DOI: https://doi.org/10.36691/RJA1497

Pharmacoeconomic analysis of bronchial asthma prophylaxis in adults and children with allergic rhinitis by means of sublingual allergen-specific immunotherapy

V.A. Lemeshco[1], S.S. Ratushnak[2], F.V. Gorkavenko[2], E.V. Nazarova[3], N.I. Ilina[3], V.V. Omelyanovskiy[1, 2, 4]

[1] Russian Medical Academy of Continuous Professional Education, Moscow, Russian Federation
[2] The Center for Healthcare Quality Assessment and Control, Moscow, Russian Federation
[3] National Research Center- Institute of Immunology Federal Medical-Biological Agency of Russia, Moscow, Russian Federation
[4] Scientific and research financial institute, Moscow, Russian Federation

ABSTRACT

BACKGROUND: Allergic rhinitis is the most common chronic allergic disease worldwide, and bronchial asthma (BA) is one of the most severe complications of allergic rhinitis. Clinical studies reported that sublingual allergen-specific immunotherapy can reduce the incidence of bronchial asthma in children and adults. However, allergen-specific immunotherapy is rather expensive and is not reimbursed by the state, which transfers the cost of this therapy to patients.

AIMS: To evaluate the cost-effectiveness of allergen-specific immunotherapy in children and adults with allergic rhinitis and/or allergic rhinoconjunctivitis

MATERIALS AND METHODS: The study hypothesized based on study results by Devillier P. et al. in 2019, to which the incidence of asthma was 13.7% and 17.0% in the sublingual allergen-specific immunotherapy + symptomatic therapy and the symptomatic therapy group, respectively (odds ratio: 0.776, 95% confidence interval [0.622; 0.968]). Pharmacoeconomic study based on decision tree model. Costs taken into account are the following: allergen-specific immunotherapy, symptomatic therapy, diagnostics, and routine follow-up visits due to bronchial asthma, outpatient bronchial asthma drug therapy, and hospitalization due to bronchial asthma. The modeling horizon was 5 years, including 2 years of allergen-specific immunotherapy therapy and 3 years of follow-up.

RESULTS: The cost per patient when using allergen-specific immunotherapy in combination with symptomatic therapy was 166,711.93 rubles, whereas with symptomatic therapy was 101,700.35 rubles. The cost-effectiveness ratio for allergen-specific immunotherapy in combination with symptomatic therapy was 193,177.20 rubles per 1 prevented case of asthma, whereas 122,530.55 rubles for symptomatic therapy for 1 prevented case of bronchial asthma. Thus, the cost of 1 averted bronchial asthma case when using allergen-specific immunotherapy in combination with symptomatic therapy is 57.7% higher than with symptomatic therapy. The cost-benefit analysis result revealed that the incremental cost-utility ratio for an additional year of life adjusted for its quality when performing sublingual allergen-specific immunotherapy in combination with symptomatic therapy compared with symptomatic therapy alone in children and adults was 567,365.48 rubles, which is less than the calculated willingness to pay threshold (RUB 2,248,898.50).

CONCLUSIONS: The comparison results of the cost of 1 added quality adjusted life years and willingness to pay threshold concluded that sublingual allergen-specific immunotherapy in combination with symptomatic therapy compared to symptomatic therapy alone is potentially cost-effective in children and adults with allergic rhinitis.

Keywords: Economics; pharmaceutical; costs and cost analysis; cost-benefit analysis/methods; sublingual immunotherapy; asthma/therapy, rhinitis, allergic

For citation: Lemeshko VA, Ratushnak SS, Gorkavenko FV, Nazarova EV, Ilina NI, Omelyanovskiy VV. Pharmacoeconomic analysis of bronchial asthma prophylaxis in adults and children with allergic rhinitis by means of sublingual allergen-specific immunotherapy. *Russian Journal of Allergy*. 2021;18(4):5–17. DOI: https://doi.org/10.36691/RJA1497

 DOI: https://doi.org/10.36691/RJA1497

Оценка клинико-экономической эффективности профилактического назначения сублингвальной аллергенспецифической иммунотерапии у взрослых и детей с аллергическим ринитом с целью предотвращения развития бронхиальной астмы

В.А. Лемешко[1], С.С. Ратушняк[2], Ф.В. Горкавенко[2], Е.В. Назарова[3], Н.И. Ильина[3], В.В. Омельяновский[1, 2, 4]

[1] Российская медицинская академия непрерывного профессионального образования, Москва, Российская Федерация
[2] Центр экспертизы и контроля качества медицинской помощи, Москва, Российская Федерация
[3] Государственный научный центр «Институт иммунологии» Федерального медико-биологического агентства, Москва, Российская Федерация
[4] Научно-исследовательский финансовый институт, Москва, Российская Федерация

АННОТАЦИЯ

ОБОСНОВАНИЕ. Аллергический ринит является самым распространённым хроническим аллергическим заболеванием во всём мире, а бронхиальная астма — одним из самых тяжёлых осложнений аллергического ринита. Применение сублингвальной аллергенспецифической иммунотерапии, по данным клинических исследований, позволяет снизить частоту развития бронхиальной астмы у детей и взрослых, однако является достаточно дорогостоящим методом лечения и не возмещается за счёт государства.

ЦЕЛЬ — оценка затратной эффективности сублингвальной аллергенспецифической иммунотерапии у детей и взрослых пациентов с аллергическим ринитом и/или аллергическим риноконъюнктивитом.

МАТЕРИАЛЫ И МЕТОДЫ. Гипотеза исследования обоснована результатами работы P. Devillier и соавт. (2019), согласно которой частота развития бронхиальной астмы составляла 13,7 и 17,0% в группах комбинированной сублингвальной аллергенспецифической иммунотерапии/симптоматической терапии и симптоматической терапии в монорежиме (отношение шансов 0,776; 95% доверительный интервал 0,622; 0,968). Моделирование результатов выполнено с использованием модели древа решений. Перечень учтённых затрат: на сублингвальную аллергенспецифическую иммунотерапию, симптоматическую терапию; диагностику и плановые посещения врачей по причине бронхиальной астмы; амбулаторную лекарственную терапию бронхиальной астмы; госпитализации в связи с бронхиальной астмой. Горизонт моделирования составил 5 лет, включая 2 года сублингвальной аллергенспецифической иммунотерапии и 3 года наблюдения.

РЕЗУЛЬТАТЫ. Затраты на одного пациента при применении сублингвальной аллергенспецифической иммунотерапии в комбинации с симптоматической терапией составили 166 711,93 руб., при симптоматической терапии — 101 700,35 руб. Показатель «затраты-эффективность» (cost-effectiveness ratio) для сублингвальной аллергенспецифической иммунотерапии в комбинации с симптоматической терапией составил 193 177,20 руб. на 1 предотвращённый случай бронхиальной астмы, для симптоматической терапии — 122 530,55 руб. Таким образом, стоимость 1 предотвращённого случая бронхиальной астмы при применении сублингвальной аллергенспецифической иммунотерапии в комбинации с симптоматической терапией на 57,7% больше, чем при симптоматической терапии в монорежиме. По результатам инкрементального анализа, показатель стоимости «затраты-полезность» (incremental cost-utility ratio) за дополнительный год жизни с поправкой на её качество (quality adjusted life years) при проведении сублингвальной аллергенспецифической иммунотерапии в комбинации с симптоматической терапией по сравнению с симптоматической терапией в монорежиме у детей и взрослых составил 567 365,48 руб., что меньше значения рассчитанного порога готовности платить (2 248 898,50 руб.).

ЗАКЛЮЧЕНИЕ. По результатам сравнения стоимости 1 добавленного года жизни с поправкой на её качество с порогом готовности платить можно сделать вывод, что сублингвальная аллергенспецифическая иммунотерапия в комбинации с симптоматической терапией по сравнению только с симптоматической терапией потенциально является экономически эффективной у детей и взрослых с аллергическим ринитом.

Ключевые слова: клинико-экономический анализ; затраты-эффективность; затраты-полезность; сублингвальная аллергенспецифическая терапия; бронхиальная астма; аллергический ринит

Для цитирования: Лемешко В.А., Ратушняк С.С., Горкавенко Ф.В., Назарова Е.В., Ильина Н.И., Омельяновский В.В. Оценка клинико-экономической эффективности профилактического назначения сублингвальной аллергенспецифической иммунотерапии у взрослых и детей с аллергическим ринитом с целью предотвращения развития бронхиальной астмы // *Российский аллергологический журнал*. 2021. Т. 18. № 4. С. 5–17. DOI: https://doi.org/10.36691/RJA1497

Статья поступила 12.11.2021	Принята к печати 20.12.2021	Опубликована 22.12.2021
Received: 12.11.2021	Accepted: 20.12.2021	Published: 22.12.2021

Background

Allergic rhinitis (AR) is the most common chronic allergic disease worldwide. AR is characterized by immunoglobulin E (IgE)-mediated inflammation of the nasal mucosa in response to allergen exposures and the presence of at least two of the symptoms (nasal congestion [obstruction], nasal discharge [rhinorrhea], sneezing, and itchy nasal cavity) that appear daily for an hour or more. AR is often accompanied by other allergic diseases, such as allergic conjunctivitis, atopic dermatitis, and bronchial asthma (BA) [1]. The problem of AR is not only related to its symptoms. AR was revealed to be significantly associated with an increased risk of BA, which has a significantly greater effect on the patient's condition compared to AR [2, 3]. Of patients with AR, 15%–38% develop BA, and 55%–85% of patients with BA have AR symptoms, while the risk of BA increases with an increased AR severity and increased number of allergens to which the patient is sensitized, as well as the presence of persistent AR compared with intermittent AR [4–6]. On average, BA develops 4 years after the occurrence of AR, and the time interval gradually increases with age up to 6 years in patients aged 41–50 years [5].

Effective treatment for AR includes allergen-specific immunotherapy (ASIT), which can reduce the severity of AR symptoms and the need for pharmacotherapy, can reduce the risk of BA in adults and children, and has a long-term prophylactic effect [7–10]. ASIT is the main method of pathogenetic treatment of IgE-mediated allergic diseases, which consists of the administration of increasing the doses of an allergen that is responsible for the clinical disease manifestations in these patients. ASIT acts on both the early and late phases of the allergic response and leads to inhibition not only of the allergen-specific reaction but also tissue hyperreactivity inhibition. Due to ASIT, the migration of effector cells to the area of allergic inflammation is suppressed and the production of regulating T-lymphocytes that contribute to the induction of immunological tolerance is stimulated, which is characterized by the suppression of the proliferative and cytokine response to allergens. There can be subcutaneous (subcASIT) and sublingual (sASIT) ASIT methods [11]. The advantages of sASIT include greater ease of use, no discomfort during administration, and the possibility of outpatient treatment, as well as a more favorable safety profile compared to subcASIT.

Nowadays, sASIT is not widely used in clinical practice in Russia, which may be due, particularly, to the high cost of treatment, as well as insufficient drugs for sASIT in the lists of drugs that are reimbursed at the expense of the state. Therefore, patients incur great expenses for sASIT. The literature review revealed the presence of several Russian clinical and economic studies of ASIT; however, they either assessed subcASIT [12–15] or did not take into account the preventive effect of sASIT concerning the development of BA [16]. Thus, a wider introduction of sASIT, a clinical, and economic study is required, which would assess the economic aspects of sASIT introduction, taking into account the preventive effects on BA.

This study aimed to assess the clinical and economic efficiency of the use of sASIT in AR or allergic rhinoconjunctivitis in a mixed population of pediatric and adult patients.

Materials and methods

Substantiation of a clinical model for economic analysis

The search and selection of studies to assess the clinical efficacy of sASIT in adults and children with AR was performed following the criterion "incidence of BA". A systematic search of clinical data was performed in four databases, namely, the Scientific Electronic Library (eLibrary.ru), the Cochrane Library, Medline (PubMed), and the clinical trials registry clinicaltrials.gov. The search time range was unlimited. The date of the search was June 29, 2020.

A search on Medline (PubMed) used the search terms "SLIT", "sublingual immunotherapy", "Allergen immunotherapy", "Allergen-specific immunotherapy", "OIT", or "oral immunotherapy", and "administration, oral (MeSH Terms)", "administration, sublingual (MeSH Terms)", and "allergic rhinoconjunctivitis", "allergic rhinitis", "Perennial rhinitis", or "Seasonal rhinitis".

Inclusion criteria were the study of the efficiency of sASIT in any dosage form compared to standard pharmacotherapy in a mixed population of pediatric and adult patients with AR or rhinoconjunctivitis. An assessment of the effects of sASIT on BA incidence was to be used as one of the criteria for assessing clinical efficiency. The clinical trial had to be comparative, and the type and language of the publication were not exclusion criteria. A strict exclusion criterion was the baseline presence of BA in all or some of the study participants. The systematic search was performed independently by two researchers. Study selection and data extraction were also conducted independently by two researchers, and in cases of disagreement, a consensus was achieved with the involvement of a third researcher.

From the systematic search, 4 publications were identified based on the results of 4 studies (Fig. 1). All of the selected studies were retrospective cohort studies, which analyzed prescription registries [7, 9, 10] or medical care case registries [8]. The works by J. Schmitt et al. (2015) [8] and U. Wahn et al. (2019) [10] did not meet the requirements of the clinical and economic analysis (CEA) since their analysis of sASIT efficiency was performed with a set of drugs for sASIT, some of which are not registered in the Russian Federation. From the remaining sources [7, 9], the CEA was based on the work by P. Devillier et al. (2019) [9] due to the presence of data on the structure of prescribing symptomatic therapy in the compared groups,

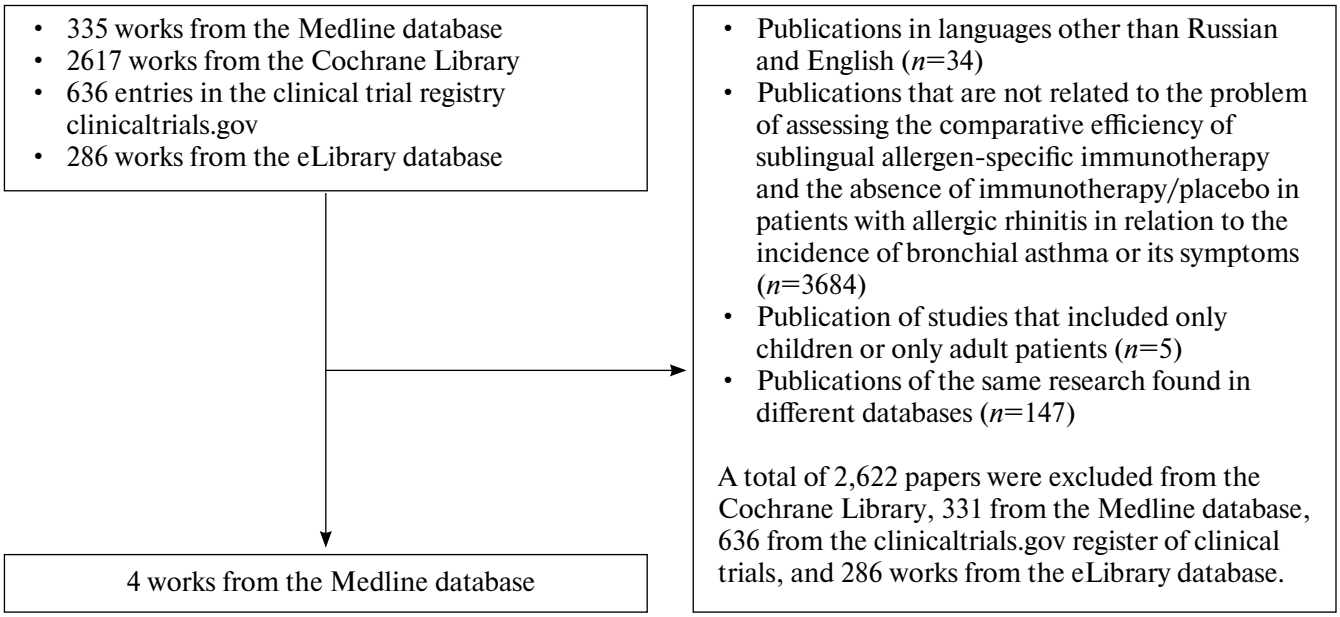

Fig. 1. Selection chart of clinical trials evaluating the comparative efficacy and/or safety of sublingual immunotherapy versus placebo and/or standard therapy in adults and children with allergic rhinitis in relation to the incidence of bronchial asthma or its symptoms.

which performed more accurate calculations and take into account the change in the structure of prescribing the symptomatic therapy. Thus, according to the results of their retrospective cohort study [9], the incidence of BA within approximately 5 years in the sASIT group was statistically significantly lower than in the symptomatic therapy group, namely 13.7% versus 17.0% (odds ratio: 0.776; 95% confidence interval: 0.622–0.968).

Additionally, the "cost-effectiveness" and "cost-utility" methods were used based on the study results by P. Devillier et al. (2019) [9] within the CEA. A decision tree model was developed for clinical and economic modeling (Fig. 2).

Clinical and economic modeling

After using one of the two compared alternatives, with a certain probability, some patients will develop BA while others will not. Each branch of the emerging decision tree from the nodes represents possible AR pathways in adults and children after using sASIT in combination with symptomatic therapy (alternative 1) or only symptomatic therapy (alternative 2). The decision tree model was developed based on Microsoft Excel.

Each branch of the decision tree was associated with the costs for the AR course for a specific scenario. The costs of the pathway are equal to the sum of the AR therapy expenses (compared alternatives: sASIT in combina-

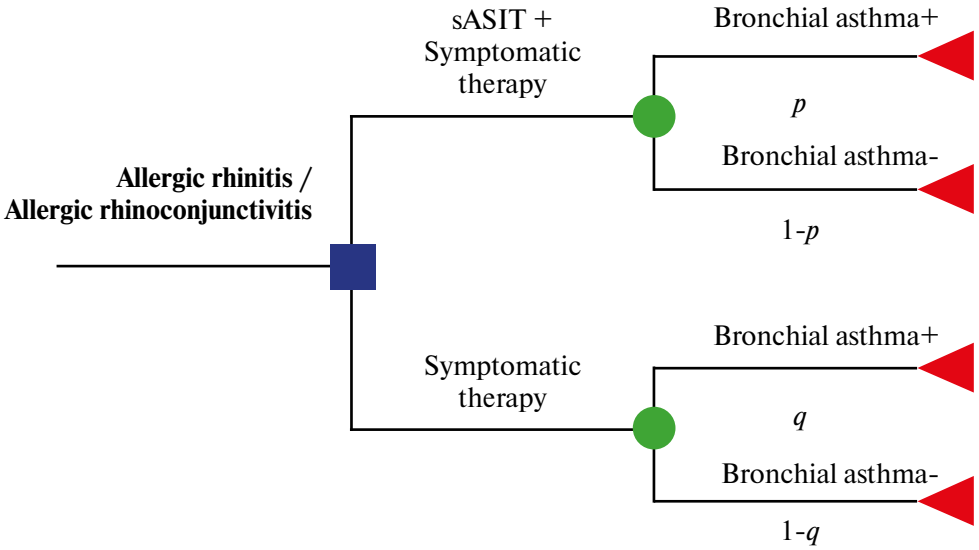

Fig. 2. Decision tree model.

Note. *p*, *q*: probability of patient getting into the symptomatic therapy group or the sublingual immunotherapy + symptomatic therapy group.

tion with symptomatic therapy or symptomatic therapy) and, in the case of BA, the costs of providing medical care in the in-patient facility and at the outpatient stage using BA drug therapy. The expected costs of sASIT in combination with symptomatic therapy and the costs of symptomatic therapy were calculated by weighing the cost of each branch against the corresponding branch probability.

The efficiency indicators for "cost-effectiveness" analysis and utility indicators for "cost-utility" analysis were determined to conduct a clinical and economic sASIT assessment. The efficacy indicators (5-year probability of BA development) were eliminated from a retrospective cohort study by P. Devillier et al. (2019) [9], in which the presence of BA, as an outcome, was determined from the records in the database on the prescription of two or more anti-asthma drugs for 1 or 2 years in a row. The time horizon for evaluating the efficiency in the study was 5 years (2 years of sASIT use and 3 years of follow-up). It should be noted that 2 years of sASIT use and 3 years of follow-up are an assumption, since, according to the study publication, the efficiency of sASIT was assessed for at least 2 years of active treatment and up to 2.92 years (35 months) of follow-up. Thus, P. Devillier et al. (2019) [9] revealed a 5-year probability of BA in the presence of sASIT in combination with symptomatic therapy as 13.7% (*p* in Fig. 2) and that during the symptomatic therapy was 17.0% (*q* in Fig. 2).

Utility indicators, particularly the quality adjusted life years (QALY), were calculated using the following equation:

$$QALY = NLY \times qlsASIT,\ ST \times dBA- + dBA+ \times \times 2.5 \times qlsASIT,\ ST + 2.5 \times qlARandBA,$$

where NLY is the number of life-years equal to the duration of the modeling horizon (5 years); qlsASIT, ST is the quality of life of patients with AR on sASIT therapy or quality of life of patients with AR on symptomatic therapy; dBA- is the probability of the absence of BA; dBA+ is the probability of developing BA; 2.5 is the time before the onset of BA equal to 2.5 years (assumption); and qlARandBA is the quality of life of patients with AR and BA.

The utility values for patients with AR who receive sASIT and symptomatic therapy were taken from C.D. Poole et al. (2014) [17]; and from the publication by P.W. Sullivan et al. (2020) [18] for patients with AR and BA.

The cost of the compared alternative approaches to AR therapy included the costs of drugs for sASIT (sASIT group); costs of symptomatic therapy for AR and rhinoconjunctivitis (sASIT group and symptomatic therapy group); costs of BA therapy that included the cost of drug therapy on an outpatient basis, the cost of hospitalization for BA exacerbations, and the cost of outpatient visits due to BA (sASIT group and symptomatic therapy group).

The entire set of drugs for sASIT was considered as sASIT, taking into account their share in the turnover structure from 2017 to 2020 in the Russian Federation [17]. The share of each drug group consisted of the sum of all drug packages in the group intended for the introductory course and the number of maintenance therapy courses. The course of maintenance therapy was calculated as the total number of packages or dosage units required for the treatment course with the average duration and intensity of dosing per year (year-round or preseasonal-seasonal). The cost calculation of sASIT was based on the dosing schedules for sASIT in their instructions for medical use.

The cost calculation of symptomatic AR therapy was performed based on the data from P. Devillier et al. (2019) [9] and our expert survey results (the methodology of the expert survey is presented below). P. Devillier et al. (2019) [9] provided information only on the symptomatic therapy drug classes that are taken by patients with AR. Thus, data on the prescribed International non-proprietary name of drugs (INN) in Russian practice and the structure of their prescription were obtained during the expert survey. According to the study, the number of prescriptions per patient per year was recalculated for each drug class. The resulting value was then used to adjust the frequency of prescription of a particular INN. Based on the expert survey results, the set of drugs for symptomatic therapy of AR included antihistamines (cetirizine, loratadine, desloratadine, levocetirizine, fexofenadine, ebastine, and bilastine), nasal glucocorticosteroids (beclomethasone, budesonide, fluticasone, and mometasone), nasal antiallergic drugs (azelastine, cromoglicic acid, and levocabastine), a combination of a glucocorticosteroid and an antibiotic for ophthalmic use (dexamethasone + tobramycin), and glucocorticosteroids for ophthalmic use (dexamethasone and hydrocortisone). The cost calculation of daily therapy with a specific drug was performed considering the cost of a drug package and weighted average by the number of released drug packages into the circulation for the first half of 2020 or 2019 without the cost data in 2020 according to the Cliphar database [19]. The calculations included the age-related characteristics of drug intake, namely dosage regimens for pediatric and adult patients (with a ratio of children and adults of 50/50), and their dosage regimes and the cost of packaging were averaged in the presence of several dosage forms and pack sizes.

The cost calculation of providing medical care for BA considered the medical procedures following the clinical guidelines for BA treatment [20]. The cost calculation of providing medical care for BA considered the hospitalization costs in a round-the-clock inpatient facility (clinical statistical group [CSG] st23.005 "BA, adults", CSG st23.006 "BA, children") and outpatient care and drug therapy costs, as well as the disease severity (mild, moderate, and severe BA). A coefficient of 0.65 was used in calculating the total cost of a hospitalization case, reflecting the minimum size of the established base rate by the constituent entities of the Russian Federation relative to the specified base rate in the federal program

of state guarantees of free provision of medical care to citizens [21].

Due to insufficient data on the rate of BA development in presence of AR, BA was assumed to gradually and evenly increase during the entire modeling period, which led the average BA duration and associated treatment costs to 2.5 years during the 5-year modeling horizon.

The hospitalization frequency was determined based on the results of an expert survey separately for each degree of BA severity; therefore, the costs for each degree of BA severity were separately calculated.

The cost calculation of outpatient visits for BA was performed considering the average standard of financial costs for 1 case of visit for the disease following the Program of State Guarantees of Free Provision of Medical Care to Citizens for 2020[1]. According to the expert survey results, the frequency of outpatient visits differs depending on disease severity; therefore, the costs of outpatient visits were also separately calculated for mild, moderate, and severe BA.

The cost calculation of drug therapy for BA exacerbations in the presence of AR included only drugs for outpatient use. According to the expert survey results, the list of drugs for BA exacerbations included short-acting β_2-agonists (salbutamol and fenoterol), long-acting β_2-agonists (formoterol), m-cholinolytics (ipratropium bromide, aclidinium bromide, tiotropium bromide, and glycopyrronium bromide), leukotriene receptor antagonists (montelukast), adenosinergic (aminophylline and theophylline), inhaled glucocorticosteroids (budesonide, fluticasone, beclomethasone dipropionate, and ciclesonide), oral glucocorticosteroids (prednisolone, methylprednisolone, and dexamethasone), fixed combinations of m-cholinergic antagonists and β_2-agonists (ipratropium bromide + fenoterol, umeclidinium bromide + vilanterol, tiotropium bromide + olodaterol), fixed combinations of inhaled glucocorticosteroids and fast-acting β_2-agonists (beclomethasone + salbutamol), and fixed combinations of inhaled glucocorticosteroids and long-acting β_2-agonists (fluticasone + salmeterol, budesonide + formoterol, beclomethasone + formoterol, and fluticasone + vilanterol). The cost calculation of daily therapy with a specific drug was performed considering the cost of a drug package and the weighted average by the number of released drug packages into the circulation for the first half of 2020 or 2019 in the absence of cost data in 2020 according to the Cliphar database [19]. The calculations took into account the age-related drug intake characteristics, namely dosage regimens for pediatric and adult patients (with a ratio of children and adults 50/50), and in the presence of several dosage forms and pack sizes, their dosage regimes and the cost of packaging were averaged.

The main result of the "cost-effectiveness" analysis was the cost calculation of one prevented BA case as the cost-effectiveness ratio (CER). Additionally, within this study, a "cost-utility" analysis was performed, particularly, the cost calculation of one additional QALY as an incremental cost-utility ratio (ICUR).

A one-way sensitivity analysis was performed, when the effect of changes in the main parameters of the model was assessed (the cost of sASIT, the efficiency of sASIT and symptomatic therapy, quality of life indicators, and the period before BA in presence of AR) on the ICUR indicator for sASIT and symptomatic therapy to test the sustainability of the obtained results of the "cost-effectiveness" analysis to key parameters changes of the model.

Expert survey methodology

An expert survey was conducted to determine the key parameters of the model, and the information about them was not available in the publications of clinical studies. The survey involved 12 allergists-immunologists. Eleven experts were interviewed in the remote form of filling out the questionnaire, and one more expert was verbally interviewed. A group of 11 experts was asked to independently complete a 2-part questionnaire with 10 questions. In part 1, experts were asked to provide an answer about the list of drugs that are used to treat AR in a mixed population of patients and the probability of their prescription. In part 2, the experts were asked to report on the required diagnostic procedures to establish BA diagnosis; the frequency of hospitalizations of the patient per year depending on BA severity (separately for children and adults); the frequency of outpatient visits to a pulmonologist per year depending on BA severity (separately for children and adults); the list of drugs for BA treatment depending on BA severity (for the combined population of children and adults). The model used the average values of the experts' answers. A separately interviewed expert provided information on the average frequency of BA exacerbations depending on its severity (for the combined population of children and adults) and the average exacerbation duration.

Results

Table 1 presents the results of the cost calculation of sASIT drugs. Based on the study design of P. Devillier et al. (2019) [9], the calculations considered that the sASIT course will last for 2 years. In the remaining 3 years of follow-up, patients will receive only AR and BA therapy. The costs presented for each of the considered INNs included the share of this INN in the structure of circulation on the Russian Federation market.

The costs of symptomatic therapy for AR and rhinoconjunctivitis included the list of groups of used drugs

[1] Decree of the Government of the Russian Federation of December 7, 2019, N 1610 "On the Program of State Guarantees of Free Provision of Medical Care to Citizens for 2020 and for the Prospected Period of 2021 and 2022". Access mode: http://publication.pravo.gov.ru/Document/View/0001201912180001. Reference date: 11/06/2021.

Table 1. Sublingual immunotherapy costs for 1 patient over 2 years

INN	Share of INN, %	Costs, rub.
Grass pollen allergens	10.66	10,812.15
Indoor allergens	7.96	7629.70
Pollen allergens of trees	69.87	44,883.10
Grass pollen allergoids	3.55	3059.30
Indoor allergoids	7.96	13,486.75
The average cost of a course of treatment with a drug for sASIT		79,871.00

N o t e. INN: international nonproprietary name of medicines; sASIT: sublingual allergen-specific immunotherapy.

and their intake frequency according to P. Devillier et al. (2019) [9]. The list of INNs included in the classes was determined in the course of an expert survey. The total costs for 1 and 5 years of AR therapy per patient are presented in Table 2.

The cost calculations of BA therapy considered the structure of BA severity for pediatric and adult patients based on the expert survey results (Table 3).

The results of costs calculation of outpatient visits due to BA, hospitalizations due to BA, and the drug therapy cost are presented in Tables 4–6, respectively.

Over the 5 years of modeling, the costs per patient for using sASIT in combination with symptomatic therapy were 166,711.93 rubles and 101,700.35 rubles for symptomatic therapy. The CER of sASIT in combination with symptomatic therapy was 193,177.20 rubles per 1 prevented BA case, and 122,530.55 rubles per 1 prevented BA case for symptomatic therapy. Thus, the cost of 1 prevented BA case when using sASIT in combination with symptomatic therapy is 57.7% higher than with symptomatic therapy. This result was justified since the sASIT technology is more efficient

Table 2. The total costs of allergic rhinitis treatment per patient

Parameter	sASIT group + symptomatic therapy	Symptomatic therapy group
Costs per 1 year, rub.	5006.39	15,098.41
Costs per 5 years, rub.	25,031.96	75,492.04

N o t e. sASIT: sublingual allergen-specific immunotherapy.

Table 3. The distribution of asthma in population by severity according to expert survey

Severity	Prevalence of bronchial asthma, %		
	children	adults	mixed population
Mild	45	36	41
Moderate	44	35	39
Severe	11	29	20

Table 4. The costs for outpatient visits for bronchial asthma

Parameter	Severity of bronchial asthma		
	Mild	Moderate	Severe
Frequency of outpatient visits, cases per year per person (expert survey)	0.53	1.28	2.7
Cost of outpatient treatment for disease [21], rub.	1414.4		
Costs during 1 year	742.56	1803.36	3818.88
Costs during 5 years	1856.4	4508.4	9547.2

Table 5. The costs of inpatient treatment for bronchial asthma

Parameter	Severity of bronchial asthma		
	Mild	Moderate	Severe
Hospitalization rate, cases per year per person (expert survey)	0.39	2.16	3.57
Cost of a completed hospitalization case [21], rub.	28,204.88		
Costs during 1 year	10,897.34	60,896.9	100,640.14
Costs during 5 years	27,243.35	152,242.26	251,600.36

Table 6. The average costs of drug therapy for bronchial asthma

Parameter	The severity of bronchial asthma		
	Mild	Moderate	Severe
Cost of therapy per day, rub.	55.23	107.40	89.95
Cost of 1 year of therapy, rub.	303.78	1772.15	2473.68
Cost of 2.5 years of therapy (5-year horizon of modeling), taking into account the distribution according to the severity of bronchial asthma, rub.	308.52	1750.00	1229.11
Total, rub.	3287.63		

and more costly; however, it is impossible to make an unambiguous conclusion about the extent to which the increase in costs is economically feasible in connection with its use.

The main result of the "cost-utility" analysis is the ICUR indicator, which amounted to 567,365.48 rubles for 1 additional QALY when performing sASIT in combination with symptomatic therapy compared to symptomatic therapy alone in pediatric and adult patients. The resulting value of 567,365.48 rubles for 1 additional QALY is less than the value of the calculated indicator of the willingness to pay the threshold (3 times gross domestic product per capita) of 2,248,898.50 rubles. Therefore, the considered technology of sASIT combined with symptomatic therapy compared to symptomatic therapy alone is potentially cost-effective in pediatric and adult patients with AR.

According to the sensitivity analysis results, not only the cost of sASIT, but also its efficiency indicators, particularly the incidence of BA, which has the greatest impact on the final results, have a significant impact on the final CER indicators. Thus, a change in the cost of sASIT from -15 to +15% caused a change in the CER value within ±8.45%, and a change in efficiency caused a change from -6.87 to +7.2%. The influence of the change in the time indicator to the BA development caused fluctuations in the CER value for sASIT in ±4.65%. In turn, change evaluation in the CER value for symptomatic therapy showed that its therapy efficiency and the time to the onset of BA have a significant effect on its value. Thus, the change in BA occurrence probability from -15 to +15% caused a change in the CER value from -13.93 to +14.82%, and the change in time before the onset of BA caused a change in ±11.29%.

The evaluation of ICUR indicator value changes showed that the greatest influence is exerted by the quality of life of patients with AR when taking symptomatic therapy (from -84.55% to -221.26%) when receiving sASIT (from -65.59% to -121.19%), patients with AR and BA (from -8.69% to + 6.76%), the cost of sASIT (± 18.43%), the efficiency of sASIT (from -16.41% to 17.28%), the efficiency of symptomatic therapy (from -19.19% to + 19.93%), and the time to the onset of BA (from -12.57% to +18.2%).

Discussion

Summary of the main research finding

This CEA is the first Russian study that takes into account the effect of sASIT on the probability of BA development; therefore, the final results considered the effects of therapy not only on the course of AR but also the preventive effect concerning BA. Additionally, in this work, not a single drug for sASIT was considered, but the entire set of drugs on the Russian Federation market.

Research limitations

The present study has several limitations that must be taken into account when interpreting the obtained results, which are related to the data that was used to create the model. Thus, the clinical study, from which the efficiency value of sASIT in combination with symptomatic therapy was taken, has several limitations. First of all, the study by P. Devillier et al. (2019) [9] is not Russian; it was conducted in France, that is, under conditions that differ from the Russian ones in the range of allergens and the duration and intensity of the pollination season, as well as the range of sensitization of the participants. Additionally, the publication does not provide a sufficient amount of data on the composition and regimens of AR and BA treatment, which can potentially affect the incidence and severity of BA, and therefore, within this CEA, the expert survey results were used to compensate for the insufficient data for some model parameters. The expert survey, as a method, has its drawbacks, including those associated with the level of significance of the obtained data and the sample size, which can also lead to a bias in the results.

The study by P. Devillier et al. (2019) [9] is a retrospective cohort, therefore the significance level of its results is lower compared to the results of randomized controlled trials. Moreover, the assessment of BA incidence in their work [9] is based on the surrogate outcome, namely, the frequency of prescriptions for BA treatment, which is a less accurate way of assessing the true incidence of BA compared to clinical examination.

A follow-up period of 5 years (2 years of treatment and 3 years of follow-up) is not ideal for evaluating a prolonged prophylactic effect. In the global practice, ASIT is performed for 3–5 years, until a decreased intensity of symptoms or their complete disappearance, a decreased

need for symptomatic therapy, and most importantly, after achieving a long-term remission at the end of treatment, on average, for 5–7 years to prevent the development of more severe disease forms and expansion of the sensitization spectrum. Therefore, according to the prospective study results by M. Marogna et al. (2010) [21], which evaluated the long-term effect of obtained sASIT after treatment for 3, 4, or 5 years, remission lasted for 7–8 years. The study involved patients with respiratory allergies, who were monosensitized to dust mites; the follow-up period was 15 years. The subjects were distributed into 4 groups. Group 1 received symptomatic drug therapy, and the other three groups received sASIT for 3, 4, or 5 years, respectively. The clinical effect (assessment of symptoms and consumption of symptomatic therapy) was considered to be persistent as long as the clinical indicators remained below 50% of the baseline value, and then patients underwent another course of treatment. In patients who received sASIT for 3 years, clinical benefit persisted for 7 years, whereas 8 years for those who received immunotherapy for 4 or 5 years. The emergence of new sensitization within 15 years was registered in 100% of controlled patients and in less than 1/4 of patients who receive sASIT (21%, 12%, and 11%, respectively). The sASIT course 2 was beneficially faster than course 1. This study has the longest follow-up period.

Another long-term study by U. Wahn et al. (2019) [10] evaluated the efficiency of ASIT (sASIT and subcASIT) with symptomatic therapy compared to symptomatic therapy alone. The data was sourced from a retrospective analysis of a medical database in Germany. The follow-up period was 6 years after the end of treatment. During the study period, more than half of the participants (64.5%) who received ASIT did not use symptomatic therapy compared with 47.4% of patients who used only symptomatic therapy. Additionally, 49.1% of participants in the ASIT group did not take anti-asthma therapy compared with 35.1% of participants in the control group. ASIT achieved remission of up to 6 years after treatment discontinuation, during which the consumption of symptomatic therapy for asthma and rhinitis was significantly reduced, as well as the risk of starting the new anti-asthma drugs. Thus, based on the results of these studies, it can be assumed that the cost-effectiveness in the long-term follow-up will be significantly higher than that demonstrated in this study. Establishing the clinical and economic efficiency of ASIT for a period that exceeds 5 years is a promising task for further clinical and economic research.

When interpreting the results of calculating the cost of BA drug therapy, it should be considered that the calculations included only the cost of therapy during the period of BA exacerbations, while the cost of basic therapy was not taken into account. The basic therapy was not considered due to objective difficulties in collecting significant data on real clinical practice. The cost calculation of basic therapy without taking into account the decreased treatment adherence was associated with the risks of overestimating the actual costs of basic BA therapy. The current version of the calculations should be considered as a conservative scenario, in which the clinical and economic efficiency of sASIT is underestimated. Accounting for the correct cost of basic therapy can be considered an urgent task in conducting subsequent clinical and economic ASIT studies.

An additional limitation was that the quality of life values that are used for calculating the QALY was not obtained in the Russian population and did not include the preferences of the Russian population. In the absence of national tariffs for determining the health-related quality of life, the use of international tariffs is one of the approaches to determine the health-related quality of life. This approach is not optimal, as different populations assess health-related quality of life differently, and the use of international tariffs can lead to biased estimates.

Conclusion

The CEA calculated the economic consequences of using sASIT in pediatric and adult patients, taking into account that sASIT will affect not only the course of AR (the model considered a gradual decrease in the consumption of symptomatic therapy in the sASIT group, which indirectly indicates a decreased AR symptom severity) but also reduce the risk of BA. Thus, in the study, the cost of 1 prevented BA case was determined when using sASIT in combination with symptomatic therapy, which was 57.7% higher than with symptomatic therapy alone. This result is justified in that the considered sASIT technology is more efficient and costly. The main result of the "cost-utility" analysis is the ICUR indicator, which amounted to 567,365.48 rubles for 1 additional QALY when performing sASIT in combination with symptomatic therapy compared to symptomatic therapy alone in pediatric and adult patients. The resulting value of 567,365.48 rubles per 1 additional QALY is significantly lower than the value of the calculated indicator of the willingness to pay the threshold of 2,248,898.50 rubles. Therefore, the considered sASIT technology with symptomatic therapy compared to symptomatic therapy alone is potentially cost-effective in pediatric and adult patients with AR over a 5-year follow-up period. Considering the data of international studies on ASIT efficiency with a longer follow-up period than in the publication on which the CEA was performed, a greater economic benefit in the longer term can be predicted. Confirmation of these predictions requires new clinical and economic studies with a longer follow-up period of assessment.

Additional information

Funding source. This study was not supported by any external sources of funding.

Competing interests. The authors declare that they have no competing interests.

Authors' contribution. V.A. Lemeshko — oversaw the project, designed the study, performed systematic literature review, performed calculations, wrote the manuscript with input from all authors; S.S. Ratushnyak, F.V. Gorkavenko — designed the study, performed systematic literature review, performed calculations, wrote the manuscript with input from all authors; E.V. Nazarova — oversaw the project, designed the study, wrote the manuscript with input from all authors, edited the manuscript; N.I. Ilina, V.V. Omelyanovskiy — oversaw the project, edited the manuscript. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

REFERENCES

1. The Russian Association of Allergologists and Clinical Immunologists, the National Medical Association of Otorhinolaryngologists, the Union of Pediatricians of Russia. Clinical recommendations «Allergic rhinitis». 2019. (In Russ). Available from: https://raaci.ru/dat/pdf/allergic_rhinitis-project.pdf. Accessed: 06.11.2021.
2. Shaaban R, Zureik M, Soussan D, et al. Rhinitis and onset of asthma: a longitudinal population-based study. *The Lancet*. 2008;372(9643):1049–1057. doi: 10.1016/s0140-6736(08)61446-4
3. Bousquet J, Schünemann HJ, Samolinski B, et al. Allergic Rhinitis and its Impact on Asthma (ARIA): achievements in 10 years and future needs. *J Allergy Clin Immunol*. 2012;130(5):1049–1062. doi: 10.1016/j.jaci.2012.07.053
4. Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol*. 2002;109(3):419–425. doi: 10.1067/mai.2002.121701
5. Valero A, Pereira C, Loureiro C, et al. Interrelationship between skin sensitization, rhinitis, and asthma in patients with allergic rhinitis: a study of Spain and Portugal. *J Inv Allergol Clin Immunol*. 2009;19(3):167–172.
6. Lombardi C, Passalacqua G, Gargioni S, et al. The natural history of respiratory allergy: a follow-up study of 99 patients up to 10 years. *Respir Med*. 2001;95(1):9–12. doi: 10.1053/rmed.2000.0945
7. Zielen S, Devillier P, Heinrich J, et al. Sublingual immunotherapy provides long-term relief in allergic rhinitis and reduces the risk of asthma: a retrospective, real-world database analysis. *Allergy*. 2017;73(1):165–177. doi: 10.1111/all.13213
8. Schmitt J, Schwarz K, Stadler E, Wüstenberg EG. Allergy immunotherapy for allergic rhinitis effectively prevents asthma: results from a large retrospective cohort study. *J Allergy Clin Immunol*. 2015;136(6):1511–1516. doi: 10.1016/j.jaci.2015.07.038
9. Devillier P, Molimard M, Ansolabehere X, et al. Immunotherapy with grass pollen tablets reduces medication dispensing for allergic rhinitis and asthma: a retrospective database study in France. *Allergy*. 2019;74(7):1317–1326. doi: 10.1111/all.13705
10. Wahn U, Bachert C, Heinrich J, et al. Real-world benefits of allergen immunotherapy for birch pollen-associated allergic rhinitis and asthma. *Allergy*. 2018;74(3):594–604. doi: 10.1111/all.13598
11. Kurbacheva O, Pavlova K, Kozulina I. Allergen-specific immunotherapy: history, methods and new options. *Medicinskii Sovet*. 2013;(3-2):10–19. (In Russ).
12. Kurbacheva O. Pharmacoeconomical analysis of allergen-specific immunotherapy. *Problemy Standartizacii v Zdravoohranenii*. 2007;(3):8–15. (In Russ).
13. Ushakova D, Drinov G, Tikhomirova S, Slastushenskaya I. Clinical and economic effectiveness of allergyspecific immunotherapy in atopic bronchial asthma. *Kremlevskaia Medicina. Klinicheskii vestnik*. 2014;(2):25–29. (In Russ).
14. Gushchin I, Kurbacheva O, Pavlova K. Economic rationality of allergen-specific immunotherapy. *Pulmonologiia*. 2005;(5):46–52. (In Russ). doi: 10.18093/0869-0189-2005-0-5-46-52
15. Sobko E, Gordeeva N, Kraposhina A, et al. Clinical efficiency and the pharmacoeconomic analysis of allergen immunotherapy at patients with mild and moderate allergic bronchial asthma. *Farmakoèkonomika*. 2015;8(2):29–37. (In Russ). doi: 10.17749/2070-4909.2015.8.2.029-037
16. Trifonova T, Popova L, Alemanova G, Bobkova E. Clinical and economic efficacy of sublingual allergenspecific immunotherapy in children with allergic rhinitis. *Prakticheskaia Medicina*. 2015;92(7):78–83. (In Russ).
17. Poole CD, Bannister CA, Andreasen JN, et al. Estimation of health-related utility (EQ-5D index) in subjects with seasonal allergic rhinoconjunctivitis to evaluate health gain associated with sublingual grass allergen immunotherapy. *Health Qual Life Outcomes*. 2014;12(1):99. doi: 10.1186/1477-7525-12-99
18. Sullivan PW, Kavati A, Ghushchyan VH, et al. Impact of allergies on health-related quality of life in patients with asthma. *J Asthma*. 2019;57(11):1263–1272. doi: 10.1080/02770903.2019.1645168
19. Klifar. Commercial database. (In Russ). Available from: http://www.cliphar.ru/. Accessed: 06.11.2021.
20. Russian Respiratory Society. Clinical recommendations "Bronchial asthma". 2019. (In Russ). Available from: https://spulmo.ru/upload/kr_bronhastma_2019.pdf. Accessed: 06.11.2021.
21. Marogna M, Spadolini I, Massolo A, et al. Long-lasting effects of sublingual immunotherapy according to its duration: a 15-year prospective study. *J Allergy Clin Immunol*. 2010;126(5):969–975. doi: 10.1016/j.jaci.2010.08.030

ЛИТЕРАТУРА

1. Российская ассоциация аллергологов и клинических иммунологов, Национальная медицинская ассоциация оториноларингологов, Союз педиатров России. Клинические рекомендации «Аллергический ринит». 2019. Режим доступа: https://raaci.ru/dat/pdf/allergic_rhinitis-project.pdf. Дата обращения: 06.11.2021.
2. Shaaban R., Zureik M., Soussan D., et al. Rhinitis and onset of asthma: a longitudinal population-based study // Lancet. 2008. Vol. 372, N 9643. P. 1049–1057. doi: 10.1016/s0140-6736(08)61446-4
3. Bousquet J., Schünemann H.J., Samolinski B., et al. Allergic Rhinitis and its Impact on Asthma (ARIA): Achievements in 10 years and future needs // Journal of Allergy and Clinical Immunology. 2012. Vol. 130, N 5. P. 1049–1062. doi: 10.1016/j.jaci.2012.07.053
4. Guerra S., Sherrill D.L., Martinez F.D., Barbee R.A. Rhinitis as an independent risk factor for adult-onset asthma // Journal of Allergy and Clinical Immunology. 2002. Vol. 109, N 3. P. 419–425. doi: 10.1067/mai.2002.121701

5. Valero A., Pereira C., Loureiro C., et al. Interrelationship between skin sensitization, rhinitis, and asthma in patients with allergic rhinitis: a study of Spain and Portugal // Journal of Investigational Allergology & Clinical Immunology. 2009. Vol. 19, N 3. P. 167–172.
6. Lombardi C., Passalacqua G., Gargioni S., et al. The natural history of respiratory allergy: a follow-up study of 99 patients up to 10 years // Respiratory Medicine. 2001. Vol. 95, N 1. P. 9–12. doi: 10.1053/rmed.2000.0945
7. Zielen S., Devillier P., Heinrich J., et al. Sublingual immunotherapy provides long-term relief in allergic rhinitis and reduces the risk of asthma: a retrospective, real-world database analysis // Allergy. 2018. Vol. 73, N 1. P. 165–177. doi: https://doi.org/10.1111/all.13213
8. Schmitt J., Schwarz K., Stadler E., Wüstenberg E.G. Allergy immunotherapy for allergic rhinitis effectively prevents asthma: results from a large retrospective cohort study // Journal of Allergy and Clinical Immunology. 2015. Vol. 136, N 6. P. 1511–1516. doi: 10.1016/j.jaci.2015.07.038
9. Devillier P., Molimard M., Ansolabehere X., et al. Immunotherapy with grass pollen tablets reduces medication dispensing for allergic rhinitis and asthma: a retrospective database study in France // Allergy. 2019. Vol. 74, N 7. P. 1317–1326. doi: 10.1111/all.13705
10. Wahn U., Bachert C., Heinrich J., et al. Real-world benefits of allergen immunotherapy for birch pollen-associated allergic rhinitis and asthma // Allergy. 2019. Vol. 74, N 3. P. 594–604. doi: 10.1111/all.13598
11. Курбачева О.М., Павлова К.С., Козулина И.Е. Аллергенспецифическая иммунотерапия: история, методы и новые возможности // Медицинский совет. 2013. № 3-2. С. 10–19.
12. Курбачева О.М. Фармакоэкономический анализ аллергенспецифической иммунотерапии // Проблемы стандартизации в здравоохранении. 2007. № 3. С. 8–15.
13. Ушакова Д.В., Дрынов Г.И., Тихомирова С.В., Сластушенская И.Е. Клиническая и экономическая эффективность аллергенспецифической иммунотерапии при атопической бронхиальной астме // Кремлевская медицина. Клинический вестник. 2014. № 2. С. 25–29.
14. Гущин И.С., Курбачева О.М., Павлова К.С. Экономическая целесообразность аллергенспецифической иммунотерапии // Пульмонология. 2005. № 5. С. 46–52. doi: 10.18093/0869-0189-2005-0-5-46-52
15. Собко Е.А., Гордеева Н.В., Крапошина А.Ю., и др. Клиническая эффективность и фармакоэкономический анализ аллергенспецифической иммунотерапии у пациентов с аллергической бронхиальной астмой легкого и среднетяжелого течения // Фармакоэкономика. Современная фармакоэкономика и фармакоэпидемиология. 2015. Т. 8, № 2. С. 29–37. doi: 10.17749/2070-4909.2015.8.2.029-037
16. Трифонова Т.А., Попова Л.Ю., Алеманова Г.Д., Бобкова Е.В. Клинико-экономическая эффективность сублингвальной аллергенспецифической иммунотерапии у детей с аллергическим ринитом // Практическая медицина. 2015. № 7. С. 78–83.
17. Poole C.D., Bannister C.A., Andreasen J.N., et al. Estimation of health-related utility (EQ-5D index) in subjects with seasonal allergic rhinoconjunctivitis to evaluate health gain associated with sublingual grass allergen immunotherapy // Health and Quality of Life Outcomes. 2014. Vol. 12, N 1. P. 99. doi: 10.1186/1477-7525-12-99
18. Sullivan P.W., Kavati A., Ghushchyan V.H., et al. Impact of allergies on health-related quality of life in patients with asthma // Journal of Asthma. 2020. Vol. 57, N 11. P. 1263–1272. doi: 10.1080/02770903.2019.1645168
19. Клифар. Коммерческая база данных. Режим доступа: http://www.cliphar.ru/. Дата обращения: 06.11.2021.
20. Российское респираторное общество. Клинические рекомендации «Бронхиальная астма». 2019. Режим доступа: https://spulmo.ru/upload/kr_bronhastma_2019.pdf. Дата обращения: 06.11.2021.
21. Marogna M., Spadolini I., Massolo A., et al. Long-lasting effects of sublingual immunotherapy according to its duration: a 15-year prospective study // Journal of Allergy and Clinical Immunology. 2010. Vol. 126, N 5. P. 969–975. doi: 10.1016/j.jaci.2010.08.030

AUTHORS' INFO

Corresponding author:
Filipp V. Gorkavenko; address: Khohlovsky lane 10, bldg. 5, Moscow 109028, Russia;
ORCID: https://orcid.org/0000-0002-4586-2451;
eLibrary SPIN: 4274-4456;
e-mail: fill-gor@yandex.ru

Co-authors:
Valeriya A. Lemeshko;
ORCID: https://orcid.org/0000-0002-7452-6940;
eLibrary SPIN: 6391-6847;
e-mail: lera.lemeschko@yandex.ru

Svetlana S. Ratushnyak;
ORCID: https://orcid.org/0000-0001-7967-5112;
eLibrary SPIN: 7419-7690; e-mail: svetlanarshk@gmail.com

Evgeniya V. Nazarova, MD, Cand. Sci. (Med.);
ORCID: https://orcid.org/0000-0003-0380-6205;
eLibrary SPIN: 4788-7407; e-mail: evallergo@yandex.ru

ОБ АВТОРАХ

Автор, ответственный за переписку:
Горкавенко Филипп Васильевич;
адрес: Россия, 109028, Москва, Хохловский пер., вл. 10, стр. 5;
ORCID: https://orcid.org/0000-0002-4586-2451;
eLibrary SPIN: 4274-4456; e-mail: fill-gor@yandex.ru

Соавторы:
Лемешко Валерия Александровна;
ORCID: https://orcid.org/0000-0002-7452-6940;
eLibrary SPIN: 6391-6847;
e-mail: lera.lemeschko@yandex.ru

Ратушняк Светлана Сергеевна;
ORCID: https://orcid.org/0000-0001-7967-5112;
eLibrary SPIN: 7419-7690; e-mail: svetlanarshk@gmail.com

Назарова Евгения Валерьевна, к.м.н.;
ORCID: https://orcid.org/0000-0003-0380-6205;
eLibrary SPIN: 4788-7407; e-mail: evallergo@yandex.ru

Natalia I. Ilina, MD, Dr. Sci. (Med.), Professor;
ORCID: https://orcid.org/0000-0002-3556-969X;
eLibrary SPIN: 6715-5650; e-mail: instimmun@yandex.ru

Vitaly V. Omelyanovskiy, MD, Dr. Sci. (Med.), Professor;
ORCID: https://orcid.org/0000-0003-1581-0703;
eLibrary SPIN: 1776-4270;
e-mail: vvo@rosmedex.ru

Наталья Ивановна Ильина, д.м.н., профессор;
ORCID: https://orcid.org/0000-0002-3556-969X;
eLibrary SPIN: 6715-5650; e-mail: instimmun@yandex.ru

Омельяновский Виталий Владимирович,
д.м.н., профессор;
ORCID: https://orcid.org/0000-0003-1581-0703;
eLibrary SPIN: 1776-4270; e-mail: vvo@rosmedex.ru