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Direct comparative study of the effectiveness of mepolizumab and dupilumab in patients with severe non-allergic eosinophilic asthma

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Abstract

Introduction. Biologics for severe asthma (SA) treatment are widely used in real clinical practice. But there are very few direct comparative studies at the moment.

Aim. To compare mepolizumab and dupilumab effectiveness in patients with non-allergic eosinophilic SA in real clinical practice using regional register of Sverdlovsk region.

Materials and methods. The data of patients with non-allergic eosinophilic SA treated with dupilumab (n = 23) and mepolizumab (n = 19) were analyzed. Therapy effectiveness was determined according to BARS and patients' proportion who achieved asthma remission, dynamics of ACT, AQLQ, FEV_1, blood eosinophils, frequency of short-acting bronchodilators use and systemic glucocorticosteroids (SGCS) demand, frequency of asthma exacerbations and hospitalizations.

Results. Within 12 months of targeted therapy a good response to biologics according to BARS in 77.8% of patients on dupilumab and in 82.4% of patients on mepolizumab (p = 1.000) was revealed. Remission of SA (without FEV_1) was achieved in 62.5% of patients in dupilumab group and in 68.8% of patients in mepolizumab group (p = 1.000). Remission of SA (with FEV_1) was achieved in 43.8% of patients on dupilumab and in 56.2% of patients on mepolizumab (p = 0.724). There were statistically significant improvements for all separately analyzed indicators in each observation group. Statistically significant differences after a year of therapy between groups were recorded in terms of eosinophil levels (p < 0.001) and nasal symptoms assessed using the SNOT-22 questionnaire (p = 0.048) in favour of mepolizumab.

Conclusions. Patients with non-allergic eosinophilic SA have good response to both dupilumab and mepolizumab. The drugs equally improve disease control, life quality, reduce the need for relievers and SGCS, show a similar safety level.

Keywords: severe bronchial asthma, targeted therapy, biologics, remission of severe bronchial asthma

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Прямое сравнительное исследование эффективности меполизумаба и дупилумаба у пациентов с тяжелой неаллергической эозинофильной бронхиальной астмой

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РЕЗЮМЕ

Введение. Генно-инженерные биологические препараты (ГИБП) для лечения тяжелой бронхиальной астмы (ТБА) достаточно широко используются в реальной клинической практике. Но прямых сравнительных исследований на данный момент крайне мало.

Цель. Сравнить эффективность меполизумаба и дупилумаба у пациентов с неаллергической эозинофильной ТБА в реальной клинической практике на примере территориального регистра Свердловской области.

Материалы и методы. Проанализированы данные пациентов с неаллергической эозинофильной ТБА, получавших дупилумаб (n = 23) и меполизумаб (n = 19). Определялась эффективность терапии по системе BARS и доле пациентов, достигших ремиссии ТБА, динамике АСТ-теста, опроснику AQLQ, уровню $ОФВ_1$, эозинофилов крови, кратности применения короткодействующих бронходилататоров (КДБД) и потребности в системных глюкокортикостероидах (СГКС), частоте обострений БА и госпитализаций.

Результаты. За 12 месяцев таргетной терапии хороший ответ на терапию по BARS выявлен у 77,8% пациентов на дупилумабе и у 82,4% пациентов на меполизумабе (p = 1,000). Ремиссии ТБА без учета $ОФВ_1$ достигли 62,5% пациентов группы дупилумаба и 68,8% пациентов группы меполизумаба (p = 1,000). Ремиссия ТБА с учетом $ОФВ_1$ достигнута у 43,8% пациентов на дупилумабе и у 56,2% пациентов на меполизумабе (p = 0,724). По всем отдельно анализируемым показателям

установлены статистически значимые улучшения в каждой группе наблюдения. Статистически значимые различия через год терапии между группами зарегистрированы по уровню эозинофилов (p < 0,001) и по назальным симптомам, оцененным с помощью опросника SNOT-22 (p = 0,048) в пользу меполизумаба.
Выводы. Пациенты с неаллергической эозинофильной ТБА одинаково хорошо отвечают на терапию дупилумабом и меполизумабом. Препараты в равной степени улучшают контроль над заболеванием, качество жизни, уменьшают потребность в КДБД и СГКС, показывают сходный уровень безопасности.

Ключевые слова: тяжелая бронхиальная астма, таргетная терапия, генно-инженерные биологические препараты, ремиссия тяжелой бронхиальной астмы

Для цитирования: Наумова ВВ, Бельтюков ЕК, Ковтун ОП, Быкова ГА, Смоленская ОГ, Штанова АА, Степина ДА. Прямое сравнительное исследование эффективности меполизумаба и дупилумаба у пациентов с тяжелой неаллергической эозинофильной бронхиальной астмой. *Медицинский совет*. 2023;17(20):18–27. https://doi.org/10.21518/ms2023-308.

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INTRODUCTION

Patients with severe asthma (SA) according to GINA[1] make up 5–10% of all the patients with asthma [1], which is of great socio-economic importance due to the increased risk of exacerbations, disability and death [2]. The last decades have been marked by the appearance of a new class of drugs, monoclonal antibodies, which are already in routine practice. Randomized clinical trials have shown that treatment with biologics are effective and safe [3–7]. Observational studies in real clinical practice confirm the effectiveness of targeted therapy [3]. Five biologics have FDA-approved indications for moderate to severe atopic asthma (omalizumab), moderate to severe asthma with an eosinophilic phenotype or steroid-dependent asthma (dupilumab), or severe asthma with an eosinophilic inflammatory profile (mepolizumab, reslizumab, benralizumab). These genetically engineered biological drugs (GEBDs) are targeted at different parts of T2 inflammation [3]. To date, indirect comparative studies of biologics have been performed, according to the results of which there are no significant differences between molecules [8–11] or there is a predominance of any biological drug in certain indicators [12–14]. A limitation of these studies is the lack of direct comparison of biologics. Therefore, we conducted a direct comparison of the effectiveness of two biologics.

The aim of the study – to compare mepolizumab and dupilumab effectiveness in patients with non-allergic eosinophilic SA in real clinical practice using regional register of Sverdlovsk region.

MATERIALS AND METHODS

A comparative prospective, open, non-randomized study was conducted. The study was approved by the Local Ethics Committee of Ural State Medical University. Patients were included in the study after signing their voluntary informed consent.

The study involved adult patients (⩾ 18 years) with severe non-allergic eosinophilic bronchial asthma (BA), who received biological therapy within the territorial register of patients with SA in the Sverdlovsk region. Exclusion criteria were as follows: age under 18 years, expected duration of therapy less than 12 months, severe concomitant diseases (symptomatic arterial hypertension, coronary artery disease, functional class III and IV of chronic heart failure, hepatic cirrhosis, suspected or verified oncological diseases, tuberculosis). When patients were included in the registry, the diagnosis of SA was confirmed according to the criteria of the American Thoracic Society and the European Respiratory Society (ATS/ERS, 2014) [15] with further amendments[2]. The phenotype of non-allergic eosinophilic asthma was determined by a combination of a negative allergic history, negative results of allergy tests (including Phadiatop test), and peripheral blood eosinophil levels > 150 cells/μl.

The drugs were prescribed according to the instructions: mepolizumab - subcutaneously at a dose of 100 mg once every 4 weeks, dupilumab – an initial dose of 600 mg, then 300 mg subcutaneously every 2 weeks. Patient recruitment took place from June 2019 to April 2022. The database was analyzed in April 2023.

The effectiveness of each drug was evaluated (before-after analysis), and the effectiveness of two drugs was compared with each other in terms of individual and integral indicators. Data for evaluating the effectiveness were collected initially before therapy, after 4 and 12 months of taking biological drug.

To assess the overall picture of the effectiveness of targeted drugs after 12 months of therapy, we used the Biologics Asthma Response Score (BARS) scoring system proposed by K. Milger et al. [16], and also determined the achievement of SA remission by patients [17].

We used a three-component BARS system without taking FEV_1 into account. Determining the response to therapy in each patient included calculating the sum of points according to the dynamics of ACT test, the presence of systemic glucocorticosteroids (SGCS) and exacerbations of BA for 12 months of therapy, divided by the number of indicators (*Table 1*). When the result of calculations BARS ⩾ 1.5, the response to therapy was

[1] Global Initiative for Asthma. Global strategy for asthma management and prevention. National Institutes of Health. Diagnosis and Management of Difficult-to-Treat and Severe Asthma in Adolescent and Adult Patients. National Heart, Lung, and Blood Institute. Revised 2019. http://www.ginasthma.org. Accessed Septemper, 02, 2023.

[2] Global Initiative for Asthma. Global strategy for asthma management and prevention. National Institutes of Health. Revised 2023. Available at: https://www.ginasthma.org.

● ***Table 1.*** Biologics Asthma Response Score (BARS) scoring
● ***Таблица 1.*** Расчет баллов по системе Biologics Asthma Response Score (BARS)

Indicator	Good response 2 points	Satisfactory response 1 point	Insufficient response 0 points
Dynamics of ACT	• An increase of 3 points or more and a total score ⩾ 20 • Increase by 6 points or more	• Increase by 3–5 points, but total score < 20	• No increase or increase less than 3 points
Dynamics of asthma exacerbations (if the patient did not have exacerbations of BA at baseline and during targeted therapy, then this criterion was not taken into account)	• No exacerbations in 12 months • Reduction in the number of exacerbations ⩾ 75%	• Reducing the number of exacerbations by 50-74%	• Less than 50% reduction in exacerbations
Dynamics of SGCS taking (if the patient did not take SGCS at baseline and during targeted therapy, then this criterion was not taken into account)	• The patient initially took SGCS (permanently or in courses) and canceled against the background of GEBD	• SGCS continued, dose reduced	• The patient did not take SGCS initially; against the background of GEBD, he took SGCS
Total score	⩾ 1.5	0.5 – 1.33	< 0.5

Notes. ACT – Asthma Control Test, BA – bronchial asthma, GEBD - genetically engineered biological drug, SGCS – systemic glucocorticosteroids.

recognized as good, at 0.5–1.33 – satisfactory, < 0.5 – insufficient.

Based on the concept of "BA remission as a goal of treatment" [17], we included the absence of asthma exacerbations, the absence of SGCS intake, scores in the ACT test and optionally FEV_1 in the integral indicator "SA" remission. A patient was considered to have achieved SA remission if he had no exacerbations, no SGCS intake, ACT score ⩾ 20 points, optional FEV_1 ⩾ 80% after 12 months of therapy with a targeted drug.

Also, the effectiveness of the drugs was evaluated according to individual indicators: the level of disease control according to the ACT questionnaire, the decrease in the proportion of patients with uncontrolled asthma, the quality of life (AQLQ questionnaire), respiratory function (forced expiratory volume in the first second (FEV_1)), the need for short-acting bronchodilators (SABA) and SGCS, the number of exacerbations and hospitalizations due to asthma exacerbations. The effect of biologics on nasal symptoms was assessed (SNOT-22 and VAS questionnaires).

STATISTICAL ANALYSIS

Statistical analysis was performed using StatTech v. 3.1.6 (Developer – StatTech LLC, Russia).

Quantitative variables were assessed for normality using the Shapiro-Wilk test (when the number of subjects was less than 50).

Quantitative variables following a normal distribution were described using mean (M) and standard deviation (SD), 95% confidence interval (95% CI) for the mean were estimated.

Quantitative variables following non normal distribution were described using median (Me) and lower and upper quartiles (Q1 – Q3).

Categorical data were described with absolute and relative frequencies.

Student's t-test was used to compare two groups on a quantitative variable if it was normal distribution and Mann-Whitney U-test was used if distribution differed from normal.

Comparison of frequencies in the analysis of 2 by 2 contingency tables was performed using Fisher's exact test (for expected values less than 10).

One-way repeated measures analysis of variance was used to compare three or more matched samples in regard to normally distributed quantitative variables. Statistical significance of dependent variable changes over time was assessed using the Pillai's Trace and paired Student's t-test with Holm correction as post hoc methods.

Wilcoxon test was used for comparison of quantitative variable following non normal distribution between two matched samples.

When comparing three or more matched samples distribution of which was different from normal_quantitative variable Friedman test was used along with Conover-Iman test with Holm correction as a post hoc method.

Comparison of binary variables in more than two paired samples was performed using Cochran Q-test and McNemar test with Holm correction as a post hoc method.

RESULTS

As of April 2023, the registry included 66 patients with non-allergic eosinophilic SA - J45.1. Women predominated 87.9% (n = 58) among the patients. The mean age was 55.5 ± 9.88 years (95% CI 53.07–57.93). The majority of patients (n = 23, 34.8%) received dupilumab, 19 patients (28.8%) received mepolizumab, 15 patients (22.7%) received benralizumab, and 9 patients (13.6%) received reslizumab.

Groups of patients in the registry with a diagnosis of non-allergic eosinophilic SA (J45.1) who received mepolizumab and dupilumab were comparable in terms of asthma onset age, age of targeted therapy initiation, body mass index (BMI), presence of concomitant pathology, and hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs), laboratory and functional indicators (*Table 2*).

When determining the response to therapy according to the BARS system, a good response (⩾ 1.5 points) was recorded in 77.8% of patients in the dupilumab group and in 82.4% of patients in the mepolizumab group,

● ***Table 2.*** Characteristics of patients with severe non-allergic eosinophilic bronchial asthma taking mepolizumab and dupilumab
● ***Таблица 2.*** Характеристика пациентов с тяжелой неаллергической эозинофильной бронхиальной астмой, получающих меполизумаб и дупилумаб

Indicators	Total n = 42	Mepolizumab n = 19	Dupilumab n = 23	p
Women, n (%)	36 (85.7)	15 (78.9)	21 (91.3)	0.384
Men, n (%)	6 (14.3)	4 (21.1)	2 (8.7)	
Average age, years, M ± SD (95% CI)	54.36 ± 11.02 (50.92–57.79)	57.05 ± 10.99 (51.76–62.35)	52.13 ± 10.78 (47.47–56.79)	0.152
Average age of asthma onset, years, M ± SD (95% CI)	36.45 ± 13.98 (32.10–40.81)	37.89 ± 16.23 (30.07–45.72)	35.26 ± 12.07 (30.04–40.48)	0.550
BMI, kg/m^2, M ± SD (95% CI)	29.45 ± 5.04 (27.83–31.06)	28.95 ± 5.14 (26.39–31.50)	29.85 ± 5.05 (27.61–32.09)	0.580
Allergic rhinitis, n (%)	2 (4.8)	1 (5.3)	1 (4.3)	1.000
CRSwNP, n (%)	25 (59.5)	13 (68.4)	12 (52.2)	0.353
CRSsNP, n (%)	8 (19.0)	1 (5.3)	7 (30.4)	0.054
Atopic dermatitis, n (%)	1 (2.4)	1 (5.3)	0 (0.0)	0.452
Hypersensitivity to NSAIDs, n (%)	24 (57.1)	11 (57.9)	13 (56.5)	1.000
Total IgE, IU/l, Me (Q1–Q3)	94.1 (30.6–176.7)	74.0 (30.1–274.0)	94.1 (39.0–152.1)	0.987
Phadiatop, PAU/l, Me (Q1–Q3)	0.08 (0.02-0.20)	0.10 (0.03-0.33)	0.05 (0.02-0.12)	0.475
Peripheral blood eosinophils, cells/μl, Me (Q1–Q3)	460.0 (292.0–680.0)	575.0 (368.8–942.5)	496.0 (323.0–685.5)	0.280
FEV_1, %, M ± SD (95% CI)	62.0 ± 20.7 (55.5–68.5)	67.2 ± 24.7 (52.9–81.4)	58.2 ± 20.6 (46.8–69.6)	0.295

Notes. BMI – body mass index, CRSwNP – chronic rhinosinusitis with nasal polyps, CRSsNP – chronic rhinosinusitis without nasal polyps, NSAIDs – non-steroidal anti-inflammatory drugs, FEV1 – forced expiratory volume in the first second.

a satisfactory response (0.5–1.33 points) – in 22.2% and 17.6%, respectively (p = 1.000).

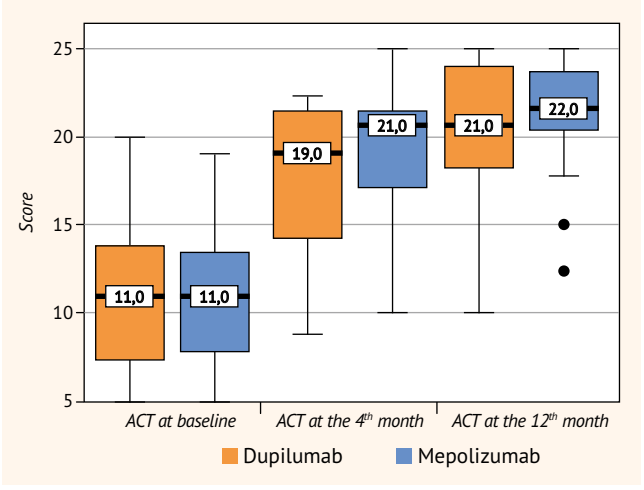
Remission of SA (three-component indicator, without FEV_1) was achieved in 62.5% of patients in the dupilumab group, in the mepolizumab group – in 68.8% (p = 1.000). When lung function (FEV_1 ⩾ 80%) was included in the definition of SA remission, 43.8% of patients treated with dupilumab and 56.2% of patients treated with mepolizumab achieved remission (p = 0.724).

During the year of targeted therapy, mean ACT scores increased significantly in the dupilumab group from 11.0 (Q1–Q3: 7.8–13.2) to 21.0 (Q1–Q3: 18.2–24.2) (p < 0.001) and in the mepolizumab group from 11.0 (Q1– Q3: 8.0–12.5) to 22.0 (Q1–Q3: 20.5–24.0) (p < 0.001). No significant differences between the groups were found in any of the control points of observation (*Fig. 1*).

The proportion of patients with uncontrolled asthma in both groups significantly decreased during 12 months of therapy (p < 0.001). The proportion of uncontrolled asthma decreased from 100% to 20% in the mepolizumab group, and from 93.8% to 37.5% in the dupilumab group. There were no significant differences between the groups in all the three observation points (*Fig. 2*).

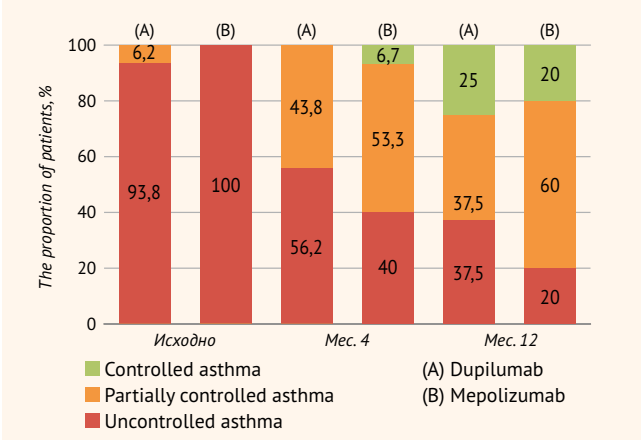
During 12 months of therapy with GEBDs, patients showed an improvement in pulmonary function. FEV_1 increased from 58.2% ± 20.6% (95% CI 46.8–69.6) to 78.5% ± 19.3% (95% CI 67.8–89.2) in the dupilumab group (p < 0.001). FEV_1 increase was from from 67.2% ± 24.7% (95% CI 52.9–81.4) to 79.9% ± 16.6% (95% CI 70.3–89.4) in the mepolizumab group (p = 0.034). There were no statistically significant differences between the groups in each control point (*Fig. 3*).

● ***Figure 1.*** Dynamics of ACT scores in patients with severe non-allergic eosinophilic bronchial asthma receiving dupilumab and mepolizumab for 12 months
● ***Рисунок 1.*** Динамика баллов в АСТ у пациентов с тяжелой неаллергической эозинофильной бронхиальной астмой, получавших дупилумаб и меполизумаб в течение 12 месяцев

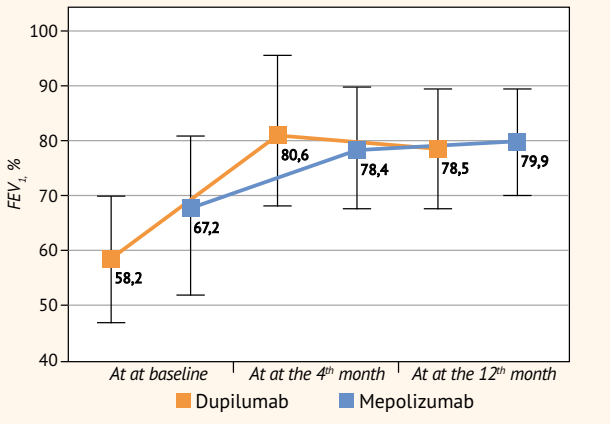


Notes. ACT – Asthma Control Test

● ***Figure 2.*** Dynamics of asthma control level in patients with severe non-allergic eosinophilic bronchial asthma receiving dupilumab and mepolizumab for 12 months
● ***Рисунок 2.*** Динамика уровня контроля у пациентов с тяжелой неаллергической эозинофильной бронхиальной астмой, получавших дупилумаб и меполизумаб в течение 12 месяцев



● ***Figure 3.*** Dynamics of FEV1 level in patients with severe non-allergic eosinophilic bronchial asthma receiving dupilumab and mepolizumab for 12 months
● ***Рисунок 3.*** Динамика уровня ОФВ1 у пациентов с тяжелой неаллергической эозинофильной бронхиальной астмой, получавших дупилумаб и меполизумаб в течение 12 месяцев



Notes. FEV_1 – forced expiratory volume in the first second

With improved disease control in both groups, there was an improvement in the quality of life according to the AQLQ questionnaire ($p < 0.001$). The dynamics of score changes were more pronounced in the dupilumab group, but there were no statistically significant differences between the groups in any of the control points (*Fig. 4*).

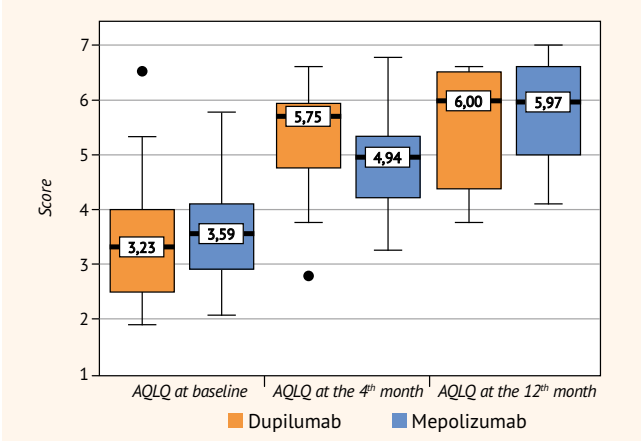
During the year of biological therapy, patients in both groups were significantly less likely to use drugs that relieve symptoms ($p < 0.001$) (*Fig. 5*). The need for the use of SGCS also decreased. Prior to the initiation of targeted therapy, 75% of patients in the dupilumab group and 64.3% of patients in the mepolizumab group required SGCS (on an ongoing basis or courses during exacerbations). One year after the start of targeted therapy, the proportion of patients taking SGCS decreased in the dupilumab group to 12.5% ($p < 0.001$) and in the mepolizumab group to 14.3% ($p = 0.008$). There were no statistically significant differences between the groups (*Fig. 6*).

One year before therapy, 77.3% (n = 17) of patients in the dupilumab group and 90.9% (n = 16) in the mepolizumab group experienced an asthma exacerbation. During the year, only one asthma exacerbation was registered in each group on targeted therapy. There was a decrease in the average number of exacerbations per patient per year in the dupilumab group by 4.7 times ($p = 0.018$), in the mepolizumab group by 12.8 times ($p = 0.005$). There were no statistical differences between the groups at baseline ($p = 0.793$) and at the 12th month of therapy ($p = 0.563$) (*Fig. 7*).

The number of hospitalizations decreased in both groups, but statistical significance was not achieved (*Fig. 8*).

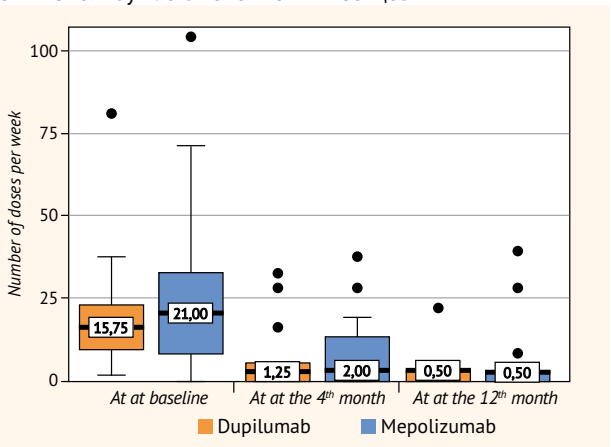
During therapy with dupilumab, the level of eosinophils increased from 496.0 cells / μl (Q1–Q3: 323.0–685.5) to

● ***Figure 4.*** Quality of life level dynamics (AQLQ) in patients with severe non-allergic eosinophilic bronchial asthma receiving dupilumab and mepolizumab for 12 months
● ***Рисунок 4.*** Динамика качества жизни у пациентов с тяжелой неаллергической эозинофильной бронхиальной астмой, получавших дупилумаб и меполизумаб в течение 12 месяцев

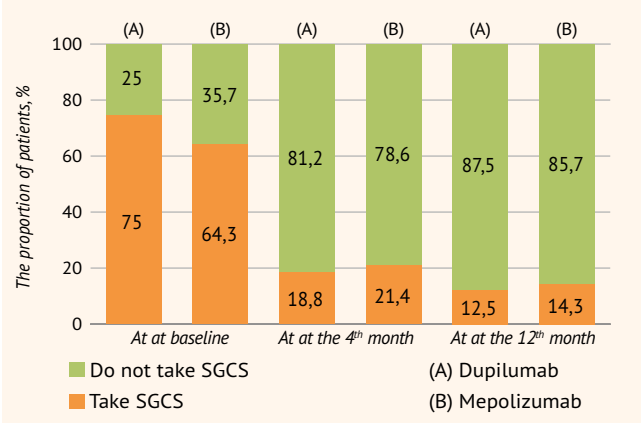


Notes. AQLQ – Asthma Quality of Life Questionnaire

● ***Figure 5.*** Dynamics of relievers demand in patients with severe non-allergic eosinophilic bronchial asthma receiving dupilumab and mepolizumab for 12 months
● ***Рисунок 5.*** Динамика потребности в короткодействующих бронходилататорах у пациентов с тяжелой неаллергической эозинофильной бронхиальной астмой, получавших дупилумаб и меполизумаб в течение 12 месяцев

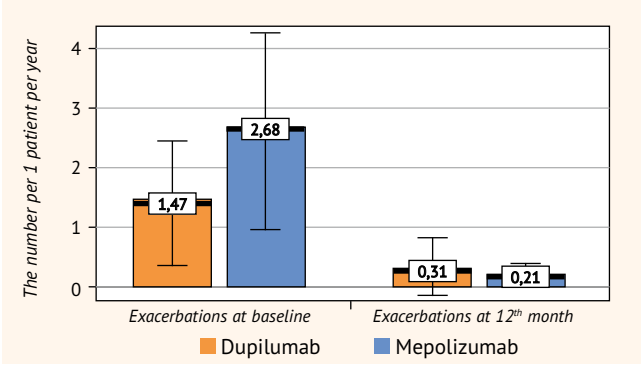


● ***Figure 6.*** Dynamics of systemic glucocorticosteroids demand in patients with severe non-allergic eosinophilic bronchial asthma receiving dupilumab and mepolizumab for 12 months
● ***Рисунок 6.*** Динамика потребности в системных глюкокортикостероидах у пациентов с тяжелой неаллергической эозинофильной бронхиальной астмой, получавших дупилумаб и меполизумаб в течение 12 месяцев

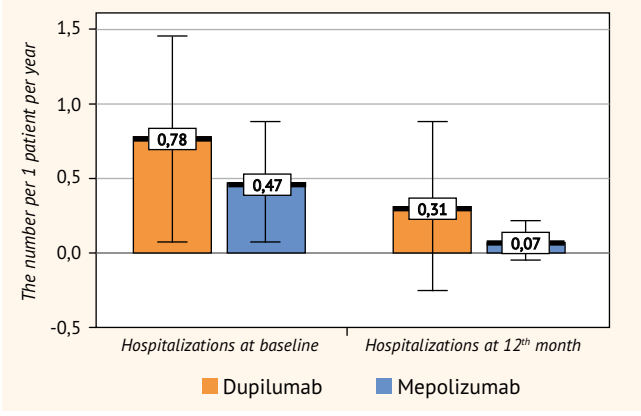


Notes. SGCS – systemic glucocorticosteroids

● ***Figure 7.*** Dynamics of exacerbation number in patients with severe non-allergic eosinophilic bronchial asthma receiving dupilumab and mepolizumab for 12 months
● ***Рисунок 7.*** Динамика обострений у пациентов с тяжелой неаллергической эозинофильной бронхиальной астмой, получавших дупилумаб и меполизумаб в течение 12 месяцев



● ***Figure 8.*** Dynamics of hospitalization number in patients with severe non-allergic eosinophilic bronchial asthma receiving dupilumab and mepolizumab for 12 months
● ***Рисунок 8.*** Динамика количества госпитализаций у пациентов с тяжелой неаллергической эозинофильной бронхиальной астмой, получавших дупилумаб и меполизумаб в течение 12 месяцев



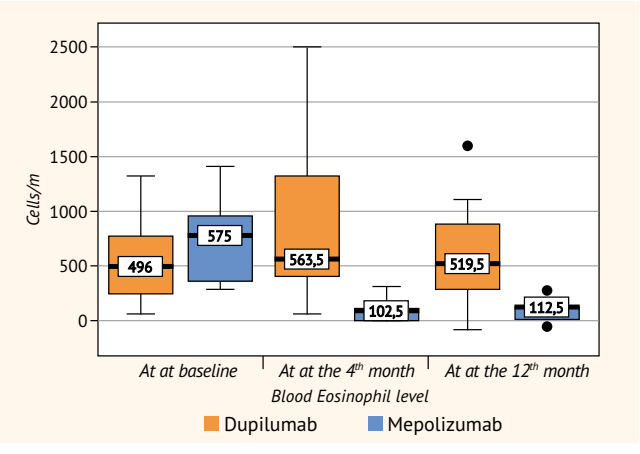
563.5 cells / μl (Q1–Q3: 430.8–1381.5) by 4th month of therapy, with a further decrease to 519.5 cells / μl (Q1– Q3: 305.5–800.0) by the 12th month of therapy. Changes were not statistically significant (p = 0.305). There was a significant decrease in the level of peripheral blood eosinophils from 575.0 cells/μl (Q1–Q3: 368.8–942.5) to 102.5 cells/μl (Q1–Q3: 26.4–148.0) at the 4th month and 112.5 (Q1–Q3: 89.5–132.2) at the 12th month (p < 0.001) in patients treated with mepolizumab. The difference between the indicators of the two groups was statistically significant at the 4th and 12th months of therapy (p < 0.001) (*Fig. 9*).

Along with the dynamics of bronchial asthma, we assessed the dynamics of nasal symptoms. According to the SNOT-22 questionnaire, at baseline, patients in the dupilumab and mepolizumab groups scored 50.6 ± 30.5 (95% CI 34.3–66.8) and 48.7 ± 33.1 (95% CI 30.3–67.0) points, respectively. By the 12th month of therapy, there was a decrease in the mean score to 31.4 ± 21.1 (95% CI 20.1– 42.6) in the dupilumab group (p = 0.008) and to 18.2 ± 13.3 (95% CI 10.8–25.6) in the mepolizumab group (p < 0.001). There were no statistically significant differences between the groups at baseline and at month 4, but at month 12 the dynamics in the mepolizumab group was more pronounced (p = 0.048) (*Fig. 10*).

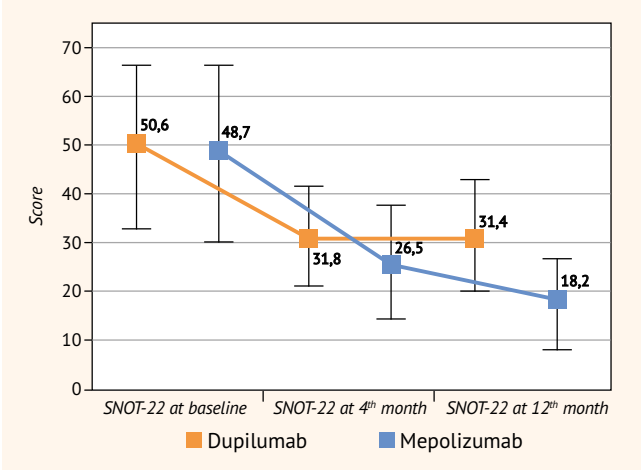
The decrease in nasal symptoms according to VAS for the year of targeted therapy in both groups was statistically significant from 7.0 points at baseline to 3.0 points at the 12th month, there was no difference between the groups (*Fig. 11*).

Among all patients of both study groups (n = 42), adverse events (AEs) were registered in 28.6% of patients (n = 12). AEs were observed in 26.1% of patients (n = 6) in the dupilumab group and in 31.6% of patients (n = 6) in the mepolizumab group, no statistical difference was found (p = 0.742). Three patients had one AE each (pain at the injection site, increased blood pressure,

● ***Figure 9.*** Dynamics of peripheral blood eosinophil level in patients with severe non-allergic eosinophilic bronchial asthma receiving dupilumab and mepolizumab for 12 months
● ***Рисунок 9.*** Динамика уровня эозинофилов периферической крови у пациентов с тяжелой неаллергической эозинофильной бронхиальной астмой, получавших дупилумаб и меполизумаб в течение 12 месяцев

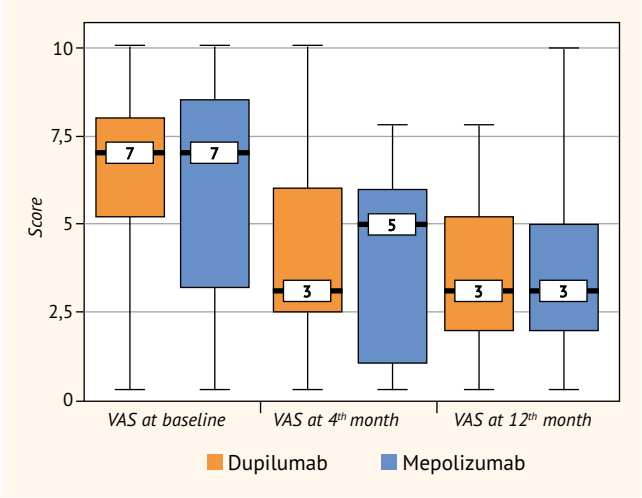


● ***Figure 10.*** Dynamics of SNOT-22 scores in patients with severe non-allergic eosinophilic bronchial asthma receiving dupilumab and mepolizumab for 12 months
● ***Рисунок 10.*** Динамика баллов в опроснике SNOT-22 у пациентов с тяжелой неаллергической эозинофильной бронхиальной астмой, получавших дупилумаб и меполизумаб в течение 12 месяцев



Notes. SNOT-22 – Sino-Nasal Outcome Test

● ***Figure 11.*** Dynamics of VAS in patients with severe non-allergic eosinophilic bronchial asthma receiving dupilumab and mepolizumab for 12 months
● ***Рисунок 11.*** Динамика баллов ВАШ у пациентов с тяжелой неаллергической эозинофильной бронхиальной астмой, получавших дупилумаб и меполизумаб в течение 12 месяцев



Notes. VAS – visual analog scale

ineffectiveness in asthma), three patients had two AEs each (dizziness and taste in the mouth, weakness and hoarseness, pain at the injection site and increased temperature) in the mepolizumab group. All adverse events were mild and did not require discontinuation of the targeted drug. Four patients had one AE each (two patients had pain at the injection site; increased blood pressure, weakness), one patient had two AEs (headache and weakness), one patient had three AEs (weakness, dizziness, decrease in blood pressure) in the dupilumab group.

DISCUSSION

In this study, we compared the effectiveness of mepolizumab and dupilumab in patients with non-allergic eosinophilic SA over 12 months of therapy. Drugs with different mechanisms of action on T2 inflammation were selected for comparison. Benralizumab and reslizumab were not included in the study due to the small number of patients receiving these biologics. Head-to-head comparative studies are rare, as within T2 high asthma, patients can differ significantly phenotypically and endotypically. For comparison, we selected patients with eosinophilia not associated with allergic inflammation. We did not randomize and this reduces the value of the study. One of the important criteria for choosing a drug was the patient's ability to come twice a month for an injection of the drug and, accordingly, twice a month to undergo a minimum examination before the injection, which to some extent gave a random character to the choice of a biological drug.

When assessing the response to therapy according to the BARS system, we received a good response (≥ 1.5 points) in 77.8% of patients in the dupilumab group and in 82.4% of patients in the mepolizumab group. This is higher than that of K. Milger et al., who generally received a good response in the group of patients on targeted therapy 61.4% [18]. Also, the proportion of patients who achieved remission in our study was higher (for the dupilumab group 43.8% and for the mepolizumab group 56.2%) than in K. Milger et al. (for anti-IL4R, 13 – 23% and for the group of anti-IL5 drugs – 38%). The tendency for anti-IL5 drugs to be superior and the proportion of patients with remission to decrease persists when FEV_1 indicator is taken into account. The influence of respiratory function on the achievement of remission is explained by fixed airway obstruction in some patients.

Despite the fact that when comparing groups in terms of the proportion of patients with uncontrolled asthma, no statistical difference was found at all stages of observation, there was a more pronounced decrease in the proportion of uncontrolled asthma in the mepolizumab group (up to 20% vs 37.5% in the dupilumab group by the 12th month of therapy). Also, a patient with fully controlled asthma appeared already at the 4th month of therapy among patients receiving mepolizumab. But the absolute and relative number of patients with complete asthma control slightly prevailed in the dupilumab group at the 12th month of therapy.

The dynamics of eosinophil level is explained by the mechanism of biologics action. Thus, as expected, there was a decrease in peripheral blood eosinophils in patients treated with mepolizumab. Mepolizumab blocks the binding of interleukin 5 to the receptor complex, which leads to a decrease in the production and survival of eosinophils [19]. In patients treated with dupilumab, we observed a non-significant increase in the number of eosinophils. It can be explained by the fact that dupilumab blocks the migration of eosinophils into tissues by inhibiting the production of eotaxins mediated by IL-4 and IL-13 and adhesion molecules of vascular cell [20].

In our study, annual treatment with biologics was accompanied by a significant reduction in the frequency of SA exacerbations in patients: by 4.7 times (p = 0.018) in the dupilumab group, and by 12.8 times (p = 0.005) in the mepolizumab group. However, no statistically significant difference was found between the effectiveness of these drugs. Some studies favour mepolizumab [21, 22] or dupilumab [23] as the best drug to reduce exacerbations. In a study by A. Akenroye et al. patient groups were distributed according to the number of blood eosinophils, and dupilumab therapy was statistically most effective for patients with both eosinophil counts ⩾300 cells/μL and those with eosinophil counts from 150 to 299 cells/μL (p > 0.001) [24]. One of the first studies directly comparing reslizumab, dupilumab and mepolizumab in patients with severe eosinophilic asthma revealed an advantage in reducing the frequency of exacerbations for reslizumab, although statistical significance was not obtained [25]. Most large meta-analyses and systematic reviews agree that the use of any biologics effectively reduces the frequency of exacerbations in patients with SA [3, 9, 24–29]. Thus, targeted therapy for SA at the 5th stage according to GINA is characterized by a better control of symptoms and the absence or decrease in the frequency of exacerbations requiring hospitalization. In our study, after initiation of biological therapy, the number of hospitalizations per 1 patient per year after 12 months of treatment was 0.31 ± 1.01 in the dupilumab group, and 0.07 ± 0.26 in the mepolizumab group, which is less than before biologics start (0.78 ± 1.32 and 0.47 ± 0.74, respectively). However, these changes were not significant enough (p > 0.05). Other studies have shown a significant reduction in the rate of hospitalizations in patients with SA while taking mepolizumab, dupilumab and other GEBDs, without a statistically significant difference between the drugs [3, 9, 27–31].

The need for relievers significantly decreased during the year in both groups (p < 0.001). In a study by R. Faverio et al. dupilumab significantly reduced the use of SABA and other relievers [32], which is consistent with our data. The same dynamics was revealed on the use of SGCS in our study. SGCS use was decreased to 12.5% in the dupilumab group (p < 0.001), and to 14.3% in the mepolizumab group (p = 0.008); no statistically significant differences were found between therapy with each drug. According to some studies, the number of SGCS prescriptions is significantly lower in patients receiving dupilumab compared to patients receiving mepolizumab [33–35]. Other studies describe the complete cessation of SGCS during treatment with any GEBD [35–37].

Against the background of 12 months of targeted therapy respiratory function (FEV_1) increased by 1.34 times to 78.5% ± 19.3 in the dupilumab group (p < 0.001) and by 1.18 times to 79.9% ± 16.6% in the mepolizumab group (p = 0.034), without statistically significant differences between the groups. Our results are in complete agreement with other studies, including meta-analyses and systematic reviews, which describe a statistically significant improvement in FEV_1 with mepolizumab and dupilumab, with the latter having a more pronounced effect on FEV_1 compared with mepolizumab, but without a statistically significant difference [24, 25, 27–29, 38, 39].

According to Toma S. et al., gradation of scores in SNOT-22 corresponds to the severity of nasal symptoms: > 50 severe, 20 – 49 moderate, < 20 mild symptoms [40]. Initially both groups were on the border of moderate and severe nasal symptoms. The reduction in scores appeared to be about the same by the 4th month, but there was no further change in the dupilumab group by the 12th month, and the scores continued to decrease to mild nasal symptoms in the mepolizumab group. Similar conclusions were made by L. Chong et al. in a systematic review of GEBDs use for the treatment of chronic rhinosinusitis: only the mepolizumab group showed a significant decrease in SNOT-22 scores after 3 months of use [41]. In other meta-analyses, dupilumab compared with mepolizumab, on the contrary, showed better results in reducing the severity of nasal symptoms at the end of the 3rd and 4th months of biologics use [42, 43]. In general, compared with placebo, all GEBDs significantly reduce the severity of nasal symptoms as assessed by SNOT-22 [44].

A similar trend was noted for VAS, i.e. the maximum improvement in nasal symptoms in the dupilumab group was observed by the 4th month and then maintained at the same level, and the dynamics of symptom improvement was present throughout the entire observation period in the mepolizumab group. In a retrospective study by C. Mümmler et al., also the greatest improvement in VAS symptoms at the 4th month of therapy is observed in the dupilumab group, on average -3 points (p < 0.001), while in the mepolizumab group the decrease is -1 point (p < 0.01). However, during follow-up, mepolizumab showed an increase in positive dynamics, on average -2 points (p < 0.001), in contrast to dupilumab, the effectiveness of which decreased over time (p < 0.001) [45], which is consistent with the results of our study. However L. Chong et al. in systematic review said that there was no significant improvement in the condition of patients according to VAS during treatment with mepolizumab, and the positive effect of dupilumab had only moderate statistical significance [41].

CONCLUSION

Thus, patients with non-allergic eosinophilic SA respond equally well to dupilumab and mepolizumab therapy and achieve disease remission. The drugs equally improve disease control, improve quality of life, reduce the need for SABA and SGCS, show a similar safety level. A slight advantage was found for dupilumab in terms of the effect on respiratory function, and mepolizumab for the number of asthma exacerbations and nasal symptoms (according to SNOT-22).

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