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Regulation in the sphere of circulation of extemporaneously compounded medicines under modern conditions of Russia

V.V. Ryazhenov[1], E.A. Maksimkina[1], V.S. Fisenko[2], A.V. Alekhin[3,4], V.V. Tarasov[1], M.G. Raisyan[1], E.R. Zakharochkina[1], K.A. Chizhov[1], R.Y. Garankina[1]

[1] Sechenov First Moscow State Medical University (Sechenov University),
2, Trubetskaya Str., bldg 8, Moscow, Russia, 119991
[2] Ministry of Health of the Russian Federation,
3, Rakhmanovsky Lane, GSP-4, Moscow, Russia, 127994
[3] Limited Liability Company "UK Pharmaclone Group",
12, Krasnopresnenskaya embankment, office 1542B, Moscow, Russia, 123610
[4] Bauman Moscow State Technical University,
5, 2nd Baumanskaya Str., bldg 1, Moscow, Russia, 105005

E-mail: rimma-garankina@yandex.ru

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The aim of the work was to analyze the current regulatory legal framework governing the manufacture of drugs in pharmacies, and a comprehensive review of the current state of their manufacture; a disclosure of problems and search for the ways to improve the sphere of circulation of extemporaneously compounded medicines (ECMs).

Materials and methods. The national legislation of the Russian Federation and the regulatory framework of the medicines common market of the Eurasian Economic Union in the field of an extemporaneous drugs circulation formed a regulatory base of the work. To collect and analyze the information data, the materials presented on the official websites of the Ministry of Health of Russia, the Ministry of Industry and Trade of Russia have been used. The results of the scientific publications for the previous 10 years (2014–2024) have also been analyzed.

Results. The article deals with the current state issues of the drug products manufactured in pharmacies, in the sphere of circulation. The analysis of the legislative base on ECMs has been carried out, the problems of the normative legal regulation of the pharmacy drugs manufacturing have been identified. The introduction of new relevant concepts into Federal Law No. 61-FZ "On Circulation of Medicines" — "extemporaneous drug products", "extemporaneous manufacturing", "extemporaneous production" — has been proposed. The authors' definition of the "pharmaceutical sovereignty" concept was given in the course of the study. Based on the results of the study, the possibilities and ways of improving the mechanisms of the state regulation of the drugs extemporaneous manufacturing in the current political and economic conditions have been identified.

Conclusion. The operational management and systematization of the regulatory legal framework of the ECMs circulation sphere based on the regulatory science is the most important factor in increasing the affordable, effective, personalized pharmaceutical care. An important element of the mobilization model of the economy is strengthening of the state regulation, development of the domestic production capacities and technologies, including taking into account extemporaneous manufacturing of drugs and small-scale production.

Keywords: extemporaneously compounded medicines; drugs manufacturing; extemporaneous formulations; extemporal production; pharmacy; drug supply; pharmaceutical sovereignty; drug sovereignty.

Abbreviations: ECMs — extemporaneously compounded medicines; DF — dosage form; CPR — certificate of product registration; SRMs — State Register of Medicines; EEU —Eurasian Economic Union; DS — drug substance; RCPEA — Russian Classification of Products by Economic Activities; SPh — State Pharmacopoeia; LGWS — List of goods, works and services; UDCM — Unified directory-catalog of medicines; WIPO — World Intellectual Property Organization.

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Регулирование в сфере обращения экстемпоральных лекарственных препаратов в современных условиях России

В.В. Ряженов[1], Е.А. Максимкина[1], В.С. Фисенко[2], А.В. Алехин[3,4], В.В. Тарасов[1], М.Г. Райсян[1], Е.Р. Захарочкина[1], К.А. Чижов[1], Р.Ю. Гаранкина[1]

[1] Федеральное государственное автономное образовательное учреждение высшего образования «Первый Московский государственный медицинский университет имени И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет), Россия, 119991, г. Москва, ул. Трубецкая, д. 8, стр. 2
[2] Министерство здравоохранения Российской Федерации, Россия, 127994, ГСП-4, г. Москва, Рахмановский пер, д. 3
[3] Общество с ограниченной ответственностью «УК Фармаклон Групп», Россия, 123610, г. Москва, Краснопресненская набережная, д. 12, офис 1542В,
[4] Федеральное государственное бюджетное образовательное учреждение высшего образования «Московский государственный технический университет имени Н.Э. Баумана (национальный исследовательский университет)», Россия, 105005, г. Москва, 2-я Бауманская ул., д. 5, с. 1

E-mail: rimma-garankina@yandex.ru

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Цель. Анализ действующей нормативной правовой базы, регулирующей изготовление лекарственных препаратов (ЛП) в аптечной организации (АО) и всесторонний обзор текущего состояния их изготовления. Раскрытие проблем и поиск путей совершенствования сферы обращения экстемпоральных лекарственных препаратов (ЭЛП).
Материалы и методы. Нормативную базу работы составило национальное законодательство Российской Федерации и регуляторной базы общего рынка лекарственных средств Евразийского экономического союза в сфере обращения экстемпоральных ЛП. Для сбора и анализа информационных данных использованы материалы, представленные на официальных сайтах Министерства здравоохранения России, Министерства промышленности и торговли России. Так же были проанализированы результаты научных публикаций за последние 10 лет (2014–2024 гг.).
Результаты. В статье рассматриваются вопросы современного состояния сферы обращения ЛП, изготовленных в АО. Проведён анализ законодательной базы по ЭЛП, определены проблемы нормативного правового регулирования аптечного изготовления ЛП. Предложено введение новых актуальных понятий в федеральный закон № 61-ФЗ «Об обращении лекарственных средств» — «экстемпоральные лекарственные препараты», «экстемпоральное изготовление», «экстемпоральное производство». В ходе проведённого исследования дано авторское определение понятию «фармацевтический суверенитет». По результатам исследования определены возможности и предложены пути совершенствования механизмов государственного регулирования экстемпорального изготовления лекарственных препаратов в современных политических и экономических условиях.
Заключение. Оперативное управление и систематизация нормативной правовой базы сферы обращения ЭЛП на основе регуляторной науки — важнейший фактор повышения доступной, эффективной, персонализированной лекарственной помощи. Важным элементом мобилизационной модели экономики является усиление государственного регулирования, развитие отечественных производственных мощностей и технологий, в том числе с учётом экстемпорального изготовления ЛП и мелкосерийного производства.
Ключевые слова: экстемпоральные лекарственные препараты; изготовление лекарственных препаратов; экстемпоральное изготовление; экстемпоральное производство; аптечная организация; лекарственное обеспечение; фармацевтический суверенитет; лекарственный суверенитет
Список сокращений: ЛП — лекарственный препарат; ЭЛП — экстемпоральный лекарственный препарат; ЛФ — лекарственная форма; ЛС — лекарственное средство; АО — аптечная организация; РУ — регистрационное удостоверение; ГРЛС — Государственный реестр лекарственных средств; ЕАЭС — Евразийский экономический союз; ФС — фармацевтическая субстанция; ОКВЭД — Общероссийским классификатором видов экономической деятельности; ГФ — Государственная фармакопея; КТРУ — каталог товаров, работ и услуг; ЕСКЛП — Единый структурированный справочник-каталог лекарственных препаратов; ВОИС — Всемирная организация интеллектуальной собственности.

INTRODUCTION

The current state of functioning of the pharmaceutical market is a reflection of the general situation under sanctions restrictions [1]. The presence of defective drugs in pharmacies reduces the availability of the drug provision and personalized care [2–5]. In this regard, the key task of state structures is to search for methods [6–8] and tools [9, 10] to fulfil constitutional obligations to protect health and provide medical care[1].

The drugs manufactured in pharmacies, or extemporaneously compounded medicines (ECMs), are not only an important but also a necessary

[1] The Constitution of the Russian Federation. Article 41. (adopted by popular vote on Dec 12, 1993 with amendments approved during the nationwide vote on July 01, 2020)

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component of quality drug therapy in health service delivery [11–14]. The advantages of ECMs are an individual dosage of the active substance, the possibility of combining a required amount of active substances in one dosage form (DF), a replacement or elimination of excipients (preservatives, fillers, stabilizers), an ergonomic DF selection [15–18]. ECMs have a short shelf life, up to a maximum of 30 days[2], and due to the lack of a profitability of their mass production, are not produced by the pharmaceutical industry [19–23]. These drugs are most in demand in paediatric and geriatric populations (especially for newborns and premature infants, polymorbid gerontological patients) [24–27], in dermatology, oncology, palliative care [28], for patients with high-cost nosologies, including those with orphan diseases [29–32]. A physician prescription of individual extemporaneous drugs allows patients and medical organizations to purchase necessary amounts of ECMs, which helps to achieve financial and budgetary efficiency for patients and medical organizations [33–36].

The Pharmacies engaged in the manufacture of ECMs, are an essential link in the value-based, personalized pharmaceutical care. It should be noted that, as of 2023, active manufacturing pharmacies across the country are represented by 460 to 890 entities and represent less than 0.5% of all pharmacies licensed for pharmaceutical activities [37]. For example, in Germany and Austria, all pharmacies are engaged in the manufacture of drugs, due to the mandatory license condition to include a manufacturing department in the structure of pharmacies [38–40]. In Poland, 99% of pharmacies are involved in the manufacture of drugs[3].

The expansion of the compounding (magistral formula) determines the need to update the technological base, to offer the necessary list of drug substances (DSs) on the market with the necessary packaging for pharmacies involved in the drugs manufacturing [41]. With this in mind, the most important role in the field of the drug manufacturing is assigned to the professional staff with modern competences that correspond to the development of the pharmaceutical market [42].

Recently, the regulatory framework for ECMs has undergone many additions and changes, but for the effectiveness of the regulatory practice, a systemic "roadmap" that takes into account all external threats and internal challenges, is needed.

THE AIM of the work was to analyze the current regulatory legal framework governing the drugs formulation in pharmacies, and a comprehensive review of the current state of their manufacture; a disclosure of problems and search for the ways to improve the sphere of circulation of extemporaneously compounded medicines (ECMs).

MATERIALS AND METHODS

Regulatory legal acts of the Russian Federation in the field of health care and circulation of drugs were chosen as objects of the study; the following methodological tools were used: empirical, theoretical and quantitative. As an empirical base, available data from the official website of the Ministry of Health of Russia[4], statistical data[5], a reference legal system "ConsultantPlus" on a contractual basis of Sechenov University, were studied.

The search was conducted using the following keywords: "extemporaneously compounded medicines", "drugs manufacturing", "extemporaneous formulations", "extemporal production", "pharmacy", "drug supply", "pharmaceutical sovereignty", "drug sovereignty", "compounding".

To analyze the results of scientific publications by other authors, the sources of information of the National Electronic Library — elibrary.ru, Google search engine were used. The search for legislative documents, literature was carried out for the period from 2014 to 2024. This period includes the sphere of ECMs circulation, before and after the entry into force of Federal Law No. 502-FZ[6] dated 05.12.2022, in terms of pharmacy manufacturing of drugs.

In accordance with the carried out search query, a total of 357 sources of information were found. The authors classified 50 sources as the most relevant.

In the course of the research, a set of scientific methods of systemic, logical, structural, comparative types of analysis was applied.

RESULTS AND DISCUSSION

Manufacturing of drugs in pharmacies in accordance with part 33 of Article 4 (Federal Law No. 61-FZ), refers to pharmaceutical activities, including wholesale trade of drugs, their storage, transportation and (or) retail trade of drugs, including a remote method, their dispensing, storage, transportation, manufacturing[7].

The term "extemporaneously compounded medicines" has been widely used in pharmaceutical practice since historical times, but till present, it has not been properly legislated. Although it should be noted that the sectoral law on the circulation of drugs defines about 20 concepts of drugs. *"Ex tempore"* (from

[2] Order of the Ministry of Health of the Russian Federation dated May 22, 2023 No. 249n (as amended on May 22, 2023) "Rules for the manufacture and release of medicines for medical use by pharmacies licensed for pharmaceutical activities".

[3] Zhukova O. Pharmacies in Poland. Available from: https://pharmvestnik.ru/articles/apteki-poljshi.html. Russian

[4] Ministry of Health of the Russian Federation. Available from: https://minzdrav.gov.ru

[5] Federal State Statistics Service of Russia. Available from: https://minzdrav.gov.ru

[6] Federal Law No. 502-FZ dated 05.12.2022 "On Amendments to Article 56 of the Federal Law on the Circulation of Medicines".

[7] Federal Law No. 61-FZ dated 12.04.2010 "On the Circulation of Medicines".

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Latin — as needed), more than ever emphasizes the importance of ECMs in the system of the drug supply under the conditions of mobilization economics and strengthening the drug sovereignty of the country. In this regard, the introduction of a new concept in Article 4 of Federal Law No. 61-FZ — "extemporaneously compounded medicines" — was proposed. According to the definition, ECMs are medicinal products in the DF of the drugs manufactured in pharmacies according to doctors' prescriptions or requirements of medical organizations, providing a personalized approach in the treatment of a particular patient' or a group of patients' disease, taking into account their anatomical and physiological and age-specific features. In the authors' opinion, the systematization of all terms and definitions used in relation to these drugs (drugs manufactured in pharmacies; extemporaneous dosage forms, extemporaneously compounded medicines, drugs, etc.) and the approval of the new concept of "extemporaneously compounded medicines" will do a lot. They will contribute to the improvement of the development processes of an integrated state vertical of the normative legal regulation of the ECMs circulation sphere.

Changes in Legislation

In September 2023, the amendments introduced by Federal Law No. 502-FZ[8] dated Dec 05, 2022 to Article 56 "Manufacturing and dispensing of drugs" of the Federal Law "On Circulation of Medicines", came into force in the Russian Federation. To date, the manufacture of ECMs for medical use is allowed only to pharmacies and prohibited to individual entrepreneurs, which limits the activity of small businesses and is still a debatable topic among the professional community.

The most important challenge under the sanctions regimes is the ban on the possibility to manufacture drugs registered under the national procedure in the Russian Federation. Moreover, with the entry into force of Federal Law No. 1-FZ[9] dated Jan 30, 2024 in early 2024, this ban also applies to the manufacture of drugs registered on the common market of the Eurasian Economic Union (EAEU).

The introduced legislative amendment allowing the use of finished DFs included in the State Register of Medicines (SRMs) and the Unified directory-catalog of medicines (UDCMs)[10] of the EAEU[11], is an undoubted achievement in the manufacture of drugs, but it solves only a part of the identified problems of the drug supply.

The authors believe that authorizing the manufacture of the drugs registered in the Russian Federation, as well as in the EAEU countries, should have the following key advantages:

1. Elimination of defective items in pharmacies;
2. Expansion of personalized pharmaceutical care for different groups of patients;
3. Reduction of entry barriers for new entities to the extemporaneous manufacturing market and reduction of their financial risks.

Licensing for manufacture of drugs

Manufacture of drugs is a licensable type of a pharmaceutical activity.

Licensing shall be subject to:

- manufacture of drugs for a medical use, except for the manufacture of radiopharmaceutical drugs for a medical use;
- manufacture of radiopharmaceuticals for a medical use.

In accordance with the Regulation on Licensing, three sections of license requirements for the manufacture of drugs in pharmacies can be distinguished:

- availability of a production facility or facilities (premises, buildings, structures) and the equipment at the place of pharmaceutical activities, belonging to the right of ownership or another legal basis providing for the right of possession and the right to use;
- requirements to education and qualification of pharmacies' employees;
- compliance of the licensee with the requirements of the legislation.

It should be noted that the current licensing regulations have completely eliminated the requirements of special education, qualifications and work experience for pharmacies supervisors directly involved in the dispensing, storage and manufacture of drugs[12].

In the authors' opinion, the exclusion of professional requirements for pharmacies supervisors does not contribute to the quality fulfilment of the tasks and mission assigned to pharmacies, undermines the prestige of a pharmaceutical specialist and pharmaceutical education in general, and reduces the level of employees' trust in the supervisor at the professional level.

The causal link of this cancellation can be seen in the status of pharmacies as a trading enterprise, in accordance with the Russian Classification of Products by Economic Activities (RCPEA), "retail trade in

[8] Federal Law No. 502-FZ dated Dec 05, 2022 "On Amendments to Article 56 of the Federal Law on the Circulation of Medicines".
[9] Federal Law No. 1-FZ dated Jan 30, 2024 "On Amendments to the Federal Law "On the Circulation of Medicines" and Articles 1 and 4 of the Federal Law "On Amendments to the Federal Law "On the Circulation of Medicines" and the Federal Law "On Amendments to the Federal Law "On the Circulation of Medicines".
[10] The State Register of Medicines of the Russian Federation. Available from: https://grls.minzdrav.gov.ru/Default.aspx
[11] The Unified Register of Registered Medicines of the Eurasian Economic Union. Available from: https://portal.eaeunion.org/sites/commonprocesses/ru-ru/Pages/DrugRegistrationDetails.aspx
[12] Decree of the Government of the Russian Federation dated March 31, 2022 No. 546 "On Approval of the Regulations on Licensing pharmaceutical activities".

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pharmaceutical products" belongs to the section "Retail Trade" (code 52.31)[13].

Order No. 529n of the Ministry of Health of Russia "On approval of the nomenclature of medical organizations" dated Aug 6, 2013, excluded the types of pharmacies from the nomenclature [14], although in the earlier order No. 627 dated Oct 07, 2005, all types of pharmacy institutions were present[15].

In the authors' opinion, it would be logical for RCPEA to include pharmacies "Activities in the field of health care and social services" in section Q. It is important to note the distinctive features of a drug as a drug, and, according to the requirements of order No. 647n[16] of the Ministry of Health of Russia dated Aug 31, 2016, professional pharmaceutical counseling is a prerequisite for the sale of drugs and all products of the pharmacy assortment. There are currently four professional standards that define the qualification requirements for specialists to carry out pharmaceutical activities. The content analysis of the current professional standards — "Pharmacist"[17], "Senior pharmacist"[18], "Management specialist in pharmaceutical business"[19], "Pharmacy technician"[20], — makes it possible to identify generalized labour functions and the labour functions for all the processes related to the manufacture of drugs, including the functions of quality assurance of drugs in pharmacies, pharmaceutical counseling and informing medical specialists. In general, professional standards establish requirements for professional education, special conditions for the admission to pharmaceutical activities, necessary knowledge, skills and labour actions. All these ultimately determine the goal of Pharmacies activities - to provide the population with safe and effective drugs, including ECMs.

New rules for manufacture of drugs

In pursuance of part 1 of Article 56 (Federal Law No. 61-FZ dated Apr 12, 2010), a delegated act approving new rules for manufacturing and dispensing drugs for a medical use was adopted — Order No. 249n of the Ministry of Health of Russia dated May 22, 2023, replacing Order No. 751n of the Ministry of Health of Russia dated Oct 26, 2015.

For the first time, these rules approved the peculiarities of manufacturing drugs from DFs, the procedure for manufacturing radiopharmaceutical drugs, and introduced a new section – a quality system of drug manufacturing.

The license requirement to have a person in charge of the implementation and maintenance of the quality system in pharmacies and the introduction of a new section on the quality system for the manufacture of drugs in the new regulations, are important prerequisites for the improvement of regulatory processes along the track of transformation of the current rules for the manufacture and dispensing into a prospective good practice for the manufacture and dispensing of drugs. In the authors' opinion, the adoption of good manufacturing and dispensing practices for drugs will serve to improve the efficiency and safety of manufactured drugs as a complete quality management system for this activity.

In accordance with paragraph 54 of Chapter IV "Peculiarities of manufacturing drugs from finished dosage forms" (Order No. 249n of the Ministry of Health of Russia), "...it is allowed to manufacture powders from finished dosage forms (tablets, capsules) that provide an immediate release of drugs. It is not allowed to manufacture powders from finished dosage forms (tablets, capsules) of a prolonged action and covered with intestinal soluble coating". In accordance with paragraph 56 of Chapter IV, "...the manufacture of solutions for injections and infusions from finished dosage forms of an industrial production is prohibited". In the authors' opinion, in this chapter, it is advisable to specify peculiar properties of manufacturing a wider nomenclature of dosage forms from finished dosage forms.

Chapter X of the current regulations states a specified procedure for the manufacture of radiopharmaceutical's.

Regulation of sanitary regime

A mandatory requirement of Order No.249n of the Ministry of Health of Russia is the compliance during the manufacture of medicinal products with conditions that meet sanitary and epidemiological requirements approved by the Decree of the Chief State Sanitary Doctor of the Russian Federation dated Dec 24, 2020 No. 44[21].

[13] Resolution of the State Standard of the Russian Federation dated 6.11.2001 No. 454-st "On the adoption and implementation of the RCPEA".

[14] Order of the Ministry of Health of the Russian Federation dated Aug 6, 2013 No. 529n "On approval of the nomenclature of medical organizations".

[15] Order of the Ministry of Health and Social Development of the Russian Federation dated Oct 07, 2005 No. 627 "On approval of the Unified Nomenclature of State and Municipal healthcare institutions".

[16] Order of the Ministry of Health of the Russian Federation dated Aug 31, 2016 No. 647n "On Approval of the Rules of Proper Pharmacy practice of medicines for medical use".

[17] The order of the Ministry of Labor of Russia dated 09.03.2016 No. 91n "On the approval of the professional standard "Pharmacist"".

[18] Order of the Ministry of Labor of the Russian Federation dated May 22, 2017 No. 427n "On approval of the professional standard "Pharmacist-analyst"".

[19] Order of the Ministry of Labor of the Russian Federation dated May 22, 2017 No. 428n "On approval of the professional standard "Management specialist in pharmaceutical business"".

[20] Order of the Ministry of Labor of the Russian Federation dated May 31, 2021 No. 349n "On approval of the professional standard "Pharmacist"".

[21] Resolution No. 44 of the Chief State Sanitary Doctor of the Russian Federation dated 12/24/2020 "On Approval of Sanitary Rules SP 2.1.3678-20 "Sanitary and epidemiological requirements for the operation of premises, buildings, structures, equipment and transport, as well as the operating conditions of business entities engaged in the sale of goods, performance of works or provision of services".

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While the regulation of the sanitary regime in pharmacies was previously approved by regulatory legal acts of the Ministry of Health of Russia, today, the authorization has been delegated to Rospotrebnadzor. A control of compliance with the rules on the sanitary regime remained under the jurisdiction of Roszdravnadzor.

Chapter V "Sanitary and Epidemiological Requirements for the Provision of Services by Pharmacy Organizations" is dedicated to the pharmacy section of the sanitary rules. The chapter contains only 24 paragrapharmacies, half of which relate to the pharmacies engaged in the manufacture of medicines.

Quality system of drugs manufacturing

As mentioned above, as a part of the systematic approach to the quality assurance of drug manufacturing, the chapter "Quality System for Drug Products Manufacturing" with a comprehensive approach to quality measures and development of standard operating procedures (SOPs) was introduced into pharmacies in accordance with the requirements of the General Pharmacopoeial Monographs (GPhMs) and Pharmacopoeial Monographs (PhMs).

In accordance with paragraph 7 of Chapter II "Quality System for the Manufacture of Drugs" (Order No. 249n of the Ministry of Health of the Russian Federation), the head of a pharmacy is obliged to appoint a responsible person for the implementation and maintenance of the quality system. The head's functions should include monitoring the effectiveness of the quality system and updating the SOPs, confirming the quality of manufactured drugs, as well as guaranteeing the manufacture of drugs in accordance with the SOPs. The person responsible for the implementation and assurance of the pharmacy quality system shall verify the compliance of each manufactured drug with the established requirements before and during their release.

In accordance with part 5 of Article 13 (Federal Law No. 61-FZ) and Clause 5 of Decision No. 78 of the Council of the Eurasian Economic Commission dated Nov 3, 2016, manufactured drugs are not subject to the state registration and registration on the common market of the EAEU's medicinal products[22]. Due to the absence of a mandatory registration of manufactured drugs at the national and interstate levels, the quality system of manufacturing drugs in pharmacies should be constantly updated with the introduction of necessary preventive and corrective measures to guarantee the quality and safety of finished products. Consequently, an important factor in ensuring the quality and safety of ECMs, taking into account all relations arising during the technological process of their manufacturing and dispensing, a compliance with the authorization and supervisory requirements of regulatory authorities, is the need for special education and professional competences of the supervisors of compounding pharmacies.

It should be also noted that the current delegated act does not have a single annex and, in the authors' opinion, this fact may complicate the process of manufacturing ECMs in terms of time and systematization of the regulatory information required for the manufacture of drugs. Previously, current Order No. 751n of the Ministry of Health of the Russian Federation dated Oct 26, 2015, contained 15 necessary annexes[23].

In general, attention should be paid to the relevance of the transition to the quality management system in the field of ECMs circulation — from the rules of manufacturing and dispensing of ECMs to the rules of good practice of extemporaneous manufacturing and the concept of determining the levels of risk in their manufacture [8].

In conjunction with regulatory legal acts governing the pharmaceutical industry and the market, the main tool for standardizing the quality of medicinal products is the State Pharmacopoeia of the Russian Federation (SPh RF). The fulfilment of the requirements specified in the SPh RF for the quality of drugs is mandatory for all subjects of the drug circulation, including the pharmacies manufacturing ECMs.

The current edition since 1 September 2023 is the SPh RF, XV edition[24]. All PhMs of the current pharmacopoeia are oriented to the requirements of the EAEU Pharmacopoeia; the norms are set in accordance with the international standards.

Taking into account the importance and necessity of tasks solution of drugs pharmacy manufacturing, the Ministry of Health of Russia has developed and approved 10 GPhMs[25], enacted since Sep 1, 2023. In connection with the widespread use of extemporaneous prescriptions in paediatric practice, the approval of GPhM 'Pharmacy Manufactured Drugs for Children' is particularly relevant. The list of the main regulatory legal acts governing the sphere of the ECMs circulation is presented in Table 1.

[22] Decision of the Council of the Eurasian Economic Commission dated Nov 03, 2016 No. 78 "On the Rules for registration and examination of medicines for medical use".

[23] Order of the Ministry of Health of the Russian Federation dated Oct 26, 2015 No. 751n "On approval of the Rules for the manufacture and release of medicines for medical use by pharmacy organizations, individual entrepreneurs licensed for pharmaceutical activities".

[24] Order of the Ministry of Health of the Russian Federation dated July, 20, 2023 No. 377 "On Approval of General Pharmacopoeial Monographs and Pharmacopoeial Monographs".

[25] Order of the Ministry of Health of the Russian Federation dated 08/25/2023 No. 448 "On Approval of General Pharmacopoeial Articles and Pharmacopoeial Articles and Amendments to Order of the Ministry of Health of the Russian Federation dated July 20, 2023 No. 377 "On Approval of General Pharmacopoeial Monographs and Pharmacopoeial Monographs".

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Table 1 – Main regulatory legal acts in the sphere of circulation of extemporaneously compounded medicines

Name of regulatory legal act	Functions / regulations governing the scope of ECMs circulation	Comments on hierarchy
Constitution of the Russian Federation	They defines the foundations of the political, legal and economic system of the state: • Art. 39 guarantees the social security in case of illness, disability; • Art. 41 gives the right to health care and medical assistance.	Constitution of the Russian Federation has supreme legal force, is represented by direct regulatory legal acts and is applied throughout the country
Federal law No. 323-FZ dated Nov 21, 2011	Realization of the constitutional right of citizens to health care and medical assistance, including drug provision and social protection: • Art.18 gives the right to health care; • Art. 19 gives the right to medical assistance; • Ch. 5 “Organization of Health Protection”.	Federal laws have a supreme legal authority after the Constitution of the Russian Federation and federal constitutional laws; they are directly applicable in the entire territory of the Russian Federation.
Federal Law No. 323-FZ “On the fundamentals of public health protection in the Russian Federation” dated Nov 21, 2011	Realization of the constitutional right of citizens to health care and medical assistance, including drug provision and social protection: • Part 33, Art. 4. Pharmaceutical activities (manufacturing of DPs is related to pharmaceutical activities); • Art. 8. Licensing of drugs and pharmaceutical activities; • Clause 1, Part 5, Art. 13. State registration of drug products (drugs manufactured by pharmacies are not subject to state registration); • Clause 1, Part 1, Art. 46. Labeling of drugs (drugs manufactured by pharmacies are an exception for their labeling); • Art. 56. Manufacturing and dispensing of drugs (manufacturing of drugs is allowed to be carried out by pharmacies having a relevant license; manufacturing of drugs using finished dosage forms is allowed; manufacturing of drugs registered in the Russian Federation and the EAEU, is not allowed); • Art. 57. Prohibition of sale of falsified drugs, substandard drugs, counterfeit drugs.	
Resolution of the Government of the Russian Federation No. 547 “On Approval of the Regulations on Licensing of Pharmaceutical Activities” dated March 31, 2022.	It specifies the procedure for licensing pharmaceutical activities: • manufacture of drugs for medical use, except for the manufacture of radiopharmaceutical drugs for medical use; • manufacture of radiopharmaceuticals for medical use.	Delegated RLAs, adopted in pursuance of the law
Order of the Ministry of Health of the Russian Federation No. 249n “Rules for manufacturing and dispensing drugs for medical use by pharmacy organizations holding a license for pharmaceutical activities”, dated May 22, 2023.	It regulates the rules of manufacturing, quality system and rules for dispensing ECMs in accordance with approved sections: I. General Provisions. II. Quality system of ECMs manufacturing. III. Peculiarities of manufacturing of drugs from pharmaceutical substances. IV. Peculiarities of manufacturing of drugs from finished dosage forms. V. Quality control of drugs. VI. Expiry dates for manufactured drugs. VII. Rules of dispensing and labeling of drugs. VIII. Controls on dispensing of drugs. IX. Features of the manufacture of homeopathic drugs. X. Procedure for the manufacture of radiopharmaceuticals.	

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Name of regulatory legal act	Functions / regulations governing the scope of ECMs circulation	Comments on hierarchy
Resolution of the Chief State Sanitary Doctor of the Russian Federation No. 44 "On Approval of Sanitary Rules SR 2.1.3678-20 "Sanitary and Epidemiological Requirements for the Operation of Premises, Buildings, Structures, Equipment and Transport, as well as the Conditions of Activity of Business Entities Engaged in the Sale of Goods, Performance of Work or Provision of Services", dated Dec 24, 2020.	It defines sanitary and epidemiological requirements in the implementation of pharmaceutical activities in accordance with the approved section: V. Sanitary and epidemiological requirements when providing services by pharmacies.	Delegated RLAs, adopted in pursuance of the law
Order of the Ministry of Health of the Russian Federation No. 377 "On approval of general pharmacopoeial Monographs and pharmacopoeial Monographs", dated July 20, 2023.	A list of quality indicators and quality control methods is defined.	
Order of the Ministry of Health of the Russian Federation No. 448 "On approval of general pharmacopoeial Monographs and pharmacopoeial Monographs, dated Aug 25, 2023; and amendments to Order of the Ministry of Health of the Russian Federation No. 377 "On approval of general pharmacopoeial Monographs and pharmacopoeial Monographs", dated July 20, 2023.	The following GPMs have been developed and approved: • GPhM.1.8.0001 Medicinal preparations of pharmacy manufacture. • GPhM.1.8.0003 Non-sterile pharmaceutical preparations of pharmacy manufacturing in the form of liquid dosage forms. • GPhM.1.8.0004 Non-sterile preparations of pharmacy manufacturing in the form of soft dosage forms. • GPhM.1.8.0005 Non-sterile preparations of pharmaceutical manufacturing in the form of solid dosage forms. • GPhM.1.8.0006 Sterile pharmaceutical preparations of pharmacy manufacturing. • GPhM.1.8.0002 Pharmacy-manufactured drugs for children. • GPhM.1.4.1.0043 Selection of dosage forms for children. • GPhM.1.11.0004 Extemporaneously compounded radiopharmaceuticals. • GPhM.1.8.0007 Homeopathic drugs of pharmacy manufacturing. • GPhM.1.4.1.0018 Infusions and decoctions.	

Note. RLA — regulatory legal act; ECMs — extemporaneously compounded medicines; GPhM — General Pharmacopoeial Monographs.

Regulation peculiarities of extemporaneously compounded medicines manufacturing

It should be noted that the prescription and use of ECMs is actually "off-label" — outside the instructions for a medical use and outside the general characterisation of drugs. Taking into account that the off-label efficacy and safety monitoring is currently carried out within the framework of pharmacovigilance and applies only to the registered drugs, it is necessary to improve regulatory processes to establish norms for monitoring these ECMs indicators [43, 44].

Pursuant to Art. 44 of Federal Law No. 248-FZ dated July 31.07.2020[26], Decree of the Government of the Russian Federation No. 1049 dated June 29, 2021[27], Order of Roszdravnadzor No. 9508 dated Dec 21, 2023[28], a risk-based approach is applied when conducting a state control of pharmacies with the right to manufacture drugs, including aseptic drugs. Pharmaceutical activities for manufacturing drugs are categorized as activities with a significant risk category, therefore, scheduled pharmacies supervisory activities are carried out once in 3 years. Supervisory activities help to identify risk-oriented points in the pharmacies

[26] Federal Law No. 248-FZ dated July 31, 2020 "On State Control (Supervision) and Municipal Control in the Russian Federation".

[27] Decree of the Government of the Russian Federation dated June 29, 2021 No. 1049 "On Federal State Control (Supervision) in the field of circulation of medicines".

[28] Order of the Federal Service for Healthcare Supervision dated Dec 21, 2023 No. 9508 "On Approval of the Program for the Prevention of Risks of Harm (Damage) to Legally Protected Values in the implementation of Federal State Control (Supervision) in the field of circulation of medicines for medical use in 2024".

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involved in drugs manufacturing, which contributes to improving the quality of a pharmaceutical supply to the population [45].

New regulatory legal acts (Order of the Ministry of Health of Russia No. 249n and the GPhM approved and enacted by Order of the Ministry of Health of Russia No. 377) could not significantly change the expected positive dynamics of compounding pharmacies and their increase in quantity and quality.

Constraints and risks for compounding pharmacies

A possible factor to reduce the financial risk for compounding pharmacies and increase their motivation to compound ECMs would be to amend Art. 164.2 of the Tax Code of the Russian Federation[29]: "…when selling drugs manufactured in a pharmacy, the value-added tax rate does not apply".

The question remains open when ECMs are procured by medical organizations that do not have their own compounding pharmacies.

Attention should be paid to some peculiarities identified by the authors in the course of their work:

- drug dispensing to medical organizations can be carried out exclusively by manufacturers of drugs and drugstores (Art. 54, No. 61-FZ);
- absence of ECMs state registration (Art. 13, No. 61-FZ);
- determination of the remaining ECMs shelf life;
- determination of price formation;
- entry of List of goods, works and services (LGWS) into the Unified directory-catalog of medicines (USCMP) with ECMs prescriptions and pharmacy manufacturing as services.

Thus, a procurement participant must have records in the pharmaceutical license indicating both manufacturing and dispensing of drugs and drugstores. Due to the absence of a certificate of product registration (CPR) for ECMs, the customer has no right to demand a copy of the RC and hand it over with the goods. There is a direct violation of the legislation on the contract system and on the circulation of drugs. Taking into account the limited shelf life of ECMs, it is necessary to indicate the shelf life depending on the specific dosage form of ECMs.

It should be also noted that it is necessary for pharmaceutical substance manufacturers to define the functionally required dosage forms for pharmacies involved in drugs manufacturing. At present, the State Register of Medicines (SRMs) mostly includes pharmaceutical substances in large packages, which are acceptable for the production of drugs. According to the analytical company RNC Pharma[30], for 9 months last year, 60% of pharmaceutical substances were imported from China, 15% from India and 23%, the most expensive ones, from Europe. The Ministry of Industry and Trade together with Vnesheconombank of Russia (VEB.RF), the Russian state development corporation that provides financing for social and economic projects, initiated a programme to support projects for the production of more than 145 pharmaceutical substances with preferential loans for pharmaceutical manufacturers.

The most important issue for the production of effective and safe drugs is the solution of compounding pharmacies staffing, the development of thematic cycles on ECMs for pharmaceutical and medical specialists. In this regard, it is necessary to jointly develop system solutions of the Ministry of Health of Russia and the Ministry of Education of Russia on the market demand for pharmaceutical personnel, especially pharmacy technicians and senior pharmacists. The position of pharmacy technicians according to the approved nomenclature of pharmaceutical workers by order of the Ministry of Health of the Russian Federation dated May 02, 2023 No. 205n[31] (as amended on May 02, 2023) was supposed to be valid only until Dec 31, 2025, which did not correspond to the personnel policy in the light of legislative changes in the manufacture of medicines. The logical changes made to this order dated Dec 04, 2023 eliminated these time limits. The position of senior pharmacists can be occupied by a specialist with professional retraining in "Pharmaceutical chemistry and pharmacognosy", if there is information about the accreditation of a specialist in "Pharmacy" and (or) training in internship / residency in "Pharmacy management and economics". A pharmacy technician and a senior pharmacist can hold an administrative position of the head of a structural unit or department of pharmacies, in addition to which a senior pharmacists may work or combine positions of a pharmacist and a pharmacy technician. The novelty of this order is a long-awaited authorization for the pharmacy head to work as a pharmacy technician. Thus, the regulator has simplified the procedure of transition from one specialty to another, which makes it possible to expand the positions held and interchangeability of specialists in labour collectives.

In order to form support measures for the law on compounding pharmacies, a special working group was set up under the Health Protection Committee of the State Duma of Russia, with the participation of deputies of the legislative assembly, representatives of

[29] The Tax Code of the Russian Federation (as amended, effective from June 1, 2024).

[30] RNC Pharma. Available from: https://rncph.ru/news/month/2023-9

[31] Order of the Ministry of Health of the Russian Federation dated May 02, 2023 No. 205n "On approval of the Nomenclature of positions of medical workers and pharmaceutical workers".

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the Ministry of Health and the Ministry of Industry and Trade of Russia, the pharmaceutical industry and patient organizations.

Due to the fact that pharmaceutical activities concerning ECMs manufacturing for pharmacies are unprofitable and there remains a risk of their closure, the working group has prepared an adopted draft law[32] of amendments to the federal law "On Circulation of Medicines", the work continues on drafts to the federal laws "On the Basics of Health Protection of Citizens", "On Compulsory Medical Insurance in the Russian Federation", the Civil Code and the Tax Code.

The aim of the package of amendments to federal laws is to increase the demand for pharmaceutically manufactured drugs by including them in clinical recommendations, treatment standards and in specialist training programs. In addition, treatment with ECMs should be included in state guarantee programs with an appropriate funding under the system of a preferential drug provision.

In connection with the revival of ECMs manufacturing, the issue of the intellectual property protection is also relevant.

In the scientific article "The new role of extemporaneous manufacturing in regulating access of drugs to the market", the authors reviewed the patent legislation abroad, including the EAEU countries in relation to ECMs manufacturing in pharmacy organizations [10].

The authors found out that the norm on the exceptions related to patent rights concerning pharmacy drugs manufacturing, is legislated in many member countries of the World Intellectual Property Organization (WIPO). The statements stipulated in Clause 5 of Article 1359 of the Civil Code of the Russian Federation, are not an infringement of the exclusive right to an invention, utility model or industrial design, they imply a single ECM production in pharmacies on prescriptions of doctors using the invention[33]. In the presence of a license, a pharmaceutical substance included in the SRMs for medical use may be used in the ECMs manufacturing in pharmacies.

Due to the fact that a compounding pharmacy cannot produce pharmaceutical substances on its own, it is necessary to legislate that a single production of pharmaceutical substances by a manufacturer will not be recognized as an infringement of the exclusive right to an invention, utility model or industrial design.

[32] Draft Law No. 798952-7 "On Amendments to Article 56 of the Federal Law on the Circulation of Medicines (regarding the Manufacture of Medicines)".

[33] The Civil Code of the Russian Federation (part four)" dated Dec 18, 2006 No. 230-FZ with amendments and additions.

Improvement of legislative base in the sphere of extemporaneously compounded medicines circulation

The logical consequence of the above is the legislative statements in the federal sectoral law "On Circulation of Medicines" and the following new concepts — "extemporaneous manufacturing" for pharmacies and "an extemporal production" for pharmaceutical manufacturers of drugs, proposed by the authors of this article.

Extemporaneous manufacturing is the value-oriented manufacture of extemporaneous drugs according to individual prescriptions or requested by a medical organization for a specific patient or a specific range of patients according to established prescriptions.

Extemporaneous manufacturing is a small-scale production of extemporaneous drugs according to the needs of a defined range of patients according to established prescriptions, and specific patients with a defined nosology for personalized pharmaceutical care according to individual prescriptions.

In the light of this research, a relevant and necessary definition of "pharmaceutical sovereignty" has been provided. It implies the ability of the state to control its pharmaceutical industry, including both extemporaneous manufacturing and an extemporaneous production, to ensure their sustainable development with the priority tasks of the drug supply. Of course, pharmaceutical sovereignty includes national drug sovereignty, but the definition is considered from a broad perspective, including the search for new molecules, development of the latest innovative drugs, modernization of the technological process and other external and internal factors in the conditions of the external sanctions pressure.

It should be noted that the rate of extemporaneous prescriptions from all incoming prescriptions to pharmacies in European countries is about 10%, in the USA — up to 5% [10].

In order to expand production departments in pharmacies in all subjects, to meet regional needs in ECMs [46], it is possible to develop a passport, approve and launch the federal project "Extemporaneous drugs: manufacturing and production". The project can be an important link in strengthening national pharmaceutical sovereignty, an important addition to the state programme "Pharma-2030" and a strategic factor of a sustainable development of the health care system as a whole. It should be noted that the current strategy shifts the focus towards measures to support drugs manufacturers through subsidisation, venture financing, and cheaper credit resources[34]. In the plans for the implementation of this state programme, the RF Government Order No. 753-r of 30.03.24 envisages the

[34] Decree of the Government of the Russian Federation dated July 06, 2023 No. 1495-r "On the Strategy for the development of the pharmaceutical industry of the Russian Federation for the period up to 2030".

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development of a mechanism for calculating the need of the healthcare system for drugs, based on which the actual demand will be formed, which will allow planning the processes of development and (or) organization of their production. It is also necessary to note the creation of interdepartmental working groups to ensure the interaction between the medical community and the manufacturing sector, with the participation of regulators, to raise awareness of domestic drugs among medical professionals and to receive feedback from specialists on the results of the use of drugs[35]. These support measures can significantly boost the development of extemporaneous manufacturing and production at regional levels and make the federal project sustainable.

In the authors' opinion, extemporaneous manufacturing and production should be regulated by the state, taking into account the primary objectives of the drug supply. However, there are already pioneers in opening commercial pharmacies, for example, the R-Pharm group of companies opened its first innovative manufacturing pharmacy "R-Pharm Compound". It should be noted that the National Project should outline the conditions for commercial organizations to enter the ECMs market. Extemporaneous manufacturing and production, in our opinion, should be regulated by the state, taking into account the primary tasks of drug supply.

The carried out analysis of the legal regulation of pharmaceutical activities concerning the manufacture of drugs in pharmacies showed a great deal of work done by the standard-setting activity, revealed some financial risks and barriers to entry into the ECMs market, professional requirements for pharmaceutical personnel and the main aspects of the further improvement of the legal framework to regulate the sphere of ECMs circulation [47–50].

CONCLUSION

The operational management and the degree of the regulatory impact in the field of the ECMs circulation is the most important factor in increasing the affordable, effective, personalized pharmaceutical care. Extemporaneous manufacturing and an extemporaneous production, a quality management system and dispensing of ECMs should be based on the evidence-based methods and tools, fulfil state objectives in the field of the drug provision, be economically beneficial for the patient, production structures and lead to the reduction of budgetary allocations for the drug provision. Manufacturing of drugs in pharmacies, a small-scale production of ECMs, are important elements of the development of domestic production capacities and technologies and improvement of the drug supply to the population of the country.

[35] Decree of the Government of the Russian Federation dated March 30, 2024 No. 753-r "Action Plan for the implementation of measures to implement the Strategy for the Development of the Pharmaceutical Industry of the Russian Federation for the period up to 2030".

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Vasily V. Ryazhenov — problem setting, critical analysis of scientific and normative legal documents, introduction of intellectual content remarks, editing of the article; Elena A. Maksimkina — collection and analysis of scientific and methodological literature, critical analysis of scientific and methodological literature, introduction of intellectual content remarks, editing of the article; Victor S. Fisenko — collection of scientific and methodological literature, critical analysis of scientific and normative legal documents, methodological literature, introduction of intellectual content remarks, editing of the article; Aleksey V. Alekhin — collection of scientific and methodological literature, critical analysis of scientific and methodological literature, introduction of intellectual content remarks, editing of the article; Vadim V. Tarasov — collection of scientific and methodological literature, critical analysis of scientific and methodological literature, introduction of intellectual content remarks, editing of the article; Maria G. Raisyan — collection of scientific and methodological literature, critical analysis of scientific and methodological literature, introduction of intellectual content remarks, editing of the article; Elena R. Zakharochkina — collection of scientific and methodological literature, introduction of intellectual content remarks, editing of the article; Kirill A. Chizhov — data collection and analysis, editing and design of the article; Rimma Yu. Garankina — problem setting, concept, collection and critical analysis of scientific literature and regulatory legal documents, collection and analysis of data, interpretation of results, writing, editing and design of the article, final approval of the manuscript.

All the authors confirm that their authorship meets the ICMJE international criteria (all the authors have made substantial contributions to the conceptualisation, research and preparation of the article, and have read and approved of the final version before the publication).

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AUTHORS

Vasily V. Ryazhenov – Doctor of Sciences (Pharmacy), Head of the Department of Regulatory Relations in the Field of Circulation of Drug Products and Medical Devices, Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0002-1278-5883. E-mail: ryazhenov v_v_2@staff.sechenov.ru

Elena A. Maksimkina – Doctor of Sciences (Pharmacy), Professor of the Department of Regulatory Relations in the Circulation of Medicines and Medical Devices, Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0003-1802-8928. E-mail: maksimkina.e@mail.ru

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Victor S. Fisenko – First Deputy Minister of Health, Russian Federation, Ministry of Health of the Russian Federation (Russian Ministry of Health), ORCID ID: 0009-0002-0918-737X. E-mail: fisenkovs@minzdrav.gov.ru

Aleksey V. Alekhin – General Director of "Farmaklon Group Management Company" LLC, Assistant of BMT-3 Department, Bauman Moscow State Technical University. ORCID ID: 0009-0003-5882-8994. E-mail: Ava@pharmaclon.ru

Vadim V. Tarasov – Doctor of Sciences (Pharmacy), Professor, Director of the Institute of Translational Medicine and Biotechnology, Professor of the Department of Pharmacology, Nelyubin Bauman Institute of Pharmacy, Sechenov First Moscow State Medical University (Sechenov University). ORCID: 0000-0002-9394-7994. E-mail: tarasov_v_v@staff.sechenov.ru

Maria G. Raisyan – Candidate of Sciences (Pharmacy), Associate Professor of the Department of Regulatory Relations in the Field of Circulation of Medicines and Medical Devices, Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0001-5768-8166. E-mail: raysyan_m_g@staff.sechenov.ru

Elena R. Zakharochkina – Candidate of Sciences (Pharmacy), Associate Professor of the Department of Regulatory Relations in the Field of Circulation of Medicines and Medical Devices, Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0009-0003-6791-8908. E-mail: zakharochkina_e_r@staff.sechenov.ru

Kirill A. Chizhov – 1st year student, A.P.Nelyubin Institute of Pharmacy, Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0009-0008-7757-1609. E-mail: chizhow.kirill2016@yandex.ru

Rimma Yu. Garankina – Candidate of Sciences (Pharmacy), Associate Professor of the Department of Regulatory Relations in the Field of Circulation of Medicines and Medical Devices, Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0003-4312-8672. E-mail: garankina_r_yu@staff.sechenov.ru

REVIEWS

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Treatment approaches to pulmonary lymphangioleomyomatosis: From surgical extirpation to molecular biology

I.V. Polovnikov, G.Yu. Yukina, E.G. Sukhorukova

Pavlov First Saint Petersburg State Medical University,
Bld. 6, 8, Lev Tolstoy Str., Saint Petersburg, Russia, 197022

E-mail: policrats@mail.ru

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The aim of the work was to collect and systematize the data on the treatment approaches to pulmonary lymphangioleiomyomatosis (LAM) based on insights into the pathogenesis of the disease.

Materials and methods. 70 original sources have been selected from analyzed 1 157 articles and monographs (including duplicates). The search for the sources was carried out in the databases of PubMed, eLibrary.ru, Cyberleninka for a fifty-year period of publications (from 1973 to August 2023), with an emphasis on more current publications and the ones in highly rated scientific journals.

Results. The review presents the treatment approaches to LAM, based both on clinical observations of the disease course and on the experimental data on its probable pathogenesis. The collected data are presented in the chronological order, starting from radical methods based on the idea of an unconditional connection between the development of LAM and the female sex hormones. Special attention has been paid to the drugs from the group of mTOR inhibitors, including their safety profile. In addition, the results of the studies demonstrating new promising methods of the LAM drug therapy, both combining the use of mTOR inhibitors with other drugs, and the ones based on the isolated use of alternative groups of drugs, are presented in the work.

Conclusion. The currently used methods of the drug therapy and the proposed new methods are aimed at only treating an already established disease, and the effective drug prevention of LAM now seems almost impossible due to the lack of a complete understanding about its pathogenesis and, more importantly, its etiology. This issue is the most relevant in determining further prospects for the development of pharmacotherapeutic approaches to LAM.

Keywords: lymphangioleiomyomatosis; treatment; biochemistry; pathogenesis; etiology

Abbreviations: LAM — lymphangioleiomyomatosis; TSC — tuberous sclerosis complex; VEGF-D — vascular endothelial growth factor D; MIAA — methylimidazoleacetic acid; iNOS — inducible NO synthase; SGCs — systemic glucocorticosteroids; TB — tuberous sclerosis; Cox2 — cyclooxygenase-2; RAAS — renin-angiotensin-aldosterone system; ACE — angiotensin-converting enzyme; AGT — angiotensinogen; Ang1 — angiotensin 1; Ang2 — angiotensin 2; AT-R — angiotensin receptor; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blocker; IL — interleukin; MMPs — matrix metalloproteinases; MCP1 — monocyte chemoattractant protein 1; PKB — protein kinase B; ERK — extracellular signal-regulated kinases; TGFβ — transforming growth factor beta; SASP — senescence-associated secretory phenotype; CatK — Cathepsin K; SREBP — sterol regulatory element-binding protein; CAs — carbonic anhydrases; NBC — bicarbonate Sodium (Natrium) cotransporter; SPHK1 — sphingosine kinase 1.

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ОБЗОРЫ

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Подходы к лечению лимфангиолейомиоматоза лёгких: от радикальной хирургии до молекулярной биологии

И.В. Половников, Г.Ю. Юкина, Е.Г. Сухорукова

Федеральное государственное образовательное учреждение высшего образования
«Первый Санкт-Петербургский государственный медицинский университет им. академика И.П. Павлова»
Министерства здравоохранения Российской Федерации,
197022, Россия, Санкт-Петербург, ул. Льва Толстого, д. 6–8

E-mail: policrats@mail.ru

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Цель. Сбор и систематизация данных о подходах к лечению лимфангиолейомиоматоза (ЛАМ) лёгких, основанных на представлениях о патогенезе заболевания.

Материалы и методы. Проанализировано 1157 статей и монографий (включая дубли), из которых отобраны 70 оригинальных источников. Поиск источников осуществляли в базах PubMed, eliabrary.ru, CyberLeninka. Глубина поиска составила 50 лет — с 1973 г. по август 2023 г. Авторы акцентировали внимание на актуальных публикациях в высокорейтинговых научных журналах.

Результаты. В обзоре представлены подходы к лечению ЛАМ, основанные как на клинических наблюдениях за течением заболевания, так и на экспериментальных данных о вероятном его патогенезе. Собранные данные представлены в хронологическом порядке, начиная с радикальных методов, основанных на представлениях о безусловной связи развития ЛАМ с воздействием женских половых гормонов. Отдельное внимание уделено препаратам из группы ингибиторов mTOR, в том числе их профилю безопасности. Помимо этого, приведены результаты исследований, демонстрирующих новые перспективные методы лекарственной терапии ЛАМ, сочетающие в себе как применение ингибиторов mTOR с другими препаратами, так и основанных на изолированном использовании альтернативных групп медикаментов.

Заключение. Используемые на настоящий момент методы лекарственной терапии и предлагаемые новые методы направлены лишь на лечение уже сформировавшегося заболевания, а проведение эффективной медикаментозной профилактики ЛАМ сейчас представляется практически невозможным ввиду отсутствия полного понимания патогенеза заболевания и, что более важно, — его этиологии. Данный вопрос является наиболее актуальным в определении дальнейших перспектив развития фармакотерапевтических подходов к ЛАМ.

Ключевые слова: лимфангиолейомиоматоз; лечение; биохимия; патогенез; этиология

Список сокращений: ЛАМ — лимфангиолейомиоматоз; TSC — комплекс туберозного склероза; VEGF-D — фактор роста эндотелия сосудов D; MIAA — метилимидазолускусная кислота; ЖБАЛ — жидкость, полученная при проведении бронхоальвеолярного лаважа; iNOS — индуцибельная NO-синтаза; СГКС — системные глюкокортикостероиды; ТС — туберозный склероз; ЦОГ2 — циклооксигеназа 2 типа; РААС — ренин-ангиотензин-альдостероновая система; АПФ — ангиотензин превращающий фермент; АТГ — ангиотензиноген; Анг1 — ангиотензин 1; Анг2 — ангиотензин 2; Анг-R — рецепторы к ангиотензину; иАПФ — ингибитор ангиотензин превращающего фермента; АРБ — ангиотензина рецепторов блокатор; ИЛ — интерлейкин; ММП — матриксные металлопротеиназы; МХБ1 — моноцитов хемоаттрактантный белок 1 типа; ПК-В — протеинкиназа типа В; ERK — киназы, регулируемые внеклеточными сигналами; TGFβ — трансформирующий фактор роста бета; SASP — секреторный фенотип, связанный со старением; CatK — катепсин К; SREBP — белок связывающий регуляторный элемент стерола; СА — карбангидраза; NBC — контранспортёр бикарбонат-анионов и катионов натрия; SPHK1 — сфингозин киназа 1.

INTRODUCTION

Lymphangioleiomyomatosis (LAM)[1] is a rare disease affecting lungs, kidneys and pelvic organs, classified by WHO as a mesenchymal tumor and considered a metastatic low-grade neoplasm that originates from cells (LAM cells) with a biallelic mutation in the gene of a tuberous sclerosis complex (TSC) [1,2]. Previously, there had been a well-established belief that this disease affected only women [3], but in recent years there have been described several cases of LAM in men [4]. Nevertheless, the incidence even among females, whose proportion among patients with LAM prevails significantly, varies from 3.35 to 7.76 cases per 1 million women [5].

The issue of treating LAM is relevant, but it is better

[1] Ilkovich MM. Diffuse and parenchymal lung diseases. Moscow: GEOTAR-Media; 2021. DOI: 10.33029/9704-5908-9-DPL-2021-1-440. Russian

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to highlight briefly the main reliable biochemical markers that are identified during a laboratory LAM diagnosis and reflecting its pathogenesis (at least partly), before the immersion into therapy approaches.

The main biochemical marker in blood plasma, that is associated with lung damage by LAM, is vascular endothelial growth factor D (VEGF-D). The generally accepted concentration of it is 800 pg/mL [6, 7]. However, a meta-analysis of researches on the diagnostic effectiveness of the VEGF-D concentration in blood plasma in LAM with the PROSPERO design (protocol No. CRD42020164137) and with the QUADAS-2 method (Quality Assessment of Diagnostic Accuracy Studies, version 2) shows that the determination of VEGF-D has a high specificity and a moderate sensitivity for a LAM diagnosis. It means that a high concentration of VEGF-D confirms a LAM diagnosis, while a low concentration does not exclude it. Moreover, there was noted that the variability of VEGF-D concentration from 440 to 1239 pg/mL is permissible due to the possible influence of a number of factors on this indicator (including a sample preparation and other aspects of the analysis) [8]. Along with VEGF-D, it is proposed to use the methylimidazoleacetic acid (MIAA), that is declared as a histamine metabolite [9].

Currently, in the routine practice of a LAM diagnosis, there is a concentration determation of metalloproteinases type 2 (mainly in the blood serum) and type 9 (both in the blood serum and urine), which is more applicable for assessing the effectiveness of therapy, but not for a primary diagnosis [10–12]. Herewith, the researchers develop and test molecular “nanosensors”, that allow the assessment of the enzyme activity in real time by determining the level of specific “sensory markers” in the urine. The essence of the “nanosensors” action is in their specific interaction with metalloproteinases, whereupon the specific compound is eliminated from the body through the urine [13]. This may be interesting not only to be used in clinical practice, but also in scientific research.

It has also been shown that in LAM patients, the blood plasma concentration of osteopontin is significantly higher in comparison with healthy people, which is explained by the participation of this protein in the process of a signal transmission from CD44v6 receptors [14].

Moreover, three serum proteins can be identified as potential diagnostic markers: fibronectin, von Willebrand factor and kallikrein III [15]. A recent study of the blood plasma of patients with an established LAM diagnosis is interesting due to using a nuclear magnetic resonance method to identify a wide range of biochemical markers. Based on the results of this study, the authors identified two potential blood plasma LAM markers — methionine and acetic acid [16].

It has also been shown that in the LAM patients, concentrations of the cytokines CCL2 (MCP-1), CXCL1 (GRO1) and CXCL5 (ENA-78) that are determined in the fluid obtained during the bronchoalveolar lavage, is higher. The main difficulty in introducing the identified markers into the routine practice is the standardization of methods for collecting that fluid due to the impossibility of accurately determining the degree of the material dilution [17].

A surfactant analysis in the mice demonstrates a significant activity increase in the inducible NO synthase (iNOS) in the lungs of the animals with a mutation in TSC2 that results in the nitrosylation of surfactant protein D [18], an established regulator of the alveolar macrophages activity [19].

It is also advisable to focus on the biochemical features that underlie various treatment approaches to LAM during their consideration.

THE AIM of the work was to collect and systematize the data on the treatment approaches to pulmonary lymphangioleiomyomatosis (LAM) based on insights into the pathogenesis of the disease.

MATERIALS AND METHODS

The selection of the sources was accorded to the algorithm presented at Figure 1. As a result, 70 original sources have been selected from analyzed 1 157 articles and monographs (including duplicates).

The search for the sources was carried out in the databases of PubMed, eLibrary.ru, CyberLeninka for a fifty-year period of publications — from 1973 to August 2023, with an emphasis on more current publications and publications in highly rated scientific journals. The keywords used for the search were as follows: “lymphangioleiomyomatosis” / “лимфангиолейомиоматоз” isolated and in combination with “pulmonary / лёгкие”, “(bio)marker” / “(био)маркер”, “immunology” / “иммунология”, “gene” / “ген”, “diagnosis” / “диагностика”, “therapy” / “терапия”, “experiment” / “эксперимент”, “animal model” / “модель животного”.

A primary analysis of the sources (*n*=1157) was based on a screening of their abstracts. As a result, 541 sources including original studies, clinical observations, a retrospective analysis of the clinical observations data, a meta-analysis of the experimental studies and clinical observations, monographs and their individual chapters wholly or partially directly related to LAM, were selected. Next, duplicates (*n*=29) were excluded and a screening of the sources (*n* = 512) was carried out. As a result, the review includes only the sources that contained information about: biochemical and/or genetic characteristics of changes, approaches to their treatment (correction). The criteria for non-inclusion were: isolated extrapulmonary LAM

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manifestations, a clinical LAM picture (symptoms and semiotics), functional studies, methods of radiation and ultrasound examinations, approaches to collecting biological materials for the examination.

To analyze the selected sources, a descriptive and analytical method was used.

The review also includes three more sources containing information necessary to clarify individual concepts, definitions, research and diagnostic methods related to the topic of the review.

RESULTS AND DISCUSSION

The drug therapy approaches are based both on the clinical observations and on the data on the biochemical changes occurring in LAM. The data below are structured chronologically and, where it is possible, are grouped by the similarity of the action mechanism.

Radical and hormonal kinds of therapy

Due to the predominant LAM manifestation in women and due to the positive clinical experience, one of the first ideas for the "targeted" LAM therapy was a major surgery at the early stages of identifying the symptoms of the disease [20]. But later on, probably due to the widespread introduction of the hormone replacement therapy into the clinical practice and for humanistic reasons, this method got less preferable than the drug therapy.

The world experience in the LAM treatment with sex hormones shows conflicting data. Several studies *in vitro* demonstrated the effectiveness of estrogen and progesterone receptor blockers on the LAM cells development [21, 22]. An *in vivo* experiment on Eker rat uterine leiomyoma cells (line ELT3) showed the inducing effect of estradiol on metastasis of TSC2-deficient cells through matrix metalloproteinase 2. Whereas the use of fulvestrant inhibited estradiol-induced lung metastases and increased the survival of the mice with xenografts tumors treated with estradiol [22]. This consists with retrospective clinical observations [23]. However, the current results of the clinical observations indicate only a variable effectiveness of such therapy and only in women whose clinical LAM picture was dependent on the menstrual cycle phase [24], and the clinical studies actually proved the ineffectiveness of the hormonal therapy, in particular the analogue of a gonadotropin-releasing hormone [25]. Herewith, to refuse the application of estrogen-based oral contraceptives due to the fact that their effect on the growth of LAM cells has been proven experimentally [22] and by clinical observations [26], seems reasonable.

Regarding the use of systemic glucocorticosteroids (SGCs), the situation is even more ambiguous. Although LAM is called "steroid-sensitive cancer" [27], we are usually talking about estrogens and progesterone are usually in the focus of the discussion, and no data have been found on clinical observations of the SGCs effect on the course of LAM or on the experimental study of this effect. Symptomatic LAM therapy usually includes the use of inhaled glucocorticosteroids, long-acting beta-2-adrenergic agonists and anticholinergics; however, the tactics of their use need to be studied in more detail [28], and no data have been found on their effect on pathogenesis either.

In the context of the therapy effectiveness of LAM as a disease directly related to sex hormones, the question about the metastatic nature of LAM cells is still relevant. A genetic analysis of LAM cells demonstrates their similarity to myometrial cells, from which the authors who have studied this issue conclude that they are likely to have a metastatic nature. Herewith, they note that there is need for further research. However, they point out that even if the development of LAM cells is determined as *in situ*, it will be possible to use the PBX1/HOXD11 markers as targets for a specific kind of therapy by the drugs that are an alternative to mTOR inhibitors that characterize myometrial cells [29]. This is serine-threonine protein kinase, acting as a subunit of intracellular multimolecular signaling complexes that regulate the cell growth well-known since 1991. More details about this group of drugs will be discussed below.

mTOR inhibitors

The key link in the LAM pathogenesis is considered mTOR. Its constitutive activation is a result of mutation in TSC-genes (typical for LAM-cells) that leads to a proliferation stimulation of mutant cells, and the leading pathogenetic drug therapy is its inhibitors — sirolimus and everolimus [1]. But there are also the data on the non-drug inhibition of mTOR, based on the artificial deficiency of amino acids, demonstrated *in vitro* in cell cultures [30].

A retrospective analysis of the clinical data from the patients with verified LAM included in the Chinese LAM registry from 10 May 2017 to 31August 2020 (n=399), demonstrates that the use of sirolimus significantly reduces the risk of recurrent pneumothorax in the LAM patients. However, the authors keep the question about the significance of pneumothorax to start sirolimus therapy, and note that this requires a further study [31]. On the other hand, it has been shown that even relatively low sirolimus doses (with plasma concentrations below 5 ng/ml) demonstrate a clinical efficacy comparable to the use of high doses of this drug (with plasma concentrations of 5–15 ng/mL) [32]. In general, the use of sirolimus demonstrates a satisfactory safety profile according to a retrospective analysis of adverse events caused by the use of the drug in patients included in the LAM registry of Peking Union Medical College Hospital (PUMCH), Beijing, China (n=142) [33].

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Based on the same registry, there is a retrospective study of the course of pregnancy against the background of taking Sirolimus at the established diagnosis of LAM (*n*=30). Based on its results, the authors draw a non-confident conclusion that although the use of sirolimus is probably associated with a high risk of a spontaneous abortion. In their study, this connection is not observed reliably [34]. Herewith, there is a clinical observation of a woman at the established diagnosis of LAM, who endured successfully two pregnancies, the second during therapy with sirolimus, gave birth to two healthy children and demonstrated a clinical stability of the disease [35].

The presence of a risk of adverse events caused by taking mTOR inhibitors, including a combination with another method of treating LAM (a lung transplantation) and in the context of an increase of a risk of developing infectious diseases due to a weakened immune response [36] forces further research into their effectiveness and the search for alternative treatment methods.

Regarding the effect on the prognosis of a lung transplantation, the data on the relative safety of the sirolimus and everolimus use both in the period up to and after the lung transplantation, have been previously published [37]. However, the results of the recent survey (2022) of several centers where a lung transplantation is carried out demonstrate that now it is impossible to unequivocally conclude both about the need to continue therapy with mTOR inhibitors in patients included in the waiting list for a lung transplant, and about the impact of taking these drugs on “an anastomotic failure” after a lung transplantation [38].

Regarding the issue of increasing the risk of developing infectious diseases, the greatest interest nowadays is the condition of patients on therapy with mTOR inhibitors in the context of the ongoing COVID-19 pandemic. It was shown that patients with tuberous sclerosis (TS) and LAM on therapy with mTOR inhibitors did not have a higher risk of contracting COVID-19 [39]. In the outcomes of COVID-19 in the patients at the previously established diagnosis of LAM, there are no significant differences between those who were treated with mTOR inhibitors and those who received other therapy, either [40]. A case of a 29-year-old patient at the previously established diagnosis of LAM, who fell ill with COVID-19 and tolerated it relatively satisfactorily on Sirolimus therapy, has been also described in detail [41].

In addition, the development of bronchial hyperreactivity induced by sirolimus has been described, with a description of the supposed pathogenesis of this adverse event development [42].

Overall, it remains an open question as to whether such therapy is necessary or at least defining clear criteria for the need of it. This describes the clinical case of a 36-year-old patient with a verified diagnosis of LAM after a series of spontaneous pneumothoraxes, but after that the course of the disease independently stabilized without taking any specific therapy [43]. This can point out the invalidity of the thesis about mTOR being not the only one key link in the LAM pathogenesis.

The search for new treatment approaches to LAM can be divided into two directions — the isolated use of alternative drugs or their combination with mTOR inhibitors.

mTOR inhibitors in combination

Statins

As far back as 2007, an experiment demonstrated the effectiveness of a combination of mTOR inhibitors and statin drugs (in particular atorvastatin), including by inhibition of prenylation of the GTP-binding protein RHEB, which is involved in the regulation of the cell cycle [44]. Later, experiments *in vitro* [45] and *in vivo* [46] demonstrated the effectiveness of the combination of mTOR inhibitors with Simvastatin, and its greater effectiveness was noted in comparison with atorvastatin [47].

In clinical studies of the proposed combination of simvastin+sirolimus and simvastin+everolimus, multidirectional dynamics is noted: on the one hand, it is possible to achieve a stabilization of the lung diffusion capacity and lungs volumes; on the other hand, a decrease of the speed criteria of the external respiration function [48].

Hydroxychloraquine

The combined effects of mTOR inhibitors and hydroxychloroquine are studied actively. Their extreme similarity in their effect on polyamine metabolism was shown in an *in vitro* experiment on the cells obtained from LAM patients. In this regard, the authors also propose to consider the assessment of polyamine metabolism as a biochemical criterion for the effectiveness of the LAM therapy, and point out that the safety of the combined use of drugs has already been proven, but a therapeutic effect assessment requires a further study [49].

Bisphosphonates

Another option for mTOR therapy “adding-on” is the use of bisphosphonates, particularly zoledronic acid, based on clinical observations. The same combination demonstrates its effectiveness in an *in vivo* experiment on a LAM model in female mice with a subcutaneous injection of TSC-deficient cells [50].

Phytoalexin

Another combination is phytoalexin Resveratrol, which demonstrates a wide range of clinical effects [51]. Clinical trials have demonstrated its safety in combination

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with sirolimus, but its efficacy evaluation in comparison with monotherapy requires further research [52].

Alternative to mTOR inhibitors

In the context of the "isolated" LAM therapy, first, it is necessary to mention the drugs effect on VEGF. An *in vivo* experiment on female mice after the intranasal administration of a suspension of cells obtained from the chylous effusion of a patient with an established diagnosis of LAM, demonstrated the effectiveness of the intramuscular administration of antibodies to VEGF receptors [53]. The similar data were presented in another *in vivo* experimental model in female mice after the injection into the tail vein of a suspension of cells obtained from the renal tubular cystadenoma of TCS2-mutant mice [54].

As the tissues affected by the LAM cells show a deficiency of the collagen type IVa5, their effect on the activity of the LAM cells was appreciated in an *in vitro* experiment on the heterogeneous LAM cells and in an *in vivo* experiment, when the tumor cells of the line LNM35 AAV-EGFP-expressing were engrafted into the ears of the female mice. The results of the study demonstrate a decrease in the cells proliferative activity in response to the use of the protein, that is named by the authors as Lamstatin. Its active center, CP17, is represented by the following amino acid composition — VCNFASRNDYSYWLSTP between amino acids 66 and 82 in the collagen chain [55].

Because of the established effect of the matrix metalloproteinases (MMPs) inhibition by doxycycline, its use in the treatment of LAM was explored. Despite its high effectiveness according to the laboratory studies [8], later on, its ineffectiveness in the LAM treatment was proven by a systematic clinical analysis [56].

Based on the previously established data that the LAM cells express cyclooxygenase-2 (COX-2), and the use of celicoxib in an *in vivo* experiment on the mice demonstrates its effectiveness [57], in 2020, a safety study of this drug in the LAM patients, who had not previously received the treatment, was carried out with positive results. The clinical effectiveness of the drug was not assessed [58].

It was revealed that LAM cells have a local renin-angiotensin-aldosterone system (RAAS) (Fig. 2), and a retrospective analysis of the clinical cases showed that the patients with therapy by angiotensin-converting enzyme (ACE) inhibitor drugs are less prone to a decreased lung function [59]. However, it should be separately noted that determining the level of ACE, a well-known since the end of the last century marker for the diagnosis of sarcoidosis [60], — has been recognized as uninformative for the LAM diagnosis [11].

An *in vitro* experiment on the ELT3V-line cells showed that the exposure to an angiotensin II receptor inhibitor (Losartan) regulates a synthetic activity of TSC2-deficient cells, causing their death by changing the level of expression of the Klotho protein, which is probably involved in aging processes [61]. Moreover, in an *in vitro* experiment on the cells obtained from the chylous effusion of a LAM patient, it was demonstrated that LAM cells in general have a secretory phenotype associated with aging senescence-associated secretory phenotype (SASP), that manifests itself in the activation of β-galactosidase and in increasing the secretion in Cathepsin K (CatK), IL-6 and IL-8. SASP can play a key role in the migration of LAM cells and the transformation of granulomas into cysts. In this light, the identified molecules can be targeted for specific LAM therapy, aimed at reducing the risk of a cystic transformation of the lungs and its progression [62]. It has also been shown that the main producers of one of the SASP — CatK — components are fibroblasts that are associated with LAM, and its activation is possible only at a relatively low pH level (<7.0). The necessary "acidification" of the environment is ensured by the LAM cells themselves by an increased expression of membrane transport proteins that ensure the export of hydrogen cations and the manifestation of the Warburg effect, which is caused by the mTOR dysregulation (Fig. 3) [63]. In addition, "aging" of LAM cells also manifests itself in lipid metabolism changes by SREBP (sterol regulatory element-binding protein), which is an mTOR effector [64].

An *in vitro* experiment on heterogeneous cell cultures and on mice with subcutaneous injections of ELT3-V3-line cells showed that TSC2 deficiency causes an abnormal sphingolipid metabolism, which can be a target for other specific LAM therapy. In particular, these are the enzyme sphingosine kinase 1 (SPHK1), the receptor complex S1PR3, and the phosphorylated sphingosine S1Pthat "binds" them. The effectiveness of PF-543 hydrochloride in inhibiting SPHK1 and the effectiveness of the S1PR3 antagonist (TY52156) have been demonstrated in suppressing the tumor activity of TSC2-deficient cells, in particular, that of LAM cells (Fig. 4) [65].

As has been shown, that the tissues affected by LAM have increased the expression of PD-L1 (CD274), a ligand that suppresses the T-cell immune response. The authors believe that this fact can explain the situation when the immune system is not aggressive towards LAM cells. An *in vivo* experiment demonstrated a statistically significantly better survival of mice that had been treated by PD-L1 inhibitors, which can also form the basis of an alternative route for the treatment of LAM [66], including a form of inhaled drugs[2].

[2] Amosu M.M., McCright J.C., Yang B.E., de Oro Fernandez J.G., Moore K.A., Gadde HS. Inhaled CpG increases survival and synergizes with checkpoint inhibition in lymphangioleiomyomatosis. bioRxiv. 2023;2023.02.06.527331. Preprint. DOI: 10.1101/2023.02.06.527331

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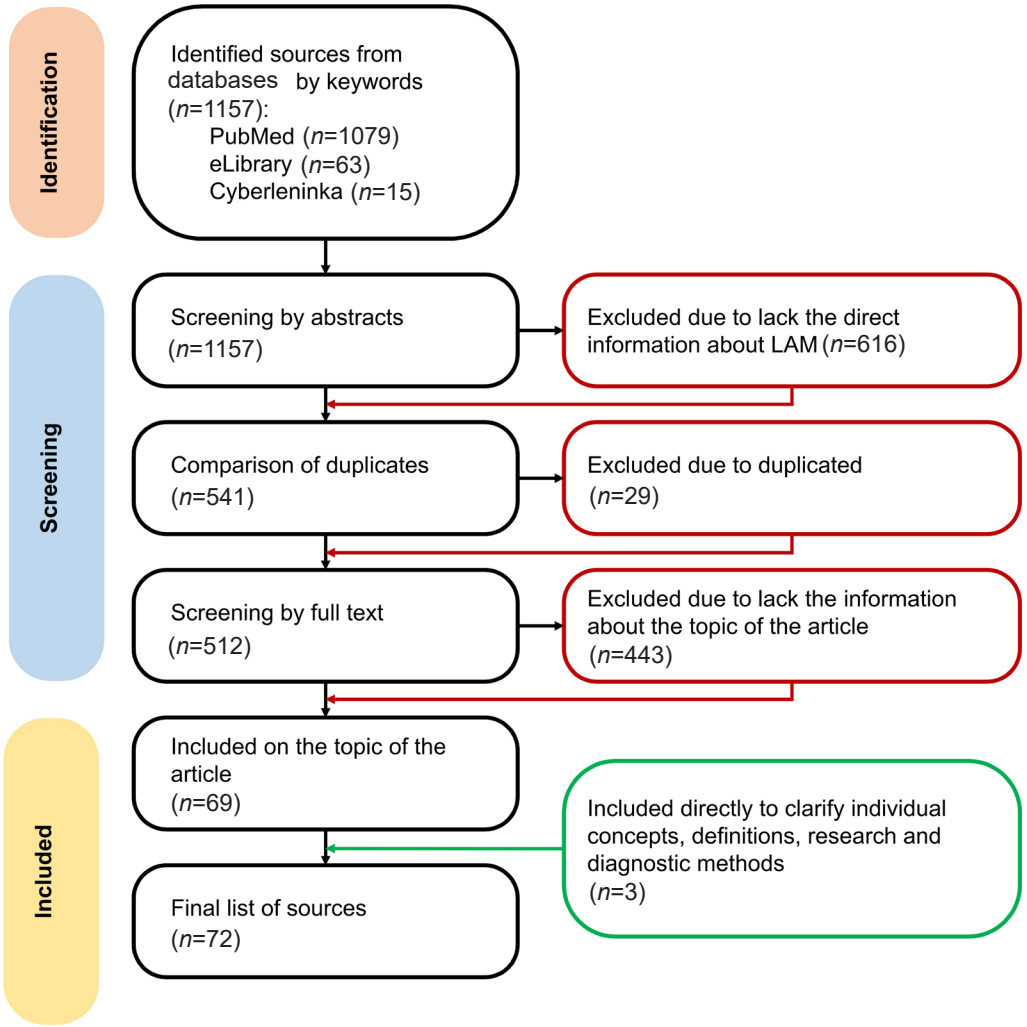

Figure 1 – Scheme for selecting sources to be included in the review.

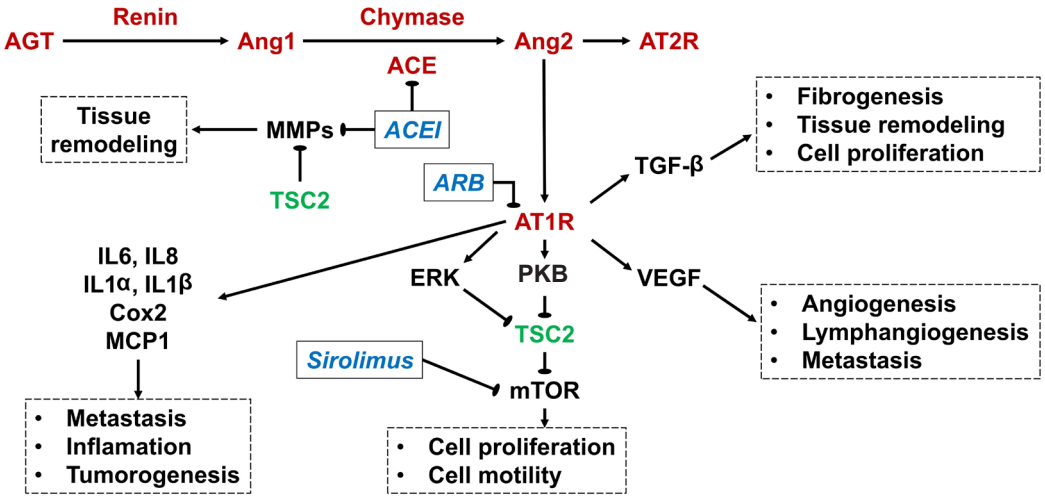

Figure 2 – Local renin-angiotensin-aldosterone system of LAM cells and its targets for drug therapy.

Notes: Adopted from [59]. AGT — angiotensinogen; Ang1 — angiotensin 1; Ang2 — angiotensin 2; AT*R — angiotensin receptor (1; 2 types); ACE — angiotensin-converting enzyme; ACEI — ACE inhibitor; ARB — angiotensin receptor blocker; Cox2 — cyclooxygenase-2; IL* — interleukin (1; 6; 8 types); MMPs — matrix metalloproteinases; MCP1 — monocyte chemoattractant protein 1; PKB — protein kinase B; TSC2 — gene of tuberous sclerosis complex; mTOR — mechanistic/mammalian target of rapamycin; TGFβ — transforming growth factor beta; VEGF — vascular endothelial growth factor.

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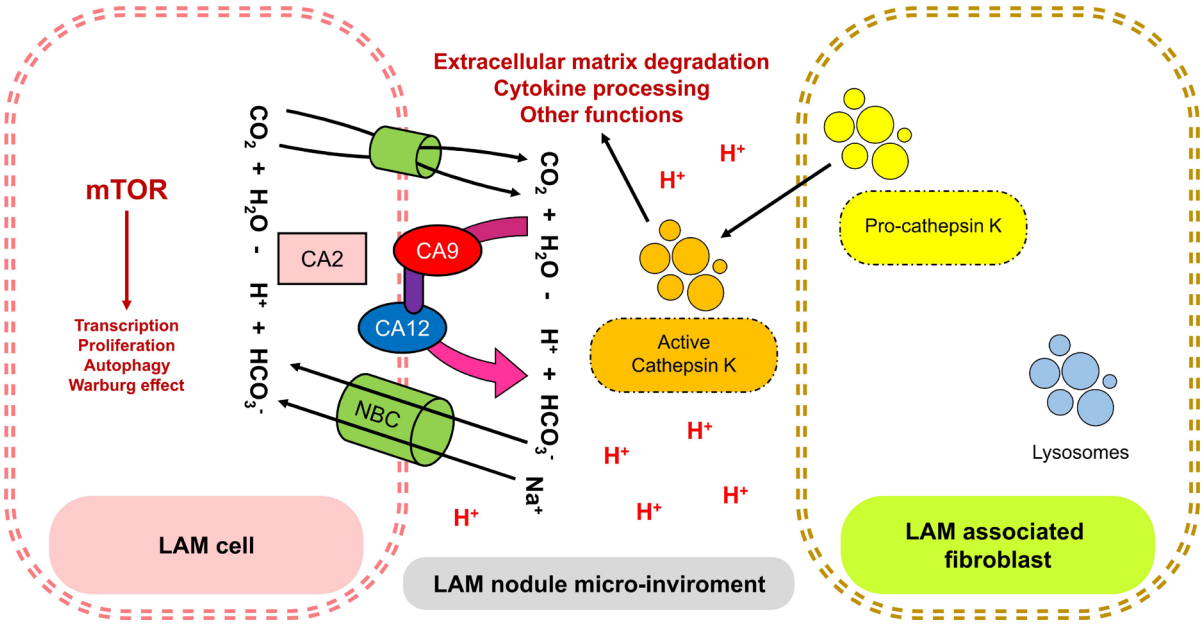

Figure 3 – The mechanism of Cathepsin K activation in LAM cells micro-environment.
Notes: Adapted from data in [63]. CA* — carbonic anhydrases (2, 9, 12 types); NBC — bicarbonate Sodium (Natrium) cotransporter.

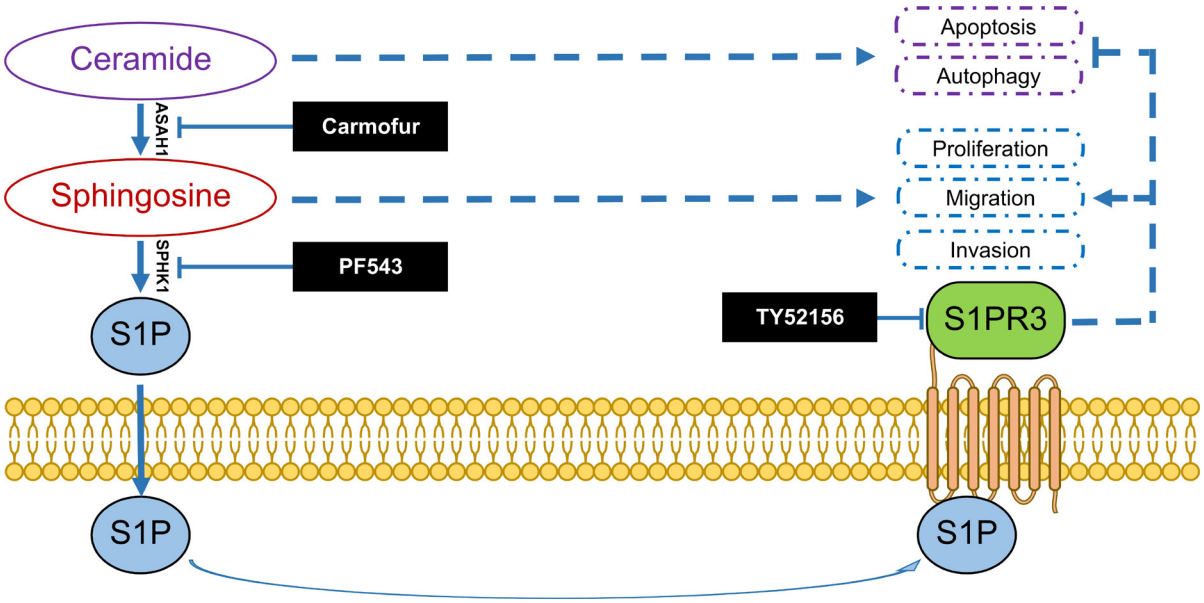

Figure 4 – Abnormal sphingolipid metabolism in LAM cells with potential targets for drug therapy.
Notes: Adapted from data in [65]. Explanations are in the text.

Another potential target for the LAM therapy is Galectin-3, a tumor growth factor, an elevated amount of which was found in LAM cells [67].

In June 2023, a great study of the cytostatic drug Sorafenib was published. It was carried out on a cell culture obtained from the human lungs affected by LAM and extirpated during the transplantation. The cells were cultured and then engrafted into the cell culture obtained from healthy lungs that mimicked the own lung tissue and a stromal component. As a result, the invasion of LAM cells and the effect of the specified cytostatic drug on this process were assessed. Finally, the invasion of LAM cells and the effect of the indicated cytostatic drug on this process were estimated. A pronounced inhibitory effect of Sorafenib on the invasion process was observed, which the authors associate with VEGF, transforming growth factor beta (TGFβ) signaling and the Wnt signaling pathway[3].

According to the recent study, the genes *IGF1*, *SERPINE1*, and *CXCL12* have been recognized as key links in the pathogenesis of the inflammatory response

[3] Koc-Gunel S., Gautam L.K., Calvert B.A. Sorafenib inhibits invasion of multicellular organoids that mimic Lymphangioleiomyomatosis nodules. Preprint. DOI: 10.1101/2023.06.12.544372

and intense LAM proliferation. The results of the research can form the basis for a new pathogenetic LAM therapy [68].

In addition, in the *in vitro* experiment on ELT3-V3-line cell cultures that had been obtained from Eker rat uterine leiomyoma and ELT3-T3-line cells, it was shown that in the LAM cells there was a violation of the expression of glutaredoxin-1. As a result, a cell apoptosis was inhibited, which provoked a tumor growth. The mechanism of the identified changes was described and it had been proven that it was not associated with mTOR. It is assumed that the use of the drugs that normalize the production of glutaredoxin-1 can create a new treatment approach to LAM [69].

Concluding the discussion of the LAM therapy, it is worth mentioning the survival trends of patients. Overall, based on the analysis of the outcomes of the LAM patients at Asian Medical Center (Seoul, Republic of Korea) from July 2001 to February 2020, and compared with the data from other studies, there is a trend towards an increase in the percentage of a ten-year survival of the patients: approximately 80% in 2000–2001, 86% in 2007, 90.9% in 2020 [70].

CONCLUSION

In the search for the treatment approaches to LAM, the researchers have traveled a truly thorny path from radical and even barbaric methods that cripple the body of an already ill person, to the methods based on a deep understanding of molecular biology and having a relatively more acceptable safety profile. However, all currently used methods of the drug therapy and the proposed new methods are aimed at only treating an already established disease, and an effective drug prevention of LAM now seems almost impossible due to the lack of a complete understanding about its pathogenesis and, more importantly, its etiology.

This issue is the most relevant in determining further prospects for the development of pharmacotherapeutic approaches to LAM.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Ilya V. Polovnikov — creation of the idea, work with the key aim and objectives, data collection, analysis and interpretation, writing the manuscript, preparing the article for the publication, collection and reworking of data visualization; Galina Y. Yukina — work with the key aim and objectives, data collection, analysis and interpretation, preparing the article for the publication, provision an access to the databases for analysis; Elena G. Sukhorukova — work with the key aim and objectives, data collection, analysis and interpretation, critical revision of the data visualization. All the authors have made equial and equivalent contributions to the preparation of the publication.

All the authors confirm that their authorship meets the international ICMJE criteria (all the authors have made a significant contribution to the development of the concept, research and preparation of the article, read and approved the final version before the publication).

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AUTHORS

Ilya V. Polovnikov – pulmonologist, senior laboratory assistant of the department of pathological anatomy with a pathology clinical department, Pavlov First Saint Petersburg State Medical University. ORCID ID: 0000-0002-8633-8496. E-mail: policrats@mail.ru

Galina Yu. Yukina – Candidate of sciences (Biology), associate professor, head of the scientific laboratory of pathomorphology of the scientific and clinical center of pathomorphology, Pavlov First Saint Petersburg State Medical University. ORCID ID: 0000-0001-8888-4135E-mail: pipson@inbox.ru

Elena G. Sukhorukova – Candidate of sciences (Medicine), senior researcher at the scientific laboratory of pathomorphology of the scientific and clinical center of pathomorphology, Pavlov First Saint Petersburg State Medical University. ORCID ID: 0000-0001-5521-7248. E-mail: len48@inbox.ru

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The current state of the problem of treatment adherence in patients with osteoporosis

A.M. Beitullaev[1], E.A. Egorova[1], A.V. Petrov[1], K.V. Bubley[1], A.V. Matveev[2], A.A. Bikbaev[3], A.G. Gevorkyan[3], T.K. Maltsev[3], M.N. Usamova[4]

[1] Order of the Red Banner of Labour Medical Institute named after S.I. Georgievsky of Crimean Federal University named after V.I. Vernadsky, 5/7 Lenin Blvd., Simferopol, Republic of Crimea, Russia, 295021
[2] Russian Medical Academy of Continuing Professional Education, 2/1 Barrikadnaya Str., Moscow, Russia, 125993
[3] Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University, 11 Kalinin Ave., Pyatigorsk, Russia, 357532
[4] Implant Studio, Limited Liability Company "Positive", 2A Kalinin Ave., Pyatigorsk, Russia, 357500

E-mail: asan25.2001@gmail.com

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Compliance with the recommendations of a health professional by patients with chronic diseases is observed only in 50% of cases, and therefore, the problem of compliance is very relevant. The widespread occurrence of osteoporosis (OP) in Russia and the world, as well as the existing problem of reducing patient compliance, requires an analysis of existing data on the level of treatment adherence in patients with OP.

The aim. To analyze the current state of adherence to therapy in patients with OP.

Materials and methods. The article provides an overview of the available publications on the mentioned objective. Various databases and search engines were used to search for research by Russian and foreign authors: elibrary.ru, CyberLeninka, Russian National Library (RNB), PubMed, Scientific&Scholarly Research Database (Scilit), Google Academy. The information was searched by keywords and phrases: "osteoporosis", "osteoporosis", "adherence to therapy/treatment", "adherence to treatment", "compliance", "compliance", as well as the corresponding MeSH terms.

Results. The current state of the OP problem has been studied, and the pharmacotherapy currently used in this pathology has been considered. The data on the compliance of patients with OP, the factors that negatively affect the adherence of patients, as well as the methods that contribute to the growth of this indicator, are analyzed, and the expediency of their use is demonstrated.

Conclusion. The problem of adherence to treatment of patients with OP is an important issue of modern healthcare. One of the most effective ways to improve compliance is to increase patients' awareness of the disease, its course, methods and expediency of pharmacotherapy. There is an urgent need to develop accessible and search for new methods to increase treatment adherence in patients with OP.

Keywords: osteoporosis; treatment commitment; compliance; patient awareness

Abbreviations: OP — osteoporosis; AR — adverse reaction.

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Современное состояние проблемы приверженности лечению пациентов с остеопорозом

А.М. Бейтуллаев[1], Е.А. Егорова[1], А.В. Петров[1], К.В. Бублей[1], А.В. Матвеев[2], А.А. Бикбаев[3], А.Г. Геворкян[3], Т.К. Мальцев[3], М.Н. Усамова[4]

[1] Ордена Трудового Красного Знамени Медицинский институт им. С.И. Георгиевского федерального государственного автономного образовательного учреждения высшего образования «Крымский федеральный университет им. В.И. Вернадского», Россия, 295021, Республика Крым, г. Симферополь, б-р Ленина, д. 5/7
[2] Федеральное государственное бюджетное образовательное учреждение дополнительного профессионального образования «Российская медицинская академия непрерывного профессионального образования» Министерства здравоохранения Российской Федерации, Россия, 125993, г. Москва, ул. Баррикадная, д. 2/1, стр. 1
[3] Пятигорский медико-фармацевтический институт – филиал федерального государственного бюджетного образовательного учреждения высшего образования «Волгоградский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Россия, 357532, г. Пятигорск, пр-кт Калинина, д. 11
[4] Имплант Студио, Общество с ограниченной ответственностью «Позитив», Россия, 357500, г. Пятигорск, пр. Калинина, д. 2А

E-mail: asan25.2001@gmail.com

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Соблюдение рекомендаций медицинского работника пациентами при хронических заболеваниях наблюдается лишь в 50% случаев, в связи с чем, проблема комплаентности является очень актуальной. Широкая распространённость остеопороза (ОП) в России и мире, а также существующая проблема снижения комплаентности пациентов требует проведения анализа существующих данных об уровне приверженности лечению у пациентов с ОП.

Цель. Провести анализ текущего состояния уровня приверженности терапии у пациентов с ОП.

Материалы и методы. В работе осуществлен обзор доступных публикаций по упомянутой тематике. Для поиска исследований российских и зарубежных авторов использовали различные базы данных и поисковые системы: elibrary.ru, КиберЛенинка, Российская национальная библиотека (РНБ), PubMed, Scientific&Scholarly Research Database (Scilit), Академия Google. Поиск информации проводился по ключевым словам и фразам: «остеопороз», «osteoporosis», «приверженность терапии/лечению», «adherence to treatment», «комплаентность», «compliance», а также соответствующим MeSH терминам.

Результаты. Изучено современное состояние проблемы ОП, рассмотрена фармакотерапия, применяющаяся в данное время при упомянутой патологии. Проанализированы данные о комплаентности пациентов с ОП, факторы, негативно влияющие на приверженность больных, а также методы, способствующие росту данного показателя, а также продемонстрирована целесообразность их применения.

Заключение. Проблема приверженности лечению пациентов с ОП является важным вопросом современного здравоохранения. Одним из наиболее эффективных способов улучшения комплаентности является повышение осведомлённости пациентов о заболевании, его течении, методах и целесообразности проводимой фармакотерапии. Существует острая необходимость в разработке доступных и поиске новых методов повышения приверженности лечению пациентов с ОП.

Ключевые слова: остеопороз; приверженность лечению; комплаентность; осведомлённость пациентов

Список сокращений: ОП — остеопороз; НР — нежелательная реакция; ЛП — лекарственный препарат.

INTRODUCTION

According to the International Classification of Diseases, Tenth Revision (ICD-10)[1], diseases of the musculoskeletal system include various syndromes and nosologicals caused by inflammatory and metabolic lesions of the musculoskeletal system. These pathologies have a significant negative impact on the working capacity of the population, the economy, and the mental health of society [2]. In the structure of morbidity of the adult population of Russia, pathologies of the musculoskeletal system occupy one of the leading places [3], as well as 3rd place in terms of overall

[1] International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Available from: https://icd.who.int/browse10/2019/en

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prevalence after diseases of the circulatory system and respiratory organs[2]. The increase in morbidity and disability among various age groups emphasizes the need for priority attention to methods of prevention and treatment of the above-mentioned pathology [4].

Osteopathies and chondropathies account for only about 2% of the total number of diseases of the musculoskeletal system [3]. This is quite explainable by the low level of diagnosis and the long latent course of the pathological process, which causes a delay in patients seeking medical help [1]. Osteoporosis (OP), being the most common metabolic bone disease [5, 6], is characterized by a decrease in bone mass and a violation of the microarchitecture of bone tissue, which increases the risk of fractures even with minimal trauma[3] [7]. This disease leads to millions of fractures worldwide every year, worsening the physical and psychological condition of patients, reducing the quality and shortening the duration of life [8, 9]. At the end of 2019, there were about 42 million patients with OP registered in the world, and by 2034 this number may exceed 200 million [10]. OP is a widespread disease in Russia [11–13], affecting about 14 million people, which is about 10% of the population [14]. While about 25% (34 million people) are at risk of osteoporotic fractures. Previously analyzed data, including the results of X-ray densitometry, show that 33.8% of women and 26.9% of men over 50 years of age in Moscow have signs of OP [15].

The risk group for the development of OP mainly includes elderly individuals. The reasons for the spread of OP among this category are related to changes in lifestyle and physiological changes in the body, as well as the development of inflammatory processes that negatively affect bone strength [5]. There are various factors causing the development of OP, including biological (gender, age, genetic predisposition), environmental, and behavioral (presence of bad habits, diet with insufficient calcium content, lack of physical activity) [16].

According to ICD-10 more than 20 forms of OP are distinguished, the most common of which is postmenopausal OP, caused by a decrease in estrogen levels [17]. Diagnosis of OP in postmenopausal women is based on the presence of a fragility fracture or low bone mineral density in the anamnesis, which is measured using densitometry [18]. After a hip fracture, many women lose the ability to move independently, and the risk of death within a year after the injury doubles [19]. Women are more susceptible to the development of OP due to a decrease in the level of progesterone and estrogen, which is observed in this category of patients from 40–45 years of age [20].

The chronic nature of the disease requires prolonged pharmacotherapy, which, in turn, increases the risk of adverse reactions (ARs) from medicines and may also reduce the level of adherence to treatment in patients.

"Compliance" is usually considered as adherence to the regimen and scheme of treatment prescribed by a doctor, while "adherence to therapy" is a characteristic of the patient's behavior during treatment and the correspondence of this behavior to the doctor's recommendations [21]. These concepts are close in meaning, so they can be considered synonymous [22]. According to the World Health Organization, adherence to a healthcare professional's recommendations by patients with chronic diseases is observed in only 50% of cases[4]. Poor adherence to therapy is a complex problem that requires a multidisciplinary approach, requiring the involvement of various specialists for positive recovery dynamics and support for the quality of life of patients [23].

The widespread prevalence of OP in Russia and worldwide, as well as the existing problem of reduced patient compliance, prompted the authors to analyze existing data on the level of adherence to treatment in patients with osteoporotic pathology.

THE AIM. To analyze the current status of adherence to treatment in patients with OP.

MATERIALS AND METHODS

A review of available publications on the mentioned topic was carried out. Each author independently selected literary sources, after which a joint decision was made on the inclusion of a scientific publication in the analysis. Various databases and search engines were used to search for studies by Russian and foreign authors: elibrary.ru, CyberLeninka, Russian National Library, PubMed, Scientific&Scholarly Research Database (Scilit), Google Scholar, while PubMed and CyberLeninka were used by the authors as priority sources of information, the rest of the listed ones were additional. The search period covered all mentions of keywords available in the databases, from January 1, 1886 to October 31, 2024.

[2] Healthcare in Russia. 2023: Federal State Statistics Service. Available from: https://rosstat.gov.ru/folder/210/document/13218

[3] WHO. Kanis JA, on behalf of the WHO Scientific Group. Assessment of osteoporosis at the primary health-care level. Technical Report. WHO Collaboraiting Centre, University of Sheffield, UK; 2008:288. Available from: https://frax.shef.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf

[4] WHO. Adherence to Long-term Therapies: Evidence for Action. World Health Organization;2003:198. Available from: https://doi.org/10.5144/0256-4947.2004.221

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The selection of publications on the review of drug therapy for OP was carried out using keywords and phrases: “osteoporosis,” “safety of pharmacotherapy,” “side effects,” “adverse reactions”; names of medicines and pharmacological groups used for OP (“bisphosphonates,” “denosumab,” etc.), as well as corresponding MeSH terms[5].

The search for information to carry out an analysis of the state of adherence to treatment in patients with OP was carried out using keywords and phrases: “osteoporosis,” “adherence to therapy/treatment,” “compliance,” as well as corresponding MeSH terms.

The process of selecting studies devoted to the problem of adherence to therapy in patients with OP is presented in Figure 1 and is based on the recommendations of the PRISMA system (Preferred Reporting Items for Systematic reviews and Meta-Analyses), 2020 [24].

The stage of identification of publications and pre-screening analysis implied the presence in the publication of several keywords on the topic, for example, “osteoporosis” and “adherence to treatment,” “side effects” and “bisphosphonates.”

The screening stage involved excluding publications from the sample that were published before 2020, thus, the data for the last 5 years were primarily reviewed. It should be noted that if a publication published before January 2020 contained data that, in the authors’ opinion, are of key importance for the analysis, then such work underwent screening.

The stage of analyzing the acceptability of selection criteria involved assessing the relevance of information in the publication on the topic. The assessment involved the analysis by several authors of controversial publications for inconsistencies in the narrative or insufficiently reliable information, assessing the level of citation of publications, which may be one of the criteria for reliability and relevance, after which a collective conclusion was made.

RESULTS AND DISCUSSION

Drug therapy for osteoporosis: efficacy and safety profile

The chronic course of OP requires long-term pharmacotherapy aimed to improve the quality of life and prolonging remission of the disease[6, 7].

In medical practice, several pharmacological groups of medicines are used that affect various mechanisms of regulation of bone homeostasis, such as monoclonal antibodies, bisphosphonates, calcitonin, and molecular action drugs. The main goal of pharmacotherapy is to conduct primary (prevention of the first fracture in patients from a high-risk group) and secondary (prevention of repeated fracture) prevention of bone deformation [19]. Bisphosphonates — synthetic analogs of pyrophosphate, an endogenous regulator of bone mineralization, are the main medicines in this case [25, 26]. They act on osteoclasts, disrupting their metabolism and adhesion of tumor cells to the bone matrix, which suppresses their migration, invasion, and angiogenesis. Medicines are often used to treat metabolic bone diseases, including bone loss caused by glucocorticoids and other hormonal medicines [27]. Bone resorption is suppressed at the maximum level approximately 3 months after the start of oral bisphosphonate therapy. This effect remains stable throughout the pharmacotherapy [27].

Despite the fact that this class of medicines demonstrates high efficacy in reducing the risk of fractures in OP [28], the use of bisphosphonates may be accompanied by frequent and serious ARs: osteonecrosis of the jaw, atrial fibrillation, atypical femoral fractures [29–31]. Parenteral administration of bisphosphonates can also cause side effects such as fever, increased fatigue, myalgia, headache [30]. In turn, the resulting ARs require additional safety control of pharmacotherapy.

Denosumab, which is included in the clinical guidelines for the treatment of various forms of OP, is currently one of the most frequently prescribed medicines, reducing the activity of osteoclasts and, unlike bisphosphonates, does not damage the intracellular structures of the osteoclast [32]. The medicine has high efficacy in the treatment of OP, in particular, positive treatment dynamics are observed in the lumbar spine, its use reduces the risk of fractures and reduces pain syndrome [33, 34], and promotes an increase in bone mineral density [35]. Safety data for denosumab are quite convincing even after many years of its use: rare ARs are observed, such as the development of erysipelas, eczema. Clinical manifestations of serious ARs are the risk of multiple fractures after discontinuation of the medicine [36].

[5] MeSH. Medical Subject Headings 2024 [Internet]. Available from: https://meshb.nlm.nih.gov
[6] Clinical Guidelines No. 87. Osteoporosis. Ministry of Health of the Russian Federation. Available from: https://cr.minzdrav.gov.ru/recomend/87_4
[7] Clinical Guidelines No. 614. Pathological fractures complicating osteoporosis. Ministry of Health of the Russian Federation. Available from: https://cr.minzdrav.gov.ru/recomend/614_2

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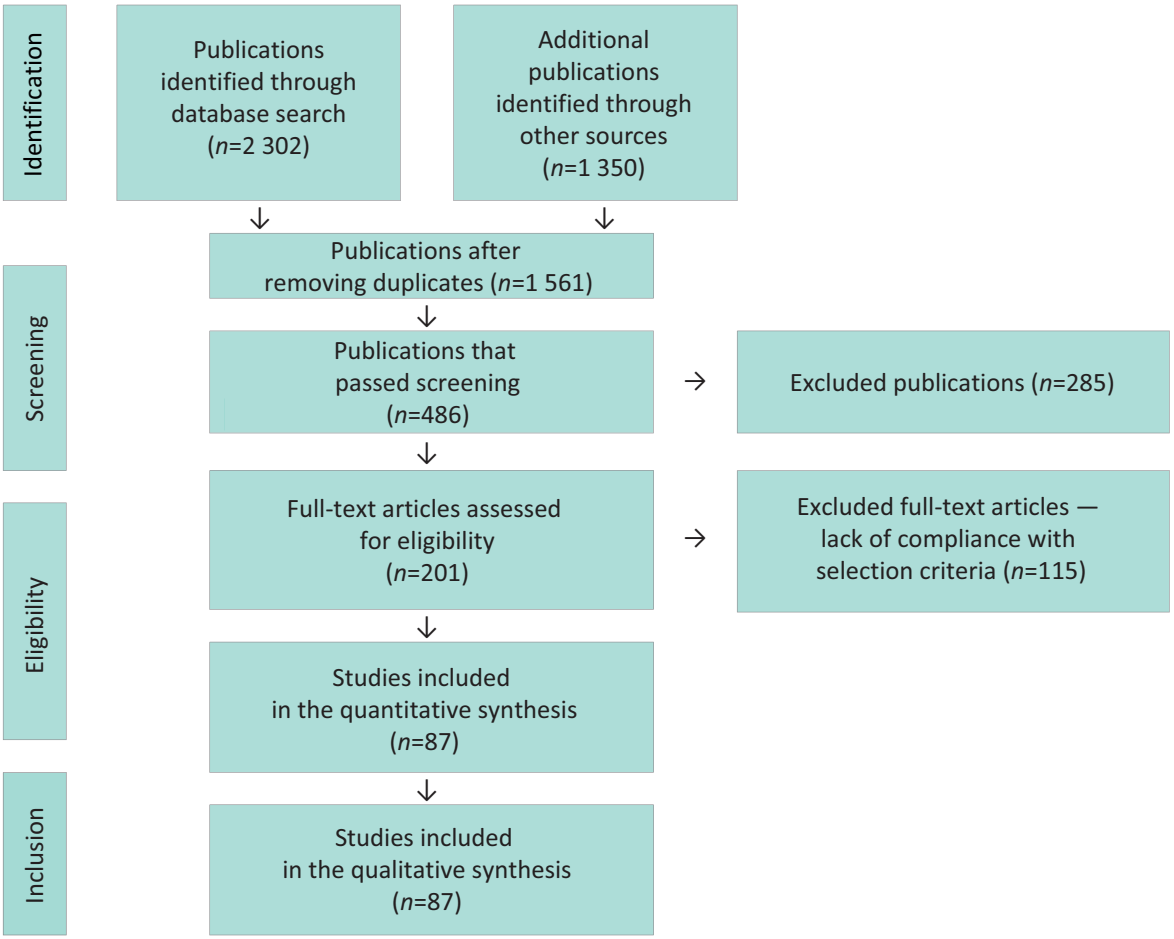

Figure 1 – Flowchart of source selection

Teriparatide remains the main medicine for the treatment of OP. It significantly reduces the risk of non-vertebral fractures, significantly stimulates bone formation, increases the mineral density of bone tissues in the lumbar spine and femoral neck in the long term [37]. The medicine is characterized by good tolerability [38] and a low frequency of severe ARs, which allows us to talk about its safe use in patients, including comorbid elderly patients [39]. Ars, caused be the medicine, are classified by researchers as non-serious, most often observed from the digestive and musculoskeletal systems [40]. The medicine can be used after the development of severe ARs, such as osteonecrosis of the jaw and atypical femoral fracture, against the background of the use of bisphosphonates as it is of the first line of treatment for OP [41]. Teriparatide may be an alternative pharmacotherapy option [42], and also demonstrates high rates of efficacy when combined with denosumab, providing an increase in bone mineral density and fracture prevention [34, 43].

Another medicine of choice in the treatment of OP is strontium ranelate. It is a first-line medicine in the treatment of postmenopausal OP in women, and can be safely used for a long time (up to 8 years) [44]. Reviews of studies evaluating pharmacotherapy for OP with strontium ranelate demonstrate an adequate level of efficacy [45], which is shown, first of all, due to the distinctive anti-resorptive and bone-forming effect on bone remodeling, which leads to an improvement in bone density indicators [46]. However, in the periodically updated safety report of the European Medicines Agency, there were described increased risks of developing myocardial infarction with the use of strontium ranelate, in connection with which a decision was made to limit its medical use[8], and in some countries the production of this medicine was discontinued due to concerns about its safety [47].

The combination of calcium and colecalciferol is an integral part of the pharmacotherapy of patients with OP. Increased calcium intake is required for primary and secondary prevention of OP, reducing the risk of hip fractures and maintaining bone mineral density [48]. Vitamin D deficiency can contribute to an increased risk of developing OP and its consequences, reducing the ability to physical activity in elderly people [49, 50]. Increased calcium intake is necessary

[8] PSUR assessment report. Strontium ranelate. EMA/PRAC/136656/2013. European medicines agency, 11 April 2013. Available from: https://www.ema.europa.eu/en/documents/variation-report/protelos-h-c-560-psu-0031-eparassessment-report-periodic-safety-update-report_en.pdf

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throughout the treatment of OP, which is achieved by increasing the amount of food with this trace element or using calcium medicines. The use of colecalciferol is recommended when its deficiency is established. The course begins with therapeutic doses with further transfer of the patient to preventive pharmacotherapy[9]. Thus, the use of a combination of calcium and vitamin D plays a key role in the prevention and treatment of various forms of OP, primarily by preventing fractures [51].

Continuous use of these medicines can lead to the development of various ARs in patients. As a rule, researchers describe ARs that can be classified as non-serious in terms of severity: flu-like syndrome, arthralgia, nausea, epigastric pain, constipation [52], fatigue, loss of appetite, metallic taste in the mouth [53]. At the same time, there are suspicions of a possible link between high calcium intake and an increased risk of developing cardiovascular diseases, such as stroke, myocardial infarction, while other researchers refute this assumption [54]. Nevertheless, some authors studying various methods of pharmacotherapy for OP emphasize that the efficacy and results of treatment depend on their use in combination with calcium and vitamin D preparations [32, 44].

The numerous data on ARs of medicines used for the treatment of OP found in the literature sources predetermine the need to study the problem of compliance of patients with OP, since the side effects of these medicines can affect adherence rates.

Adherence to treatment in patients with osteoporosis

Recently, awareness of the importance of adhering to the treatment regimen has increased, since a low level of compliance leads to consequences both for an individual patient (a decrease in the level of efficacy of pharmacotherapy, an increase in the level of morbidity and mortality) and for the healthcare system in whole, leading to an increase in financial costs [55]. There are three key stages of adherence to treatment: initiation of treatment (taking a new medicine), adherence (the degree to which the amount of medicine taken by the patient corresponds to the prescribed one), and discontinuation of therapy (termination of MP intake for any reason). At each of these stages, there are various factors that can affect patient compliance, both negatively and positively [56]. Non-compliance with the rules of medicine intake is a universal problem of a large number of diseases of a chronic nature, an additional problem is the difficulty of assessing the level of compliance, since there is inconsistency in the studied factors that determine the deviation of patients from the prescribed therapy and, as a result, their subsequent analyzes [57]. The most common methods of increasing the level of adherence to therapy are reducing the number of emerging ARs of medicines, simplifying the pharmacotherapy regimen, digitalization of healthcare, communication with the patient and conducting psychological consultations, however, it is additionally required to take into account the specifics of a particular disease and the characteristics of each patient [58].

The problem of adherence of patients with OP to treatment is relevant, there is a decrease in the compliance of patients over time after the fracture occurred. Only a third of patients continue to take calcium and vitamin D medicines for 3 or more years, and only half of them adhere to the medicine dosage regimen prescribed by the doctor [59]. The level of adherence in patients with OP, as in most people suffering from chronic diseases, is unstable: according to various estimates, in the first year of treatment it ranges from 34 to 75%, in subsequent years — from 18 to 75% [60]. Low adherence to treatment leads to a decrease in the increase in bone mineral density and less suppression of bone metabolism in patients with OP, which leads to a higher frequency of fractures, an increase in the number of hospitalizations and healthcare costs [60]. Healthcare professionals prescribing medicine therapy should take into account not only the characteristics of the patient, the course of the disease, but the patient's financial capabilities, which can also serve to reduce adherence to treatment. In the case of OP, factors that reduce the level of patient adherence to therapy are additionally the chronic nature of the disease, long-term pharmacotherapy, a large number of medicines prescribed simultaneously [61]. Doctors and healthcare professionals should focus on maintaining the persistence of patients, which is a fundamental factor in adherence to therapy [62], and also look for other ways to increase compliance.

Measuring adherence rates allows to analyze the profile of the use of medicines prescribed for OP, assess the presence of deviations between the prescription of medicines in medical practice and clinical guidelines outlined in the guidelines for doctors. Periodic monitoring of such indicators is an important tool for optimizing pharmacotherapy for OP and right allocation of healthcare resources [63]. Various questionnaires for patients are used to assess adherence to treatment. The most common for patients with OP are the Treatment Satisfaction Questionnaire for Medication (TSQM), the EuroQol-5 questionnaire, which assess the efficacy of the treatment, the side effects that occur, the convenience of using medicenes, the overall satisfaction of patients with the treatment, as well as their quality of life [64]. Researchers need to rationally use various methods of conducting the survey to obtain more reliable data. A modern approach to studying the level of compliance is the use of machine

[9] Clinical Guidelines No. 87. Osteoporosis. Ministry of Health of the Russian Federation.

learning models, such as ExtraTree, SMOTE-SVM, which are used to predict adherence to treatment in patients and, therefore, adjust pharmacotherapy [65].

The use of medicines with significant time intervals between doses, such as bisphosphonates, as a rule, allows you to increase compliance and achieve the necessary treatment results [66]. Special care and frequency of taking oral dosage forms of bisphosphonates, which is necessary due to the low bioavailability of medicines are a factor reducing compliance [67]. Medicines for more convenient use and increasing the level of adherence to therapy, are being developed with the most infrequent dosing frequency, for example, ibandronic acid at a dosage of 150 mg 1 time/month [68], and the results of studies show that the prescription of medicines in a monthly or weekly regimen leads to a significant increase in the number of patients adhering to the regimen, rather than with daily use. [69]. Other researchers note that patients receiving oral forms of medicines are less likely to adhere to the treatment regimen than patients receiving them by subcutaneous or intravenous administration [70]. Therefore, the choice of the route of administration of medicines is also an important factor for increasing compliance.

However, possible manifestations of ARs of bisphosphonates, in particular, serious side effects [29–31], are factors that force the patient to abandon the prescribed therapy [71]. A possible way to solve the problem of low compliance due to developing ARs may be a transition to safer medicines, for example, to denosumab, which can be used for a long time, without requiring breaks in treatment [72]. Teriparatide also demonstrates lower risks of developing ARs compared to oral bisphosphonates, indicating a favorable safety profile of the medicine [73].

In some cases, refusal of therapy is associated with the patient's fears due to the expectation of the development of possible ARs, even if they themselves have not encountered them — fear of side effects is one of the main reasons for stopping the prescribed treatment [74]. In a study by Roh et al. it is emphasized that the level of non-compliance with the treatment regimen in patients with insufficient awareness is significantly higher (47%) than in patients with sufficient information about OP and the pharmacotherapy used (29%) [75]. In this case, increasing the patient's awareness of the disease and methods of therapy can contribute to increased compliance [76], for example, through the "Patient School" [77]. Familiarizing the patient with the features of the medical interventions carried out by the attending physician is a multi-stage process, including research, collecting a history of life and further determining the health problem, its comprehensive assessment taking into account the level of influence of the pathology on the quality of life, drawing up a treatment plan, studying the degree of benefit of the patient's awareness for himself [78]. The use of methods to increase patient awareness allows to reduce the frequency of hospitalizations and disability rates, temporary loss of working capacity of the population [79], as well as improving the prognosis of the course of the disease and the quality of life of patients [80]. Participation of patients in the "School for Patients with Osteoporosis" contributes to increasing their awareness of the rules and duration of medicines' use, reducing the risk of developing ARs, which makes patients control the necessary level of vitamin D in the body, performing physical exercises, assessing an effective method of influencing the results of OP therapy [81]. Group consultations of patients, conducted for a long time, have a positive effect on achieving the goals of therapy: involving patients in the process of treatment, providing individual assessments of the risk of developing fractures (for example, using the FRAX®[10] algorithm system) and the ability to make decisions on pharmacotherapy independently can significantly increase patient compliance [82].

An additional factor that improves the level of adherence to therapy is the involvement of caregivers or relatives of patients in the treatment process, since they, as a rule, better perceive information from a healthcare professional, help patients solve problems of a technical nature (road to the hospital, purchase of medicines, search for training materials, etc.). Researchers report that in solitary patients the number of fractures in the 3rd year of observation is higher (6.2%) than in people who are helped by caregivers and relatives (1.1%) [83].

The results of the pharmacotherapy and the level of adherence to therapy can be influenced by other factors, for example, the excessive burden on the healthcare system like the period of the coronavirus infection pandemic. Healthcare professionals reported a reduction in the number of densitometric studies (this is evidenced by 50.6% of respondents), an increase in the number of remote consultations for both new (62.3%) and regular patients (81.7%), a lower quality of medical care provided for fracture prevention (51.7%), as well as interruption of the course of injectable bisphosphonate therapy (45.4%) and denosumab (6.3%) [84]. Delaying the use of denosumab may increase the risk of developing vertebral fractures; no such AR was found on bisphosphonate therapy, which can accumulate in patients for a long time, so patients could be transferred to alternative pharmacotherapy options. [85]. The International OP Foundation and the National OP Foundation also conducted a survey of medical and pharmaceutical workers and, in addition to the above factors, focused on the problem of medical supply disruptions causing difficulties in the selection of pharmacotherapy

[10] FRAX®. Fracture Risk Assessment Tool. Available from: https://frax.shef.ac.uk/FRAX/tool.aspx?lang=rs

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[86], which leads to a decrease in the efficacy of OP treatment. Coronavirus infection in patients with OP also leads to negative consequences both on the course of the underlying disease and on the therapy being carried out: the risks of hypercoagulation complications require cancellation or use with caution of raloxifene and estrogen, increasing the risk of thrombosis, metabolic disorders in bone tissue, observed in patients with OP, can exacerbate the course of coronavirus infection [87].

CONCLUSION

So, the problem of adherence to treatment in patients with OP is an important issue in modern healthcare. Compliance can be influenced by a number of factors, such as insufficient awareness of patients about the need for pharmacotherapy, ARs and the chronic nature of the disease. Low rates of adherence of patients to the prescribed therapy lead to aggravation of the course of OP, the occurrence of fractures, and a decrease in the quality of life of patients.

One of the most effective ways to improve compliance is to increase patients' awareness of the disease, its course, methods, and the need for pharmacotherapy. Healthcare professionals can provide this information to patients through the "Patient Schools." This method demonstrates high efficacy in improving the prognosis of the course of the disease, the quality of life of patients, reducing the level of complications of the disease (the need for hospitalization, the resulting loss of working capacity, disability). There is an urgent need to develop new accessible methods to improve adherence to treatment in patients with OP.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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AUTHORS

Asan M. Beitullaev — 2-year postgraduate student, assistant at the Department of Basic and Clinical Pharmacology of the Order of the Red Banner of Labour Medical Institute named after S.I. Georgievsky of Crimean Federal University named after V.I. Vernadsky. ORCID ID: 0000-0002-8059-7075. E-mail: asan25.2001@gmail.com

Elena A. Egorova – Candidate of Sciences (Pharmacy), Associate Professor of the Department of Basic and Clinical Pharmacology of the Order of the Red Banner of Labour Medical Institute named after S.I. Georgievsky of Crimean Federal University named after V.I. Vernadsky. ORCID ID: 0000-0003-4012-2523. E-mail: egorovapharm@mail.ru

Andrey V. Petrov – Doctor of Sciences (Medicine), Professor of the Department of Internal Medicine No. 2 of the Order of the Red Banner of Labour Medical Institute named after S.I. Georgievsky of Crimean Federal University named after V.I. Vernadsky. ORCID ID: 0000-0002-6398-2545. E-mail: petroff14@yandex.ru

Konstantin V. Bubley – 2-year resident, Assistant at the Department of Internal Medicine No. 2 of the Order of the Red Banner of Labour Medical Institute named after S.I. Georgievsky of Crimean Federal University named after V.I. Vernadsky. ORCID ID: 0000-0002-8960-602X. E-mail: bubley.99@mail.ru

Aleksander V. Matveev – Candidate of Sciences (Medicine), Associate Professor of the Department of Clinical Pharmacology and Therapy, Head of the Educational Center for Fundamental and Translational Medicine of the Russian Medical Academy of Continuing Professional Education. ORCID ID: 0000-0002-6636-3950. E-mail: avmcsmu@gmail.com

Aleksey A. Bikbaev – 6th year student at the Faculty of Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. ORCID ID: 0009-0001-8419-0766. E-mail: al.bikbaev@mail.ru

Artem G. Gevorkyan – 5th year student at the Faculty of Dentistry of the Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. ORCID ID: 0009-0003-2729-1872. E-mail: Artem1110690@yandex.ru

Tom K. Maltsev – 5th year student at the Faculty of Dentistry of the Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. ORCID ID: 0009-0008-6540-4272. E-mail: tom.maltsev.01@mail.ru

Maryam N. Usamova – dentist at Implant Studio (Positiv LLC), Pyatigorsk (Russia). ORCID ID: 0009-0008-0929-2376. E-mail: m.usamova@mail.ru

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Targeted therapy of bronchial asthma in children and adolescents: A narrative review

M.S. Matevosova[1], L.I. Agapitov[1], I.A. Averina[1, 2], I.V. Sokolova[2], S.V. Zotova[2], R.A. Chernigovsky[1, 2]

[1] Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University, 11 Kalinin Ave., Pyatigorsk, Russia, 357532

[2] Clinical Hospital No. 10 – branch of North Caucasus Federal Scientific and Clinical Center, 26 Lenin Str., Lermontov, Russia, 357341

E-mail: milalean2001@gmail.com

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The aim. To evaluate the results of clinical studies on the efficacy and safety of bronchial asthma (BA) therapy with genetically engineered biologicals (GEBP) in children and adolescents.

Materials and methods. For writing this review article, a search for full-text publications was conducted in the PubMed database. Studies on the efficacy and safety of biologicals — monoclonal antibodies, in the treatment of BA refractory to therapy with inhaled glucocorticosteroids and beta-2-agonists, in children and adolescents from 2010 to 2025 were analyzed using the following key queries"bronchial asthma", "monoclonal antibodies", "anti-IgE antibody", "anti-IL-receptor antibody", "anti-thymic stromal lymphopoietin antibody", "adolescents", "children".

Results. The observed continuing and steady increase in the incidence of BA, the involvement of several organ systems in the pathological process, the difficulty in choosing treatment tactics, the high cost of therapy, and the need to monitor the patient's condition place this disease in a special place among modern medical problems. To date, advances in genetic engineering have made it possible to introduce GEBPs — monoclonal antibody drugs, into medical practice as one of the steps in the treatment of poorly controlled and resistant to first-line therapy BA of moderate and severe severity. According to recent clinical studies among children and adolescents, biologicals to varying degrees can affect symptom control, lung function, frequency of exacerbations, requests for emergency medical care and hospitalizations, as well as reducing the dosages of glucocorticosteroids and beta-2-agonists used.

Conclusion. To date, positive results have been noted in the use of monoclonal antibodies in the treatment of BA, but clinical trial data among children and adolescents are limited. There is also insufficient information about the consequences of the mechanism of influence of these drugs in relation to long-term inhibition of the immune system and a decrease in the content of eosinophils in the blood serum in the developing child's body. To formulate a final conclusion, further study of the long-term efficacy and safety of biologicals in pediatric practice is necessary in order to combat this serious public threat.

Keywords: bronchial asthma; monoclonal antibodies; immunoglobulin E; interleukins; thymic stromal lymphopoietin; pediatrics

Abbreviations: BA — bronchial asthma; GEBP — genetically engineered biological products / biologicals; GCs — glucocorticosteroids; GINA — Global Initiative for Asthma; IgE — immunoglobulin E; FEV1 — forced expiratory volume in 1 second; IFN-α — interferon-alpha; IL — interleukin-4; TSLP — thymic stromal lymphopoietin.

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Таргетная терапия бронхиальной астмы у детей и подростков: описательный обзор

М.С. Матевосова[1], Л.И. Агапитов[1], И.А. Аверина[1,2], И.В. Соколова[2], С.В. Зотова[2], Р.А. Черниговский[1,2]

[1] Пятигорский медико-фармацевтический институт – филиал федерального государственного бюджетного образовательного учреждения высшего образования «Волгоградский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Россия, 357532, г. Пятигорск, пр-кт Калинина, д. 11

[2] Клиническая больница № 10 – филиал федерального государственного бюджетного учреждения «Северо-Кавказский федеральный научно-клинический центр Федерального медико-биологического агентства России», Россия, 357341, г. Лермонтов, ул. Ленина, д. 26

E-mail: milalean2001@gmail.com

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Цель. Провести оценку результатов клинических исследований, посвящённых изучению эффективности и безопасности терапии бронхиальной астмы (БА) генно-инженерными биологическими препаратами (ГИБП) у детей и подростков.

Материалы и методы. Для написания данной обзорной статьи был проведён поиск полнотекстовых публикаций в базе данных PubMed. Были проанализированы работы по изучению эффективности и безопасности применения биологических препаратов — моноклональных антител, в лечении БА, рефрактерной к терапии ингаляционными глюкокортикостероидами и бета-2-агонистами, у детей и подростков с 2010 по 2025 гг. с использованием следующих ключевых запросов: «bronchial asthma», «monoclonal antibodies», «anti-IgE antibody», «anti-IL-receptor antibody», «anti-thymic stromal lymphopoietin antibody», «adolescents», «children».

Результаты. Наблюдаемый продолжающийся и неуклонный рост заболеваемости БА, вовлечённость нескольких систем органов в патологический процесс, сложность выбора тактики лечения, высокая стоимость терапии и необходимость в мониторинге состояния пациента ставят рассматриваемое заболевание на особое место среди современных проблем медицины. На сегодняшний день достижения в области генной инженерии позволили внедрить в медицинскую практику ГИБП — препараты моноклональных антител, в качестве одной из ступеней лечения плохо контролируемой и резистентной к терапии препаратами первой линии БА средней и тяжёлой степени тяжести. По данным последних клинических исследований среди детей и подростков, биологические препараты в разной степени способны влиять на контроль симптомов, функцию лёгких, частоту обострений, обращений за неотложной медицинской помощью и госпитализаций, а также снижение дозировок применяемых глюкокортикостероидов и бета-2-агонистов.

Заключение. На сегодняшний день отмечаются положительные результаты применения моноклональных антител в терапии БА, однако данные клинических исследований среди детей и подростков ограничены. Также недостаточно информации о последствиях механизма действия данных препаратов в отношении длительного ингибирования иммунной системы и снижения содержания эозинофилов в сыворотке крови в развивающемся организме ребенка. Для формулирования окончательного вывода необходимо дальнейшее изучение долгосрочной эффективности и безопасности применения биологических препаратов в педиатрической практике в целях борьбы с этой серьезной общественной угрозой.

Ключевые слова: бронхиальная астма; моноклональные антитела; иммуноглобулин Е; интерлейкины; тимический стромальный лимфопоэтин; педиатрия

Список сокращений: БА — бронхиальная астма; ГИБП — генно-инженерные биологические препараты; ГКС — глюкокортикостероиды; GINA — Глобальная инициатива по борьбе с астмой; IgE — иммуноглобулин Е; ОФВ1 — объём форсированного выдоха за 1 секунду; ИФН-α — интерферон-альфа; ИЛ — интерлейкин-4; ТСЛП — тимический стромальный лимфопоэтин.

INTRODUCTION

Bronchial asthma (BA) is a heterogeneous disease characterized by chronic airways inflammation. Currently, BA is one of the most common pathologies among children and adolescents. The basis for the disease development is a hyperactive immune response of the body to the effects of specific environmental factors — causally significant triggers [1].

To date, the observed tendency of increasing asthma incidence is directly related to the level of urbanization and the environmental situation in the world [2]. Thus, according to epidemiological data,

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in 2019, the disease was observed in 262 million people [3]. In 2020, the Centers for Disease Control and Prevention published data on the prevalence of BA in the United States: the disease is noted in 25.25 million patients, of which 4.2 million are children. Already in 2021, there is an increase in the latter indicator — 4.68 million people. In Russia[1], as of 2022, 313 thousand children suffering from this pathology were registered[2]. According to the forecasts of the World Health Organization (WHO), there will be a further increase in the number of patients, and already in 2025 there will be more than 400 million people suffering from BA in the world [4].

The disease significantly reduces the quality of life of patients, having a negative impact not only on indicators of physical health, but also on daily activities: academic performance in school and additional sections, playing sports, interacting with peers, socialization in society, which is an important and integral stage in the life of every child [5, 6]. Undoubtfully, this affects the mental state of the growing organism, causing such symptoms as depressed mood, increased fatigue, and loss of strength. The connection between the disease and mental disorders in adulthood is under consideration, it finds its confirmation again in one of the recent studies: major depressive disorder, bipolar affective disorder, generalized anxiety disorder, panic disorder, specific phobias, as well as post-traumatic stress disorder, overeating and alcohol abuse are more common in patients suffering from BA than in the general population [7].

A significant number of patients (10% of patients according to the latest epidemiological data [8], of which 5% are children and adolescents [9]) have refractory asthma, the therapy with first-line drugs — high doses of inhaled glucocorticosteroids (GCs) and beta-2-agonists — does not lead to proper symptom control, which requires the search for new, more effective drugs [10]. In addition, the mechanism of action of GCs is characterized by its non-selectivity — hormonal drugs have a negative impact on many organs and tissues. Long-term use of this pharmacological group entails the development of a number of undesirable reactions and side effects, significantly reducing the quality of life of patients. Thus, studies among people taking GCs show an increased risk of complications from a number of organ systems: musculoskeletal (fractures, osteoporosis, myopathy), cardiovascular (arterial hypertension, heart failure, coronary heart disease, myocardial infarction), endocrine (obesity, diabetes mellitus, amenorrhea), digestive (gastric and duodenal ulcer). Vision organs complications are noted — glaucoma and cataracts. Growth retardation is most often observed in children. Acne appears on the skin, dryness and peeling are observed. Taking GCs is associated with the risk of developing mental disorders such as depression and anxiety. Cases of increased infectious diseases are also described, which is associated with the immunosuppressive effect of this group of drugs [11]. Daily intake of GCs in high doses contributes to the suppression of adrenal function according to the mechanism of negative feedback due to exogenous hormones in the body [12]. It was found that even short-term therapy can lead to the development of these adverse events [13]. Therapy with high doses of beta-2-agonists also demonstrates ambiguous results in a number of studies. To date, a conclusion has been formulated about the minimum effective dose of drugs for this pharmacological group in the treatment of BA in adults and adolescents, but it has not yet been determined in young children [14]. Moreover, taking this group of drugs can lead to side effects associated with a stimulating effect on the sympathetic nervous system, which is especially dangerous in patients of the age group under consideration.

Currently, International Clinical Guidelines for the treatment of asthma in children and adolescents consider the prescription of biologicals — monoclonal antibodies — depending on the phenotype of the disease, in order to achieve BA control that has not been achieved with drugs recommended in previous stages of treatment. The creation of genetically engineered biological products (GEBPs) is undoubtedly a revolutionary breakthrough and one of the main achievements of modern medicine. Their introduction into clinical practice has opened up new opportunities and made a major step forward in the treatment of many pathologicals. The mechanism of action of this pharmacological group lies in their interaction with specific molecules that are key links in pathogenesis, which prevents the development of pathology and improves the quality of life of patients.

THE AIM. To evaluate the results of clinical studies on the efficacy and safety of monoclonal antibody therapy for bronchial asthma in children and adolescents.

MATERIALS AND METHODS

The search of full-text publications was conducted in the PubMed database. Studies on the use of monoclonal antibodies in the treatment of BA refractory to therapy with inhaled GCs and beta-2-

[1] Most Recent Asthma Data. CDC. Available from: https://www.cdc.gov/asthma/most_recent_data.htm
[2] Russian Research Institute of Health. Available from: https://mednet.ru

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agonists in children and adolescents from 2010 to 2025 were analyzed using the following key queries: “bronchial asthma”, “monoclonal antibodies”, “anti-IgE antibody”, “anti-IL-receptor antibody”, “anti-thymic stromal lymphopoietin antibody”, “adolescents”, “children”. As a result, 1296 sources were found. Exclusion criteria were: non-full-text articles (*n*=21), as well as works that do not directly address the topic of the review (*n*=1 222). As a result, 53 scientific works were included in this review.

RESULTS AND DISCUSSION

Monoclonal antibodies to immunoglobulin E

In the International Clinical Guidelines of the Global Initiative for Asthma (GINA), children over 6 years of age with refractory moderate to severe BA, uncontrolled by high doses of inhaled GCs and long-acting beta-2-agonists, are recommended to take a humanized monoclonal antibody to immunoglobulin E (IgE) — omalizumab[3]. Omalizumab not only interacts with IgE, reducing their content in the blood serum, but also inhibits the binding of these molecules to high-affinity FCER1 receptors on mast cells, basophils and dendritic cells (Fig. 1.). Thus, the release of biologically active substances — inflammatory mediators — by the listed immunocompetent cells is prevented [15].

Nowadays, there are a number of scientific papers on the evaluation of the efficacy and safety of this drug in pediatric practice. In a study involving 38 children aged 7 to 16 years, 35 of whom (92.1%) completed it, children were injected with omalizumab subcutaneously at a dosage of 75 to 375 mg every 2 or 4 weeks. As a result, 29 patients (76.3%) had good BA control, based on the results of the Japanese pediatric BA Control Program Questionnaire [16].

After 6 months of treatment, according to the results of a study among children and adolescents with severe BA, a decrease in the number of exacerbations was recorded during omalizumab therapy compared to the previous year (1.03 and 7.2, respectively). After another year of observation, the number of exacerbations was 0.8. In addition, it was noted that the frequency of hospitalizations decreased by 96%. No adverse events were reported [17].

Omalizumab also demonstrated efficacy and safety in study involving 6 patients with moderate to severe BA aged 10 to 13 years. The drug was administered subcutaneously at a dosage of 150 to 600 mg every 2 or 4 weeks. Already after 16 weeks, an increase in the score in the Asthma Control test was registered by 55%, and one of the subjects had complete symptom control. In 3 patients, the dosage of inhaled GCs used decreased by 28.2%. The number of exacerbations decreased in 76.93% of participants, and no hospitalizations were observed [18].

According to the latest clinical observations, viral respiratory infections contribute to the exacerbation of BA symptoms. In studies, omalizumab has demonstrated an enhanced response of the non-specific immune system defense factor — interferon-alpha (IFN-α), which reduced the frequency of virus-induced respiratory infections, as well as their duration in children and adolescents with BA [19, 20].

However, despite the fact that omalizumab therapy has demonstrated high efficacy, and studies examining its safety have not found statistically significant differences in the incidence of adverse events among patients taking this monoclonal antibody and placebo (p <0.05) [21, 22], further research is needed to study the development of side effects, as well as the long-term effect of the drug in pediatric practice.

Monoclonal antibodies to interleukin-4 and interleukin-13

The GINA also consider the use of a humanized monoclonal antibody to the α-chain of the interleukin-4 (IL-4) receptor, capable of, among other things, inhibiting the activity of interleukin-13 (IL-13) — dupilumab, in children over 6 years of age with BA. IL-4, being a signaling molecule, activates T-helpers involved in the implementation of the inflammatory reaction, and IL-13 stimulates the synthesis of periostin by epithelial cells of the bronchi (Fig. 2). Periostin participates in the contraction of smooth muscles of the bronchi and hyperplasia of cells of endoepithelial glands [23]. Consequently, exposure to these targets prevents the development of bronchospasm and mucus hypersecretion, which makes it impossible to implement a hyperactive reaction of the upper respiratory tract in response to a specific allergen or other causative triggers [24].

To date, there are few studies on the efficacy of dupilumab, limited to adult and adolescents patients. According to the results of one such scientific work, 0.46 exacerbations per year were recorded in subjects older than 12 years who took the drug at a dosage of 200 mg every 2 weeks. Among patients who took placebo, this figure was 0.87 per year. Also, in the group of subjects taking dupilumab, an improvement in lung function was noted: the value of forced expiratory volume in 1 sec (FEV1) increased by 0.32 L. The drug showed

[3] Global Initiative for Asthma. Global strategy for asthma management and prevention. Available from: https://ginasthma.org/wp-content/uploads/2024/05/GINA-2024-Strategy-Report-24_05_22_WMS.pdf

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its effectiveness regardless of the initial content of eosinophils in the serum of studied participants [25]. The most common side effects of dupilumab were injection site reactions (pain, tissue swelling, hyperemia and itching), inflammation of the mucous membrane of the eyes, herpetic infection of the oral cavity, and joint pain [26]. In a study among patients with GCs-dependent BA, a decrease in the dosage of GCs used was recorded (70.1%) compared with the results in the placebo group (41.9%): 80% of individuals in the control group reduced the dosage by 50%, and 48% of subjects completely stopped taking hormone therapy [27].

It was also found that taking dupilumab helps to improve the quality of life in patients with concomitant allergic diseases. Thus, in patients with severe uncontrolled BA and concomitant allergic rhinitis, taking dupilumab at a dosage of 300 mg 2 times/week contributed to a significant improvement in symptoms [28]. Recent studies have revealed that taking dupilumab for concomitant atopic dermatitis contributes to a significant improvement in the clinical picture. The mechanism of alleviating the symptoms of concomitant atopic dermatitis with dupilumab is that systemic blockade of the α-chain of the IL-4 receptor helps to reduce the level of type 2 memory B cells — precursors of B-lymphocytes, and, consequently, IgE in the blood serum [29]. Thus, in one study among children aged 6 months to 5 years suffering from concomitant moderate to severe atopic dermatitis, relief of symptoms was observed as early as 16 weeks of the trial: improvement in the area of eczema and severity index by ≥75% [30]. Among patients with chronic rhinosinusitis with nasal polyps, taking dupilumab demonstrated an improvement in the quality of life of participants. During the survey of patients, there was a significant decrease in the severity of obstruction and discharge from the nose, impaired sense of smell, and a feeling of facial pressure [31]. There is a need for further evaluation of the effectiveness of this monoclonal antibody among children under 12 years of age.

Earlier studies have also been conducted on a drug capable of directly inhibiting IL-13 — lebrikizumab. This humanized monoclonal antibody demonstrated a significant improvement in the clinical picture, according to the results of a recent study among adolescents aged 12 to 17 years with refractory and uncontrolled BA. Over 52 weeks, 113 asthma exacerbations were observed: 31 cases in patients receiving lebrikizumab at a dosage of 125 and 37.5 mg, and 51 cases in participants from the placebo group. As a result, it was concluded that taking lebrikizumab at a dosage of 125 mg contributed to a 51% reduction in the frequency of exacerbations, and at a dosage of 37.5 mg — a 40% reduction. The number of patients with adverse events was the same in both groups of subjects [32]. However, in studies among adult patients, a significant number of subjects experienced adverse events (79%), serious adverse events (8%), and adverse events leading to drug withdrawal (3%). In addition, phase 3 clinical trials did not demonstrate a significant improvement in the clinical picture and a decrease in the frequency of BA exacerbations, even in the group of patients with higher levels of diagnostic markers, therefore, further work with this monoclonal antibody was no longer carried out [33].

Further study of the efficacy and safety of the drug from this group of monoclonal antibodies — tralokinumab — was also discontinued, as this GEBP did not have a significant effect on the frequency of BA exacerbations (only 44%) and improvement in lung function (12.2%) in patients with severe refractory BA compared with placebo [34]. To date, lebrikizumab and tralokinumab are not used in the treatment of BA in children and adolescents due to limited and inconsistent data on their efficacy and safety.

Monoclonal antibodies to interleukin-5

Interleukin-5 (IL-5) is a pro-inflammatory cytokine that promotes the activation and increased lifespan of eosinophils, which is one of the key links in the pathogenesis of BA. Studies on this group of monoclonal antibodies are limited to BA with eosinophilia, as this factor is considered to be prognostic [35]. The IL-5 inhibitor — reslizumab, as well as a humanized monoclonal antibody to the α-chain of the receptor of this signaling molecule — benralizumab, demonstrated mixed results in clinical studies among patients older than 12 years.

The use of reslizumab, according to the results of phase 3 studies among patients aged 12 years and older, contributed to a decrease in the annual frequency of BA exacerbations by 50–59% compared with placebo [36]. However, a number of trials have reported adverse events and side effects, including an increase in the content of the enzyme creatine phosphokinase in the blood serum [37], which confirms the need for further monitoring. Benralizumab was used among patients older than 12 years. During a phase 3 trial involving 728 people (866 patients received benralizumab, and 440 received placebo), it was concluded that the use of this monoclonal antibody led to a decrease in the frequency of exacerbations in the control group (*n*=221). The most common side effect was nasopharyngitis — 39% in the

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control group, 21% in the placebo group [38]. However, data on its safety among children and adolescents are limited. To date, in clinical practice, reslizumab and benralizumab are used in the treatment of BA in patients older than 18 years.

From the group of humanized monoclonal antibodies to IL-5 receptors, mepolizumab is the drug of choice for the treatment of BA in children older than 6 years. The mechanism of action is shown in Figure 3.

The study of phase 2 was conducted to evaluate the efficacy and safety of this humanized monoclonal antibody in 36 children with severe BA and eosinophilic airway inflammation. Mepolizumab was administered subcutaneously at a dose of 40 mg (for children weighing less than 40 kg) and 100 mg (for children weighing more than 40 kg) once every 4 weeks. On the 12 weeks, the content of eosinophils in serum and sputum in patients receiving the drug under consideration at a dosage of 40 mg was reduced by 89%, and in patients receiving a dosage of 100 mg, by 83% from the baseline level. More than one exacerbation of BA was observed in 10 patients, 4 of them were hospitalized, and 6 patients reported adverse events [39]. In 2024, the results of work on evaluating the effectiveness of this drug among 16 patients aged 7 to 17 years were published. During therapy with mepolizumab, 3 patients had oral GCs treatment canceled, and another 3 patients had their daily dosage reduced. A decrease in the level of eosinophils in the blood serum was also recorded (on average, by 0.85×109/L) [40]. Data from a study examining the risk/benefit ratio of mepolizumab have also recently been published — in most children, this indicator remained favorable for 10 years of therapy [41]. However, further research is needed to formulate a final conclusion regarding the efficacy and safety of mepolizumab among patients for this age group.

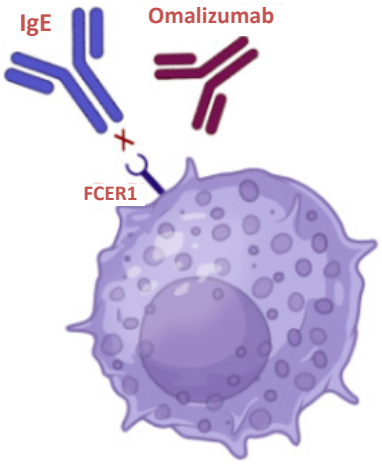

Figure 1 – Mechanism of action of omalizumab
Note: Drawn using the “BioRender” program.

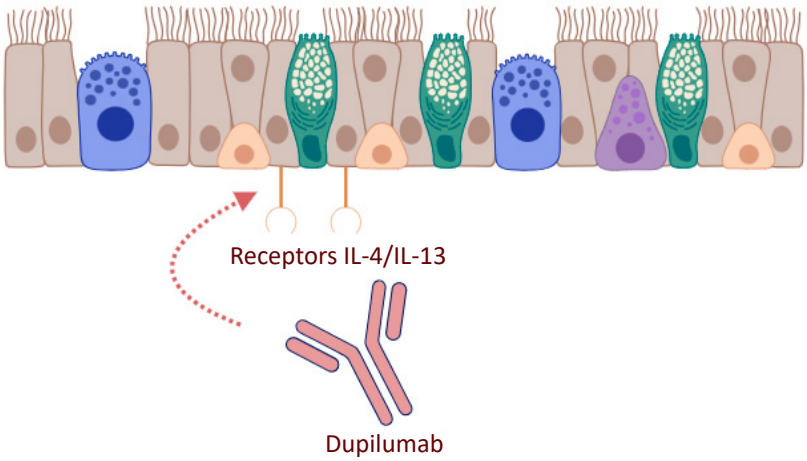

Figure 2 – Mechanism of action of dupilumab
Drawn using the “BioRender” program.

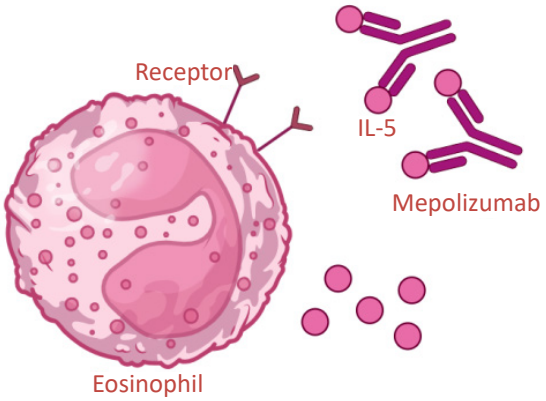

Figure 3 – Mechanism of action of mepolizumab
Note: Drawn using the “BioRender” program.

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Table 1 – Results of studies of monoclonal antibodies for the treatment of asthma in children and adolescents

Drug	Mechanism of action	Age of participants	Dose	Result	Reference
Omalizumab	Binds to IgE, reducing its content in the blood serum, inhibits the binding of IgE to FCER1 receptors on mast cells, basophils and dendritic cells.	From 7 to 16 years	75–375 mg every 2 or 4 weeks	Good BA control was recorded in 76.3% of patients. The frequency of hospitalizations decreased by 88%. Among the undesirable phenomena, infectious diseases of the upper respiratory tract were observed, but their frequency did not increase with prolonged use of the drug.	[16]
		From 6 years	75–375 mg every 2 or 4 weeks	After 6 months of treatment, a decrease in the number of exacerbations was noted compared to the previous year (1.03 and 7.2, respectively). After a year, the number of exacerbations was 0.8. The frequency of hospitalizations decreased by 96%. No adverse events were observed.	[17]
		From 10 to 13 years	150–600 mg every 2 or 4 weeks	After 16 weeks, an increase in the sum of points in the BA control test by 55% was recorded, one of the subjects had complete symptom control. In 50% of patients, the dosage of GCs used decreased by 28.2%. The number of exacerbations decreased in 76.93% of participants, no hospitalizations were observed.	[18]
Dupilumab	Binds to the α-chain of the IL-4 receptor, inhibits the activity of IL-13	From 12 years	200 mg every 2 weeks	0.46 exacerbations per year were recorded in subjects compared with the placebo group – 0.87 per year. The FEV1 indicator increased by 0.32 liters.	[25]
		From 6 to 11 years	200 mg every 2 weeks	Adverse events were observed: reactions at the injection site of the drug, inflammation of the conjunctiva, herpetic infection of the oral cavity, joint pain, increased levels of eosinophils in the blood serum.	[26]
		From 6 months to 5 years		After 16 week of testing, symptomatic relief was observed: improvement in eczema area and severity index by ≥75%.	[30]
Mepolizumab	Binds to the α-chain of the IL-5 receptor	From 6 to 11 years	40 mg (with body weight <40 kg) and 100 mg (with body weight >40 kg) 1 time every 4 weeks	At week 12, the content of eosinophils in the blood serum and sputum in patients taking the drug at a dosage of 40 mg was reduced by 89%, in patients receiving a dosage of 100 mg—by 83% of the initial level. More than one BA exacerbation was observed in 10 children out of 36, 4 of them were hospitalized, and adverse events were recorded in 6 patients.	[39]
		From 7 to 17 years	40 mg (with weight <40 kg) and 100 mg (with body weight >40 kg) 1 time every 4 weeks	3 out of 16 patients discontinued GCs treatment, and in another 3 patients, their daily dosage was reduced. The drug contributed to a decrease in the frequency of hospitalizations. A decrease in the content of eosinophils in the blood serum was recorded (on average by 0.85×109/L).	[40]
Tezepelumab	Binds to TSLP of the airways	From 12 years old	210 mg every 4 weeks	The exacerbation rate was 0.93 per year in the tezepelumab group and 2.1 in the placebo group. The FEV1 index at week 52 of the trial was 0.23 l in patients taking the drug and 0.09 l in patients taking placebo. The effect of therapy was recorded at 2 week of the study and tended to persist throughout the treatment period.	[47]
		From 12 years old	210 mg every 4 weeks	In 4 out of 65 participants, adverse events from the cardiovascular system (atrial fibrillation) were recorded, as well as the addition of viral and bacterial infectious diseases (gastroenteritis, tonsillitis, lung abscess). 39 patients experienced side effects, the most common of which was nasopharyngitis.	[48]

Note: BA — bronchial asthma; IL — interleukin; GCs — glucocorticosteroids; FEV1 — forced expiratory volume in 1 second; TSLP — thymic stromal lymphopoietin.

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Monoclonal antibodies to thymic stromal lymphopoietin

Updated International Clinical Guidelines also include the use of humanized monoclonal antibody thymic stromal lymphopoietin (TSLP), the main regulator of inflammatory processes of the respiratory tract — tezepelumab, in children over 12 years of age with severe refractory asthma. TSLP is a mediator synthesized in large quantities by epithelial cells of the respiratory tract when exposed to environmental factors [42]. It was found that basophils, dendritic and mast cells are also involved in the synthesis of this signaling molecule [43]. TSLP participates in the differentiation of T-helpers, and also promotes the activation of Janus kinase 1 and 2, which, in turn, transmit activating signals to a number of pro-inflammatory cytokines — IL-4, IL-5 and IL-13 [44]. Thus, inhibition of TSLP, a potential therapeutic target in severe asthma, by a monoclonal antibody prevents the production of these signaling molecules, thereby preventing the development of an inflammation [45].

Tezepelumab has shown its effectiveness in the treatment of refractory and uncontrolled BA among adult patients. Participants were divided into 4 groups: 145 patients used the drug at a dose of 70 mg every 4 weeks, 145 patients — at a dose of 210 mg every 4 weeks, 146 patients — 280 mg every 2 weeks, 148 patients made up the placebo group. As a result, a decrease in the frequency of exacerbations was observed for 52 weeks of the study — by 61, 71 and 66% in each group, respectively, in comparison with placebo. Indicators of external respiration also improved: the value of FEV1 before taking a bronchodilator was higher in all groups receiving tezepelumab than in the placebo group (the difference was 0.12, 0.11 and 0.15 L, respectively) [46]. According to the results of a recent study among patients aged 12 years and older to assess the effectiveness of the drug under consideration at a dosage of 210 mg, the frequency of BA exacerbations was 0.93 per year in the tezepelumab group and 2.1 in the placebo group. There was also an improvement in lung function: the FEV1 indicator at 52 weeks of the trial was 0.23 L in patients taking the drug and 0.09 L in patients taking placebo. This effect of therapy was recorded on the 2nd week of the study and tended to persist throughout the treatment period [47]. However, according to the results of clinical trials to assess the safety of this monoclonal antibody among 65 subjects, 4 had adverse events from the cardiovascular system (atrial fibrillation), as well as the addition of viral and bacterial infectious diseases, such as gastroenteritis, tonsillitis and lung abscess. 39 patients experienced side effects, the most common of which was nasopharyngitis [48]. These data confirm the need for further study of the efficacy and safety of this GEBP in children and adolescents.

Genetic Engineering is constantly evolving, developing new promising biologicals for more effective and safer therapy for severe treatment-resistant asthma. Currently, research is being conducted on the first inhaled humanized monoclonal antibody to TSLP — ecleralimab. The inhaled route of administration has several advantages over intravenous and subcutaneous injections — low probability of side effects due to non-systemic administration, the presence of an effect and a high rate of its achievement when administered in small doses, as well as ease of use and lack of trauma [49]. Ecleralimab has shown its effectiveness in a study among adult patients with BA: a decrease in sputum eosinophil content by 64% was observed as early as 7 h and by 52% 24 hours after exposure to the provoking factor [50].

In addition, the use of GIBPs therapy in the treatment of BA helps to improve the mental well-being of patients [51, 52]. Thus, one recent study found that patients responding to monoclonal antibody therapy experienced a reduction in symptoms and a decrease in the severity of major depressive and generalized anxiety disorders [53].

The summary of the results of clinical studies on the use of monoclonal antibodies for the treatment of BA in children and adolescents shown in Table 1.

CONCLUSION

Thus, the creation of GEBPs — monoclonal antibodies, has created new opportunities for the treatment of patients with refractory and uncontrolled BA. The use of monoclonal antibodies as targeted therapy contributes to proper symptom control, improved clinical picture, improved quality of life, as well as socialization and realization of their abilities in studies, creativity, sports, in many other areas of activity. It allows us to conclude that GEBPs have a positive impact not only on physical well-being, but also on the mental health of patients.

However, despite the fact that there are positive results of the usage of these drugs, an important question remains open about the consequences of prolonged inhibition of non-specific immune defense factors and a decrease in the content of eosinophils in the context of the developing immune system of the child's body. Unfortunately, the data from modern clinical trials and scientific research papers in this area are limited to adult patients, which does not allow us to formulate a final conclusion about the long-term effectiveness and safety of using monoclonal antibodies in pediatric practice today.

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AUTHORS

Milana S. Matevosova – student of the Faculty of Medicine of Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. ORCID ID: 0009-0002-0324-7933. E-mail: milalean2001@gmail.com

Leonid I. Agapitov – Doctor of Sciences (Medicine), Professor of the Department of Therapeutic Disciplines of Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. ORCID ID: 0000-0001-5562-6594. E-mail: lagapitov@rambler.ru

Irina A. Averina – Candidate of Sciences (Medicine), senior lecturer of the Department of Therapeutic Disciplines of Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University; Head of the Pediatric Department of Clinical Hospital No. 10 – branch of North Caucasus Federal Scientific and Clinical Center (Lermontov, Russia). ORCID ID: 0000-0002-8713-5017. E-mail: iradoc77@mail.ru

Irina V. Sokolova – Deputy Head of the Medical Department of Clinical Hospital No. 10 – branch of North Caucasus Federal Scientific and Clinical Center (Lermontov, Russia). ORCID ID: 0009-0001-9461-8199. E-mail: irina.sokir@yandex.ru

Svetlana V. Zotova – Head of the children's clinic of Clinical Hospital No. 10 – branch of North Caucasus Federal Scientific and Clinical Center (Lermontov, Russia). ORCID ID: 0009-0001-0905-1627. E-mail: zotovasv77@gmail.com

Roman A. Chernigovsky – teacher of the Department of Therapeutic Disciplines of Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University; Pediatrician of the pediatric department of Clinical Hospital No. 10 – branch of North Caucasus Federal Scientific and Clinical Center (Lermontov, Russia). ORCID ID: 0009-0003-3828-5670. E-mail: gjgjgj26gjgjgj@gmail.com

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