Научно-практический журнал
ФАРМАЦИЯ И ФАРМАКОЛОГИЯ

ОРИГИНАЛЬНАЯ СТАТЬЯ

DOI: 10.19163/2307-9266-2021-9-3-235-248

УДК 658.8+614.275

ECONOMIC ASPECTS OF APPLICATION OF THE RUSSIAN BIOSIMILAR OMALIZUMAB IN PATIENTS WITH ATOPIC BRONCHIAL ASTHMA OF MODERATE TO SEVERE CLINICAL COURSES

V.S. Krysanova[1,2,3], A.D. Ermolaeva[1,3], T.N. Ermolaeva[1], M.V. Davydovskaya[1,4], K.A. Kokushkin[1,3]

[1] Scientific and Practical Center for Clinical and Economic Analysis, the Ministry of Health of Moscow Region
4A, Karbyshev Str., Krasnogorsk, Moscow Reg., Russia, 143403
[2] Medical Institute of Continuing Education, Moscow State University of Food Production
11, Volokolamsk Hwy., Moscow, Russia, 125080
[3] Sechenov First Moscow State Medical University
8, Trubetskaya Str., Moscow, Russia, 119991
[4] Pirogov Russian National Research Medical University
1, Ostrovityanov Str., Moscow, Russia, 117997

E-mail: v.krysanova@mail.ru

Received 19 May 2021 Accepted 20 June 2021

A certain success in the treatment of bronchial asthma is associated with the introduction of monoclonal antibodies into the treatment process. They made it possible to improve the control of the disease. A number of original genetically engineered biological drugs, such as benralizumab, reslizumab, dupilumab, mepolizumab and omalizumab, are currently registered in Russia. In 2020, this list was supplemented by the first Russian biosimilar drug omalizumab – Genolar® (JSC Generium, Russia). High rates of the development of modern medicine are closely related to the use of biosimilars. The prescription of biosimilars today often makes it possible to provide a larger number of patients with modern drugs at lower costs.

The aim of the study was a comprehensive pharmacoeconomic assessment of the application of the domestic biosimilar drug omalizumab in the treatment of patients suffering from moderate and severe atopic bronchial asthma.

Materials and methods. At the first stage, an information search in the available databases (Cochrane Library, MedLine, Embase, eLIBRARY) was carried out. According to the results obtained, a meta-analysis (Agache I. et al.) was found out; within its framework, the efficacy and safety of the use of several monoclonal antibodies was assessed. Dupilumab was chosen as the reference drug. Pharmacoeconomic analyses were carried out using a "Cost-Minimization Analysis" (CMA) and a "Budget Impact Analysis" (BIA). Taking into account various options of bronchial asthma, the developed algorithm for providing medical care to adult patients with atopic asthma made it possible to assess the costs, including direct medical and indirect costs.

Results. The cost analysis demonstrated the advantage of using the Russian biosimilar omalizumab in patients with atopic asthma compared to dupilumab due to financial savings of up to 40%. The Budget Impact Analysis showed that the use of the domestic biosimilar omalizumab, even taking into account the annual increase in the number of patients (8%), will save up to 109,641,409.64 rubles (or 3%) compared to the current practice.

Conclusion. The use of the domestic biosimilar omalizumab in patients with moderate to severe atopic bronchial asthma is a clinically effective and economically justified approach to organizing medical care for adult patients in Russia.

Keywords: bronchial asthma; biosimilar; omalizumab; dupilumab; costs; pharmacoeconomic analysis

Abbreviations: BA – bronchial asthma; BIA – Budget Impact Analysis; IGCSs – inhaled glucocorticosteroids; OGCSs – oral glucocorticosteroids; GEBDs – genetically engineered biologic drugs; VEDs – vital and essential drugs; GETE – Global Evaluation of Treatment Effectiveness; CMA – cost minimization analysis; A – Ambulance / EMS – Emergency medical services; RICU – resuscitation and intensive care unit; ALV – artificial lung ventilation; CHI – compulsory health insurance; GDP – gross domestic product; VAT – value added tax; PSGs – Programme on State Guarantees; DRG – diagnostic related groups; IIC – input intensity coefficient; INN – international non-proprietary name; TN – tradename

For citation: V.S. Krysanova, A.D. Ermolaeva, T.N. Ermolaeva, M.V. Davydovskaya, K.A. Kokushkin. Economic aspects of application of the russian biosimilar omalizumab in patients with atopic bronchial asthma of moderate to severe clinical courses. *Pharmacy & Pharmacology.* 2021;9(3):235-248. **DOI:** 10.19163/2307-9266-2021-9-3-235-248

Для цитирования: В.С. Крысанова, А.Д. Ермолаева, Т.Н. Ермолаева, М.В. Давыдовская, К.А. Кокушкин. Экономические аспекты применения российского биоаналога омализумаба у пациентов с атопической бронхиальной астмой среднетяжелого и тяжелого течения. *Фармация и фармакология.* 2021;9(3):235-248. **DOI:** 10.19163/2307-9266-2021-9-3-235-248

RESEARCH ARTICLE

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

ЭКОНОМИЧЕСКИЕ АСПЕКТЫ ПРИМЕНЕНИЯ РОССИЙСКОГО БИОАНАЛОГА ОМАЛИЗУМАБА У ПАЦИЕНТОВ С АТОПИЧЕСКОЙ БРОНХИАЛЬНОЙ АСТМОЙ СРЕДНЕТЯЖЕЛОГО И ТЯЖЕЛОГО ТЕЧЕНИЯ

В.С. Крысанова[1,2,3], А.Д. Ермолаева[1,3], Т.Н. Ермолаева[1], М.В. Давыдовская[1,4], К.А. Кокушкин[1,3]

[1] Государственное бюджетное учреждение Московской области «Научно-практический центр клинико-экономического анализа Министерства здравоохранения Московской области»
143403, Россия, Московская область, г. Красногорск, ул. Карбышева, 4А
[2] Медицинский институт непрерывного образования Федеральное государственное бюджетное образовательное учреждение высшего образования «Московский государственный университет пищевых производств»
125080, Россия, г. Москва, Волоколамское шоссе, 11
[3] Федеральное государственное автономное образовательное учреждение высшего образования «Первый Московский государственный медицинский университет имени И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет)
119991, Россия, г. Москва, ул. Трубецкая, 8
[4] Федеральное государственное автономное образовательное учреждение высшего образования «Российский национальный исследовательский медицинский университет имени Н.И. Пирогова» Министерства здравоохранения Российской Федерации
117997, Россия, г. Москва, ул. Островитянова, д. 1

E-mail: v.krysanova@mail.ru

Получено 19.05.2021 Принята к печати 20.06.2021

Определённый успех в лечении бронхиальной астмы связан с внедрением в лечебный процесс моноклональных антител, которые позволили улучшить контроль заболевания. На территории России в настоящее время зарегистрирован целый ряд оригинальных генно-инженерных биологических препаратов, таких как бенрализумаб, реслизумаб, дупилумаб, меполизумаб и омализумаб. В 2020 году этот список пополнил первый российский биоаналог препарата омализумаб – Генолар® (АО «Генериум», Россия). Высокие темпы развития современной медицины тесно связаны с применением биоаналогов. Назначение биоаналогов сегодня зачастую дает возможность обеспечить большее количество пациентов современными препаратами за счет более низкой стоимости.

Цель. Проведение комплексной фармакоэкономической оценки применения отечественного биоаналогичного препарата омализумаба при лечении пациентов, страдающих атопической бронхиальной астмой среднетяжелого и тяжелого течения.

Материалы и методы. На первом этапе был проведен информационный поиск в доступных базах данных (Cochrane Library, MedLine, Embase, eLIBRARY), по результатам которого был обнаружен мета-анализ Agache I., с соавторами, 2020 г., в рамках которого проводилась оценка эффективности и безопасности применения нескольких моноклональных антител. В качестве препарата сравнения был выбран дупилумаб. Фармакоэкономический анализ проводился с применением метода «минимизации затрат» и анализа влияния на бюджет. Разработанный алгоритм оказания медицинской помощи взрослым пациентам с атопической бронхиальной астмой, учитывающий ее различные варианты, позволил провести оценку затрат, включающую прямые медицинские и непрямые затраты.

Результаты. Анализ затрат продемонстрировал преимущество применения российского биоаналога омализумаба у пациентов с атопической бронхиальной астмой по сравнению с дупилумабом в связи с экономией финансовых средств до 40%. Анализ влияния на бюджет показал, что применение отечественного биоаналога омализумаба даже с учетом ежегодного прироста числа пациентов (8%) позволит сэкономить до 109 641 409,64 руб. (или 3%) по сравнению с текущей практикой.

Заключение. Применение отечественного биоаналога омализумаба у пациентов с атопической бронхиальной астмой среднетяжелого и тяжелого течения является клинически эффективным и экономически выгодным подходом к организации медицинской помощи взрослым пациентам на территории России.

Ключевые слова: бронхиальная астма; биоаналог; омализумаб; дупилумаб; затраты; клинико-экономический анализ

Список сокращений: БА – бронхиальная астма; АВБ – анализ влияния на бюджет; иГКС – ингаляционные глюкокортикостероиды; пГКС – пероральные глюкокортикостероиды, ГИБП – генно-инженерные биологические препараты, ЖНВЛП – жизненно необходимые и важнейшие лекарственные препараты; GETE – глобальная оценка эффективности лечения (Global Evaluation of Treatment Effectiveness); СМА – анализ «минимизации затрат» (cost-minimization analysis); СМП – скорая медицинская помощь; ОРИТ – отделения реанимации и интенсивной терапии; ИВЛ – искусственная вентиляция легких; ОМС – обязательное медицинское страхование; ФФОМС – Федеральный фонд обязательного медицинского страхования; ВВП – валовый внутренний продукт; НДС – налог на добавленную стоимость; ПГГ – программа государственных гарантий; КСГ – клинико-статистические группы; КЗ – коэффициент затратоемкости; МНН – международное непатентованное наименование; ТН – торговое наименование

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DOI: 10.19163/2307-9266-2021-9-3-235-248

INTRODUCTION

Bronchial asthma (BA) is a serious medical and social problem that occurs in almost 262 million people [1]. Regardless of age, when treated insufficiently, patients with this disease are subject to various restrictions of daily life, a decrease in its quality, or even, in extreme cases, death[1]. Recently, there has been a higher increase in the prevalence of BA and the mortality rate from it in developing countries [2]. As evidenced by official statistics[2,3] and the results of epidemiological studies, an increase in the number of patients with this pathology is also typical of the domestic population [3–5].

A high prevalence, a long-term chronic course of the disease, the need for constant drug therapy – all these factors determine a high social significance of BA [6, 7]. Asthma is a significant socioeconomic burden for low- and middle-income countries [3]. The term "a socio-economic burden" refers not only to high costs of treatment (direct medical costs), but also to the costs associated with both temporary and permanent kinds of disability (direct non-medical costs), limitation of physical and social activities, and, as a consequence, a decrease in the quality of life of patients and their families (indirect costs) [8]. As defined by the World Health Organization, the global burden of disease is measured in terms of the number of years of life lost as a result of disability. This concept combines the years of life lost due to a state of health that does not meet the criteria for full health, and the years of life lost due to premature mortality [9].

According to the data published in 2019, among all diseases, BA was placed high in terms of the socio-economic burden: among the children aged 0 to 9 years (the 19th place); among the adults aged 50 to 74 years (the 28th place); in the group of 75 years and older (the 24th place). In the overall picture of the global burden of all the diseases, BA amounted to 0.85% of all life years lost as a result of disability (Disability Adjusted Life years, DALY) [10]. In 2019, the uncontrolled asthma caused the loss of 752 thousand years of quality-adjusted life years (QALYs) in the United States [11]. Medical expenses for the struggle against BA in the United States in the period from 2008 to 2013 only amounted to about 50.3 billion US dollars [12], in Greece in 2019 the economic losses due to BA amounted to 727 million euros [13].

Asthma is a common cause of absenteeism from school and work days. A retrospective analysis showed that in the United States, school-age children with BA are 1.54 times more likely to miss classes. That leads to a more frequent absenteeism on the part of their parents – they miss their work 1.16 times as often. This results in an annual loss of about 7 million school days [14]. This indicator also correlates with the severity of asthma. So in the work by Song H.J. et al. in 2020 [15] it was reported that for a year, 1 patient with mild, moderate and severe BA accounts for 0.76, 2.31 and 7.19 lost school and work days, respectively. In terms of indirect costs, it leads to additional expenses per person in the amount of 106, 321 and 1000 US dollars per year. A severe course of asthma deserves special attention, since in this case the focus should be not only on significant economic costs, but also on a significant decrease in the quality of life and an increase in the risk of death [16, 17]. For example, in Turkey, about 4.4 thousand US dollars is spent annually per patient with severe asthma [18]. A retrospective analysis for the period of June–November, 2016 in Spain showed that severe asthma results in an average loss of 9.1 working days per patient per year, while the average direct costs are about 7.5 thousand euros per patient per year. Taking into account indirect costs, the amount increases to 8.6 thousand euros per year [19].

According to American researchers, the socioeconomic burden of uncontrolled asthma in adolescents and adults over the next 20 years will be about US dollars 963.5 billion and 15.46 million lost QALYs [11]. It should be notified that all these are related to preventable losses, since they are associated with insufficient control of the disease.

A disease control is the most important criterion for the effectiveness of BA therapy; it implies a stable state with minimum symptoms of BA or their absence. That leads to a significant decrease in the likelihood of exacerbation and, accordingly, hospitalization, which reduces the burden of disease for both patients and the healthcare system. [20, 21].

Therefore, this problem is considered not only as a medical one, but also as an important problem of the organization and economics of the health care system of the Russian Federation [21]. In the general structure of the disease, about 5–10% [22] of patients can be attributed to suffering from severe BA. Such patients do not answer well the standard medical therapy or achieve control over the disease only with the use of inhaled glucocorticosteroids (IGCSs) in high doses and / or oral corticosteroids (OGCSs)[4]. As a rule, severe BA is associated with an increase in the frequency of using resources of

[1] Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021. Available from: http://www.ginasthma.org/.

[2] Aleksandrova G.A., Golubev N.A., Tyurina E.M., Oskov Yu.I., Shelepova E.A., Polikarpov A.V., Kadulina N.A., Belyaeva I.M., Gladkikh T E.E., Shcherbakova G.A., Semenova T.A. The incidence of the entire population of Russia in 2019 with a diagnosis established for the first time in life. Statistical materials. Part I. M .: Department of Monitoring, Analysis and Strategic Development of Health Care of the Ministry of Health of the Russian Federation, Federal State Budgetary Institution "Central Research Institute for Organization and Informatization of Health Care" of the Ministry of Health of the Russian Federation. 2020. Available from: https://mednet.ru/napravleniya/mediczinskaya-statistika. Russian

[3] Aleksandrova G.A., Golubev N.A., Tyurina E.M., Oskov Yu.I., Shelepova E.A., Polikarpov A.V., Kadulina N.A., Belyaeva I.M., Gladkikh T E.E., Shcherbakova G.A., Semenova T.A. The incidence of the entire population of Russia in 2019. Statistical materials. Part II. Moscow: Department of Monitoring, Analysis and Strategic Development of Health Care of the Ministry of Health of the Russian Federation, Federal State Budgetary Institution "Central Research Institute for Organization and Informatization of Health Care" of the Ministry of Health of the Russian Federation. 2020. Available from: https://mednet.ru/napravleniya/mediczinskaya-statistika. Russian

[4] Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021.

the health care system due to more frequent exacerbations and, accordingly, more frequent visits to medical institutions at various levels [23].

Progress in the treatment of severe asthma was achieved against the background of the introduction of monoclonal antibodies into the treatment process. The development of genetically engineered biological drugs (GEBDs) has made it possible to achieve disease control in the most difficult to treat group of patients [24].

A number of GEBDs, such as benralizumab, reslizumab, dupilumab, mepolizumab, and omalizumab, are currently registered in the Russian Federation [25]. The efficacy and safety of these drugs have been proven in numerous clinical studies; they are included in the list of vital and essential drugs (VEDs)[5] and federal clinical guidelines[6].

Given the significant pace of development, modern medicine is currently closely related to the use of biosimilars. Prescribing biosimilars today often makes it possible to provide more patients with vital and essential drugs at lower costs. The market analysis demonstrates the possibility to achieve significant budget savings after the release of biosimilar drugs [26]. The development and research of biosimilars in the Russian Federation are carried out in accordance with international requirements in order to prove their comparability in terms of quality, safety and efficacy to the original drug [27].

In 2020, a domestic biosimilar of the drug omalizumab, TN Genolar® (JSC Generium, Russia)[7], was registered in Russia. Its efficacy, safety and immunogenicity were demonstrated in a double-blind, parallel-group, randomized, phase III study conducted from June 2018 to December 2019 (NCT04607629 Clinicaltrials.gov Database). On the basis of 25 clinical centers, 191 patients took part in the study. They were randomized into 2 groups in the 2:1 ratio: the 1st (n = 127) was treated with TN Genolar® for 52 weeks ± 3 days; and the 2nd (n = 64) was treated with TN Xolar® for 26 weeks ± 3 days [28].

The main criterion for the effectiveness of therapy in this study was the proportion of patients with a research physician rating "excellent" or "good" on the scale of the Global Evaluation of Treatment Effectiveness (GETE) after 26 weeks of therapy. In both studied populations (PP (per protocol) and FAS (full analyzes set)), no statistically significant differences were found out (p> 0.05); according to the GETE scale, in the 1st group it was 57.4%, in the 2nd – 45.2% (p = 0.132). The calculated one-sided 95% confidence interval in order to test the statistical hypothesis of the research that the studied drug is "not worse" than the reference drug in the PP-population was –0.5–25.0% (p = 0.116) and –1, 1–24.2% (p = 0.134) – in the FAS population. The safety analysis showed the comparability of the analyzed drugs in terms of the incidence of adverse events. Based on the results of the detection frequency analysis of common antidrug antibodies to omalizumab, the absence of the antibody production in response to the administration of the studied drugs was shown.

Based on the results of the clinical study [28], it can be concluded that the drugs TNs Genolar® (JSC Generium, Russia) and Xolar® (Novartis Pharma AG, Switzerland) are clinically comparable in patients with moderate to severe atopic BA.

Thus, a high prevalence of asthma, as well as the difficulties associated with achieving control over the disease, a low adherence of patients to long-term multicomponent therapy necessitate the search for new ways to solve the problem of drug provision. However, a high cost of drugs demonstrates the importance of proper allocation of financial resources when choosing targeted BA therapy. The appearance of the first biosimilar omalizumab on the domestic pharmaceutical market will gradually increase the provision of patients with effective and modern drug therapy while saving financial resources of the Russian Federation healthcare system.

THE AIM of the study was a comprehensive pharmacoeconomic assessment of the application of the domestic biosimilar drug omalizumab in the treatment of patients suffering from moderate to severe atopic bronchial asthma (BA).

The research objectives were as follows:

1. conduct a search and analysis of scientific publications on the clinical efficacy and safety of omalizumab in atopic asthma in adult patients;
2. determine the population of patients suffering from atopic BA and requiring the prescription of immunobiological drugs, based on the published data on the incidence and prevalence of BA in the world and in Russia;
3. develop a scheme for providing care to adult patients with atopic asthma, taking into account the application of the analyzed approaches to drug therapy;
4. analyze direct and indirect costs of therapy for patients with atopic BA;
5. conduct a comparative clinical and economic analysis of the use of the analyzed drugs in patients with atopic BA;
6. analyze the impact of prescribing immunobiological drugs to patients with atopic BA, on the budget taking into account the current and simulated practice;
7. analyze the sensitivity of the results obtained to changes in the initial parameters.

The research hypothesis is the following: the application of the domestic biosimilar omalizumab in adult patients with atopic asthma is a clinically effective and economically justifiable strategy for organizing patient care in the Russian healthcare system.

[5] Order of the Government of the Russian Federation of October 12, 2019 No. 2406-r "On approval of the list of vital and essential drugs, as well as lists of drugs for medical use and the minimum range of drugs required for the provision of medical care" (as amended by Government orders RF from 26.04.2020 N 1142-r, from 12.10.2020 N 2626-r, from 23.11.2020 N 3073-r). Russian

[6] Clinical guidelines of the Ministry of Health of the Russian Federation. Bronchial asthma. Russian Respiratory Society. 2019. Available from: https://spulmo.ru/upload/kr_bronhastma_2019.pdf. Russian

[7] Instructions for the use of the medicinal product for medical use Genolar®. [Electronic resource]. Available from: http://grls.rosminzdrav.ru. Russian

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DOI: 10.19163/2307-9266-2021-9-3-235-248

MATERIALS AND METHODS

Study design

The pharmacoeconomic methods "Cost-Minimization Analysis" (CMA) and a "Budget Impact Analysis" (BIA) were used.

At the first stage of the study, an information search in the available databases (Cochrane Library, MedLine and Embase, Russian information and analytical system eLIBRARY) was carried out. That was the search for the data on the efficacy and safety of the application of various types of GEBDs as targeted therapy in patients with atopic BA.

According to the results obtained, a systematic review with a meta-analysis by Agache I. et al. 2020 [29] was found out. Within its framework, the efficacy and safety of the use of three genetically engineered biologic drugs – benralizumab, dupilumab, omalizumab – was assessed. Based on the hypothesis of the study, within the framework of this investigation, a comprehensive pharmacoeconomic assessment of the use of various GEBDs in this indication was carried out. The drug dupilumab was chosen as the reference drug, since in the published indirect comparative analysis by Bateman E.D. et al., 2020 [30], there was no statistically significant difference between omalizumab and dupilumab in terms of reducing the exacerbations frequency.

The "cost-minimization analysis" (CMA) is a special case of the "cost-efficacy analysis" in which two or more technologies that have identical efficacy and safety but different costs, are compared [31]. The "cost minimization" is calculated according to the formula:

$$CMD = Cost1 – Cost2,$$

where: CMD (cost-minimization difference) is a cost difference indicator, Cost1 and Cost2 are direct and indirect costs for the use of the 1st and 2nd technologies.

To assess the level of costs, in the course of the clinical and economic analysis, an algorithm for the provision of medical care to adult patients with atopic BA was developed. Since this form of asthma is characterized by frequent exacerbations, the resources of the health care system associated with their management, were assessed in the study. Their average annual frequency was calculated as the product of the frequency of exacerbations against the background of the absence of GEBDs therapy [32, 33] and the Incidence Rate Ratio (IRR), obtained on the basis of the meta-analysis by Agache I. et al., 2020 [29]. The tactics of management of exacerbations (the conditions for the provision of medical care) was determined on the basis of the previously published data [34, 35]. According to this algorithm, the provision of medical care to 1 adult patient with atopic BA was taken into account. The time horizon of the study was 1 year. The general research scheme is shown in Fig. 1.

Description of model assumption

1. Within the framework of the study, only patients with atopic asthma receiving one of the analyzed variants of GEBDs, were considered.

2. Outside of the exacerbation (a controlled course), patients with atopic BA receive basic therapy and GEBDs; to control the therapy course, they are observed by a doctor in an outpatient clinic.

3. In case of an exacerbation, a patient with atopic BA, in addition to the emergency medical care (EMC), can receive medical care in inpatient conditions, if necessary, with assistance in the conditions of the resuscitation intensive care unit (RICU) and artificial lung ventilation (ALV).

To conduct a pharmacoeconomic analysis, the position of "state" was chosen. In this regard, the analysis estimated direct medical costs paid from the budget funds and / or the funds from the compulsory health insurance (CHI) system and indirect costs.

Within the framework of the study, the costs of providing care to patients with atopic asthma included several types.

Direct medical costs are targeted drugs (GEBDs); basic drug therapy; monitoring therapy (outpatient supervision); ambulance / EMC; treatment of exacerbation in a day and round-the-clock hospital, assistance in RICU conditions.

Indirect costs are in the form of loss of gross domestic product (GDP) associated with premature mortality in patients with atopic asthma.

At the first stage, direct medical costs of GEBDs were determined, analyzed within the framework of this study. The dosage regimen of drugs was determined taking into account the official instructions for use[8,9,10], the costs of drug therapy were determined per 1 patient for one year. Based on the data of the Register of Patients with Severe Bronchial Asthma (as at December 31, 2020)[11], the average monthly doses of the analyzed drugs were determined: for omalizumab it was 383 mg, for dupilumab – 567 mg.

[8] Instructions for the use of the medicinal product for medical use Genolar®. [Electronic resource]. Available from: http://grls.rosminzdrav.ru. Russian

[9] Instructions for the use of a medicinal product for medical use Ksolar® [Electronic resource]. Available from: http://grls.rosminzdrav.ru. Russian

[10] Instructions for the use of a medicinal product for medical use Dupixent® [Electronic resource]. Available from: http://grls.rosminzdrav.ru. Russian

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ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

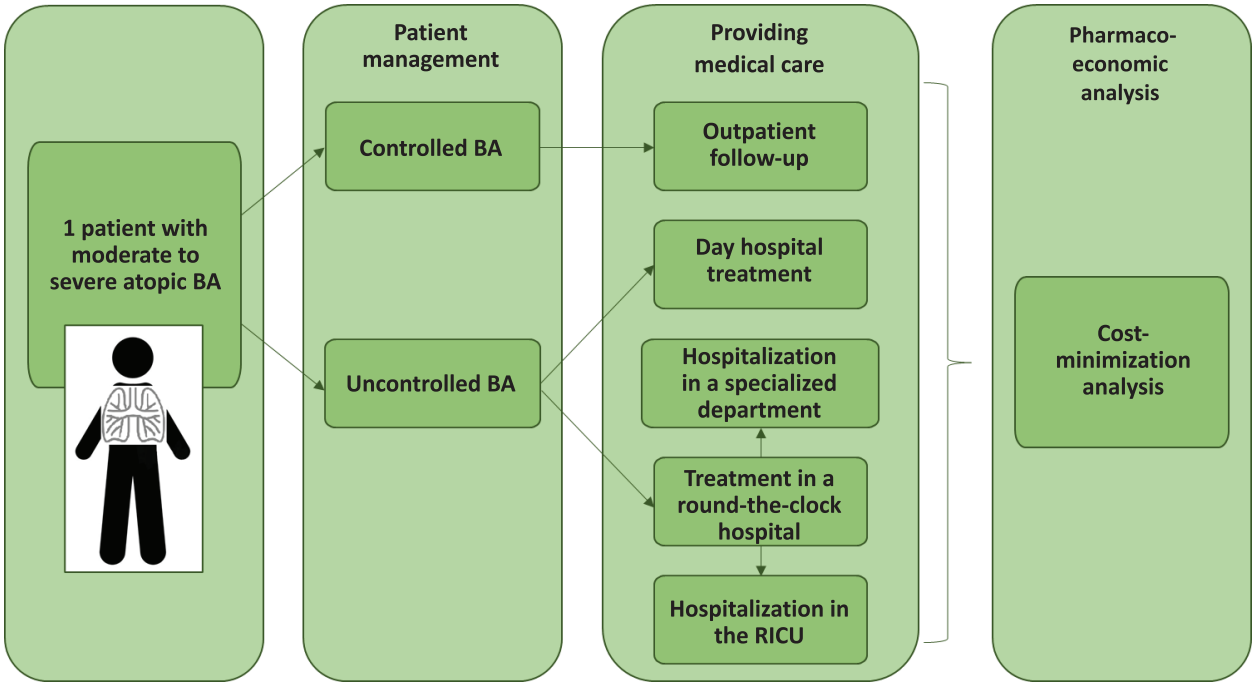

Figure 1 – General research scheme

Table 1 – Direct medical non-drug costs

Medical service	Cost, rub.	Reference source
Calling the ambulance brigade	2 713.40	Programme on State Guarantees, 2021
Disease treatment in the provision of medical care on an outpatient basis	1 505.10	Programme on State Guarantees, 2021
Basic rate for a round-the-clock hospital hospital	37 382.3	Programme on State Guarantees, 2021
Basic rate for a day hospital	22 261,5	Programme on State Guarantees, 2021
Bronchial asthma, adults (DRGs st23.005; IIC = 1.1)	26 971.33	Methodological recommendations on methods of paying for medical care at the expense of the compulsory health insurance fund, 2021
Diseases of the respiratory system (DRGs ds23.001; IIC = 0.9)	12 021.,21	Methodological recommendations on methods of paying for medical care at the expense of the compulsory health insurance fund, 2021
Influenza and pneumonia with organs dysfunction syndrome (DRGs st12.013; IIC = 4.4)	106 913.38	Methodological recommendations on methods of paying for medical care at the expense of the compulsory health insurance fund, 2021

Table 2 – Results of the indicators analysis of the effectiveness of the considered GEBDs per 1 patient suffering from atopic moderate to severe BA, within 1 year

Indicator	Dupilumab	Omalizumab
Weighted average frequency of exacerbations per year, number of cases	0.50	0.49
Hospitalization rate, number of cases	0.13	0.13
Frequency of hospitalizations in RICU, number of cases	0.005	0.005
Death rate, number of cases	0.00003	0.00003

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Table 3 – Results of the costs analysis of drug therapy with GEBDs per patient with atopic BA per year

INN	TN	Dosage form / dosage / packaging	Dosage regimen	Per month costs of therapy, rub.	Per year costs of therapy, rub.
Dupilumab	Dupixent	Solution for subcutaneous administration, 175 mg / ml, 1.14 ml (2)	Initial dose – 400 mg (2 injections of 200 mg), then – 200 mg every 2 weeks	80 534.19	966 410.34
		Solution for subcutaneous administration, 150 mg / ml, 2 ml – syringe with a needle protection system (2)	Initial dose – 600 mg (2 injections of 300 mg), then – 300 mg every 2 weeks		
Omalizumab	Genolar	Lyophilisate for preparation of a solution for subcutaneous administration, 150 mg (1)	From 75 to 600 mg, once every 2 or 4 weeks	46 586.37	559 036.47

Table 4 – Results of direct medical and indirect costs analysis for the management per patient with atopic BA per year

Indicator	Dupilumab	Omalizumab
Direct medical costs, rub.		
Costs for GEBDs therapy, rub.	966 410.34	559 036.47
Basic therapy costs, rub.	15 959.00	15 959.00
Costs for control over injections, rub.	18 061.20	18 061.20
Exacerbation costs without hospitalization, rub.	4 354.31	4 324.56
Exacerbation costs with hospitalization (excluding RICU), rub.	3 468.85	3 445.15
Exacerbation costs with hospitalization (including RICU), rub.	572.93	569.02
Costs for EMS, rub.	1 346.36	1 337.16
Total, rub.	1 010 172.99	602 732.56
Indirect costs, rub.		
Lost GDP resulting from premature deaths, rub.	59,50	59.10
Total, rub.	59,50	59.10
Total costs, rub.	1 010 232,49	602 791.65

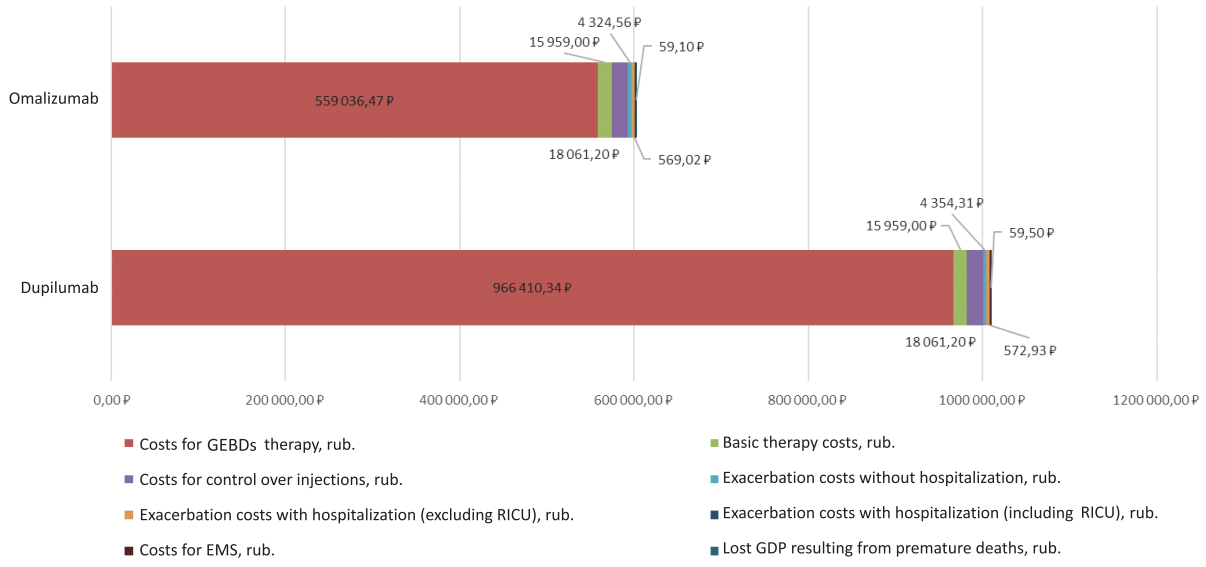

Figure 2 – Results of assessing costs for providing medical care per patient with atopic BA per year

Table 5 – Impact of different variants of GEBDs use in patients with atopic asthma on the budget: results of analysis

Indicator	Current practice	Share,%	Simulated practice 1	Share,%	Simulated practice 2	Share,%
			Omalizumab			
Medicinal product	TN Xolair®		TN Xolair®+TN Genolar®.		TN Genolar®.	
Number of patients, persons	5608	93%	6040	93%	6040	93%
Costs, rub.	3 783 840 662,93		3 858 091 061,99		3 640 861 581,16	
Medicinal product			Dupilumab			
Number of patients, persons	422	7%	455	7%	455	7%
Costs, rub.	426 318 110,36		459 655 782,50		459 655 782,50	

The analyzed medicinal products are included in the VED list. The cost of 1 package for them was calculated based on the price registered in the State Register of maximum selling prices[12], taking into account the weighted average size of the maximum wholesale markup approved in various regions of the Russian Federation (the population was also taken into account) and the added tax Cost (VAT)[13,14,15]. For pharmaceuticals in the Russian Federation, VAT is 10% (preferential taxation); the maximum wholesale markup is 11.39%.

Basic calculations were made on the basis of the following prices for medicines (excluding VAT and the maximum wholesale markup) for 1 package:

1. Omalizumab (Genolar®), lyophilisate for the preparation of a solution for a subcutaneous administration, 150 mg – 14,890.61 rubles;

2. Dupilumab (Dupixent®), solution for a subcutaneous administration, 150 mg/ml, 2 ml (2) – 69,552 rubles;

3. Dupilumab (Dupixent®), solution for a subcutaneous administration, 175 mg/ml, 1.14 ml (2) – 46,368 rubles.

Based on the determined cost of 1 package of the drug, the cost of 1 mg of the active substance was calculated to determine the costs of one-month therapy, taking into account the average monthly doses, then the costs of the annual course of therapy (12 months) was calculated.

The costs of basic therapy for a patient with atopic asthma were determined on the basis of the previously published studies [36]; they amounted to 15,959 rubles per patient per year.

Taking into account the form of release for GEBDs, the costs of monitoring therapy were also taken into account, since according to the instructions for medical use, this group of drugs should be administered under the supervision of medical personnel, however, for the drug dupilumab, the possibility of self-administration by the patients is provided.

It was assumed that for all the drugs under consideration, the frequency of visits for medical care in an outpatient setting should be once per month. The costs of monitoring therapy were calculated on the basis of the standard of financial costs for 1 treatment for a disease on an outpatient basis in accordance with the Programme on State Guarantees (PSGs) for the provision of free medical care to citizens for 2021[16].

At the next stage, the costs associated with the management of patients during the period of exacerbation of atopic asthma, were determined. In BA exacerbations, the study included the provision of several types of medical care: in the event of an exacerbation, the patient made an emergency call, after which he could undergo treatment either in a day hospital or in a round-the-clock hospital. When providing medical care in a round-the-clock hospital, if necessary, the patient received assistance in an RICU with artificial lung ventilation.

The costs for emergency medical care and inpatient treatment were determined on the basis of the standard of financial costs at the expense of the compulsory medical insurance funds according to the PSGs for the provision of free medical care to citizens for 2021. Herewith, the Methodological recommendations on methods of paying for medical care at the expense of the compulsory medical insurance funds[17] of the Federal

[12] State register of maximum selling prices of the Russian Federation. [Electronic resource]. Available from: http://grls.rosminzdrav.ru/PriceLims.aspx. Russian

[13] Information on the maximum tax of wholesale mark-ups and the maximum tax of retail mark-ups to prices for vital and essential medicines established in the constituent entities of the Russian Federation (data as of 19.02.2021). The site of the Federal Antimonopoly Service of Russia. [Electronic resource] Available from: https://fas.gov.ru/documents/687611. Russian

[14] Federal State Statistics Service. Estimated resident population as of January 1, 2021. Available from: https://www.gks.ru/folder/12781. Russian

[15] Tax Code of the Russian Federation (part two) of 08/05/2000 No. 117-FZ. Article 164. Tax rates. P. 2. Available from: http://www.consultant.ru/document/cons_doc_LAW_28165/35cc6698564adc4507baa31c9cfdbb4f2516d068/. Russian

[16] Decree of the Government of the Russian Federation of December 28, 2020 No. 2299 "On the program of state guarantees for free provision of medical care to citizens for 2021 and for the planning period of 2022 and 2023." [Electronic resource] Available from: http://government.ru/news/41272/. Russian

[17] Methodical recommendations on methods of payment for medical care at the expense of compulsory medical insurance funds. Minutes of the meeting in absentia of the members of the working group dated December 29, 2020 No. 06/11/8 [Electronic resource] Official website of the Federal Compulsory Medical Insurance Fund. Available from: http://www.ffoms.ru/. Russian

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Compulsory Medical Insurance Fund and Methodological recommendations of the Federal State Budgetary Institution "Centre of expertise and quality control of medical care" were taken into account[18]. It was assumed that the number of emergency calls was equal to the number of exacerbations of atopic asthma within 1 year. All cases of inpatient treatment were compared with the corresponding diagnostic related groups (DRGs), for which the input intensity coefficients (IIC) had been determined. All calculations for inpatient care (round-the-clock and day hospitals) were carried out according to the following formula:

$$AC = AS \times IIC \times CC,$$

where: AC is the average cost of a completed hospitalization case included in the DRGs in medical organizations (their structural units) providing medical care in inpatient conditions at the expense of compulsory medical insurance funds; AS is the average standard of financial costs for 1 case of hospitalization in medical organizations (their structural subdivisions) providing medical care in inpatient conditions at the expense of compulsory medical insurance; IIC is the input intensity coefficient of DRGs, to which the given case of hospitalization is attributed; CC is the correction coefficient reflecting a lower level of the base rate from the standard of financial costs established by the PSGs (for a day hospital it is 0.6, for a round-the-clock hospital – 0.65).

General characteristics of direct medical costs included in the analysis (excluding drug therapy) are presented in Table 1.

Indirect costs were calculated per patient per year. The lost state GDP due to the losses of premature mortality was calculated based on the probability of deaths in patients with exacerbations of atopic asthma who are on ALV, multiplied by the amount of the lost GDP per day, equal to 6208.23 rubles per day[19,20].

Based on the calculations carried out, the BIA was further carried out, which is a part of a comprehensive drugs assessment and is aimed at assessing the financial consequences of the use of certain drugs or medical devices[21].

Taking into account the fact that BA is a chronic disease that requires constant and long-term treatment, the time horizon for BIA was also 1 year. The main characteristics of the population in which the use of the analyzed medical technology (domestic biosimilar omalizumab) is expected, are as follows: patients aged 18 years and older suffering from moderate to severe atopic bronchial asthma, who are to be prescribed immunobiological drugs.

According to the Department of Health Monitoring, Analysis and Strategic Development of the Federal State Budgetary Institution "Central Research Institute for Organization and Informatization of Health Care" of the Russia Ministry of Health, the number of BA diagnoses determined for the first time in patient lives in 2019, amounted to 122,897 cases, or 83.7 cases per 100 thousand people. In 2019, the total number of asthma registered cases was 1,592,596 people. Among the general population of patients with asthma, about 68% have atopic asthma [37]; about 5–10% have a severe form (for modeling the population, it was assumed to be 8%) [38, 39], thus the number of patients with severe atopic asthma in the Russian Federation is about 86,637. According to the "Register of patients with severe bronchial asthma in the Russian Federation," about 8% of patients with severe asthma receive therapy with GEBDs [40, 41]. The proportion of the patients receiving GEBDs omalizumab and dupilumab (INNs) is about 87%, while the correlation between these drugs is 93% and 7%[22], respectively. Based on the analyzed data, it can be established that the population of patients with severe atopic asthma receiving therapy with GEBDs omalizumab and dupilumab (INNs) can be about 6,030 people.

At the final stage of the study, a sensitivity analysis was carried out. Its aim was to reveal the sensitivity of the study results to the changes in the initial parameters.

RESULTS AND DISCUSSION

In the review, it was revealed that so far there had been no direct comparative clinical studies for the analyzed drugs.

In the systematic review by Agache I. et al., 2020 [29], the efficacy and safety of treatment for severe al-

[18] Omelyanovskiy VV, Avksentyeva MV, Sura MV, et al. Guidelines for the comparative clinical and economic assessment of a medicinal product (new edition). Approved by order of the Federal State Budgetary Institution "CEKKMP" of the Ministry of Health of Russia dated December 29, 2018 No. 242-od. Moscow, 2018 46 p. Available from: https://rosmedex.ru/wp-content/uploads/2019/06/MRKE%60I_novaya-redaktsiya_2018-g..pdf. Russian

[19] Omelyanovskiy VV, Avksentyeva MV, Sura MV, et al. Methodological recommendations for calculating costs when conducting clinical and economic studies of drugs. Approved by order of the Federal State Budgetary Institution "CEKKMP" of the Ministry of Health of Russia dated December 29, 2017 No. 185-od. Moscow, 2017, 24 p. Available from: https://rosmedex.ru/wp-content/uploads/2018/02/Metodicheskie-rekomendatsii-po-raschetu-zatrat-pri-provedenii-kliniko-e%60konomicheskih-issledovaniy-lekarstvennyih-preparatov-2017.pdf. Russian

[20] On the approval of the Methodology for calculating economic losses from mortality, morbidity and disability of the population [Electronic resource] Order of the Ministry of Economic Development of Russia No. 192, Ministry of Health and Social Development of Russia No. 323n, Ministry of Finance of Russia No. 45n, Rosstat No. 113 dated 10.04.2012 (registered with the Ministry of Justice of Russia 28.04.2012 No. 23983). Available on the reference legal system "ConsultantPlus" Russian

[21] Omelyanovskiy VV, Avksentyeva MV, Sura MV, et al. Methodological recommendations for assessing the impact on the budget in the framework of the program of state guarantees of free provision of medical care to citizens.

[22] IPO "Russian Respiratory Society". Register of patients with severe bronchial asthma (as of 31.12.20). [Electronic resource] (materials provided by JSC "Generium"). Russian

lergic asthma with the use of benralizumab, dupilumab, and omalizumab have been considered. The review included 28 studies (3 randomized controlled clinical trials (RCCTs) on benralizumab, 1 RCCT on dupilumab, and 24 RCCTs on omalizumab) in the patients aged 12 to 75 years (excluding the patient population in the omalizumab studies, the age of patients in these studies was also 6–11 years old), receiving therapy for 12–56 weeks.

The exacerbation rates for dupilumab were assessed in 1 RCCT and for omalizumab in 6 RCCTs. It was shown that all the analyzed GEBDs reduce the frequency of exacerbations with a high reliability of evidence: for benralizumab, the incidence rate (IR) was 0.63 (95% CI 0.50–0.81), for dupilumab it was 0.58 (95% CI 0, 47–0.73), for omalizumab – 0.56 (95% CI 0.45–0.69). According to the results of a systematic review, the use of benralizumab, dupilumab and omalizumab leads to a statistically significant improvement in asthma control. At the same time, the use of omalizumab and benralizumab is associated with an improvement in the quality of patient life. It has also been shown that the use of omalizumab leads to a decrease in the required dose of IGCSs and OGCSs.

To carry out the "cost minimization" analysis, a selection of criteria for efficacy affecting the level of costs was carried out. For this study, the rate of exacerbation was chosen a criterion for efficacy affecting the overall level of costs and the use of resources of the health care system.

According to the RCCTs data of Hanania N.A. et al., 2011 [32], the frequency of exacerbations in patients with atopic asthma who do not receive GEBDs, is 0.88 per year; relative to this indicator, the number of exacerbations was determined against the background of omalizumab therapy, taking into account the data obtained in the meta-analysis carried out by Agache I. et al., 2020 [29].

According to the RCCTs data by Corren J. et al., 2019 [33], the frequency of exacerbations in patients with atopic asthma who do not receive GEBDs, is 0.736 in one group and 0.975 in the other group per year. Relative to these values, the average number of exacerbations was determined against the background of dupilumab therapy, taking into account the data obtained in the framework of meta-analysis by Agache I [29].

The number of hospitalizations was determined on the basis of the number of exacerbations, taking into account the frequency of hospitalizations equal to 27% [37], while about 4% of patients require hospitalization in the RICU. About 5% of all patients with BA exacerbation require tracheal intubation and ALV; in case of ALV, the lethality of patients can reach 9.8% [34]. The details are presented in Table 2.

The results of the costs analysis of drug therapy with the use of GEBDs per patient with atopic BA per year are presented in Table 3. The difference in the costs for drug therapy with GEBDs is 407,373.87 rubles, or 42% in favor of the domestic biosimilar omalizumab.

The lowest total costs are associated with the provision of medical care to patients with atopic BA when using the domestic biosimilar omalizumab (602, 791.65 rubles), the highest – when using dupilumab (1,010,232.49 rubles) (Table 4 and Fig. 2). At the same time, the difference in favor of the domestic biosimilar (TN Genolar®) was 407,440.84 rubles, or 40% per year per patient. For all analyzed GEBDs, the largest share in the structure of direct medical costs is accounted for the drugs themselves, the share of costs reaches a maximum of 96% (for dupilumab).

Thus, the costs analysis demonstrated the advantage of using the domestic biosimilar omalizumab in patients with atopic asthma compared to dupilumab, since its use is associated with the lowest costs per patient with moderate to severe atopic asthma per year. The difference was 40%.

As a part of the BIA, the approximate size of the target population was calculated (6030 people). However, the data obtained may not fully reflect the real picture of the number of patients with atopic asthma who need GEBDs therapy. There is still a cohort of patients who have comorbid conditions (i.e., atopic dermatitis, rhinosinusitis polyposa, or idiopathic urticarial) in which GEBDs are also required. In this regard, it is difficult to determine the exact size of the patient population.

To assess the level of costs within the framework of the analysis of real and simulated practice, the costs of treating patients with atopic asthma have been calculated. The results are presented in Table 5. Within the framework of the BIA, it was assumed that 2 options would be considered for the simulated practice. Currently, the main share of INN omalizumab is the original drug TN Xolar®. After the appearance of the biosimilar by TN Genolar® on the domestic pharmaceutical market, its application structure will undergo changes. Based on this assumption, several options were considered – the use of INN omalizumab preparations in a 1:1 ratio and the use of only the domestic biosimilar by TN of Genolar®. At the same time, taking into account the modeling horizon of 1 year, it was taken into consideration that the annual increase in patients would be about 8% according to official statistics, which would lead to an increase in the population to 6495 patients.

BIA demonstrated that the costs for the current practice of providing medical care to patients requiring therapy with the use of GEBDs by INNs omalizumab and dupilumab amounted to 4,210,158,773.29 rubles. For the 1st option (TN Xolar® + TN Genolar® 50/50) of the simulated practice, the costs amounted to 4,317,746,844.48 rubles, for the 2nd option (TN Genolar® 100%) – to 4,100,517,363.65 rubles. Thus, the BIA demonstrated that the use of the domestic biosimilar omalizumab, even taking into account the annual increase in the number of patients (by 8%), will save up to 109,641,409.64 rubles, or 3%, compared to the current practice.

To assess the stability of the model, the values of the efficacy criteria for omalizumab and dupilumab, the cost of drugs omalizumab and dupilumab, as well as the size of the target population, were changed in the directions of decreasing and increasing. The sensitivity analysis was carried out taking into account the fact that in real prac-

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DOI: 10.19163/2307-9266-2021-9-3-235-248

tice, the indicators of the therapy efficacy may differ due to the individual characteristics of the patient, the level of adherence to therapy, etc. The cost of drugs may also differ in different regions of the Russian Federation, because each region has its own level of wholesale markups. The sensitivity analysis demonstrated the robustness of the present model to changes in the initial parameters.

Thus, this study is the first experience in conducting a comprehensive pharmacoeconomic assessment of the use of the domestic biosimilar omalizumab in patients with moderate to severe atopic BA. A review of the domestic literature showed that several pharmacoeconomic studies have already been carried out on the application of the original drug omalizumab.

So in the work by Kolbin A.S. et al., 2016 [42], the issues of the omalizumab use in children with severe uncontrolled asthma were considered. However, in the course of the work, there was only a comparison with standard therapy; no comparison of several GEBDs was carried out. It was shown that, within a 5-year horizon of modeling, the use of omalizumab would lead to additional costs in the amount of 39,821 rubles per hospitalization averted [42]. The BIA demonstrated the comparability of the total costs for 100 children with BA, 7 of which would receive omalizumab, and for 105 children with BA without any use of targeted therapy. Prior to this, in the work by Kolbin AS et al., 2015 [43], similar aspects of the use of omalizumab in relation to adult patients were considered.

In another work by Kulikov A.Yu. et al., 2018 [44], a comparative assessment of the use of several targeted drugs, omalizumab and reslizumab, was carried out. The results of the work showed that in the treatment of severe bronchial asthma with eosinophilic type of inflammation, the use of reslizumab is more cost-effective, while the study used a "cost-effectiveness" analysis. In the work by Tolkushin A.G. et al., 2019 [45], the pharmacoeconomic analysis was carried out from the position that there was no statistically significant difference in efficacy and safety between the drugs omalizumab and mepolizumab. The total direct medical costs for mepolizumab were 870 130 rubles, and for omalizumab – 1 852 063 rubles. The obtained differences in the annual costs of therapy with omalizumab in comparison with the results in the present work, can be justified by different approaches to modeling and taking into account the cost of the original drug, in calculating. The comparison of the results obtained with the annual costs of mepolizumab therapy manifests financial savings in favor of the domestic biosimilar omalizumab. A comparative pharmacoeconomic analysis conducted by Zyryanov S.K. et al., 2019 [46] already included, in addition to omalizumab and mepolizumab, reslizumab for the treatment of patients with uncontrolled atopic moderate to severe BA. The analysis demonstrated the cost-effectiveness of omalizumab compared to other drugs included in the study.

In the course of a few interesting studies, a comparative pharmacoeconomic evaluation of the application of omalizumab and dupilumab was carried out [35, 47], in the framework of which the economic advantage of using dupilumab in patients with severe asthma was demonstrated. So, in the publication by Salasyuk A.S. et al., 2019 [37], the results of their own indirect comparative analysis of the omalizumab and dupilumab effectiveness were presented, during which differences were shown in relation to the incidence of exacerbations. The hypothesis of this study was based on the indirect comparative analysis by Bateman E.D. et al., 2020 [30]. The emergence of newer information regarding a comparative efficacy, as well as the entry into the domestic pharmaceutical market of biosimilars, prompted a new study. In the course of this work, the calculations of the authors' own on the frequency of exacerbations based on the data of reliable randomized controlled clinical trials and a meta-analysis by Agache I. et al., 2020 [29], have been presented.

Thus, at present, a large amount of data on various economic aspects of the use of GEBDs in domestic conditions has been accumulated. Within the framework of all the studied publications, the issues of the original drugs use have been considered. At the same time, the use of various approaches to modeling and the choice of information sources for calculations have led to some heterogeneity of the data. In the course of the present work, the issues of using the domestic biosimilar omalizumab have been considered. Using these GEBDs will make it possible to reduce the average annual cost of BA therapy.

CONCLUSION

Based on the results of the conducted pharmacoeconomic analysis, it was found out that the use of the domestic biosimilar omalizumab in patients with moderate to severe atopic BA is a clinically effective and economically justified approach to organizing medical care for adult patients in the Russian Federation.

FUNDING

The research was carried out with the support of JSC "Generium", Russia. The sponsor had no influence on the choice of material for publication, analysis and interpretation of the data.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHORS' CONTRIBUTION

Vera S. Krysanova – concept development and study design, analysis and interpretation of the research results, text writing; Alina D. Ermolaeva – material collecting and processing; Tatyana N. Ermolaeva – development of the research concept; Maria V. Davydovskaya – scientific consulting; Konstantin A. Kokushkin – scientific consulting.

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AUTHORS

Vera S. Krysanova – Researcher of the Department of Clinical and Economic Analysis of "Scientific and Practical Center for Clinical and Economic Analysis of the Ministry of Health of Moscow Region"; post-graduate student of the Department of Clinical Pharmacology and Propedeutics of Internal Diseases, Institute of Clinical Medicine n.a. N.V. Sklifosovsky, Research Institute of Higher Education "First Moscow State Medical University n. a. I. M. Sechenov"; Lecturer at the Department of Therapy with a course in Pharmacology and Pharmacy, Medical Institute of Continuing Education, Moscow State University of Food Production. ORCID ID: 0000-0002- 0547-2088. E-mail: v.krysanova@mail.ru

Alina D. Ermolaeva – Candidate of Sciences (Pharmacy), Senior Researcher of the Department for Monitoring and Analysis of Medicinal Supply, Scientific and Practical Center for Clinical and Economic Analysis of the Ministry of Health of Moscow Region, Assistant of the Department of Organization and Economics of Pharmacy at the Institute of Pharmacy n. a. A.P. Nelyubin, Sechenov First Moscow State Medical University. ORCID ID: 0000-0001-9082-1010. E-mail: aluska.ru@mail.ru

Tatyana N. Ermolaeva – Head of the Department of Clinical and Economic Analysis of Scientific and Practical Center for Clinical and Economic Analysis of the Ministry of Health of the Moscow Region. ORCID ID: 0000-0002-3615- 0292. E-mail: ermolaeva_mzmo@mail.ru

Maria V. Davydovskaya – Doctor of Sciences (Medicine), Deputy Director for Research, Scientific and Practical Center for Clinical and Economic Analysis of the Ministry of Health of Moscow Region"; Professor of the Department of Neurology, Neurosurgery and Medical Genetics, Russian National Research Medical University n. a. N.I. Pirogov. ORCID ID: 0000-0002-8294-0893. E-mail: mdavydovskaya@gmail.com

Konstantin A. Kokushkin – Director of the Scientific and Practical Center for Clinical and Economic Analysis of the Ministry of Health of the Moscow Region; Applicant for the Department of Clinical Pharmacology and Propedeutics of Internal Diseases, Institute of Clinical Medicine n.a. N.V. Sklifosovsky, First Moscow State Medical University n. a. I. M. Sechenov. ORCID ID: 0000-0002-6758-2389. E-mail: kokushkinka@gmail.com