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ДОСТИЖЕНИЕ КОНТРОЛЯ ТЯЖЕЛОЙ БРОНХИАЛЬНОЙ АСТМЫ ПРИ ИСПОЛЬЗОВАНИИ ПРЕПАРАТА ДУПИЛУМАБ

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Achievement of Control of Severe Bronchial Asthma When Using Dupilumab

Резюме

Цель исследования оценить возможность достижения контроля тяжелой бронхиальной астмы (БА) при использовании генно-инженерной биологической терапии препаратом Дупилумаб. Материалы и методы. Обследовано 32 пациента тяжелой бронхиальной астмой (8 (25 %) мужчин, средний возраст 58 [28;65]) лет, 24 (75 %) женщин, средний возраст 50 [26;62] лет), которые получали дополнительную терапию препаратом Дупилумаб в течение 12 месяцев. Конечная точка исследования 12 месяцев терапии препаратом Дупилумаб. Аллергический фенотип заболевания регистрировался у 19 (60 %) пациентов, у четверти пациентов — неаллергический и у 5 (15 %) пациентов наблюдалась смешанная БА. Результаты. До назначения генно — инженерной биологической терапии (ГИБТ) у пациентов отмечалась крайне высокая каждодневная потребность в скоропомощных препаратах — около 9 раз в сутки, регистрировались 4 и более обострений в течение предшествующих 12 месяцев до включения в исследование. Спустя 12 месяцев дополнительной терапии препаратом Дупилумаб отмечалось значительное снижение симптомов — у 22 (70 %) пациентов полностью отсутствовали приступы удушья. У 6 пациентов (19 %) в течение последующих 12 месяцев развилось 1 обострение БА, с которым пациенты справились самостоятельно при помощи небулайзерной терапии в домашних условиях. До начала генно-инженерной биологической терапии 10 человек (31 %) получали системные глюкокортикостероиды (СГКС) в дозе от 10 до 5 мг по преднизолону. Через 4 месяца 22 (70 %) пациентам, получающим гормональные препараты, удалось от них отказаться. Через 12 месяцев ни один пациент не принимал СГКС. Заключение. В течение 12 месяцев дополнительной терапии препаратом Дупилумаб пациентам удалось полностью отказаться от приема СГКС. Обострения, требующие госпитализаций, отсутствовали у всех пациентов, включенных в исследование. Полный контроль достигли 22 (69 %) исследуемых, частичный контроль — 10 (31 %). Полностью отсутствовала потребность в короткодействующий бета-агонистов (КДБА) у 27 (85 %) исследуемых.

Ключевые слова: *тяжелая бронхиальная астма, дупилумаб, достижение контроля, генно-инженерная биологическая терапия*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The aim of the study was to evaluate the possibility of achieving control of severe bronchial asthma (BA) using genetically engineered biological therapy with Dupilumab. Materials and methods. The study included 32 patients with severe bronchial asthma (8 (25 %) men, mean age 58 [28; 65]) years, 24 (75 %) women, mean age 50 [26; 62] years) who received additional therapy with Dupilumab for 12 months. The endpoint of the study was 12 months of therapy with Dupilumab. The allergic phenotype of the disease was recorded in 19 (60 %) patients, a quarter of patients had non-allergic phenotype, and 5 (15 %) patients had mixed BA. Results. Before the introduction of genetically engineered biological therapy, patients had an extremely high daily need for emergency medications — about 9 times a day, 4 or more exacerbations were recorded during the previous 12 months before inclusion in the study. After 12 months of additional therapy with Dupilumab, a significant reduction in symptoms was noted — 22 (70 %) patients did not have asthma attacks at all. In 6 patients (19 %), 1 exacerbation of bronchial asthma developed during the next 12 months, which the patients coped with independently using nebulizer therapy at home. Before the start of genetically engineered biological therapy, 10 people (31 %) received systemic glucocorticosteroids (OCS) at a dose of 10 to 5 mg of prednisolone. After 4 months, 22 (70 %) patients receiving hormonal drugs managed to stop them. After 12 months, no patients took OCS. Conclusion. During 12 months of additional therapy with Dupilumab, patients managed to completely stop taking OCS. Exacerbations requiring hospitalization were absent in all patients included in the study. Complete control was achieved by 22 (69 %) subjects, partial control was achieved by 10 (31 %). There was no need for short-acting beta-agonists (SABA) in 27 (85 %) subjects.

Key words: *severe bronchial asthma, dupilumab, achieving control, genetically engineered biological therapy*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Conformity with the principles of ethics

The Local Ethics Committee of the Krasnoyarsk Regional Clinical Hospital and the Local Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education Krasnoyarsk State Medical University named after prof. V.F. Voyno-Yasenetsky of the Ministry of Health of the Russian Federation approved the study (Protocol No. 122/2023 dated November 29, 2023). Patients received medications as regional or federal beneficiaries

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ALT — antileukotrienes, BA — bronchial asthma, BT — biological therapy, LAACA — long-acting anticholinergic agents, LABA — long-acting beta-agonists, ICS — inhaled corticosteroids, NSAIDs – non-steroid anti-inflammatory drugs, FEV_1 — forced expiratory volume in one second, SCS — systemic corticosteroids, SBA — severe bronchial asthma, FVC — maximum air volume that can be exhaled after the maximum deep inspiration.

Introduction

Bronchial asthma (BA) is the second most common chronic respiratory disease in the world reported in almost 330 million patients [1]. Approximately 1.6 million patients with BA are verified just in Russia based on official historical data [2]. However, epidemiological studies demonstrate that this parameter may be significantly higher — around 6 million people [3]. The latest studies have confirmed significant economic effects of BA burden on vulnerable social population strata. Due to this, analysis of the disease course, dedicated costs, and socioeconomic factors becomes the main studied object [4, 5].

The term “socioeconomic burden” includes not only high treatment costs (direct medical expenses), but also costs associated with both temporary or permanent

disability (direct non-medical expenses), limited physical and social activity, and, thus, decreased quality of life of patients and their family members (indirect expenses) [6]. According to the World Health Organization definition, global disease burden is measured by the number of living years lost due to disability. This definition combines living years lost due to the health condition which does not comply with full health criteria and living years lost due to premature mortality [7].

Within the latest decade, severe bronchial asthma (SBA) treatment should be significantly improved thanks to the availability of biological therapy modifying specific cellular signaling pathways. In particular, Dupilumab, a fully human monoclonal antibody, blocks interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling via specific binding with the IL-4Rα-subunit which is common for IL-4 and IL-13 receptor complexes. The drug also blocks IL-4 signaling via type I receptors (IL-4Rα/γc) and IL-4/IL-13 common signaling via type II receptors (IL-4Rα/IL-13Rα). IL-4 and IL-13 are key type 2 inflammatory cytokines (including produced by Th2-lymphocytes) involved in the pathogenesis of atopic diseases [8]. The drug was approved in adults and children over 6 years of age as additional SBA treatment [9]. According to the European Medicines Registry, Dupilumab is recommended in SBA associated with Th2-inflammation, which is characterized by high eosinophil count in peripheral blood, increased nitric oxide levels (FeNO) in the exhaled air, with the requirements for systemic corticosteroids (SCS) in adult patients with allergic BA [10].

Treatment with Dupilumab demonstrates significant therapeutic effects confirmed in many randomized clinical trials (RCTs) [11, 12]. It should be noted that the additional drug therapy provided the increased probability that SCS would not be required and improved clinical outcomes regardless of the SCS dose in patients with steroid-dependent SBA [13, 14, 15].

Aim of the study

Evaluating the possibility of achieving severe bronchial asthma control when using biological therapy with Dupilumab.

Study materials and methods

32 patients with severe bronchial asthma were included into the prospective open observational single-center study: 8 (25 %) males with an average age of 58 [28;65] years and 24 (75 %) females with an average age of 50 [26;62] years followed up in the Pulmonary-Allergy Center of KSBHI "Krai Clinical Hospital" (Krasnoyarsk, Russia). All respondents had their concomitant diseases determined, pulmonary function tests and disease control level assessed, the scope of basic therapy available was clarified as well. The primary endpoint of the study was to assess the efficacy and safety of Dupilumab, to determine the possibility of achieving SBA control. Important study milestones: before starting biological therapy (BT) and 12 months after initiating BT.

Study inclusion criteria: severe BA; age 18-75 years, reversible bronchial obstruction confirmed by pulmonary function tests; basic therapy compliance, possibility of correct basic therapy use, scope of basic therapy corresponding to Steps 4-5 (GINA 2023).

Exclusion criteria: mild or moderate BA, COPD, difficult-to-control BA, malignancies, severe renal or hepatic failure, pregnant and breastfeeding females.

The study was approved by the Local Ethics Committee of KSBHI «Krai Clinical Hospital» (Krasnoyarsk, Russia) and the Local Ethics Committee of FSBEI HE KrasSMU named after Prof. V.F. Voino-Yasenetsky, Ministry of Health of Russia (Protocol No. 122/2023 dated November 29, 2023). The patients received drug products as regional or federal benefit recipients.

All patients signed consents for personal data processing.

The diagnosis of severe BA was established based on the scope of basic anti-inflammatory therapy corresponding to Step V according to GINA 2023 guidelines that was administered to patients included into the study [9, 18].

Patients demonstrated correct inhalation technique and had high compliance with the basic therapy.

It should be noted that early disease onset (before 6 years of age) was observed in 2 (6 %) patients included in the study; before 20 years of age — in 8 (25 %) patients with SBA, over 40 years of age — in 11 (34 %) patients. Prolonged disease history is worth noting: in 22 (70 %) patients BA duration was over 20 years. Allergic disease phenotype was reported in 19 (60 %) patients, non-allergic phenotype — in a quarter of patients, and mixed BA — in 5 (15 %) patients. Allergic rhinitis was predominant in the structure of comorbidities, its prevalence was 18 (56.2 %) persons; chronic rhinosinusitis polyposa — in half of patients; non-steroid anti-inflammatory drug (NSAID) intolerance — in 7 (22 %) patients. 25 (78 %), i.e. the majority of patients with SBA were overweight, while the normal body mass index was observed in 7 persons (22 %).

Table 1. Characteristics of patients with severe bronchial asthma included in the study

Indicator		Severe BA (n = 32)
Age, years Me [IQR]		56 [33; 68]
Phenotype	Allergic	19 / 60 %
	Non-allergic	8 / 25 %
	Mixed	5 / 15 %
Gender:	Female, abs/%	24 / 75 %
	Men, abs/%	8 / 25 %
Duration of the disease, years Me [IQR]		22,0 [2,0; 55,0]
Age of disease onset, years Me [IQR]		33,0 [5,0; 56,0]
Comorbid pathology:		
Allergic rhinitis, abs/%		18 / 56,2 %
NSAID intolerance, abs/%		7 / 21,9 %
Chronic polypous rhinosinusitis, abs/%		16 / 50 %
Body mass index, kg/m^2 Me [IQR]		28,5 [21,9; 44,1]

Note: BA — bronchial asthma, NSAID — non-steroidal anti-inflammatory drugs, n — quantitative characteristic accepted in mathematics, abs — absolute number of patients

The general clinical examination included the patient's interrogation (complaints, history); physical data (visual examination, auscultation). Bronchial obstruction severity was clinically evaluated by the number of daily asthma attacks, frequency of nocturnal symptoms, number of daily β2-agonist inhalations.

All patients had the allergy examination in the history, which included skin tests and/or detection of specific IgE.

The pulmonary function parameters were recorded using the ErichEger general pletysmography device (Germany). The bronchial patency condition was evaluated using the pulmonary function tests coupled with the bronchodilator test (400 μg of salbutamol). Pulmonary function tests were arranged in accordance with the quality standards of the European Respiratory Society (ERS) and the American Thoracic Society (ATS) [19].

BA control was assessed using the ACQ-5 (Asthma Control Questionnaire — 5) questionnaire [9], which allows to determine the control level and risk of future exacerbations. The ACQ-5 test consists of 5 questions with the 6-point rating scale for answers. The total ACQ-5 score is calculated as the mean for 5 answers: 0.5-0.75 — adequate control; 0.75-1.5 — intermediate control; 1.5 — uncontrollable asthma.

BA control level was also assessed using the ACT (Asthma Control Test) test [9]. The questionnaire included 5 questions with a 5-point rating scale for answers. The total ACT score was determined as the sum of points: <20 points — no control; 20-24 points — partial control; 25 points — total control of BA symptoms.

All respondents were administered treatment corresponding to Step V (GINA 2023) [9] and demonstrated high treatment compliance. All concomitant diseases were compensated.

The criterion for administering additional Dupilumab treatment presumed not achieving BA control with the standard treatment scope. Administration of the biological agent Dupilumab is recommended in patients aged ≥12 years with the eosinophilic asthma phenotype (eosinophil count in peripheral blood ≥150 cells/μL) or in patients with hormone-dependent asthma administered oral corticosteroids (regardless of the eosinophil count in peripheral blood).

Data were statistically processed using Microsoft Office Excel, 2010 (version 14.0.7261.5000) and 2009 software. Quantifiable values were presented as medians (Me) and the interquartile range (Q1 and Q3), where Q1 corresponded to the 25th percentile, and Q3 — to the 75th percentile. When analyzing samples for normal distribution using the Kolmogoroff-Smirnoff method and the Shapiro-Wilk test, all data were distributed non-normally. In the comparative group analysis based on quantifiable signs, the non-parametric Wilcoxon test was used ($p < 0.05$). The comparative analysis of differences in qualitative signs was provided with the χ^2 test and the Yates' correction.

Cost calculations. Costs were calculated using the model built in the Microsoft Office Excel, 2010 software. The time horizon of 12 months was used for the scenario of the analysis presented in the article. Compulsory medical insurance system costs based on the existing tariffs were calculated as part of evaluating costs for each patient's treatment strategy. We evaluated only direct medical expenses in our study. Accounting for the fact that SBA is a chronic disease requiring prolonged treatment and follow-up, the analysis included the evaluation of costs at several stages, the final formula was as follows:

$$Cost = Cost\ (basic\ therapy) + Cost\ (outpatient\ treatment) + Cost\ (inpatient\ treatment) + Cost\ (ambulance\ calls),$$

where Cost is the total treatment costs,

Cost (basic therapy),

Cost (outpatient treatment),

Cost (inpatient treatment),

Cost (ambulance calls).

Medical care costs for adult patients with SBA were evaluated accounting for direct medical expenses (drug treatment and various medical care types) [16].

Study results and discussion

Clinical and functional characteristics of patients with SBA included in the study are presented in Table 2. Before initiating BT, patients had very high everyday requirements in emergency drugs — approximately 9 times a day. Patients had daytime symptoms up to 7 times a day and nocturnal awakenings due to BA attacks up to twice a night. At least 4 exacerbations were recorded within 12 months preceding the study inclusion, and most of them required inpatient hospitalization. Ambulance team calls were reported in each patient with SBA (at least 5 times during the previous year).

Significantly decreased symptoms were observed 12 months after additional Dupilumab treatment. Thus, 22 (70 %) patients had no attacks, while in 10 (30 %) patients asthma attacks developed 3-4 times a week. 1 BA exacerbation developed in 6 (18 %) patients within the following 12 months, though patients coped with them spontaneously using nebulizer therapy at home.

Clinical symptoms were objectified with ACQ-5 and ACT tests, which results (see Table 2) confirm no BA control in each patient included into the study (ACQ-5 > 1.5 points, ACT-test < 20 points).

Table 2. *Clinical and functional indicators of patients with severe bronchial asthma included in the study, before the appointment of GIBT and 12 months after the appointment of GIBT*

Indicator	Before the appointment of the GIBT	12 months after appointment GIBT	The significance of differences
	Me [Q_1; Q_3]	Me [Q_1; Q_3]	
Number of daytime attacks, o/day	7,0 [4,0; 13,0] *	1,0 [0,0; 1,0] *	P_{1-2} = 0,003
Number of night attacks, o/day	2,0 [1,0; 5,0] *	0,0 [0,0; 0,0] *	P_{1-2} = 0,008
Need for SABA, o/day	9,0 [8,0; 16,0] *	1,0 [0,0; 1,0] *	P_{1-2} = 0,003
Number of exacerbations, o/year	4,0 [3,0; 7,0] *	1,0 [0,0; 1,0] *	P_{1-2} = 0,005
Number of hospitalizations, o/year	4,0 [4,0; 7,0] *	0,0 [0,0; 0,0] *	P_{1-2} = 0,01
Number of visits to the clinic, o/year	3,0 [2,0; 6,0] *	0,0 [0,0; 1,0] *	P_{1-2} = 0,001
Number of EMS calls, o/year	5,0 [2,0; 12,0] *	0,0 [0,0; 0,0] *	P_{1-2} = 0,003
ACQ-5, point	3,0 [1,5; 5,0] *	0,0 [0,0; 1,0] *	P_{1-2} = 0,009
ACT, point	15,0 [8,0; 19,0] *	24 [22,0; 25,0] *	P_{1-2} = 0,007
FEV1, %	63,11 [21,1; 86,8]	90,6 [51,0; 119,9]	P_{1-2} = 0,1
FEV1/FVC, %	63,6 [46,9; 75,3]*	72,3 [51,2; 79,4] *	P_{1-2} = 0,055
Growth, %	21,2 [2,4; 40,3]	9,4 [4,8; 17,9]	P_{1-2} = 0,1
Growth, ml	223 [162,0; 219,0]	31,0 [0,0; 180,0]	P_{1-2} = 0,12

Note. p* — differences between groups in quantitative characteristics were carried out using the Wilcoxon test for two dependent samples (p <0.05), GIBT — genetic engineering biological therapy, SABA — short-acting beta-agonists, EMS — emergency medical care, ACQ — Asthma Control Questionnaire–5 / asthma control questionnaire, ACT — Asthma Control test / asthma control test; FEV1 — forced expiratory volume in the first second, FEV1/FVC — the ratio of the forced expiratory volume in the first second to the forced vital capacity of the lungs, o/day — number of times during the day, o/year — number of times during the previous year

The majority of patients achieved maximum control levels, with the ACQ-5 parameter of 0 points in 12 months (p=0.009). Meanwhile, ACT results increased from 15 to 22 points (p=0.007).

Before biological therapy, FEV_1 level <80 % was reported in 20 (62 %) people. 13 (41 %) people had fixed respiratory pathway obstruction, with FEV_1/FVC parameters below 70 %. When evaluating pulmonary function parameters after 12 months of additional Dupilumab treatment, FEV1 increased to reference levels in 22 (70 %) patients. Fixed respiratory pathway obstruction (FEV_1/FVC < 70 %) was determined only in 6 (18 %) patients included in the study.

12 months of additional treatment with Dupilumab led to significant decrease in the number of asthma attacks (p=0.003), nocturnal asthma attacks (p=0.008), daily SABA requirements (p=0.03), and ambulance calls (p=0.003) (Table 2).

Results of analysis of the basic therapy scope in patients with severe asthma, before initiating BT, and after 12 months after initiating BT are presented in Table 3.

Before starting biological therapy with Dupilumab, 10 (30 %) humans were administered SCS in doses of 10 to 5 mg (equivalent to prednisolone). 12 months later, no patients required daily SCS use (p=0.017). Such progressive results are associated with the fact that the majority of patients used small prednisolone doses. BT administration provided the possibility of increasing the number of patients using the double ICS + LABA combination from 10 (31 %) to 23 (72 %) (p=0.03).

Thus, almost complete control achievement did not only decrease the scope of situational SABA requirements, but also provided the possibility of complete SCS discontinuation and decreased the basic therapy scope.

Comparative analysis of direct medical expenses

During the first step, direct medical expenses for BT were determined for the current clinical practice.

For the modeled practice of using Dupilumab in adult patients with SBA, the following dosing regimen was accounted for: starting dose 600 mg subcutaneously (2 injections x 300 mg), followed by 300 mg subcutaneously once every two weeks. This means that one patient required 13 Dupilumab packages, while 32 patients — 416 packages within 12 months. The cost of 1 Dupilumab package is 87,536 rubles, thus the annual Dupilumab costs are 36,414,976 rubles per 32 patients with severe bronchial asthma.

Basic therapy costs in patients with SBA included in the study before BT initiation were 1,101,136 rubles, basic therapy costs after 12 months of BT treatment were 918,600.2 rubles (Table 4). For all drugs included into the List of Vital and Essential Drugs (LVED), registered

Table 3. *Volume of basic therapy received by patients with severe bronchial asthma, before the appointment of GIBT and 12 months after the appointment of GIBT*

Indicator	Before the appointment of the GIBT	The significance of differences GIBT	The significance of differences
Inhaled glucocorticosteroids + long-acting beta-agonists (ICS + LABA)	10 / 31 %	23 / 72 %	P_{1-2} = 0,003
Inhaled glucocorticosteroids + long-acting beta-agonists + systemic glucocorticosteroids (ICS + LABA + OCS)	7 / 22 %	0 / 0 %	P_{1-2} = 0,017
Inhaled glucocorticosteroids + long-acting beta-agonists, + antileukotrienes (ICS + LABA + ALT)	2 / 6 %	1 / 3 %	P_{1-2} =0,5
Inhaled glucocorticosteroids + long-acting beta-agonists + long-acting anticholinergics (ICS + LABA + LAMA)	5 / 16 %	5 / 16 %	P_{1-2} =0,7
Inhaled glucocorticosteroids + long-acting beta-agonists + antileukotrienes + long-acting anticholinergics (ICS + LABA + ALT + LAMA)	5 / 16 %	3 / 9 %	P_{1-2} =0,7
Inhaled glucocorticosteroids + long-acting beta-agonists + antileukotrienes + long-acting anticholinergics + systemic glucocorticosteroids (ICS + LABA + LAMA + ALT + OCS)	1 / 3 %	0 / 0 %	P_{1-2} =1
Inhaled glucocorticosteroids + long-acting beta-agonists + long-acting anticholinergics + systemic glucocorticosteroids (ICS + LABA + LAMA + OCS)	2 / 6 %	0 / 0 %	P_{1-2} =0,47

Note: p* — differences between groups in qualitative characteristics were carried out using the $\chi 2$ criterion with Yates Amendment (p <0.05), GIBT — genetic engineering biological therapy, ICS — Inhaled glucocorticosteroids, LABA — long-acting beta-agonists, LAMA — long-acting anticholinergics, OCS — systemic glucocorticosteroids, ALT — antileukotrienes.

prices with VAT and regional wholesale uplift were accounted for; distributor data were considered for other drugs. Costs were calculated based on the international nonproprietary name (INN) accounting for the dosage form.

The annual number of SBA exacerbations requiring inpatient treatment was 166 hospitalizations for all patients included into the study. According to the Tariff Agreement of the Territorial Department of Compulsory Medical Insurance of Krasnoyarsk Krai (Russia), the cost for 1 completed SBA inpatient treatment case was 50,000 rubles. Costs per 1 outpatient (therapeutic) physician visit was 405 rubles (primary visit) and 1673 rubles (repeated counseling). With that, an average of 2 outpatient visits is required for the treatment of 1 SBA exacerbation episode. It should be noted that the elective (therapeutic) physician visits are arranged 3 times yearly for all patients with SBA. Costs for 1 ambulance call concerning bronchial obstruction syndrome are 3500 rubles.

Thus, annual regional healthcare expenses for the outpatient and inpatient treatment of SBA exacerbations are 9,309,024 rubles for patients administered the standard basic therapy scope corresponding to GINA Step V. Meanwhile, after initiating BT, costs for outpatient follow-up in SBA patients achieving almost total control decreased 239-fold to 38,880 rubles (Table 5).

Thus, the total costs for treatment and medical care in the analyzed patient group before initiating BT was 10,410,160 rubles. After initiating BT with Dupilumab, total costs were 37,372,456 rubles.

Table 4. *Cost of basic therapy received by patients with severe bronchial asthma before the appointment of GIBT and 12 months after the appointment of GIBT*

Basic therapy before prescribing GIBT		Cost per month, RUB	Cost per year, RUB	Basic therapy 12 months after the appointment of GIBT		Cost per month, RUB	Cost per year, RUB
ICS + LABA, person	10	18305	219660	ICS + LABA, person	23	42101,5	505218
ICS + LABA + SGCS, person	7	13667,5	164010	ICS + LABA + OCS, person	0	0	0
ICS + LABA + ALT, person	2	4675	56100	ICS + LABA + ALT, person	1	2337,5	28050
ICS + LABA + LAMA, person	5	18622	223464	ICS + LABA + LAMA, person	5	18622	223464
ICS + LABA + ALT + LAMA, person	5	21068,5	252822	ICS + LABA + ALT + LAMA, person	3	12641,1	151693,2
ICS + LABA + LAMA + ALT + OCS, person	1	4353,7	52244,4	ICS + LABA + LAMA + ALT + OCS, person	0	0	0
ICS + LABA + LAMA + OCS, person	2	7693,4	92320,8	ICS + LABA + LAMA + OCS, person	0	0	0
LABA, person / aerosol	32/219	3376,25	40515	LABA, person / aerosol	32/55	847	10175
Итого, руб			1101136				918600,2

Note: GIBT — genetic engineering biological therapy, ICS — inhalational glucocorticosteroids, LABA — long-acting beta-agonists, ALT — antileukotrienes, OCS — systemic glucocorticosteroids, LAMA — long-acting anticholinergics, person/aerosol — number of canisters of the preparation per person, RUB — ruble

Table 5. *Costs of medical care received by patients with severe bronchial before the appointment of GIBT and 12 months after the appointment of GIBT*

	Before the appointment of the GIBT		12 months after the appointment of the GIBT	
	Quantity	Cost, RUB	Quantity	Cost, RUB
Hospitalizations	166	8 300 000	0	
Scheduled visits to the clinic	1 215	38 880	1 215	38 880
Additional visits to the clinic	128	214 144	0	
Calls to the ambulance team	216	756 000	0	
Total, RUB		9 309 024		38 880

Note: GIBT — genetic engineering biological therapy, RUB — ruble

The following formula was used to calculate the cost-effectiveness ratio [17]

$$CER = Cost : Ef,$$

(1) CER is the cost-effectiveness ratio of the technology;
(2) Cost presumes the costs associated with the technology (in money equivalent);
(3) Ef is the clinical efficacy of the technology in corresponding units. The parameter defines the scope of costs for achieving a treatment benefit unit, which is expressed, e.g., with the quality of life index. The lower the parameter, the higher is the cost benefit [17].

Complete control over SBA symptoms is equal to 1.0 of the treatment efficacy for this disease. Meanwhile, no control, frequent hospitalizations, low scores of validated questionnaires (ACT-test, ACQ-5) equals 0.2 of efficacy.

Thus, the cost-effectiveness in the group of patients with SBA before initiating BT was 52,050,800 rubles based on the formula above, while the cost-benefit 12 months after initiating BT was 37,372,456 rubles.

To conclude, the use of Dupilumab not only leads to control over disease symptoms, significantly decreasing medical care needs, increasing the quality and duration of patients' lives, but also demonstrates a more economically beneficial treatment strategy.

Discussion

According to the data obtained, after 12 months of Dupilumab treatment the maximum control level was achieved by the majority of patients: the ACQ-5 parameter was 0 points in 12 months. Meanwhile, ACT results increased from 15 to 22 points. All respondents were able to discontinue SCS completely. Such progressive results are associated with the fact that the majority of patients used small prednisolone doses. The administration of additional Dupilumab treatment statistically significantly decreases daily SABA requirements; the number of daily and nocturnal asthma attacks, and ambulance calls vs. standard treatment.

Similar results were obtained in other studies as well. Thus, significant decreases not only in the daily prednisolone dose, but also in the rate of daily exacerbations within a year were observed after Dupilumab administration in the study of Dupen C. et al. (2020) [20]. The study of Pelaia C. et al. (2021) demonstrated significant decrease in the SCS administration in already 4 weeks after the start of Dupilumab administration [21].

The possibility of administering additional treatment to patients with SBA not controlled using the standard scope of treatment is the most efficacious treatment vector. Analyzing the economic efficacy of BT use is the actual issue of modern medical community. Krysanov I.S. et al. (2020) conducted a study of target drugs used in SBA and demonstrated the least indirect and direct costs for Dupilumab treatment. The cost per 1 prevented exacerbation case for Dupilumab was significantly less than for other BT drugs [22]. In this study we have demonstrated the analysis of direct economic costs in patients with SBA administered standard basic therapy scope and additional BT with Dupilumab. We observed the increase in general expenses for the patient's drug provision, which is associated only with high Dupilumab costs. When calculating the cost-effectiveness ratio, additional BT demonstrated a more economically beneficial treatment strategy.

The current study was limited by the time frame of 12 months, and only direct economical treatment expenses were analyzed. Only SBA patients administered Dupilumab were included into the study. Long-term BT effects were not analyzed. In future studies we will recruit more patients with SBA administered Dupilumab. Patients will be included into the study for a longer follow-up period to evaluate long-term effects and economic Dupilumab efficacy.

Conclusions

The results of this study demonstrated high Dupilumab efficacy: higher symptom control parameters, improved pulmonary function parameters, and decreased scope of SCS use were reported after 12 months of therapy.

Thus, Dupilumab is an economically justified option for additional severe bronchial asthma treatment, demonstrating not only significantly decreased economic expenses, but also improved functional parameters and control levels.

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