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Organization of lipid centers in the Russian Federation — new potential

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Project of the Russian National Atherosclerosis Society

In 2016, Guidelines on the medical care organization to the patients with hereditary atherogenic lipid disorders in the regions of Russia were published, which described and presented the principles of routing patients with hereditary dyslipidemia and the organization of medical care for them within the current regulatory documents. In December 2018, the Russian Ministry of Health approved clinical guidelines for the diagnosis and treatment of familial hypercholesterolemia. Thus, persons with a severe hereditary dyslipidemia were able to get free medication with expensive lipid-lowering drugs and receive apheresis. Following the European ones, the Russian guidelines on the management of lipid metabolism disorders were updated: lower target low density lipoprotein cholesterol levels were adopted. In the Russian population, there is a high prevalence of hypercholesterolemia, including familial monogenic and polygenic types. Therefore, timely detection and routing to a lipid center or an office to a specialist (cardiologist, lipidologist), adequate and modern prescription of lipid-lowering therapy will make an important contribution not only to secondary, but also to primary prevention of atherosclerotic cardiovascular complications.

Keywords: lipid center, familial hypercholesterolemia, dyslipidemia, atherosclerosis, prevention.

Relationships and Activities: none.

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In 2016, "Methodical recommendations on the organization of medical care for patients with hereditary atherogenic disorders of lipid metabolism in the subjects of the Russian Federation" were published, which described the principles of routing and managing patients with hereditary dyslipidemia, the qualification requirements of a physician, payment methods within the current regulatory documents [1]. Over the past 5 years, certain successes have been achieved in the treatment of patients with dyslipidemia. In December 2018, the Russian Ministry of Health approved clinical guidelines on familial hypercholesterolemia (FH) [2]: persons with severe hereditary dyslipidemia can be included in the drug benefit program receiving expensive lipid-lowering drugs and apheresis. Following the European ones [3], the Russian guidelines on management of lipid metabolism disorders [4] were updated, and with them new, lower, target levels of low density lipoprotein cholesterol (LDL-C) were adopted. In the Russian population, there is a high prevalence of hypercholesterolemia, including familial monogenic and polygenic types [5-7]. Therefore, timely detection, correct routing to a lipid center or an office to cardiologist or lipidologist, adequate prescription of lipid-lowering therapy will significantly contribute not only to the secondary, but also to the primary prevention of atherosclerotic cardiovascular events (CVE).

Lipid centers and a program for lipid metabolism disorders' treatment through specialized structures, including lipid centers, is an extremely important part of a high-risk prevention strategy implementation. As part of the adult outpatient screening in Russia in accordance with the orders of the Russian Ministry of Health № 124n dated March 3, 2019 and № 173n dated March 29, 2019, persons with a total cholesterol (TC) >8 mmol/l should be followed up, while hereditary dyslipidemia should be excluded or confirmed and the target LDL-C level should be achieved [2, 8, 9]. Thus, now there are new tasks for lipid centers — not only the identification of persons with lipid metabolism disorders, including with hetero- and homozygous FH, and initiation and maintenance of statin therapy, but also their high-dose use, the introduction of novel lipid-lowering medication classes, including in combination with statins, as well as lipoprotein apheresis, allowing to achieve target LDL-C levels in most patients.

Creation of a lipid clinic network

The European Atherosclerosis Society Familial Hypercholesterolaemia Studies Collaboration (EAS-FHSC) initiative can be used as a platform for developing a network of lipid centers in Europe, including the Russian Federation. The FHSC is a pan-European database with over 62500 FH patients from various clinical centers, including 8500 children. The initiative involved 68 countries, including the Russian Federation [10]. Joint work is underway with decision-making structures such as the World Heart Federation and the World Health Organization. In Europe, much attention is paid to hypercholesterolemia, including its family forms. EAS-FHSC believes that the global burden of FH can be reduced by creating effective interaction between countries on all continents. It is necessary to create an international standardized register of patients with FH and a unified digital platform for data exchange, harmonization and analysis. All interested researchers should be able to access this data. Politicians should keep abreast of what is happening and support research. The FHSC plans to provide insights and recommendations to patients and patient organizations. After conducting training programs, it is planned to evaluate their effectiveness and create conditions for the exchange of advanced developments with each other.

Lipid clinic network creates a platform for developing unified European standards on dyslipidemia. Data from various sources are analyzed and remote virtual consultations are carried out. Each participating center has access to the EAS-FHSC network, which makes it possible to discuss the results and analyze clinical cases. Individual consultations are possible.

Organization of lipid centers in Russia

The development of a network of lipid centers in Russia is extremely relevant due to high cardiovascular mortality and insufficient effectiveness of lipid-lowering therapy, especially in refractory dyslipidemias. Severe lipid metabolism disorders are often diagnosed at late stages. In fact, there are no system for their preventive detection and counseling service for statin intolerance. The regularity and effectiveness of statin therapy is poor. According to the RECORD-3 register study in 2015, before hospitalization for acute coronary syndrome, only 19% of patients took statins, and 34% — after rehospitalization [11]. These are extremely low values, although they have slightly improved in comparison with previous RECORD registers [12, 13]. Only the rate of in-hospital statin therapy was at high level — 89,6% [11].

The second major problem is the failure of Russian patients with very high cardiovascular risk (CVR) to achieve target LDL-C levels. According to the DYSIS study, this parameter is only 12% [14].

According to the ESSE-RF study, a pronounced increase in LDL-C level >4,9 mmol/l is present in 7,7% of Russian adult population [6]. At the same time, with the same LDL-C level, the presence of FH-related mutations increases the CVE risk

several times [15]. Monogenic hypercholesterolemia can also differ in CVRSo, carriers of low density lipoprotein receptor (*LDLR*) gene mutations have the highest CVR, while carriers of apolipoprotein B-100 (*ApoB*) gene mutations — an intermediate, compared with the general population [16].

In Russia, the prevalence of heterozygous FH is 1:173 (95% confidence interval: 1:208-1:145) [2]. When recalculated, it turns out that in Russia there are more than 840 thousand patients with FH, not counting patients with other hereditary atherogenic dyslipidemias. In order to cover this entire contingent, a system for the identification and routing of patients with FH and other atherogenic dyslipidemias is needed, in which the participation of healthcare facilities at all levels is expected, with the obligatory involvement of both medical institutions conducting outpatients screening or providing cardiac care, and specialized lipid centers.

On December 11, 2014, the expert council on FH developed proposals on creating a lipid center network within the all-Russian project, to determine their structure and function, and on September 21, 2015, the expert council of Russian National Atherosclerosis Society approved the creation of lipid centers. Then, a working group and pilot regions have been identified, and the organization of interaction with authorities has begun. In 2016, guidelines were published on health care organization for patients with hereditary atherogenic lipid metabolism disorders in Russian regions, as well as for persons with severe lipid metabolism disorders without a confirmed hereditary disorder and for those with statin intolerance [1]. Over the past years, a lot of work has been done and significant changes have occurred, but many points of these guidelines are still relevant now. At the same time, after 5 years, the procedural framework of lipid centers' operation should be updated.

To date, ~20 lipid centers have been organized and operate, which is extremely small, taking into account the current statistics on lipid metabolism dispensers in Russia.

Role of the Russian register

The tasks of lipid centers include the analysis and adjustment of routine prescription of lipid-lowering therapy, especially in high and very high-risk groups, maintaining local registers of patients with severe lipid metabolism disorders, evaluating the effectiveness of lipid-lowering therapy optimization, cascade screening, entering data into the all-Russian register (RENESSANS).

The RENESSANS register was initiated to obtain consolidated information on the clinical characteristics, approaches to diagnosis and treatment of patients with severe lipid metabolism disorders, many of whom have a high or very high risk of CVE. Its purpose is to take into account and correctly manage patients not only with FH, but also with refractoriness to lipid-lowering therapy, including its intolerance. This project has a multicenter observational non-interventional design. Data is collected continuously: medical centers included in the register constantly enter information on patients into an original electronic system, where the data is converted into a depersonalized table. Centralized data upload and analysis is performed twice a year. First- and second-degree relatives are included in the cascade screening for FH.

The majority of patients are women (60%). The mean age is 54 years (mean age at diagnosis, 45 years). To date, there are more than 1700 people in the register, 10 of whom suffer from homozygous FH. More than 600 patients are classified as very high CVR. Most (>1100) patients with FH receive statin agents. Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) are taken by only 50 people so far [17]. Unfavorable outcomes are associated with male sex (relative risk increases by 2 times), coronary artery disease (7 times), a burdened history (2 times), hypertension (3 times), lipoprotein(a) level (3 times). According to the register data, the target LDL-C level can be achieved in 2% of patients using treatment, which is 10 times more than at 1 visit to the lipid center [17].

Difficulties and problems of lipid centers operation in 2016-2020

Lipid centers (offices) can be created as structural or functional units based on medical facilities of various profiles. A lipid center can be either a separate structural unit with its own position and staff, or a functional specialized medical appointment of a cardiologist or a general physician who studied a program in lipidology (36 hours) within the continuing medical education. It is the last option that seems to be optimal, since it does not require additional approvals with the Federal Compulsory Medical Insurance Fund, and all consultative and therapeutic activities provided by a lipidologist are carried out within agreed outpatient tariff rates.

An example of the effective work of lipid center as a functional unit is a specialized medical appointment of a cardiologist-lipidologist, deployed in September 2016 based on cardiology outpatient clinic of the L. S. Barbarash Kemerovo Regional Clinical Cardiology Dispensary. Initially, researchers from the Research Institute for Complex Issues of Cardiovascular Diseases worked as lipidologists of this center, which made it possible to quickly and efficiently translate advanced evidence-based approaches to prescribing lipid-lowering therapy in high and very high-risk patients into actual clinical

practice. Currently, the regional register of patients with identified severe lipid metabolism disorders numbers >190 patients. For 2021, the territorial compulsory health insurance fund in Kuzbass agreed to receive 12-month treatment it PCSK9 inhibitors for 10 patients followed up in a lipid center.

Lipid centers should also provide organizational and methodological assistance to practical healthcare, help patients in obtaining regional and federal benefits when prescribing expensive therapy. With the participation of lipid centers, combination and expensive lipid-lowering therapy should become more accessible. The issue of the availability of free molecular genetic diagnostics in hereditary lipid metabolism disorders has also ripened, possibly within the compulsory health insurance system.

The study of lipid centers profile in Russia showed that most of them are regional or municipal. The main source of funding for them is the compulsory health insurance system, which ideally should provide, if necessary, expensive drugs, such as PCSK9 inhibitors.

Difficulties were found in the follow-up of patients: conducting vascular investigations and consultations of doctors of other specialties, insufficient awareness of doctors and patients, low adherence of patients to follow-up visits to lipid center, limitation of providing effective but expensive drugs. Additional legal and research support are needed, as well as new guidelines.

The 2020 clinical guidelines on chronic coronary syndromes [18], as well as non-ST [19] and ST [20] segment elevation acute coronary syndrome, state that if the target LDL-C level cannot be achieved with highest tolerated dose of statins in combination with ezetimibe, or in patients with intolerance to HMG-CoA reductase inhibitors, it is recommended to prescribe one of the PCSK9 inhibitors to prevent CVEs [2-4, 18-20]. If during therapy with HMG-CoA reductase inhibitors at maximum tolerated doses, the LDL-C level remains significantly increased (>2,5 mmol/L), adding PCSK9 inhibitors without prior ezetimibe use should be considered [19, 20]. The principles of using all three classes of lipid-lowering drugs are harmonized with European guidelines.

The central contingent of lipid center is high and very high-risk patients, including patients requiring additional therapy to control LDL-C. These include patients with atherosclerotic diseases in combination with diabetes, FH, with multiple vascular involvement, rapid progression of atherosclerosis (2 or more vascular events within 2 years) and who have not reached the target LDL_C values. One of the options for adjusting CVR is combination lipid-lowering therapy, including PCSK9 inhibitors [2-4], which reduce the CVE risk and improve the prognosis of patients [21]. Adherence to therapy is increased by confirming the hereditary nature of lipid metabolism disorders using genetic tests.

The lipid center determines the indications for high-tech treatment methods, including PCSK9 inhibitors, and, which is very important, manage the follow-up of these patients. A special protocol has been developed taking into account the monitoring of effectiveness and safety of treatment. Check lists for primary care physicians and patients have also been developed.

Children are the most important cohort for the primary prevention of lipid metabolism disorders. An increase in LDL-C is manifested from the very birth, but in Russia there is no system for its detection. The difficulty lies in the fact that most children (with the exception of children with homozygous FH) do not have such clinical manifestations of hypercholesterolemia as xanthomas, xanthelasmas, and arcus senilis. In addition, the study of cholesterol profile is not included in the list of investigations within screening follow-up of children. Another obstacle to correcting the lipid profile in children is resistance from pediatricians and parents. Most physicians prefer delaying the initiation of lipid-lowering therapy until the age of 18. This problem can be partially solved by lipid centers. It is necessary to introduce universal screening in children aged 7 to 11 years, or to carry out selective screening. Adults should refer children and grandchildren to lipid center or medical facilities with lipid office. Physicians and adult cardiologists should refer children and grandchildren of index patients to pediatric outpatient clinics and pediatric lipid centers. Universal screening is the examination of all children in population. In European countries, it is carried out in Slovenia in newborns and children aged 5 years and is confirmed in almost half of the cases by DNA testing [22]. To detect high cholesterol levels, the German Society of Pediatrics and Adolescent Medicine recommends testing for all children aged 5 years [23]. In the United States, universal screening of children is carried out at the age of 9-11 years, because selective screening, which conducted previously, was insufficiently effective [24]. Thus, the optimal age for screening is considered to be 9-11 years, since hormonal changes during puberty in children can reduce the LDL-C level. Currently, the introduction of universal screening in Russia is being discussed. Children with suspected heterozygous FH can be screened from the age of 5 [25]. In case of suspected homozygous FH, screening is carried out as early as possible [26], for example, during immunization at the age of 1-2 years.

New day-patient treatment options

An important milestone in providing health care to patients with high and very high CVR with hyperlipidemia is the possibility of day-patient treatment for lipoprotein apheresis (from 2018) or therapy with PCSK9 inhibitors (from 2021).

In November 2017, the Russian Ministry of Health and the Federal Compulsory Medical Insurance Fund for the first time included the diagnosis-related group "Treatment of hereditary atherogenic lipid metabolism disorders using apheresis in patients with ineffectiveness of basic therapy" in the Methodological Guidelines on methods of paying for medical care at the expense of compulsory medical insurance within day-patient cardiology treatment.

In 2019-2020, this diagnosis-related group was included in the tariff agreements of at least 28 Russian regions (Altai, Krasnodar, Krasnoyarsk, Arkhangelsk, Voronezh, Volgograd, Vologda, Ivanovo, Irkutsk, Kemerovo, Omsk, Penza, Rostov, Samara, Saratov, Sverdlovsk, Tver, Tomsk, Tula, Primorsky Krai, Jewish Autonomous Oblast, the republics of Kalmykia, Crimea, Mari El, Mordovia, the Kabardino-Balkarian Republic, the cities of St. Petersburg and Sevastopol). At the same time, treatment was organized only in St. Petersburg (once every 2 weeks) and Samara (once a month).

There is a precedent when a patient from Moscow has been traveling to St. Petersburg twice a month for more than one and a half years for lipoprotein apheresis. Payment is made in accordance with the Federal Compulsory Medical Insurance Fund Order dated May 8, 2009 № 97. That is, there is possibility of treating patients from other nearby regions.

According to payment methods for health care at the expense of compulsory medical insurance funds for 2021, the current diagnosis-related group ds36.004 "Treatment with the use of biopharmaceuticals and selective immunosuppressive agents" included diagnoses of pure hypercholesterolemia (E78.0) and mixed hyperlipidemia (E78.2). Hospitals with following profiles can treat patients with these methods: therapy, cardiology, cardiac surgery, or endocrinology. An important advantage of this diagnosis-related group is the patient's stay in the hospital for only 1 day (actually, several hours), which is sufficient for subcutaneous administration of PCSK9 inhibitor. The cost of a completed case in most regions and Federal medical facilities is sufficient to cover medicines and other costs of institutions. The conditions for paying for hospitalizations for this diagnosis-related group are the presence of drug in Essential Medicines List and the corresponding indication according to product instruction and clinical guidelines. These conditions are met in 2021, since PCSK9 inhibitors are included in Essential Medicines List and in the Clinical guidelines on "Diagnostics and correction of lipid metabolism disorders in order to prevent and treat of atherosclerosis, VII revision" [4] and "Familial hypercholesterolemia" [2].

New opportunities for Federal healthcare organizations appear in 2021 in connection with the order of Russian Ministry of Health dated December 23, 2020 № 1363n.

Improving patient routing

The main challenges today are late diagnosis of lipid metabolism disorders (in case of FH, this is of decisive importance and can shorten a full-quality life to 20 years), inadequate lipid-lowering therapy (patient inaction, prescribing inadequately low statin doses, insufficient combination therapy use), and as a consequence — failure to achieve target LDL-C values and an increase in CVE risk. It is necessary to oblige all laboratories to send a patient to lipid centers or offices if total cholesterol >8,0 mmol/L is detected. The importance of cholesterol monitoring must be equated with blood glucose monitoring.

Criteria for referring a patient to a lipid center/office:

To rule out/confirm hereditary dyslipidemia, at least one criterion must be met:

1. Serum (plasma) total cholesterol >10 mmol/L and/or serum (plasma) LDL-C >8,5 mmol/L and/or serum (plasma) triglycerides >11 mmol/L.
2. Serum (plasma) total cholesterol >8,0 mmol/L and/or serum (plasma) LDL-C >5,0 mmol/L and/or triglyceride level >5,0 mmol/L and/or lipoprotein (a) level >50 mg/dl in combination with a positive family history of early (up to 55 years in men, up to 60 years in women) atherosclerotic cardiovascular disease.
3. Ineffectiveness (lowering LDL-C by less than 30%) of drug lipid-lowering therapy in highest tolerated doses for at least 3 months, including due to intolerance.
4. Prior early (up to 40 years) atherosclerotic cardiovascular disease.
5. All first-degree relatives (parents, children, siblings) of a patient with hereditary dyslipidemia.

Conclusion

There are following necessary steps to solve the problem of early detection and treatment of patients with hereditary dyslipidemias: creation of system for routing patients with severe dyslipidemia, where all levels of healthcare should be involved, with the obligatory involvement of both facilities conducting screening or providing cardiac care and specialized lipid centers; introduction of molecular genetic testing in persons with severe lipid profile

disorders into the healthcare system; creation of a cascade screening system; handling a problem of supply with a modern effective drugs; introduction of lipoprotein apheresis methods for treating patients with insufficient effectiveness of drug therapy; increase of patient medical adherence.

Each Russian region, based on its material-and-technical, staffing capabilities, the prevailing regional characteristics of healthcare system and medication provision, can create an optimal routing system for patients with dyslipidemia, create lipid offices or centers as a structural unit in medical organizations providing cardiology and therapeutic care.

Relationships and Activities: none.

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