogenic HLP.

are scarce. Therefore, there is the need for studies of various statins and ezetimibe combinations that will allow to identify the most effective treatment.

Our study assessed the effectiveness of rosuvastatin + ezetimibe therapy in patients with isolated and combined dyslipidemia that was higher in patients with isolated HLP.

Conclusion

The addition of ezetimibe to the treatment of atherogenic HLP in patients with CAD: I–II FC of stable angina in case when target level of LDL cholesterol has not been achieved led to the improvement of lipid profile parameters. Such results expand the possibilities of primary and secondary prevention of atherosclerosis progression in patients with high cardiovascular risk.

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