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A pharmaco-economic analyzis of treating severe uncontrolled child asthma with omalizumab – actual Russian clinical practice data.

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Background: *Omalizumab is the first and yet the only biopreparation for asthma which combines high efficiency and high cost. The clinical-economic expediency of using omalizumab in asthmatic children has not been previously studied in Russia.* ***Objective:*** *Our aim was to evaluate the clinical and economic expediency of using omalizumab as additive treatment (to basic or supporting therapy) in children with severe uncontrolled atopic asthma under the Russian economic conditions.* ***Methods:*** *We conducted a mathematical simulation of asthma treatment in children with an increased frequency of hospitalization (9 times per year) with an average monthly omalizumab requirement of 558 mg. The model is based on the Markov chain. The model includes direct and non-direct costs. The planning horizons were 2 and 5 years. We analyzed the efficiency and utility of the costs and their influence on the budget. The stability of received data is proven by sensitivity analysis.* ***Results:*** *Over a 5-year planning horizon the cost of an additional year of quality life (due to using omalizumab) was 1,259,185 roubles, while the "society's solvency" is 1 341 308 roubles (cost utility analysis). It takes 39,820 rubles to prevent one hospitalization with omalizumab over a 5-year planning horizon (cost efficiency analizis), which is comparable to the cost of hospitalization (43,141 rubles). Total costs for treating 100 children with asthma, 7 of which would be treated with omalizumab, were equal to the amount of money which is enough to treat 105 children without omalizumab (analysis of budgetary influence).* ***Conclusion:*** *The analyses of cost efficiency and utility have shown that the strategy of using omalizumab together with standard treatment is economically expedient. Budgetary influence analysis has not detected a significant burden on the budget.*
Keywords: *pharmacoeconomics, mathematical simulation, asthma, omalizumab.*

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RATIONALE

The prevalence of bronchial asthma (BA) in various countries ranges from 1 to 18% [1]. According to the information obtained in the framework of an epidemiological study on the program ISAAC (International Study of Asthma and Allergy in Childhood) conducted in the Russian Federation (RF), the prevalence of BA symptoms is comparable in different regions of the country, ranging from 10.6 to 16.9% [2, 3]. According to the results of an epidemiological study GA2LEN (Global Allergy and asthma European Network), the prevalence of BA symptoms in 2008-2009 in Moscow and Tomsk in adolescents aged 15-17 years was 19.9%, the prevalence of diagnosis — 7.2%; in 5.1% of adolescents the BA diagnosis was verified. [4] These figures are significantly higher than the official statistics' data on prevalence of asthma [2, 4].

The analysis of direct medical and indirect costs in children and adults with BA in the Russian Federation showed that there were 8.5 billion rubles of only medical costs [5]. Treatment of BA is complex, made up of directly drug therapy, exposure to risk factors, education of the patient and his family members (inhalation technique and regime, rules of continuous monitoring), measures to eliminate the trigger factors, specific immunotherapy, and non-drug methods [1-3]. Currently, there are various treatment strategies, depending on the severity and in accordance with the therapy steps, for children with poor control of BA. One of variants for patients with severe persistent uncontrolled asthma is the addition to the basic treatment of the humanized monoclonal antibodies to immunoglobulin E — omalizumab [1]. In randomized clinical trials (RCT), the addition of omalizumab to standard therapy clinically significantly reduced the frequency of exacerbations of BA, some studies demonstrated also a decreased need for inhaled glucocorticosteroids (IGCS) [6]. Currently we know about 11 RCTs of Omalizumab in total, nine of which included patients aged 12 to 85 years (mean age 40-43 years) [6], one — 6 to 20 years [7], and one — children of 6-11 years [8]. The results of all RCTs are in good agreement with each other in the expression of the obtained effects of omalizumab. No clinically significant dependence of the omalizumab effect on the age of patients in the range of 6-85 years is defined (including stratification of age groups in RCTs involving patients of 12-85 years), although in general the effectiveness of omalizumab in children is higher than in adults [6].

Additional financial costs associated with the use of omalizumab as an innovative medical technology require pharmacoeconomic rationale, which was the aim of the present study [9]. It should also be noted that the most informative and important for decision-making in the national health care system are the results of clinical and economic studies based on data from real clinical practice, reflecting the effectiveness and safety of drugs in individual patients.

METHODS

Mathematical model

Clinical and economic examination of the use of omalizumab in the treatment of children with BA in the Russian Federation was carried out on the basis of mathematical modeling by cost-utility analysis (CUA) and "cost-effectiveness analysis, (CEA). As the performance indicators there was the cost-utility ratio (CUR) and the cost-effectiveness ratio (CER) with the calculation of incremental coefficients (ICUR and ICER) [10, 11]. The results are evaluated in terms of "the threshold of society's willingness to pay" for the extra year of quality adjusted life years (cost-effectiveness threshold), which is calculated as triple gross domestic product (GDP) per capita. A budget impact analysis (BIA) was carried out additionally [11].

Modeling perspective

Indicators of SUA and SEA were calculated from the position (point of view) of the health system and society as a whole, the BIA is made only from the position of the health care system. The modeling used a 3.5% discount rate of treatment costs and outcomes. The discount rate of foregone GDP was equal to the refinancing rate by the Central Bank of the Russian Federation for 2015 (8.25% per year).

Initial data

Modeling was carried out on the basis of data on the experience of use of omalizumab in the Scientific Center of Children's Health (SCCH) of Russian Ministry of Health for the period of 2007-2015 (age of 6-17 years, n = 97) [unpublished data]; results of RCTs IA-05EUP (european population of children aged 6-11 years, omalizumab group — n = 421, placebo group — n = 192) [8]; results of eXpeRience prospective observational study [12]. It should be noted that IA-05EUP RCT is currently the only one in which the effect of omalizumab was investigated exclusively in the pediatric population [8]. The average age of children in the SCCH study was 14 years, according to IA-05EUP RCT data — 7 years. The average frequency of hospitalizations prior to the appointment of omalizumab — 9.4 per year according to SCCH data, and more than 2 per year according to IA-05EUP RCT. Average dose of omalizumab 558 mg/month according to SCCH (not shown in IA-05EUP RCT) is included in the model to reflect the specificity of the drug in the Russian Federation better. Values of other modeling parameters (efficiency of omalizumab, the proportion of "responders", medium dosage of inhaled IGCS, gender distribution) in researches of SCCH and IA-05EUP RCT did not differ fundamentally. According to SCCH, omalizumab increased the proportion of children with partial or full control of BA (in IA-05EUP RCT this index of effectiveness was not examined). The model also included similar results of BA control improvement, obtained in two-year eXpeRience study in predominantly adult (12 to 85 years) patients population.According to SCCH data, omalizumab allowed to reduce the average dose of IGCS in children. These data are consistent with the same effect of omalizumab described in RCT on the patient population aged 12 years or older [13]; model included the effect size obtained in RCT.

Characteristics of costs and indexes of effectiveness

The list of costs is made on the basis of the tariff agreement of the territorial funds of obligatory medical insurance in St. Petersburg for 2015; programs of state guarantees of free medical care provision to citizens for 2015 and the planning period of 2015 and 2016 [14]; public procurement [15]; State Register of limiting selling prices data [16]. Direct costs included the cost of therapy with investigational medicinal products; the cost of medical examination prior to treatment; cost of concomitant drug therapy. Indirect costs included costs of social insurance fund for the payment of temporary disability allowance; foregone GDP for the year. Criteria of treatment effectiveness: QALYs (Quality adjusted life years) — returned years of qualitative life; the incidence of severe exacerbations [17]; the level of BA control on a standard questionnaire ACQ (Asthma Control Questionnaire) [18].

Model structure

Modeling horizon was 2 years and 5 years. Modelled population: children aged 6 to 17 years with severe uncontrolled atopic BA; the average frequency of hospitalizations prior to the appointment of omalizumab and the average required dose of omalizumab corresponded the SCCH data (see above).

Medical comparison technologies

Strategy 1: standard therapy, which is understood as the combined basic therapy with long-acting β2-agonists (LABA) and IGCS; 35% of patients took leukotriene receptor antagonist (montelukast) in addition to basic therapy [8, 19].

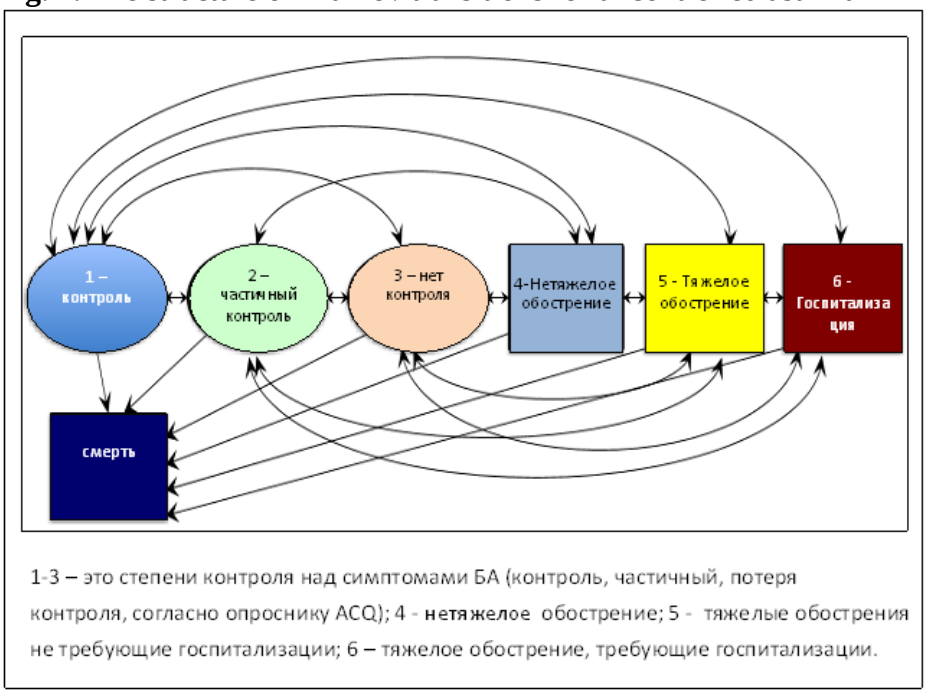
Strategy 2: omalizumab + standard therapy.

BA is a chronic disease and Markov transitions [18] are the most suitable for its modeling. We used 6 conditions for modeling:

1 — complete control of BA;
2 — partial control of BA;
3 — absence of BA control;
4 — a mild exacerbation (mild to moderate);
5 — a serious exacerbation, not requiring hospitalization;
6 — severe exacerbation requiring hospitalization [20].

Each condition may transit to any other, length of the condition from transition to transition (cycle) is 1 week (figure 1).

Fig. 1. The structure of Markov transitions for uncontrolled asthma



From left to right, top to bottom:
1 – control 2 – partial control 3 – no control 4 – mild exacerbation 5 – severe exacerbation 6 – hospitalization
Death

Note. 1-3 are degrees of BA symptoms control (control, partial control, loss of control, according to the ASQ questionnaire); 4 – mild exacerbation; 5 – severe exacerbation not requiring hospitalization; 6 - severe exacerbation requiring hospitalization.

The number of modeled population

Estimation of number of children aged 6-17 years with severe uncontrolled atopic BA was performed according to Rosstat [21] and Ministry of Health data [22, 23] on the number of Russian population and the overall incidence of asthma, as well as epidemiological data [5]. While the prevalence of atopic BA in adult patients is 69,3−72,8% [24], in children given variant of asthma occurs in 90−95% of cases [2, 3]. Estimation is presented in table 1.

Table 1. Evaluation of the number of patients with severe uncontrolled atopic BA in the Russian Federation * among those aged 6-17 years (according to [2, 3, 5])

Data sources	Number of people with BA	Estimation of the number of individuals with severe uncontrolled atopic BA
Russian Ministry of Health (patients standing on the account)	228403	20 145-21 264
Epidemiological studies	1516119	133 722-141 151

Note.*** - the population of Crimea is not counted. BA – bronchial asthma.

Markov transitions

Markov transitions for standard therapy

To simulate clinical conditions (see fig. 1) in patients with uncontrolled BA receiving standard therapy (high doses of IGCS and LABA), the transition matrixes of the pharmacoeconomic analysis performed by J. Willson et al. were used (2014) [20]. Herewith each condition was correlated with the corresponding QALYs index:

1st state — QALYs 0,937;
2 — 0.907;
3 — 0.728;
4 — 0.649;
5 — 0.570;
6 — 0.330 [20].

Adaptation of the transition matrix with an increase in the initial (prior to the appointment of omalizumab) hospitalization rates to 9.4 per year was carried out for Markov's modeling according to SCCH data. It was assumed that herewith patients receive standard therapy in full.

Markov transitions of standard therapy with the addition of omalizumab were extrapolated by applying the above-described known clinical effects of omalizumab to Markov transitions for standard therapy [8, 12, 13].

Outcomes

Clinically significant exacerbations

Acute or subacute episode of progressive deterioration of the patient's condition due to airway obstruction was considered as BA exacerbation [20]. The severity of an exacerbation was defined by the severity of symptoms, as well as the by the volume of required therapy and duration of the condition. Thus, a mild exacerbation (mild to moderate severity — state 4 in the model) was considered an acute deterioration and the occurrence of one or more BA symptoms going out of the frame of habitual indexes of previous 2 days [20], lasting for up to 2 days, requiring use of emergency drugs (salbutamol), and doubling the dose of basic therapy for a short period. Severe exacerbations lasted for 3 days or more, and were divided into two states — not requiring (condition 5 in the model) and requiring (condition 6 in the model) hospitalization. Volume of therapy for these conditions included emergency drugs, doubling the dose of basic therapy (Symbicort and Seretide, respectively), and the additional appointment of nebulizer therapy (Pulmicort and Flomax). In case of inadequate or absent effect, the model envisaged emergency measures and rapid relief of status asthmaticus (model 6 — in conditions of intensive care unit and day hospital). According to IA-05EUP RCT, omalizumab reduced the incidence of severe exacerbations not requiring hospitalization to 24.2% from initial level, and the incidence of severe exacerbations with hospitalization to 30.5% from initial level [8].

The level of BA control

In an RCT on the effectiveness of the Xolair drug for BA as the leading drug (Evaluate. Xolair for Asthma as Leading Treatment, EXALT), in adult patients with BA, the addition of omalizumab significantly improved control of the disease, according to the results of the ACQ questionnaire [20]. In IA-05EUP RCT, this effectiveness index has not been studied in children [8], but the report of the British National Institute for Health and Care Excellence (NICE) for 2013 [6] offered to extrapolate the missing results, including those on improvement of BA control, from adult RCTs involving patients from 12 to 85 years at pharmacoeconomic modeling in the pediatric population. International Society for Pharmacoeconomics and Outcomes Research (ISPOR), published in 2014 its version of omalizumab pharmacoeconomic analysis, including an analysis of the pediatric population [25], has the same point of view. We have used the results of a two-year international supervisory eXperience register (patients of 12-85 years), in which omalizumab therapy, after 48 weeks, allowed to achieve complete control of BA in 38.4% of patients and partial — in 46.6%. These conditions remained stable after 96 weeks — 41.1 and 46.0%, respectively [12].

Mortality

Mortality statistics of patients with BA in RF is not known, and that is why we used the extrapolation of risk of death compared to the normal population of patients with BA in the United Kingdom based on open data [26] in the model. The average risk of death for patients with BA out of exacerbation among age groups in relation to the general population in the UK was 0.8 (which was interpreted by us as no difference), and during status asthmaticus risk of death increased 5.7 times. In the modeling, we assumed that the mortality in a state of severe exacerbation with hospitalization in Russia also increased 5.7 times.

Reducing the dose of IGCS

At least two RCTs on adults showed the decrease in dosage of IGCS [13, 27] during therapy with omalizumab. There are no convincing data for the pediatric population yet. In this context, the probability of reducing the dose of IGCS during therapy with omalizumab was not taken into account.

Cost of medicines

According to the manufacturers data, the cost of one pack of omalizumab (150 mg) is 16 806.56 rubles. According to SCCH, children require an average amount of 558 mg of omalizumab in a month, so the average cost of treating a child with omalizumab is 15 630.10 rubles per week (cycle).

Cost of the symptoms relief with short-acting β_2 -agonist has been calculated from the frequency of needed inhalations proposed by J. Willson et al. [20]. One of the effects of omalizumab is number of short-acting β2-agonists using days reduction for 14.4% [28].

Costs of standard treatment are given in table 2.

Table 2. Cost of the standard therapy for the treatment of bronchial asthma (IGCS + LABA)

Trade name	INN, pack (number of doses)	Dosage (Age)	Price per pack, rubles	Price per cycle (7 days), rubles
Symbicort	Budesonide 160 mcg + formoterol 4.5 mcg (120	1500 mcg/day (≥ 12 years)	1006.70	1101.08

	doses)			
Seretide	Fluticasone 250 mcg + salmeterol 25 mcg (120 doses)	1171 mcg/day (≥ 12 years)	1632.10	445.94
Seretide Multidisk	Fluticasone 250 mcg + salmeterol 50 mcg (60 doses)	1171 mcg/day (≥ 12 years)	1204.93	658.45
Pulmicort	Budesonide suspension 0.5 mg/ml, 2 ml (20 vials)	1500 mcg/day (<12 years)	1028.30	359.91
Singulair	Montelukast 5 mg (1 tablet)	1 tablet per day (≤ 14 years)	35,18 (1 tablet)	42.68
Singulair	Montelukast 10 mg (1 tablet)	1 tablet per day (≥ 15 years)	40.68 (1 tablet)	50.31
Salbutamol	Salbutamol, a dose of 100 mcg (90 doses)	5 inhalations/day (≥ 12 years)	47,40	35,00
Berodual	Ipratropium bromide + fenoterol, solution for inhalation 0.25 mg + 0.5 mg/ml, 20 ml (1 vial)	1 ml per reception 3 times/day (<12 years)	210.08	220.58

Note . INN - International Nonproprietary Name. Symbicort, Seretide and Seretide Multidisk were interchangeable, the probability of use of each of them in the modeling considered equal. In case of exacerbation, doses of Symbicort, Seretide, Seretide Multidisk, Pulmicort, salbutamol and Berodual doubled. IGCS + LABA — inhaled steroids + long-acting β2-agonists.

Table 3. The average cost of all medical services per single cycle (7 days), depending on the condition

Condition	1	2	3	4	5	6
Cost of all medical services in 7 days, rub	66.97	98.17	266.87	796.16	4 172.40	24 642.16

Note. 1 - complete control, 2 - partial control, 3 – absence of control, 4 - mild exacerbation, 5 - severe exacerbation without hospitalization, 6 - severe exacerbation requiring hospitalization.

Cost of medical services

The list of necessary medical services is made on the basis of approved clinical guidelines [29, 30] and is presented in the table 3. Were included: cost of the standard therapy for the BA treatment (IGCS + LABA); ambulance and hospitalization, exacerbation, treatment of respiratory failure of 2-3-th degree; visit to pediatrician, allergist-immunologist/pulmonologist; the pediatrician house call; spirometry cost. Frequency of use depended on the condition (see figure 1).

Adverse events during treatment with omalizumab

Application instructions of omalizumab [31] do not describe any adverse events that might lead to additional costs; no pharmacoeconomic analysis of omalizumab contains such amendments [6, 25].

Treatment with systemic GCS

Foreign tactics of BA exacerbations treatment include immediate appointment of GCS orally. In Russia, the available pediatric clinical practice adheres to the strategy of doubling the dose of basic drugs, and supplementary appointment of nebulizer therapy. Systemic GCS are administered in the absence of other opportunities of cupping the condition and life-threatening exacerbations. In this model, the use of systemic corticosteroids was meant for the 6 condition — the provision of medical care in life-threatening exacerbation of asthma in the hospital (intensive care unit), the cost of systemic GCS was included in the total cost of hospitalization, estimated according to the tariff agreement of obligatory medical insurance.

Indirect costs of medical care

In case of child illness, according to the law [32], a sick-list is issued to one of the parents or to guardian, or to relative. Term of sick-list depends on the age of the child: up to 7 years — the entire period of illness in outpatient and inpatient treatment, from 7 to 15 years — up to 15 days in each case of the disease in outpatient and inpatient treatment, 16 to 17 years — up to 3 days in each case of the disease, and only in outpatient treatment. In case of outpatient treatment, first 10 days shall be reimbursed in full from the Social Insurance Fund, in case of hospitalization — in full, regardless of the duration of treatment. In addition, in the aforesaid period, GDP losses occur.

According to Rosstat and Russian Ministry of Health, among 6-17 year old children with BA, the proportion of 6-year-old was identified as 7.0%, the proportion of 7-15 year olds — as 68.5%, the proportion of 16-17-year-olds — as 24.5% [21-23]. On the basis of these data, the average duration of sick-list for adult relative was calculated in the model. It was believed that adult relative receives temporary disability allowance amounting 100% of average earnings. [32] The calculation of payments was based on Rosstat data for 2013, as data for 2014-2015 were not published. It has been assumed that severe asthma exacerbations without hospitalization results in 3 days of outpatient care of a child (by definition — worsening of BA symptoms for 3 days or more, see above), light and mild exacerbation — in 2 days (by definition — worsening of BA symptoms for 2 days, see above) [20]. The duration of hospitalization was unstable modeling value, but the average was 14 days.

Sensitivity analysis

Multilateral sensitivity analysis was conducted to test the resistance of the basic scenario results to changes. QALYs values changed within their 95% confidence interval.The cost of medicines and medical services changed within normal limits for this type of analysis from -25 to + 25% from the values in the basic scenario.

RESULTS

The cost of each treatment strategy for the patient of target group was estimated, total costs in case of the use of compared strategies were calculated. Efficiency criteria were: quality of life ("utility") and frequency of severe exacerbations requiring hospitalization. The highest total costs were recorded in case of omalizumab strategy application at the modeling horizon of 2 years — 2 033 426 rubles (only standard therapy costs 1 584 416 rubles), and at the modeling horizon of 5 years — 4 752 074 rubles (only standard therapy costs 3 780 259 rubles). As can be seen from fig. 2 and 3, omalizumab strategy reduces the cost of medical services in 2 times — from 902 863 to 442 622 rubles at a two-year modeling and from 2 162 575 to 1 059 914 rubles during five-year modeling. This decrease is possible due to the decrease in frequency of hospitalizations (see below), cost of which is more than 96% of the medical services cost.

As can be seen from table 4 , ICUR was 1 471 412 rubles for an additional quality adjusted life year at a two-year modeling horizon and 1 259 185 rubles at a five-year. In the first case, the willingness-to-pay threshold (1 341 308 rubles) was exceeded, in the second — was not.

Table 4. Cost-utility and cost-effectiveness ratios, incremental cost-utility and incremental cost-effectiveness ratios

Indicators	2 years horizon of modeling		5 years horizon of modeling	
	Standard therapy	**Omalizumab + standard therapy**	**Standard therapy**	**Omalizumab + standard therapy**
The total cost, RUR	1584416	2033426	3780259	4752074
Increase cost, RUR	Reference strategy	449 009.93	the reference strategy	971 815.19
Cumulative utility *	1,226	1,532	3,052	3,824
Increase the usefulness	Reference strategy	0.305	Reference strategy	0.772
CUR, rub.	1291842	1327619	1238514	1242686
ICUR, rub.	Reference strategy	1471412	Reference strategy	1259185
Cumulative effectiveness (number of admissions)	18.75	9.08	47.28	22.87
Effictiveness increase (decrease in the number of hospitalizations)	Reference strategy	9.67	Reference strategy	24.40
CER, RUR	84493	223896	79958	207757
ICER, RUR	Reference strategy	46433	Reference strategy	39821

Note . * - QALYs, quality adjusted life years. CUR - the ratio of costs to the quality adjusted life years, ICUR - additional costs for 1 quality adjusted life year, CER - the ratio of costs to reduction in the number of hospitalizations, ICER - additional costs for 1 reduced hospitalization.

Strategy of treatment with omalizumab prevented 9.7 cases of severe exacerbations with hospitalization per patients within 2 years and 24.4 cases — within 5 years; reduced the mortality of patients by 0.06% within 2 years and by 0.22% for 5 years; reduced the percentage of patients with the absence of BA control by 19.7% at the end of 2 years and by 19.5% after 5 years of modeling.

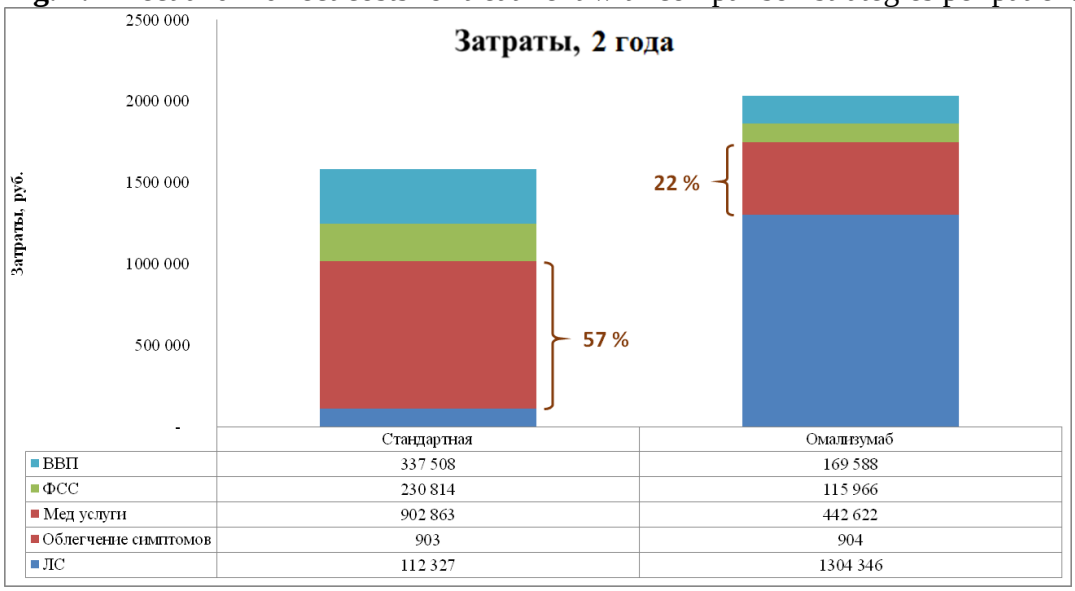
Preventing of one hospitalization per year due to use of omalizumab costs additional 46 433 rubles (ICER indicator) at a two-year horizon of modeling, or 39 821 rubles at a five-year horizon (see table 4), which is comparable to the cost of hospitalization — 43 141 rubles (CHI tariff agreement).

Budget impact analysus (BIA) is made from the point of view of regional and federal budgets and includes only direct costs. It is shown that the additional costs for the treatment of ~ 7% of children with omalizumab equaled to the cost of treatment 5 children out of 100 without omalizumab (table 5).

Table 5. Analysis of the impact on the budget per 100 treated patients with severe uncontrolled BA (9 hospitalizations per year), the modeling horizon - 2 years

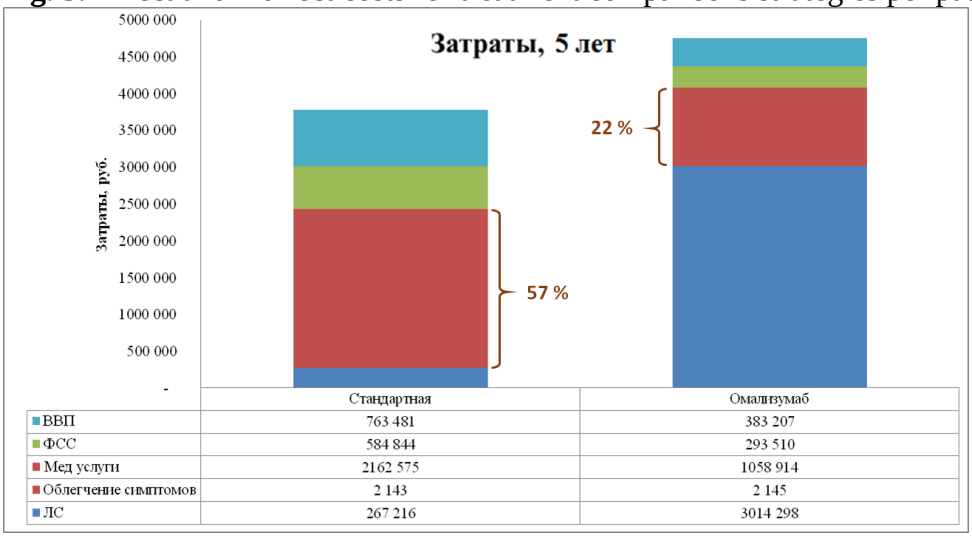
The sum of direct costs per patient for 2years	Only standard therapy	1 016 093		
	Standard therapy + omalizumab	1 747 872		
The proportion of patients with omalizumab added to standard therapy		10.0%	7.1%	6.8%
The amount of costs when using	Only standard therapy	101 609 339	101 609 339	101 609 339
	Standard therapy + omalizumab	108 927 120.32	106 804 963.72	106 585 430
Additional costs for the use of omalizumab		-7 317 781	-5 195 625	-4 976 091
The number of patients that can be treated if cancel omalizumab		-7	-5	-4

Fig. 2. Direct and indirect costs for treatment with comparison strategies per patient for 2 years



Costs, RUR; Costs, 2 years
Standard, Omalizumab
GDP, SIF, Medical services, Relief of symptoms, Drugs

Fig. 3. Direct and indirect costs for treatment comparisons strategies per patient over 5 years



Sensitivity analysis

ICUR and ICER indexes for a five-year horizon of modeling behaved consistently and did not exceed the society's willingness-to-pay threshold in 70% of iterations.

DISCUSSION

Summary of key research findings

Cost-utility and cost-effectiveness analyzes have shown that the strategy of "omalizumab + standard therapy" is economically expedient. Analysis of the impact on the budget did not reveal a significant burden on the budget.

Key findings discussion

Clinical and economic expediency evaluation of use of omalizumab as additional therapy (to the basic or maintenance therapy) in children with severe uncontrolled atopic BA was carried out in the Russian economic conditions. An important feature of the present study was that the modeling was based on the data on the omalizumab use experience in SCCH of the Russinan Ministry of Health for the period of 2007-2015 (т = 97). Omalizumab is registered both in Russia and abroad, and from March 2016 it is introduced in the list of vital and essential medicines in Russia. The study considered two horizons of modeling — 2 years and 5 years. Herewith, the treatment strategy with only standard therapy was compared with standard therapy treatment strategy with the addition of omalizumab. The model included direct and indirect costs. Main efficacy parameters were quality of life and incidence of severe exacerbations. Level of BA control and asthma mortality level were additionaly asessed. Original Markov transitions used in the modeling were obtained by other authors on the extensive representative sample of patients with BA in controlled conditions [20] and tailored to our needs.

As a result, ICUR and ICER were below the "society's willingness-to-pay threshold" in children with a high frequency of hospitalization (9 per year) and average dose of omalizumab 558 mg/month. The cost of preventing one hospitalization per year was 46 432.60 rubles in 2-year modeling and 39 820.70 rubles in five-year modeling. Adding omalizumab to therapy of 6.8-7.1% of patients will result in an additional cost, on which it is possible to treat 5 of 100 patients with only standard therapy.

In the scientific literature there are pharmacoeconomic evaluations of the expediency of using omalizumab abroad. NICE systematic review of omalizumab [6] brings the results of six pharmacoeconomic studies. All six studies included adult populations of patients with uncontrolled BA, herewith children aged 12-17 were considered as "adults", with minimal age correcting factor or without any. In five of the six studies, ICUR was evaluated as the main parameter, and its asessment varied considerably in different studies. Only in one study from Canada healthcare perspective, omalizumab was found economically expedient in all patients with uncontrolled BA [33]. Two studies concluded the possible economic expediency of using omalizumab in the subgroup of severe patients in the US [34] and Sweden [35]. In another study, use of omalizumab in the United States was considered inappropriate until the manufacturer will achieve a significant reduction in the price of the drug [36]. Two studies concluded that omalizumab is economicaly inexpedient in the US [37] and Italy [38]. NICE brings its own pharmacoeconomic evaluation and recognizes omalizumab economically expedient with the healthcare perspective of the UK, but only for severe subgroups of patients [6]. One of the recent pharmacoeconomic analyzes was carried out by ISPOR in 2014 with the EU and the UK healthcare perspective [25]. Omalizumab is recognized as cost-effective for both adults and children with severe form of BA [25]. Herewith, a separate analysis was conducted only for children aged 6-11 years, while children aged 12-17 were attributed to the adult population.

Thus, this pharmacoeconomic study, conducted from the position of Russian healthcare, corresponds to the pharmacoeconomic evaluations from other countries: the use of omalizumab is appropriate in the subgroups of severe patients. The distinctive featre of this work is creation of a separate model for children of 6-17 years on the basis of data on Russian pediatric practice of BA treatment.

CONCLUSION

The strategy of "omalizumab plus standard therapy" is economically expedient in children with high demand for the emergency medical care and hospitalization.The estimated proportion of these children does not exceed 7.1% among children with BA, and the use of omalizumab in this subgroup will not lead to a significant burden on the budget.

SOURCE OF FINANCING

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CONFLICT OF INTEREST

Over the past 3 years, A.S. Kolbin participated in research projects, followed by the preparation of reports on health technology assessment, in writing papers and preparing presentations on clinical and economic analysis for the following companies (in alphabetical order): Allergan, Amgen, Astellas, Boehringer Ingelheim, Novartis, Novo Nordisk, Pfizer, Roche, P-Pharma, Sanofi-Aventis.

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REFERENCES

1. ginasthma.org [Internet]. GINA. Global Strategy for Asthma Management and Prevention [updated 2016; cited 2016 Aug 21]. Available from: http://ginasthma.org/.
2. *Аллергия у детей: от теории — к практике* / Под ред. Л.С. Намазовой-Барановой. — М.: Союз педиатров России; 2010–2011. — 668 с. [*Allergiya u detei: ot teorii — k praktike*. Ed by L.S. Namazova-Baranova. Moscow: Soyuz pediatrov Rossii; 2010–2011. 668 p. (In Russ).]
3. Вишнева Е.А., Намазова-Баранова Л.С., Алексеева А.А., и др. Детская астма: ключевые принципы достижения контроля на современном этапе // *Педиатрическая фармакология*. — 2013. — Т.10. — №4. — С.60–72. [Vishneva EA, Namazova-Baranova LS, Alekseeva AA, et al. Infant asthma: key principles of control attainment in the modern stage. *Pediatric pharmacology*. 2013;10(4):60–72. (In Russ.)] doi: 10.15690/pf.v10i4.756.
4. Намазова-Баранова Л.С., Огородова Л.М., Томилова А.Ю., и др. Распространенность астмаподобных симптомов и диагностированной астмы в популяции подростков // *Педиатрическая фармакология*. — 2009. — Т.6. — №3. — С.59–65. [Namazova-Baranova LS, Ogorodova LM, Tomilova AYu, et al. Prevalence of asthma-like symptoms and diagnosed asthma in the population of adolescents. *Pediatric pharmacology*. 2009;6(3):59–65. (In Russ).]

5. *Социально-экономическое бремя бронхиальной астмы и хронической обструктивной болезни легких в Российской Федерации* / Бюллетень Экспертного совета по здравоохранению Комитета Совета Федерации по социальной политике и здравоохранению Федерального собрания Российской Федерации. — М.: ФОЛСТЭК; 2010. — 16 с. [*Sotsial'no-ekonomicheskoe bremya bronkhial'noi astmy i khronicheskoi obstruktivnoi bolezni legkikh v Rossiiskoi Federatsii*. Byulleten' Ekspertnogo soveta po zdravookhraneniyu Komiteta Soveta Federatsii po sotsial'noi politike i zdravookhraneniyu Federal'nogo sobraniya Rossiiskoi Federatsii. Moscow: FOLSTEK; 2010. 16 p. (In Russ).]
6. nice.org.uk [Internet]. *Omalizumab for treating severe persistent allergic asthma (review of technology appraisal guidance 133 and 201)*. National Institute for Health and Clinical Excellence; 2013. 64 pp.
7. Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-ige) for asthma in inner-city children. *N Engl J Med*. 2011;354(11):1005−1015. doi: 10.1056/nejmoa1009705.
8. Lanier B, Bridges T, Kulus M, et al. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol*. 2009;124(6):1210−1216. doi: 10.1016/j.jaci.2009.09.021.
9. *Основные понятия в оценке медицинских технологий. Методическое пособие* / Под ред. А.С. Колбина, С.К. Зырянова, Д.Ю. Белоусова. — М.: Издательство «ОКИ»; 2013. — 42 с. [*Osnovnye ponyatiya v otsenke meditsinskikh tekhnologii. Metodicheskoe posobie*. Ed by A.S. Kolbin, S.K. Zyryanov, D.Yu. Belousov. Moscow: Izdatel'stvo «OKI»; 2013. 42 p. (In Russ).]
10. Приказ Минздрава РФ от 27 мая 2002 г. № 163 «Об утверждении отраслевого стандарта «Клинико-экономические исследования. Общие положения». [Federal Law of Russian Federation №163 of 27 May 2002. «Ob utverzhdenii otraslevogo standarta «Kliniko-ekonomicheskie issledovaniya. Obshchie polozheniya». (In Russ).] Доступно по http://www.webapteka.ru/phdocs/doc2667.html. Ссылка активна на 20.07.2016.
11. Mauskopf JA, Sullivan SD, Annemans L, et al. Principles of good practice for budget impact analysis: report of the ISPOR task force on good research practices — budget impact analysis. *Value Health*. 2007;10(5):336−347. doi: 10.1111/j.1524-4733.2007.00187.x.
12. Braunstahl GJ, Chen C, Maykut R, et al. The eXpeRience registry: The real-world effectiveness of omalizumab in allergic asthma. *Respir Med*. 2013;107(8):1141−1151. doi: 10.1016/j.rmed.2013.04.017.
13. Soler M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J*. 2001;18(2):254–261. doi: 10.1183/09031936.01.00092101.
14. spboms.ru [интеренет]. Официальный сайт Территориального фонда ОМС Санкт-Петербурга [Official website of Territorial'nogo fonda OMS Sankt-Peterburga. (In Russ).] Доступно по: https://spboms.ru/. Ссылка активна на 20.07.2016.
15. zakupki.gov.ru [интеренет]. Официальный сайт Единой информационной системы в сфере закупок. [Official website of Edinoi informatsionnoi sistemy v sfere zakupok. (In Russ).] Доступно по: http://www.zakupki.gov.ru/epz/main/public/home.html. Ссылка активна на 20.07.2016.
16. grls.rosminzdrav.ru [интеренет]. Государственный реестр лекарственных средств. Безопасность лекарственных препаратов. [Государственный реестр лекарственных средств. Безопасность лекарственных препаратов. (In Russ).]Доступно по: http://grls.rosminzdrav.ru/Default.aspx. Ссылка активна на 20.07.2016.
17. EuroQol Group. EuroQol — a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199–208. doi: 10.1016/0168-8510(90)90421-9.
18. Juniper EF, O'Byrne PM, Guyatt GH, et al. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14(4):902–907. doi: 10.1034/j.1399-3003.1999.14d29.x.

19. Bousquet J, Siergiejko Z, Świebocka E, et al. Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma. *Allergy*. 2011;66(5):671–678. doi: 10.1111/j.1398-9995.2010.02522.x.
20. Willson J, Bateman ED, Pavord I, et al. Cost effectiveness of tiotropium in patients with asthma poorly controlled on inhaled glucocorticosteroids and long-acting β-agonists. *Appl Health Econ Health Policy*. 2014;12(4):447–459. doi: 10.1007/s40258-014-0107-8.
21. gks.ru [интеренет]. Федеральная служба государственной статистики. Официальная статистика. [Federal State Statistics Service. Russia in figures. (In Russ).] Доступно по: http://www.gks.ru/. Ссылка активна на 20.07.2016.
22. Минздрав РФ. *Общая заболеваемость детского населения России (0−14 лет) в 2014 году. Статистические материалы*. Часть VI. — М.; 2015. — 145 с. [Minzdrav RF. *Obshchaya zabolevaemost' detskogo naseleniya Rossii (0−14 let) v 2014 godu. Statisticheskie materialy*. V.4. Moscow; 2015. 145 p. (In Russ).]
23. Минздрав РФ. *Общая заболеваемость детского населения России (15−17 лет) в 2014 году. Статистические материалы*. Часть X. — М.; 2015. — 149 с. [Minzdrav RF. *Obshchaya zabolevaemost' detskogo naseleniya Rossii (15−17 let) v 2014 godu. Statisticheskie materialy*. V.10. Moscow; 2015. 149 p. (In Russ).]
24. Чучалин А.Г. *Пульмонология. Национальные руководства*. — М.: ГЭОТАР-Медиа; 2009. — 957 с. [Chuchalin AG. *Pul'monologiya. Natsional'nye rukovodstva*. Moscow: GEOTAR-Media; 2009. 957 p. (In Russ).]
25. Faria R, McKenna C, Palmer S. Optimizing the position and use of omalizumab for severe persistent allergic astma using cost-effectiveness analysis. *Value Health.* 2014;17(8):772–782. doi: 10.1016/j.jval.2014.07.009.
26. Watson L, Turk F, James P, Holgate ST. Factors associated with mortality after an asthma admission: A national United Kingdom database analysis. *Respir Med*. 2007;101(8):1659–1664. doi: 10.1016/j.rmed.2007.03.006.
27. Holgate ST, Chuchalin AG, Hébert J, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy*. 2004;34(4):632–638. doi: 10.1111/j.1365-2222.2004.1916.x.
28. Bardelas J, Figliomeni M, Kianifard F, Meng X. A 26-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the effect of omalizumab on asthma control in patients with persistent allergic asthma. *J Asthma*. 2012;49(2):144–152. doi: 0.3109/02770903.2011.648296.
29. *Федеральные клинические рекомендации по оказанию медицинской помощи детям с бронхиальной астмой*. — М.: Союз педиатров России; 2016. — 33 с. [*Federal'nye klinicheskie rekomendatsii po okazaniyu meditsinskoi pomoshchi detyam s bronkhial'noi astmoi*. Moscow; 2016. 33 p. (In Russ).]
30. Приказ Министерства здравоохранения РФ от 20 декабря 2012 г. N 1119н «Об утверждении стандарта скорой медицинской помощи детям при астме». [Federal Law of Russian Federation №1119н of 20 December 2012. «Ob utverzhdenii standarta skoroi meditsinskoi pomoshchi detyam pri astme». (In Russ).] Доступно по: http://base.garant.ru/70338538/. Ссылка активна на 20.07.2016.
31. Инструкция по применению лекарственного препарата для медицинского применения Ксолар лиофилизат для приготовления раствора для подкожного введения, 150 мг. — М.: МинздравРФ; 2014. [Instruktsiya po primeneniyu lekarstvennogo preparata dlya meditsinskogo primeneniya Ksolar liofilizat dlya prigotovleniya rastvora dlya podkozhnogo vvedeniya, 150 mg. Moscow: MinzdravRF; 2014. (In Russ).]
32. Федеральный закон от 29 декабря 2006 г. N 255-ФЗ «Об обязательном социальном страховании на случай временной нетрудоспособности и в связи с материнством» (с изменениями и дополнениями). [Federal Law of Russian Federation №255-F3 of 29 December 2006. «Ob obyazatel'nom sotsial'nom strakhovanii na sluchai vremennoi

netrudosposobnosti i v svyazi s materinstvom» (as amended and supplemented). (In Russ).] Доступно по: http://base.garant.ru/12151284/#help. Ссылка активна на 20.07.2016.
33. Brown R, Turk F, Dale P, Bousquet J. Cost-effectiveness of omalizumab in patients with severe persistent allergic asthma. *Allergy*. 2007;62(2):149−153. doi: 10.1111/j.1398-9995.2006.01310.x.
34. Oba Y, Salzman GA. Cost-effectiveness analysis of omalizumab in adults and adolescents with moderate-to-severe allergic asthma. *J Allergy Clin Immunol*. 2004;114(2):265−269. doi: 10.1016/j.jaci.2004.05.049.
35. Dewilde S, Turk F, Tambour M, Sandström T. The economic value of anti-IgE in severe persistent, IgE-mediated (allergic) asthma patients: adaptation of INNOVATE to Sweden. *Curr Med Res Opin*. 2006;22(9):1765–1776. doi: 10.1185/030079906x132389.
36. Wu AC, Paltiel AD, Kuntz KM, et al. Cost-effectiveness of omalizumab in adults with severe asthma: results from the Asthma Policy Model. *J Allergy Clin Immunol*. 2007;120(5):1146−1152. doi: 10.1016/j.jaci.2007.07.055.
37. Campbell JD, Spackman DE, Sullivan SD. The costs and consequences of omalizumab in uncontrolled asthma from a USA payer perspective. *Allergy*. 2010;65(9):1141–1148. doi: 10.1111/j.1398-9995.2010.02336.x.
38. Dal Negro RW, Pradelli L, Tognella S, et al. Cost-utility of add-on omalizumab in difficult-to-treat allergic asthma in Italy. *Eur Ann Allergy Clin Immunol*. 2011;43(2):45–53.