

CERTAIN ISSUES OF MEDICAL AND ECONOMIC EFFECTIVENESS OF TREATMENT OF ORPHAN DISEASES

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A lack of the single criterion for classifying rare diseases as a group of orphan diseases is the main current problem. First, it is associated with rare detection of symptoms among patients, especially children. Second, specialists have a limited number of methods of detecting orphan diseases. As the disease is considered rare, it is not profitable for pharmaceutical companies to produce the preparations which are purchased not in large numbers, but in single packages, because expenses on clinical trials and marketing advertising exceed return of investment. The market of orphan drugs in Russia is at the stage of development and formation. Medical organizations that carry out medicinal therapy of patients with orphan diseases require a clear set of regulatory documents ensuring provision of medical and pharmaceutical aid. Special attention should be paid to drawing up the lists of medicinal preparations to treat the patients. Personified accounting of patients with detected orphan diseases is an important stage for medical and pharmaceutical organizations. Modern diagnostics of orphan diseases at early stages, especially in children, exploration of specialized genetic methods of research and making them accessible for the population constitute an essential problem.

Key words: orphan diseases, rare diseases, clinical and economic method, drug provision, treatment problems, burden on the budget

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НЕКОТОРЫЕ ПРОБЛЕМЫ МЕДИКО-ЭКОНОМИЧЕСКОЙ ЭФФЕКТИВНОСТИ ЛЕЧЕНИЯ ОРФАННЫХ ЗАБОЛЕВАНИЙ

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В настоящее время основной проблемой остается отсутствие единого критерия отнесения редких заболеваний к группе орфанных заболеваний. Во-первых, это сопряжено с редким выявлением симптомов у пациентов, в особенности у детей. Во-вторых, специалисты располагают ограниченным числом способов определения орфанных заболеваний. Так как заболевание считается редким, фармацевтическим компаниям не рентабельно производить препараты, которые покупаются не массово, а единичными упаковками, затраты на клинические исследования, маркетинговые компании превышают их окупаемость. Рынок орфанных лекарственных препаратов в России находится на стадии развития и формирования. Для медицинских организаций, проводящих лекарственную терапию больных с орфанными заболеваниями, требуется четкий комплекс нормативно-правовых документов, обеспечивающих порядок оказания медицинской и фармацевтической помощи. Особое внимание должно быть уделено определению перечня лекарственных препаратов для лечения таких больных. Для медицинских и фармацевтических организаций важным этапом является проведение персонализированного учета больных с выявленными орфанными заболеваниями. Важной проблемой является своевременная диагностика орфанных заболеваний на ранних стадиях, особенно у детей, освоение специальных генетических методов исследования и обеспечение их доступности населению.

Ключевые слова: орфанные заболевания, редкие заболевания, клинко-экономический метод, лекарственное обеспечение, проблемы лечения, нагрузка на бюджет

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In the modern world, a term of orphan (rare) diseases attracts more and more attention. An orphan disease includes life threatening or steadily progressive diseases detected with a low frequency, which, if the treatment is lacking, can result in a lethal outcome or disability. In the Russian Federation, orphan diseases include pathologies with an occurrence rate of 1:10,000 and rarer [1].

Orphan diseases are common among a small proportion of human population. A low number of these patients makes it difficult to examine and comprehend the course of such diseases. Patients, their family members and medical community are often deprived of complete information support

[1]. Adoption of Federal Law No. 323-FL as of November 21, 2011 'On the basis of the protection of public health in the Russian Federation' was an important step. It contains a criterion of rare diseases such as the prevalence rate (at least 10 cases per 100,000 of people). The Law also regulates provisions about pharmacological support of citizens with diseases included into the list of life-threatening and chronic progressive rare (orphan) diseases, which can lead to reduced life expectancy or disability [2].

A list of rare diseases is formed by the Ministry of Health of the Russian Federation and published on the official site

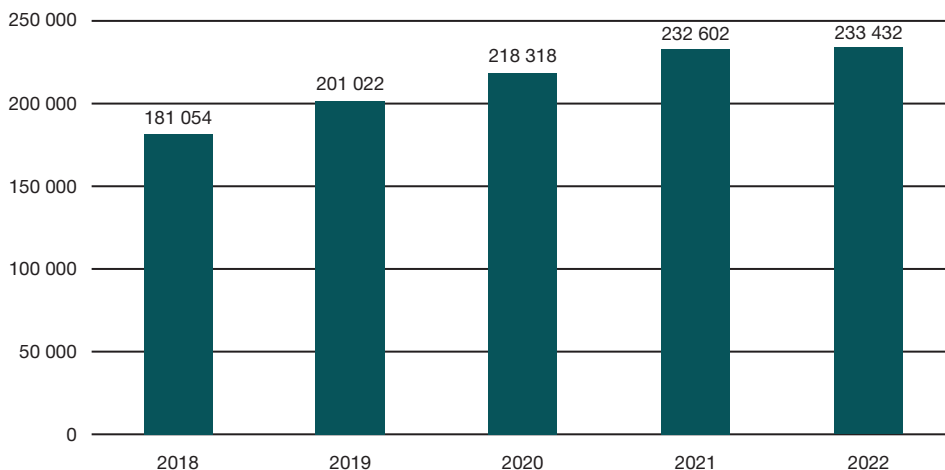


Fig. 1. Total number of patients within the High-Cost Nosologies register

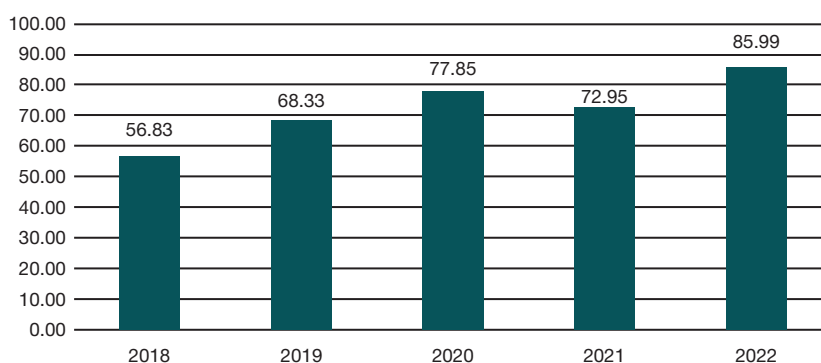


Fig. 2. Total cost of therapy, bln RUB

hereof. The list of 24 life-threatening and chronic progressive rare diseases included those with pathogenetic treatment with proven effectiveness. Such patients should be provided medicinal preparations for free. Moreover, treatment of hemophilia, cystic fibrosis, Gaucher disease and pituitary dwarfism has been financed by the '7 nosologies' state program since 2008; 7 other rare diseases have been added hereto over the last years [3].

Globally, the issue of orphan diseases has gained an increased attention lately. Specialized measures to ensure the rights of patients with orphan diseases have been applied: novel genetic concepts that prevent a disease and methods of diagnostics and treatment have been developed (orphan diseases are commonly of genetic nature). Patients are highly dependable on social, political and technological steps of a society [1].

Decision on how much the society should spend on researches of orphan agents is an ethical dilemma. On the one hand, every orphan nosology is just a small number of persons within the legal and political competence of a society. Investment of significant funds of the country into orphan diseases can be non-ethical from the utilitarian point of view, as it fails to display benefit for the society, and its alternative expenses are important from the perspective of opportunities lost for others. On the other hand, many people assert that the society has a moral obligation to help people who suffer from a serious but rare disease with no existing therapy. Moreover, medicine has a professional obligation to promote scientific knowledge in the area of novel methods of treatment. The contradicting moral obligations require totally different levels of funding of researches and developing orphan medications [4, 5].

Review of current social practices, regulatory approaches to solving the ethical and philosophical funding issue and treatment

of orphan diseases, genetization tendencies is essential for the modern world as it ensures health protection rights.

The research objective is to determine the economic burden on support of patients with orphan diseases.

Systemic analysis to structure the cited data was selected as a method; the data of the Federal State Statistics Service were used as materials.

RESEARCH RESULTS

Patients commonly treat orphan diseases during the entire life. Huge load on the state budget is associated with a high cost of therapy, lack of innovative medical preparations and technologies that make therapy possible, rather high cost of therapeutic and rehabilitation activities [1]. The territorial entities of the Russian Federation face serious financial obligations regarding provision of their citizens who have rare diseases with orphan medicines [4, 6].

It is important to notice that a total number of patients within the '14 Nosologies' register is increasing on the annual basis. Their number increased by 28.93% during the last five years; thus, therapy of these patients requires better funding (fig. 1) [5, 6].

The key indicator to estimate the use of budgetary funds within the '14 Nosologies' program is represented by the use of funding in accordance with an increase of the total number of patients who obtain therapy as per the high-cost nosology. In 2018, the state allocated 56.83 bln RUB on this group of diseases, whereas in 2022 the funding increased by 1.5 times up to 85.99 bln RUB (fig. 2) [5, 6].

It should be noted that an increased funding of therapy of adults and children has been observed in the structure of

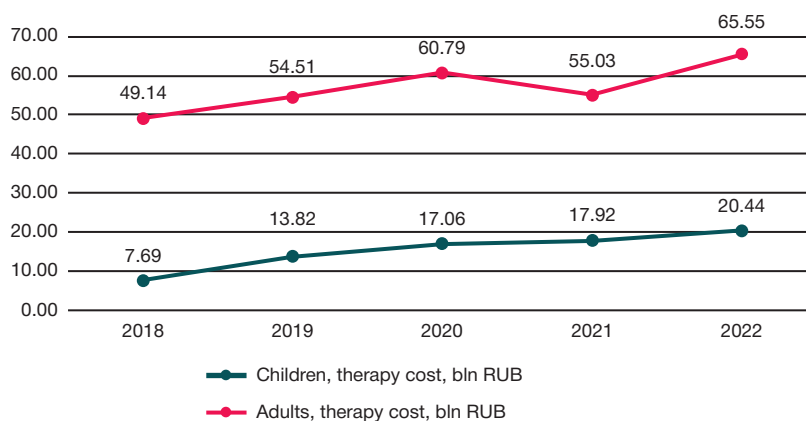


Fig. 3. Expenses on therapy of high-cost nosologies, bln RUB

the total therapy cost within the last five years [5, 6]. In 2018, 13.53% of all allocated budgetary funds were spent on pediatric therapy, whereas by 2022 funding of the patients was increased by 23.77% of the total treatment cost (Fig. 3).

DISCUSSION OF RESULTS

The most widely spread method of treatment of orphan diseases is based on achievement of health benefits considering the single index, which unites life expectancy and health-related quality of life such as quality-adjusted years of life or disability-adjusted years of life [7].

Patients with orphan diseases require constant treatment and support of life quality. However, as there are few patients compared with a general number of patients, a limited number of resources will be allocated per their disease to make the society more useful.

Uncertainty about benefits belongs to a resource-allocating problem. During economic assessment, cost and benefit uncertainty can be taken into consideration when sensitivity is analyzed. Considerable amount of money is invested into research and developments for every new chemical object, though only one of 10 developed pharmaceutical compounds is successfully sold out in the market. In its turn, testing of orphan preparations is complicated due to a shortage of patients with a disease [2]. The geographic spread of such people on a large territory constitutes a big problem in treatment of these patients. It hampers their concentration within the same specialized medical institution, where qualitative aid could be provided [8].

Patients with orphan diseases often can't implement their right for drug support as the medication has not been developed or registered in Russia yet. As drugs are usually very expensive, the state can't provide full reimbursement. Normal financing of drug supply of patients with an orphan pathology at the expense of public resources frequently hampers treatment of patients [8].

The system of preferential provision of medicines is based on state guarantees of supply of preferential or free medications for separate categories of population. The following types of preferential medical assistance are set by the state depending on belonging to the category of citizens entitled to receive state social assistance as a set of social services and group of population, the outpatient treatment of which requires dispensation of medicinal preparations and medical devices by medical prescription free of charge or with 50% discount; citizens who have certain diseases (orphan diseases, high-cost nosology) [9].

The task concerning supply of patients with orphan diseases with medicinal preparations should be solved considering the conditions of provision of medical aid to various categories of patients. In the Russian Federation, subjects in the sphere of healthcare and pharmaceutical service management organization are significantly independent when drug support of population of the subjects of the RF is provided and when budgetary means are allocated to implement various programs. Territorial programs of state guarantee of provision of medical aid and drug support of population are valid at the regional level [10].

An important parameter of pharmaco-economic effectiveness of using a medicinal agent for therapy of orphan diseases is represented by the 'threshold of payment ability'. If introduction of a new technology into treatment does not require additional expenses and even cuts expenses, the new technology is value-for-cost. But when additional means should be spent to achieve treatment benefit, the results do not allow to estimate readiness of population to pay for the therapy.

In the Russian Federation, there are three basic directions of preferential medicinal aid: provision of preferential categories of citizens with necessary medicinal preparations within a set of social services established in Federal Law as of July 17, 1999 No. 178-FZ 'Concerning state social aid'; drug supply of separate groups of population is provided free of charge or on prescription with a reduction of price in accordance with decree of the Government of the Russian Federation as of July 30, 1994 No. 890 (regional programs of preferential provision of medicines) and provision of some categories of citizens with expensive medicinal preparations as per the approved list of diseases (program of '14 high-cost nosologies') and a new trend of preferential provision of medicines for patients with orphan diseases. The systems are characterized by focus on treatment or prevention of a disease and clear regulation of the activity of all participants of the process of state social aid in the form of pharmacological support. All trends are patient-oriented. Every patient who needs the medicinal preparation should obtain it irrespective of the place of residence, property and social status. All this results in better affordability of medicinal preparations at stages of provision of medical aid and reasonable use of allocated funds [11].

Another completely unsolved problem is represented by timely diagnostics of orphan diseases. It means development of the respective base of knowledge and adoption of special research methods, formation of the personnel system and availability of genetic research [1]. Insufficient information support of patients and doctors who fail to obtain sufficient scientific and medical data can hamper identification and development of the treatment strategy of an orphan disease.

In Russia, the market of orphan medicines is at the stage of development and formation. An important step of market development includes legislative adoption of such a notion as 'orphan medicinal preparations' intended for diagnostics or pathogenetic treatment of rare diseases [12]. To expand the assortment of orphan medicinal preparations, an accelerated procedure of medicine expertise is established (art. 26 of Law No. 61-FZ). It does not mean that requirements to safety and effectiveness are decreased, but denotes that the results of preclinical and clinical trials performed outside the Russian Federation are accepted, though in accordance with the rules of good laboratory and clinical practice. Effective agents for therapy of rare diseases emerged on the Russian pharmaceutical market owing to the accelerated procedure of registration of medicinal preparations for therapy of OD.

The following consistency can be reviewed: medicinal preparations for therapy of orphan diseases are put into civil circulation in the Russian Federation 2 years after the preparations reach the market [11].

Increasing attention is paid to review of orphan diseases globally from the pediatric point of view, as they are mainly diagnosed in 2/3 of cases in childhood and often result in a fatal outcome.

An important part of all preventive activities aimed at a decrease of genetic load of population is represented by prenatal diagnostics that allows to decrease the risk of giving birth to a child with congenital and hereditary diseases. Timely detection of hereditary diseases can currently be provided by neonatal screening, which is considered as a basic liability of the state healthcare system in developed countries. It is the most effective method of diagnostics and prevention of hereditary diseases. It can be used to detect a pathology and determine the genetic risk of a hereditary disease for relatives of diagnosed infants. During the last decade, all newborns in the Russian Federation undergo neonatal screening for 5 hereditary diseases. The diseases can be diagnosed at the first screening stage without molecular and genetic researches. However, subsequent confirming molecular and genetic diagnostics that predicts the severity of clinical manifestations and corrects treatment is required taking into account the variability of a clinical picture in different mutations of the same gene. According to the Ministry of Health of the Russian Federation, diseases annually included into the screening program are diagnosed in 1,200 newborns in average [3].

Information of a patient about the results of diagnostics is always complicated and associated with potential traumas. Thus, an urgent task includes building forms of social interaction with parents and pediatric patients and searching for ways to inform the society of orphan diseases [1]. Limited

effectiveness of exact diagnostics of orphan diseases at the level of the primary link and at hospitals, absence of developed medical standards of treatment for some nosological forms, poor availability of specialized treatment for orphan patients in subjects of the Russian Federation can impair specialist-patient communication.

Patients with orphan diseases increasingly act as a classic example when the phenomenon of biosociality is being analyzed [13]. Groups of patients with orphan diseases by certain nosologies are formed, global support centers for all orphan diseases can be organized. The issue results in new forms of sociality where people are brought together and united owing to their life experience and struggle with a disease caused by certain genetic mutations. Moreover, the communities are formed on the basis of a pronounced interest of pharmaceutical companies, which commonly initiate development of medicinal preparations for various groups of patients who organize different activities devoted to orphan diseases [1].

CONCLUSIONS

Ethical aspects of prioritizing research financing do not always constitute the main issue of discussion. Assigning a legal status to orphan diseases means an undoubted progress both for medical law and for bioethics. Just distribution of resources in healthcare is still limited with the existing methods of treatment. The issue of necessary integration of knowledge, plans and researches by orphan diseases arises at the international level. Then common efforts would be coordinated and the process of etiology cognition, prevention and treatment of orphan diseases, their statistical processing, development of screening systems of diagnostics and informational aid for doctors and patients will be developed.

During the neonatal period, suitability of a wider screening for congenital and inherited metabolic diseases, and the most widely spread nosological forms of rare diseases, in particular, is not doubtful. All these conditions can be detected in the neonatal period. This will prevent severe disability of sick children reducing a number and duration of hospitalization until their transfer to outpatient treatment.

Investment into research of rare diseases offers hope to those in need and potential benefits for the future generations. The principle supports a stronger role of the state sector in taking decisions about the priority of financing the studies of orphan medicinal preparations.

Applying traditional economic assessment to therapy of orphan diseases will likely be unsuccessful, as maximization of global healthcare with national funds of separate countries will not be politically acceptable in either country.

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