EVALUATION OF TREATMENT EFFICACY IN PATIENTS WITH NON-ALCOHOLIC-STEATOHEPATITIS AND HETEROZYGOTIC FAMILIAL HYPERCHOLESTEROLEMIA

Yakimenko O., Maznichenko I.

Odessa National Medical University, Ukraine

Today, cardiovascular diseases (CVD) occupy a significant place in the structure of mortality worldwide. The main causes of CVD are atherothrombosis and hypertension. Atherothrombosis is a consequence of the development of atherosclerosis, the manifestation of which occurs as the development of acute coronary syndrome (ACS) [3,4].

It is proved that dyslipidemia is one of the leading factors in the development of CVD, which alone or in interaction with other risk factors can lead to the manifestation of an atherosclerotic process, which undoubtedly influences the course and prognosis of patients with cardiovascular diseases [3,4,7,16].

Lipid metabolism mainly occurs in the liver, abnormalities in the structure and function of the organ may cause atherogenic dyslipidemia [2,16,18]. In this condition, the liver simultaneously becomes the target organ leading to the development of non-alcoholic fatty liver disease (NAFLD), which can significantly limit the hypolipidemic therapy with statins. LDL are the main atherogenic class, due to the ability to linger in the intima of the arteries [2,11,12]. It is known that morbidity and mortality of patients with NASH has a strong correlation with morbidity and mortality from the cardiovascular diseases [3,7,16]. The pathogenesis of NAFLD and CVD is closely related, as in NAFLD there is lipid accumulation and overload, and their long stay in hepatocytes leads to inflammation of the hepatic parenchyma, steatohepatitis, which results in the release of free radicals and oxidative stress, with rapid depletion of antioxidant systems, including a cellular antioxidant - glutathione [2,5,16,18,20]. At the same time, the induction of NF-κB is activated, and hepatites are altered by hepatotoxic mediators (tumor necrosis factor-alpha (TNF)), which stimulates inflammation of the liver tissue and a decrease in insulin sensitivity [7,9,11,18].

Dyslipidemia may be primary - as a result of anomalies in genes, enzymes or transport proteins that are involved in the metabolism of lipids, and secondary, which is a consequence of hormonal imbalances, concomitant diseases and the intake of certain medicines [4].

Familial hypercholesterolemia (FHC) is a common genetic disorder caused by a gene mutation to the low-density lipoprotein (LDL) receptor, which disrupts cholesterol metabolism, leading to malignant increases in atherogenic lipid fractions, contributing to the premature development of atherosclerosis, ischemic heart disease (CHD), and early cardiovascular and cerebrovascular accidents [3,5,7,10,13]. Today, mutations in LDL, Apo-B, and PCSK9 genes are most common, but sporadic mutations of other genes involved in lipid metabolism continue to be actively studied [10,13-15]. Among the FHC, the heterozygous form of FHC (HFHC) 1: 250-500 is most common, it is characterized, as a rule, by the phenotype IIa, less often IIb according to the classification of dyslipidemia by D.Fredrickson. HFHC is an autosomal dominant type of inheritance with an average total cholesterol concentration (TC) of 9-12.9 mmol / l. The manifestation of the cardiovascular diseases, primarily ischemic heart disease (CHD), is more likely to occur in 3-4 decade of life. A severe form of FHC-homozygous FHC (HoFHC) is less common, its prevalence is 1: 250,000 - 1,000,000, as in HFHC, the type of inheritance is autosomal dominant, but in this mutation, there can be both a deep defect and a complete absence of the LDL receptor [4,6,8,13-15,17]. The concentration of TC varies from 18.0 to 31.0 mmol / l, often tuberous and tendinous xanthomas, xanthelasma, lipoid arches of the cornea are present in the patient, and in the absence of adequate therapy, premature death occurs before the age of thirty [4,6,9,10,19,20].

It is known that statin therapy is also the first line in treatment of dyslipidemia [6,13,17,19]. Patients with FHC have a lifelong high risk of developing cardiovascular accidents, therefore, statin therapy is given continuously and in the maximum tolerated doses. A number of large studies have shown that lipid-lowering therapy with statins is associated with a risk of a number of side effects including hepatobiliary system [3,4,18,19]. It is known that NAFLD is a pathological condition in which the formation of steatosis occurs, i.e. excessive accumulation of lipids in the liver tissue in the form of triglycerides [11,12,16,18]. Independently in NAFLD steatosis does not correlate with the growth of short-term morbidity and mortality, however, the progression of the disease to the NASH stage is potentially fatal, and is associated with an increased risk of fibrosis, cirrhosis, hepatic insufficiency and hepatocellular carcinoma [4,9,11,16].

Despite significant achievements in the management of patients with FHC, the problem of effective and safe therapy of HFHC with non-alcoholic steatohepatitis (NASH) remains important.

The aim of the study was to increase the efficacy of treatment of patients with nonalcoholic steatohepatitis and heterozygous familial hypercholesterolemia by developing a personalized approach to therapy using rosuvastatin 20 mg / day and the combined hepatoprotector "Gepadif" at the outpatient and inpatient stages of treatment, taking the complaints, history, physical examination methods, laboratory (general clinical, biochemical, molecular genetic investigation methods) and instrumental studies (ultrasound and echocardiographic method of investigation, electrocardiogram) as well as statistical methods.

Material and methods. A retrospective analysis of laboratory indices of blood serum lipid spectrum and indices of the liver functional activity was made in 647 patients, 245 case histories were analyzed, 124 patients with hypercholesterolemia and NASH were examined in a complex manner.

The object of the study was 55 patients (mean age 55.45 ± 5.5 years) with a clinical diagnosis of HFHC, NAFLD in the stage of steatohepatitis. The diagnosis of HFHC was made on the basis of the clinical management of the expert group on familial hypercholesterolemia of the National Lipid Association of the USA "Familial hypercholesterolemia: examination, diagnosis and treatment of adults and children," guidelines of the Association of Cardiologists of Ukraine "Dyslipidemia: diagnosis, prevention and treatment," the generalized treatment guidelines on familial hypercholesterolemia of the International Fund for Family Hypercholesterolemia. The diagnosis of NASH was made on the basis of the "Unified clinical protocol for primary, secondary (specialized) medical care: non-alcoholic steatohepatitis", the recommendations of the European Association for the Study of the Liver (EASL).

All patients who were involved in the study were divided into two groups: the first group - n=28, of whom women 57% (n=16), men 43% (n=12) received rosuvastatin 20 mg orally, once a day; the second group of patients - n=27, women 59% (n=16), men

41% (n=11) received rosuvastatin 20 mg orally, once a day and a hepatoprotector "Gepadif" 2 capsules, orally, 3 times a day. The control group consisted of 20 practically healthy persons.

The control group consisted of 20 practically healthy individuals aged 20 to 40 years who had no complaints during the consultation, there were no pathological changes during physical examination, and the indices of laboratory and instrumental methods of the investigation corresponded to the reference indices characteristic of healthy individuals.

Evaluation of the efficacy and safety of lipid-lowering therapy was assessed on the 45th and 90th days of therapy.

Verification of pathological conditions and somatic pathology was carried out according to ICD-10 classification. All examined was conducted a comprehensive examination, including assessment of complaints, history, physical (clinical) data, results of the laboratory data (blood count, urinalysis), the functional activity of the liver was assessed by determining activity of hepatic transaminase (alanine aminotransferase (ALT), aspartate-aminotransferase (AST), gamma-glutamyltransferase (GGT), alkaline phosphatase (AFP)), the lipid spectrum was determined by the photocolorithmic method (total cholesterol (TC), high-density lipoproteins (HDL), low density lipoproteins (LDL), very low density lipoproteins (VLDL), triglycerides (TG), atherogenic index (AI) creatine phosphokinase (CPK)), instrumental (ultrasound examination of the abdominal organs (US AO), electrocardiogram (ECG) echocardiography (EchoCG)) and molecular genetic examinations (personification of satin dosage by determining polymorphism of the *SLCO1B1* gene).

The study did not include patients consuming alcohol, hepatotoxic drugs with signs of viral or autoimmune hepatitis.

All patients were administered individual physical doses, according to individual tolerance to physical exertion, diet therapy.

Statistical processing of the data was carried out on the 45th and 90th day from the start of therapy, using the standard Microsoft Excel software package. Estimation of the probability of discrepancy of the mean values was carried out using Student's paired t-criterion. The results were considered statistically significant at a value of $p<0.05$.

Results and their discussion. There was made a retrospective analysis of the laboratory indices of the blood serum lipid spectrum and indices of the functional activity of the liver of 647 patients, 245 case histories were analyzed, followed by a comprehensive examination of 124 patients, of whom 55 patients (55.45±5. 5 years) with clinical diagnosis of HFHC, NAFLD in the stage of steatohepatitis.

At the time of the beginning of the study, dyslipidemia occurred in both groups, namely, an increase in TC, LDL, and a decrease in the level of HDL cholesterol, the TG level was within reference values, which generally contributed to the increase in CI and corresponded to IIa type of hypercholesterolemia according to Fredrickson.

In the patients of the first group, TC was significantly elevated relative to the control group ($p<0.001$) and was 9.39±0.73 mmol/l. The patients of the second group also experienced hypercholesterolemia - 9.4±0.74 mmol/l ($p<0.001$). The level of LDL in the blood serum was increased in both groups ($p<0.001$): in the first - 7.16±0.6 mmol/l and the 2nd - 7.21±0.17 mmol/l. The level of HDL was close to the lower limit of the basal value, both in the first and second group ($p<0.005$) and made: the 1st group - 1.5±0.4 mmol/l; the 2nd - 1.48 ± 0.34 mmol/l. The level of TG in both groups did not exceed the reference values.

When analyzing the biochemical activity of the liver transaminases of both groups before the study, it was revealed that ALT and AST were significantly increased activity in both groups in relation to the control one ($p<0.001$), in the first group the ALT was 102.5±13.74 units/l and AST - 78.32±17.97 units/l; in the second group the ALT was 99.63±20.86 units/l, and AST was 84.03±20.38 units/l, respectively.

As a result of the molecular genetic study of polymorphism of the *SLCO1B1* gene, 14 (50%) of the carriers of the wild type *c.521TT*, 11 (39.2%) were identified in the patients of the first group with the genotype *c.521TC* and 3 (10.8%) patients with the genotype *c.521CC*, in the patients of the second group, diagnostic results revealed 17 (63%) carriers of the genotype *c.521TT*, 8 (26.9%) with the genotype *c.521TC* and 2 (7.4%) with the genotype *c.521CC*.

In a comparative evaluation of the results of the lipid profile of the blood in the dynamics, on the 45th day of therapy with rosuvastatin at a dose of 20 mg the first group was found to have a tendency to decrease in the level, but they did not attain reliability: TC and LDL, in particular, TC decreased by 13.6% and was 8.11±1.35 mmol/l, and a decrease by 16.4% was observed in LDL, which was 5.99±1.0 mmol/l compared to their baseline data.

Table 1. Dynamics of biochemical blood indices in patients of the first group (M±m)

Index	Initial level	The 45th day	The 90th day
Total cholesterol (TC)	9.39±0.73 mmol/l *	8.11±1.35 mmol/l	6.65±0.97 mmol/l **
LDL	7.16±0.6 mmol/l *	5.99±1.0 mmol/l	4.24±0.82 mmol/l **
HDL	1.5±0.4 mmol/l *	1.51±0.62 mmol/l	2.06±0.43 mmol/l **
ALT	102.5±13.74 U/l *	67.54±18.57 U/l	52.57±12.56 U/l**
AST	78.32±17.97 U/l *	55.18±15.50 U/l	34.29±7.77 U/l**

*note: * - p<0.001 relative to the control group; ** - p<0.005 relative to the baseline*

Table 2. Dynamics of biochemical indices of blood in patients of the second group (M±m)

Index	Initial level	The 45th day	The 90th day
Total cholesterol (TC)	9.4±0.74 mmol/l *	7.88±0.68 mmol/l	5.1±0.59 mmol/l **
LDL	7.2±1.0 mmol/l *	5.41±0.62 mmol/l	2.23±0.58 mmol/l **
HDL	1.48±0.3 mmol/l *	2.16±0.22 mmol/l	2.56±0.29 mmol/l **
ALT	99.63±20.86 U/l *	59.07±19.46 U/l	32.16±7.83 U/l **
AST	84.03±20.38 U/l *	44.59±19.47 U/l	30.11±6.32 U/l **

*note: * - p<0.001 relative to the control group; ** - p<0.005 relative to the baseline*

When analyzing the data of biochemical studies in the patients of the first group on the 90th day of oral administration of rosuvastatin 20 mg once a day, it was revealed that the level of TC decreased by 29.2% compared to the baseline before the start of therapy, and was 6.65±0.97 mmol/l (p<0.005). The level of LDL decreased by 40.8% when compared with the baseline and was 4.24±0.82 mmol/l (p<0.005). The level of HDL increased by 37% compared with before treatment, and amounted to 2.06±0.43 mmol/l (p<0.05).

Analyzing the data of biochemical studies of hepatic transaminases of the first group, a tendency to decrease activity was revealed on the 45th day of statin therapy, but no statistically significant changes were noted. On the 90th day of treatment with rosuvastatin 20 mg/day the patients of the first group had a decrease activity in ALT by 49%, and amounted to 52.57±12.56 units/l (p<0.005); the AST activity decreased by 56.2%, which was 34.29±7.77 units/l (p<0.005) compared to the baseline.

When analyzing the effectiveness of lipid-lowering therapy with the addition of a complex hepatoprotector, there was a more pronounced tendency to the decrease of TC and LDL, in particular, the level of TC decreased by 16.2% and made 7.88±0.68 mmol/l but the levels did not reach statistical reliability in the patients of the second group on the 45th day. There was also a decrease in LDL by 25%, which made 5.41±0.62 mmol/l. The blood serum level of HDL was characterized by an increase by 45% and amounted to 2.16±0.22 mmol/l on the 45th day of therapy.

As for the indices of activity of the liver enzymes of the second group, there was a marked tendency to decrease activity in ALT on the 45th day of lipid-lowering therapy, but it was statistically insignificant: the activity of enzymes decreased by 41% and amounted to 59.07±19.46 units/l; AST also had a tendency to decrease activity and on the 45th day of lipid-lowering therapy with rosuvastatin 20 mg/day and complex hepatoprotector, was 44.59±19.47 units/l, which is 47% lower than the baseline, but the levels did not reach statistically significant values.

In the comparative analysis of the data of the biochemical indices of the lipid spectrum of the patients of the second group on the 90th day of rosuvastatin 20 mg once daily and hepatoprotector 2 capsules 3 times a day with the data obtained before the study, it was noted that the level of TC decreased by 46% and amounted to 5.1±0.59 mmol/l (p<0.005), the level of LDL significantly decreased by 68.5% and made 2.23±0.58 mmol/l in comparison with the baseline (p<0.005). When analyzing the results of HDL, it was noted that the level gradually increased and the increase was 73% on the 90th day in relation to the initial index - 2.56±0.29 mmol/l (p<0.005).

In analyzing laboratory indices of activity of hepatic enzymes of the second group, it was revealed that the activity of hepatic transaminases significantly decreased: ALT by 68% and was 32.16±7.83 units/l (p<0.005) on the 90th day of lipid lowering therapy, the activity of AST decreased by 64% and made 30.11±6.32 U/l, which allowed reaching the limits of the reference values (p<0.005).

It should be noted that despite the decrease in the leading lipid profile of both groups of patients, there was a significant more pronounced decrease in LDL cholesterol by 68.5% in the second group, which made it possible to achieve the target LDL-C level for 90 patients. It was found that the decrease in LDL in lipid-lowering therapy between the first and second groups was more pronounced in the patients of the second group that received statin with a complex hepatoprotector, the difference between the LDL-C values on the 90th day of therapy was 2.01 mmol/l, respectively. At the same time, the LDL level of the first group did not reach the target level during the therapy, and was 4.24±0.82 mmol/l.

In 90 days of lipid lowering therapy, there was revealed the advantage of statin therapy with rosuvastatin 20 mg once a day and a combined hepatoprotector based on carnitine, which was confirmed by the achievement of the target LDL level in 19 patients of the second group. At the same time there was a decrease in TC by 16% on the 45th day of therapy and by 52% in comparison with the baseline level on the 90th day of treatment. In patients of the first group, the changes in the TC index were less significant; in particular, the decrease in TC was 13.6% on the 45th day and decreased by 29.2% compared to the baseline on the 90th day of therapy.

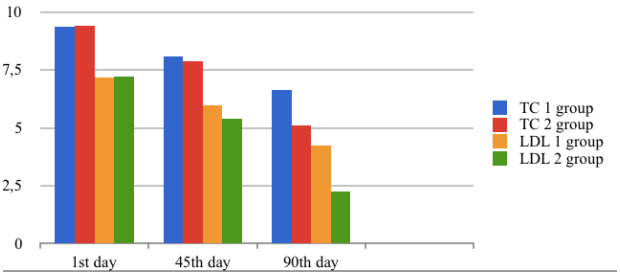

Fig. 1. Comparative analysis of the dynamics of biochemical indices of the lipidogram TC and LDL of the first and second groups

On the basis of the results of the lipidogram in all patients, there was noted a decrease in CI in both groups: CI decreased by 49% and amounted to 2.32±0.62 (p<0.005) in the patients of the first group on the 90th day, monotherapy with statin; CI decreased by 73.5% and made 1.52 (p<0.005) in the patients of the second group, which was mainly due to an increase in the HDL index. When the HDL index of the first and second groups was compared on the 90th day of therapy, it was revealed that in the first group the HDL cholesterol levels increased by 37% compared to the baseline values of 2.06±0.43 mmol/l (p<0.005), and HDL of the second group - by 73% and amounted to 2.56±0.29 mmol/l (p<0.005), which may indicate that against the background of statin therapy as well as the normalization of functioning and metabolism in hepatocytes, a more pronounced compensatory shift in favor of HDL occurs, which accelerates the exchange of atherogenic lipids, and is undoubtedly an important indicator for the prognosis.

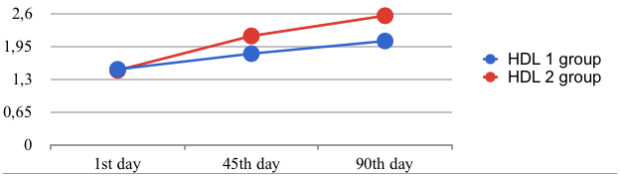

Fig. 2. Dynamics of HDL of the first and second groups

IIn conducting a comparative analysis of the clinical efficacy and safety of statin use for NASH course and the functional state of the liver, it was found that taking rosuvastamine 20 mg and hepatoprotector "Gepadif" has advantages over monotherapy with statin, which was characterized by an improvement in the subjective status in all patients of the second group, absence of complaints, in particular, a feeling of discomfort in the right hypochondrium, dyspeptic disorders. Out of the patients of the first group receiv-

ing monotherapy rosuvastatin 20 mg once a day 13 patients (48%) had complaints on heaviness in the right hypochondrium, dyspeptic disorders were in 17 (63%) patients, periodic pain in the right hypochondrium region in 7 (26%) patients were noted on the 90th day. In a number of cases, a doubled increase in the activity of hepatic transaminases was observed (ALT, AST) in the blood serum on the 90th day of therapy in patients of the first group, in 6 (22%) patients in comparison with baseline parameters.

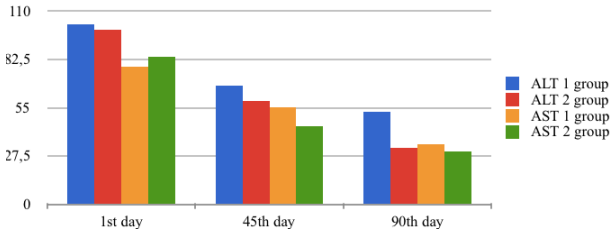

Fig. 3. Comparative analysis of the dynamics of biochemical indices of hepatic transaminases (ALT, AST) in patients of the first and second groups

Thus, in therapy of HFHC with NASH the use of rosuvastatin 20 mg orally, once in 24 hours for a long time, and hepatoprotector "Gepadif" 2 capsules 3 times with possible repetition of the hepatoprotector for the course of 90 days can ensure maximum effectiveness and safety of therapy, the therapy of choice.

Conclusions. 1. A comprehensive examination was made, including a molecular genetic diagnosis - the determination of the *SLCO1B1* gene polymorphism. Patients were chosen personalized lipid-lowering therapy and the determined maximum tolerated doses of statins.

2. When treating patients with characteristic subjective and objective manifestations of HFHC with NASH, it is advisable to use a combination of lipid-lowering therapy, consisting of rosuvastatin at a dose of 20 mg orally once per day for a long time and 2 capsules of the hepatoprotector 3 times per the course of 90 days, with possible repetition of the hepatoprotector course to achieve target levels of LDL.

3. Standard lipid-lowering therapy, including a statin (rosuvastatin 20 mg), led to a significant improvement in the subjective and objective manifestation of HFHC with NASH, but did not contribute to the achievement of target levels of LDL.

4. The use of the hepatoprotector and rosuvastatin 20 mg/day contributes to the reliable achievement of the LDL targets for 90 days of therapy <2.5 mmol/l in 22 (82%) patients, after 90 days of therapy in comparison with monotherapy with rosuvastatin 20 mg/day, which was accompanied by a significant achievement of the target lipid level in 11 (39%) patients.

5. The use of a combined hepatoprotector along with rosuvastatin contributed to a significant decrease activity in the liver transaminase levels: ALT decreased by 48.4% and amounted to 38.85±11.54 U/l for 90 days of lipid-lowering therapy, while AST decreased by 44.2% and made 32±11.54 units/l.

Prospects for further investigation. Further investigations should be directed at the search for new therapeutic targets, more effective and safe methods of treatment of the liver diseases in the course of simultaneous HFHC and NASH, taking into account the pathogenesis of NASH, which has a strong correlation with morbidity and mortality from the cardiovascular accidents. Also the search for new, more reliable markers for the manifestation of HFHC and NASH, is necessary for assessing the activity, progression of the disease, and evaluation of the effectiveness and safety of the therapy.

REFERENCES

1. Адаптована клінічна настанова, заснована на доказах «Неалкогольна жирова хвороба печінки» / Н. В. Харченко, О. М. Ліщина, Г. А. Анохіна [та ін.] // 2014. Доступно: http://old.moz.gov.ua/ua/print/dn_20140616_2.html.
2. Гиполипидемическая терапия у больных с неалкогольной жировой болезнью печени / Л. А. Звенигородцева, Н. Г. Самсонова, Н. В. Мельникова та ін. // Клиническая гастроэнтерология - №07 - 2010 - С. 25 - 33.
3. Дисліпідемії: діагностика, профілактика та лікування. Методичні рекомендації Асоціації кардіологів України / О. І. Мітченко, М. І. Лутай / 2011. - Київ - С.40
4. Латфуллин И. А. / Ишемическая болезнь сердца: основные факторы риска, лечение / И. А. Латфуллин // 2ое изд. - Изд. Казан. универ. - 2017. - Казань - 426 С.
5. Уніфікований клінічний протокол «Неалкогольний стеатогепатит». Наказ МОЗ України № 826 від 06.11.2014 року / М. К. Хобзей, Н. В. Харченко, О. М. Ліщина [та ін.] // 2014. Доступно: http://mtd.dec.gov.ua/images/dodatki/2014_826Gepatyty/2014_826_YKPMD_NSTPT.pdf.
6. The agenda for Familial Hypercholesterolemia: a scientific statement from the American Heart Association / S. S. Gidding, M. A. Champagne, S. D. de Ferranti J. Defesche, Matthew K. et all // Circulation - 132 - 2015 - P. 2167 - 2192.
7. Alkagiet S. / Association between nonalcoholic fatty liver disease and ischemic stroke / S. Alkagiet, A. Papagiannis, K. Tziomalos // World J. Hepatol. - 27 (10) - 2018. - P. 474 - 478.
8. Clinical, Anthropometric and biochemical characteristics of patients with or without genetically confirmed Familial Hypercholesterolemia / A. Lorenzo, JDLD Silva, CE James et all / Arq. Bras. Cardiol. - 110. - 2018. - P. 119 -123.
9. Clinical and histological determinate of nonalcoholic steatohepatitis and advanced fibrosis in elderly patients / M. Noureddin, K. P. Yates, I. A. Vaughn et all // Hepatology - 58(5). - 2013. - P. 1644 - 1654.
10. Clinical management of heterozygous familial hypercholesterolemia in a Polish outpatient metabolic clinic: a retrospective observational study / L. Klosiewicz-Latoszek, B. Cybulska, J. Bialobreska-Paluszkiewicz et all // Arch. Med. Sci. - 14(5) - 2018 - P. 962 - 970.
11. Cytokeratin 18, alanin aminotransferase, platelets and triglycerides predict the presence of nonalcoholic steatohepatitis / W. Can, C. Zhao, C. Shen, Y. Wan // PloS One. - 8(12). - 2013. - doi: 10.1371/journal.pone.0082092
12. 2016 ESC/EAS Guidelines for the management of dyslipidemias / Developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR) // Russ. J. Cardiol. - 5 (145) - 2017. - P. 7 - 77.
13. Familial Hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients. Clinical guidance from the National lipid Association Expert on familial Hypercholesterolemia / A. Goldberg, P. N. Hopkins, P. P. Both et all// J. Clin. Lipidology - 5. - 2011. - P. S1 - S8.
14. Prajapati R. / Familial hypercholesterolemia supravalvular aortic stenosis and extensive atherosclerosis / R. Prajapati,V. Agrawal // Indian Heart J. - Vol. 70 Issue 4. - 2018 - P. 575 - 577.
15. Guidelines for diagnosis and treatment of Familial Hypercholesterolemia 2017 / M. Harada-Shimba, H. Arai, Y. Ishogaki et all // J. Atherolscler. Thromb. - 1:25(8) - 2018. - P. 757 - 770.
16. Impaired HDL cholesterol efflux capacity in patients with

non-alcoholic fatty liver disease is associated with subclinical atherosclerosis / R. Fadaei, H. Poustchi, R. Meshkani et all // Sci. Rep. - 8(10. - 2018 - P. 11691.
17. Integrated guidance on the care of familial hypercholesterolemia from the International FH Foundation // International Journal of Cardiology - 171 - 2014 - P. 309 - 325.
18. Ipsen D. H. / Molecular mechanisms of hepatic lipid accumulation in non-alcoholic fatty liver disease / D. H. Ipsen, J. Lykkesfeldt, P. Tveden-Nyborg // Cell Mol. Life Sci. - 75 (18) 2018 - P. 3313 - 3327.
19. Pooling and expanding registries of familial hypercholesterolemia to asses gaps in care and improve disease management and outcomes: rationale and design of the global EAS Familial Hypercholesterolemia Studies Collaboration / the EAS Familial Hypercholesterolemia Studies Collaboration, A. Akram, S. R. K. Seshasai et all. // Atherosclerosis supply. - 22. - 2016. - P. 1 - 32.
20. The task Force for management of dyslipidemias of the Europian Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) // Our. Heart J. - 2011. - Vol.32. - P.1769 -1818.

SUMMARY

EVALUATION OF TREATMENT EFFICACY IN PATIENTS WITH NON-ALCOHOLIC-STEATOHEPATITIS AND HETEROZYGOTIC FAMILIAL HYPERCHOLESTEROLEMIA

Yakimenko O., **Maznichenko I.**

Odessa National Medical University, Ukraine

The aim of the study was to increase the efficacy of treatment of patients with HFHC and NASH by developing a personified approach to the therapy with rosuvastatin 20 mg/day and combined hepatoprotector at the inpatient and outpatient stages of treatment.

124 patients with clinical HFHC were examined. The object of the study was 55 patients (age 55.45±5.5 years) with a clinical diagnosis of HFHC, NASH. All patients underwent a detailed physical examination, laboratory-instrumental (general clinical, biochemical (hepatic transaminases, lipidogram, ultrasonography of the abdominal organs), molecular genetic examination (polymorphism of the *SLCO1B1* gene). Two groups of study were formed, in the first group patients received rosuvastatin 20 mg/day, in the second group - rozuvastatin 20 mg/day and combined hepatoprotector 2 capsules 3 times a day for 90 days.

The patients treated with rosuvastatin 20 mg/day and hepatoprotector were revealed a reliable decrease in the level of TC by 46%, which was 5.1±0.59 mmol/l ($p<0.005$), the level of LDL significantly decreased by 68.5% - 2.23±0.58 mmol/l ($p<0.005$), the level of HDL increased by 73% and amounted to 2.56±0.29 mmol/l ($p<0.005$). On the 90th day of therapy, the activity of hepatic transaminases reached reference values: ALT 32.16±7.83 units/l, AST – 30.11±6.32 units/l ($p<0.005$). Based on the complex examination and determination of polymorphism of *SLCO1B1*, a personified dose of statin was selected.

Keywords: heterozygous familial hypercholesterolemia, non-alcoholic steatohepatitis, statin therapy, polymorphism of the *SLCO1B1* gene.

РЕЗЮМЕ

ОЦЕНКА ЭФФЕКТИВНОСТИ ЛЕЧЕНИЯ ПАЦИЕНТОВ С НЕАЛКОГОЛЬНЫМ СТЕАТОГЕПАТИТОМ И ГЕТЕРОЗИГОТНОЙ СЕМЕЙНОЙ ГИПЕРХОЛЕСТЕРИНЕМИЕЙ

Якименко Е.А., Мазниченко Е.А.

Одесский национальный медицинский университет, Украина

Целью исследования явилось повышение эффективности лечения пациентов с гетерозиготной семейной гиперхолестеринемией (ГСГХ) и неалкогольным стеатогепатитом (НАСГ) путем разработки персонифицированного подхода к терапии с применением розувастатина 20 мг/сутки и комбинированного гепатопротектора на стационарном и амбулаторном этапах лечения.

Обследовано 124 пациента с клинической ГСГХ, из них 55 пациентов в возрасте 55,45±5,5 лет с клиническим диагнозом ГСГХ и НАСГ. Всем пациентам проведено детальное физикальное обследование, лабораторно-инструментальные общеклинические и биохимические (печеночные трансаминазы, липидограмма, УЗД органов брюшной полости), молекулярно-генетические (полиморфизм гена SLCO1B1) исследования. Сформировано две группы больных: в I группе пациенты получали розувастатин 20 мг/сутки, во II группе - розувастатин 20 мг/сутки и комбинированный гепатопротектор по 2 капсулы 3 раза в сутки 90 дней.

У пациентов, получавших терапию розувастатином 20 мг/сутки и гепатопротектором, выявлено достоверное снижение уровня общего холестерина (ОХ) на 46%, что составило 5,1±0,59 ммоль/л ($p<0,005$), уровень липопротеидов низкой плотности достоверно снизился на 68,5% - 2,23±0,58 ммоль/л ($p<0,005$), уровень липопротеидов высокой плотности увеличился на 73% и составил 2,56±0,29 ммоль/л ($p<0,005$). На 90 сутки терапии активность печеночных трансаминаз достигла референсных величин: АЛТ - 32,16±7,83 ед/л, АСТ - 30,11±6,32 ед/л ($p<0,005$). На основании комплексного обследования и определения полиморфизма SLCO1B1 подобрана персонифицированная доза статина.

რეზიუმე

არაალკოჰოლური სტეატოჰეპატიტისთდა ოჯახური ჰეტეროზიგოტური ჰიპერქოლესტერინემიით პაციენტების მკურანალობის ეფექტურობის შეფასება

ე. იაკიმენკო, ე. მაზნიჩენკო

ოდესის ეროვნული სამედიცინო უნივერსიტეტი, უკრაინა

კვლევის მიზანს წარმოადგენდა არაალკოჰოლური სტეატოჰეპატიტით და ოჯახური ჰეტეროზიგოტური ჰიპერქოლესტერინემიით პაციენტების მკურანალობის ეფექტურობის ამაღლება თერაპიის პერსონიფიცირებული მიდგომის შემუშავების გზით როზუვასტატინის (20 მგ/დღე-ღამეში) და კომბინირებული ჰეპატოპროტექტორის გამოყენებით მკურნალობის სტაციონარულ და ამბულატორიულ ეტაპებზე.

გამოკვლეულია 124 პაციენტი ოჯახური ჰეტეროზიგოტური ჰიპერქოლესტერინემიით. კვლევის ობიექტს წარმოადგენდა 55 პაციენტი (55,45±5,5 წელი) კლინიკური დიაგნოზით არაალკოჰოლური სტეატოჰეპატიტი და ოჯახური ჰეტეროზიგოტური ჰიპერქოლესტერინემია. ყველა პაციენტს ჩაუტარდა დეტალური ფიზიკალური და ლაბორატორიულ-ინსტრუმენტული გამოკვლევა (საერთო კლინიკური, ბიოქიმიური – ღვიძლის ტრანსამინაზები, ლიპიდოგრამა, მუცლის ღრუს ორგანოების ულტრაბგერითი დიაგნოსტიკა), მოლეკულურ-გენეტიკური კვლევა (გენი SLCO1B1-ს პოლიმორფიზმი). გამოიყო პაციენტთა ორი ჯგუფი. პირველი ჯგუფის პაციენტები იღებდნენ როზუვასტატინს - 20 მგ/დღე-ღამეში, მეორე ჯგუფის პაციენტები - როზუვასტატინს - 20 მგ/დღე-ღამეში და კომბინირებულ ჰეპატოპროტექტორს, დოზით 2 კაფსულა დღეში 90 დღის განმავლობაში. პაციენტებში, რომლებიც იღებდნენ როზუვასტატინს და ჰეპატოპროტექტორს გამოვლინდა საერთო ქოლე-სტერინის სარწმუნო შემცირება 46%-ით, რამაც შეადგინა 5,1±0,59 მმოლ/ლ (p<0,005); დაბალი სიმკვრივის ლიპოპროტეიდები სარწმუნოდ შემცირდა 68,5%-ით - 2,23±0,58 მმოლ/ლ (p<0,005). მაღალი სიმკვრივის ლიპოპროტეიდების დონე მოიმატა 73%-ით და შეადგინა 2,56±0,29 მმოლ/ლ (p<0,005). თერაპიის 90-ე დღეს ღვიძლის ტრანსამინაზების აქტივობამ მიაღწია რეფერენსულ სიდიდეებს: ალანინამინოტრასფერაზა - 32,16±7,83 ერთ/ლ, ასპარტატამინოტრანსფერაზა - 30,11±6,32 ერთ/ლ (p<0,005). კომპლექსური კვლევის და გენი SLCO1B1-ის პოლიმორფიზმის განსაზღვრის საფუძველზე შეირჩეყლ იქნა სტატინის პერსონიფიცირებული დოზა.

STUDY OF BONE TISSUE REPARATION AFTER A FEMUR FRACTURE DEPENDING ON THE CORRECTION OF ARTERIAL HYPERTENSION IN MODEL OBJECT RATTUS NORVEGICUS (RAT GRAY)

[1]Babalyan V., [1]Valilshchykov M., [1]Pavlov S., [2]Koshevaya E., [3]Fedota O.

[1]Kharkiv Medical Academy Of Postgraduate Education; [2]National Pharmaceutical University; [3]V.N. Karazin Kharkiv National University, Ukraine

The importance of a comprehensive study of multifactorial diseases resulting from their high prevalence among the population, physical discomfort of patients and the severity of diseases, often leading to disability, reduction quality of life and disturbance of social and psychological adaptation of patients.

The basis of many chronic diseases of non-infectious nature are both common genes and common metabolic processes. Such syntropic diseases include a wide range of cardiovascular diseases, among which diseases with hypertensive syndrome occupy a special place. Many of the genes included in the genetic network of arterial hypertension contribute to the development of other pathologies, forming the common molecular pathogenetic basis of common chronic diseases [3,5,9,11,19]. One of the pathologies associated with arterial hypertension is osteoporosis. The processes of bone remodeling and regulation of blood pressure are caused by common genetic determinants underlying the development of these diseases [3,22]. It is known that patients with osteoporosis have a higher risk of cardiovascular diseases, hypertension, than patients with normal bone mineral density (BMD). Studies conducted on model animals, including recombinant inbred rat strains, show that vascular calcification is a very complex mechanism that includes paths similar to those described in normal bone calcification [21]. In addition, the inverse relationship between vascular damage and BMD parameters can be determined both by general etiology and by factors such as tobacco smoking, low calcium intake and an unbalanced diet, low levels of vitamin D in the body, old age, and availability of diabetes [25]. The study and specification of the mechanisms of osteoporosis and cardiovascular diseases is the basis of prophylactic and therapeutic approaches in both conditions. To solve practical medical problems, it seems relevant to carry out the correction and treatment of syntropic diseases at the same time to achieve the maximum positive effect.

It is known that the most serious complication of osteoporosis is bone fractures, especially fractures of the proximal femur, which make up to 30% in the structure of inpatient trauma pathology and are a serious medical and social problem. Most patients with this pathology belong to the elderly and senile age and in 66-80% of them hypertension is noted, which can cause a delay in surgical intervention, complicate the pre- and postoperative period at all its stages, affects the rate of rehabilitation of patients, and be one of the main reasons for the unsatisfactory results of surgical treatment of fractures of the proximal femur [3,5,9,11,19].

In connection with the foregoing, it seems relevant to argue a treatment regimen involving the simultaneous correction of both pathologies using the Rattus norvegicus model object (gray rat).

The purpose of our work was to assess the role of arterial hypertension and its correction for bone tissue repair after fractures of the proximal femur with intramedullary osteosynthesis.

Materials and methods. The study was conducted on the basis of the Central Research Laboratory of the Kharkov Medical Academy of Postgraduate Education. Model object used - gray rat, Wistar and SHR lines. The average weight of the animal was 210±30 g at the age of 9 months. Three groups of rats of 10 animals each were formed. The first group (SHR 1) was a model of animals with genetically determined arterial hypertension SHR (spontaneously hypertensive rat), which was used to correct arterial hypertension in the form of enalapril monotherapy 5 ml/kg. The rats of the SHR line of the second group (SHR 2) did not receive monotherapy. The third group, the control group (Wistar), consisted of normotensive animals of the Wistar line. Blood pressure (BP), systolic blood pressure (MAP) and diastolic blood pressure (DBP) were recorded by animals using a non-invasive tail method before performing surgery and in the postoperative period using the blood pressure measurement system of small animals LE 5001 PRESSURE METER (Spain, Panlab SLU).