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Анти-IL-4,13-стратегия в терапии коморбидных пациентов на примере регионального регистра больных тяжёлой бронхиальной астмой

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АННОТАЦИЯ

Обоснование. Т2-воспаление лежит в основе бронхиальной астмы и воспалительных заболеваний носа, подтверждая концепцию «единого заболевания дыхательных путей». Препарат дупилумаб, блокируя рецептор интерлейкинов 4 и 13, способен улучшать клинико-функциональные показатели и качество жизни коморбидных пациентов с Т2-заболеваниями.

Цель — оценить эффективность анти-IL-4,13-терапии у коморбидных пациентов в региональном регистре больных тяжёлой бронхиальной астмой.

Материалы и методы. Исследование эффективности дупилумаба проводилось методом сравнения связанных совокупностей на основе территориального регистра взрослых пациентов с тяжёлой бронхиальной астмой и сопутствующими хроническими воспалительными заболеваниями носа. Как основной исход оценивали изменение среднего количества баллов в АСТ-тесте и повышение доли пациентов с частично и полностью контролируемой тяжёлой бронхиальной астмой. Оценивали также потребность в бронхолитиках и системных глюкокортикостероидах, число обострений астмы, вызовов бригад скорой медицинской помощи и госпитализаций, качество жизни (опросник AQLQ), уровень эозинофилов периферической крови, функцию внешнего дыхания. Динамику состояния пациентов с хроническими воспалительными заболеваниями носа оценивали по опросникам SNOT-22 и ВАШ. Проводили подгрупповой анализ динамики среднего количества баллов в АСТ-тесте в зависимости от фенотипа хронических воспалительных заболеваний носа.

Результаты. За 12 месяцев терапии дупилумабом АСТ увеличился с 11 (Q1–Q3: 7–13) до 20 (Q1–Q3: 18–24) баллов (p <0,001). Доля пациентов с частично и полностью контролируемой астмой увеличилась с 0 до 57,9% (p <0,001). Потребность в бронхолитиках уменьшилась с 17,5 (Q1–Q3: 5,8–24,5) до 1,0 (Q1–Q3: 0,0–2,2) дозы в неделю (p <0,001). До терапии дупилумабом 68,5% пациентов принимали системные глюкокортикостероиды, через 12 месяцев терапии — 10,5% пациентов (p <0,001). Снизилось количество обострений астмы с 2,19±1,83 (95% ДИ 1,28–3,11) до 0,22±0,55 (0,05–0,49) на пациента в год (p <0,001) и госпитализаций с 1,00±1,27 (95% ДИ 0,37–1,63) до 0,17±0,51 (95% ДИ 0,09–0,42) (p <0,001). Качество жизни по AQLQ повысилось с 2,91 (Q1–Q3: 2,43–3,86) до 5,89 (Q1–Q3: 4,70–6,58) баллов (p <0,001). Наблюдалось увеличение объёма форсированного выдоха за первую секунду с 55,38%±16,66 (95% ДИ 47,10–63,67) до 81,5%±19,14 (95% ДИ 71,98–91,02) (p <0,001). По опроснику SNOT-22 получено снижение с 47±29 (95% ДИ 34–61) до 25±18 (95% ДИ 17–34) (p <0,001), по ВАШ — с 7±2 (95% ДИ 6–8) до 4±2 (95% ДИ 3–5) (p <0,001).

Заключение. Дупилумаб продемонстрировал улучшение контроля над симптомами тяжёлой бронхиальной астмы и хроническими воспалительными заболеваниями носа, повышение качества жизни, улучшение функции дыхания, уменьшение количества обострений астмы и госпитализаций. Пациенты с тяжёлой бронхиальной астмой и сопутствующими хроническим полипозным риносинуситом, в том числе осложнённым аллергическим ринитом, лучше отвечают на терапию дупилумабом, чем пациенты с сопутствующим хроническим полипозным риносинуситом без полипов.

Ключевые слова: тяжёлая бронхиальная астма; хронический риносинусит без полипов; хронический полипозный риносинусит; аллергический ринит; дупилумаб; АСТ; AQLQ; SNOT-22; ВАШ.

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Anti-IL-4,13 strategy in management of comormid patients in the regional register of severe bronchial asthma

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ABSTRACT

BACKGROUND: T2 inflammation underlies bronchial asthma and inflammatory nasal diseases, supporting the concept of a "united airway disease." Dupilumab, by blocking interleukin-4 and -13 receptors, can improve the clinical and functional parameters and life quality of comorbid patients with T2 diseases.

AIM: To evaluate efficacy of anti-IL4R,13 therapy in patients with severe asthma with chronic inflammatory nasal diseases in real clinical practice.

MATERIALS AND METHODS: The study of dupilumab efficacy was conducted by comparing related populations based on a regional register of patients with severe asthma and concomitant chronic inflammatory nasal diseases. Asthma control achievement and decrease in the rate of patients with uncontrolled asthma were assessed as primary endpoint. The need for bronchodilators and systemic glucocorticosteroids, number of asthma exacerbations, emergency calls and hospitalizations, AQLQ scores, level of peripheral blood eosinophils, and respiratory function were also assessed. Nasal symptoms were assessed using SNOT-22 and VAS. A subgroup analysis of ACT scores was performed depending on chronic inflammatory nasal disease phenotypes.

RESULTS: Within 12 months of dupilumab therapy, ACT increased from 11 (Q1–Q3: 7–13) to 20 (Q1–Q3: 18–24) points (p <0.001). The rate of patients with partially and fully controlled asthma increased from 0 to 57.9% (p <0.001). The need for bronchodilators decreased from 17.5 doses per week (Q1–Q3: 5.8–24.5) to 1.0 (Q1–Q3: 0.0–2.2) (p <0.001). Before the dupilumab therapy, 68.5% of the patients took systemic corticosteroids and, after 12 months, 10.5% of patients (p <0.001). The number of asthma exacerbations decreased from 2.19±1.83 (95% CI 1.28–3.11) to 0.22±0.55 (0.05–0.49) (p <0.001) and hospitalizations from 1.00±1.27 (95% CI 0.37–1.63) to 0.17±0.51 (95% CI 0.09–0.42) (p <0.001). AQLQ scores increased from 2.91 (Q1–Q3: 2.43–3.86) to 5.89 points (Q1–Q3: 4.70–6.58) (p <0.001). The volume of forced exhalation in 1 sec increased from 55.38%±16.66% (95% CI 47.10–63.67) to 81.5%±19.14% (95% CI 71.98–91.02) (p <0.001). SNOT-22 scores decreased from 47±29 (95% CI 34–61) to 25±18 (95% CI 17–34) points (p <0.001) and the VAS score from 7±2 (95% CI 6–8) to 4±2 (95% CI 3–5) (p <0.001).

CONCLUSIONS: Dupilumab improved asthma and nasal symptoms control, improved quality of life and respiratory function, and reduce asthma exacerbations and hospitalizations. Patients with severe asthma and comorbid allergic rhinitis and chronic rhinosinusitis with polyps responded better to dupilumab therapy than patients with chronic rhinosinusitis without polyps.

Keywords: severe bronchial asthma; allergic rhinitis; chronic rhinosinusitis with nasal polyps; chronic rhinosinusitis without nasal polyps; dupilumab; ACT; AQLQ; SNOT-22; VAS.

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Список сокращений

ACT — asthma control test
AQLQ — Asthma Quality of Life Questionnaire
AR — allergic rhinitis
CIDN — chronic inflammatory diseases of the nose
CRS — chronic rhinosinusitis
CRSwNP — chronic rhinosinusitis with nasal polyps
FEV_1 — forced expiratory volume in 1 second
SBA — severe bronchial asthma
sCCs — systemic corticosteroids
SNOT-22 — Sinonasal Outcome Test
VAS — visual analog scale

BACKGROUND

Severe asthma is a complex, heterogeneous condition that affects 3%–10% of patients with asthma [1]. Eosinophilic asthma is one of the most common, severe, and difficult-to-treat subtypes of asthma, often associated with comorbid inflammatory diseases of the nose such as chronic rhinosinusitis (CRS) with nasal polyps [2].

CRS is a group of disorders with multifactorial etiologies, involving immune and epithelial barrier components influenced by the microbiome, environmental and genetic factors that result in the inflammation of the sinonasal mucosa [2–4].

Clinically, inflammatory diseases of the nose in patients with asthma are associated with more severe sinonasal symptoms and poorer quality of life. Asthma with nasal polyposis is also more difficult to control because these patients are more prone to exacerbations, increased airway obstruction, and more extensive eosinophilic inflammation [2–4].

An underlying systemic inflammatory link between diseases of the nose and asthma provides compelling evidence for systemic treatment with novel biologics targeting major type 2 inflammatory pathways [1, 3]. However, clear criteria on the selection of patients for a particular targeted drug have not yet been established, and the search for markers of response to biological therapy is ongoing.

This paper presents an analysis of the effectiveness of anti-IL-4,13 therapy in patients with severe bronchial asthma (SBA) and chronic inflammatory diseases of the nose (CIDN).

The study aimed to evaluate the effectiveness of anti-IL-4,13 therapy in comorbid patients from the SBA regional register.

METHODS AND MATERIALS

Study design

This open-label, observational, prospective, nonrandomized study examined the efficacy of dupilumab in comorbid patients from the regional SBA register by comparing linked samples (pre-post analysis).

Eligibility criteria

The study was conducted based on the regional SBA register of the Sverdlovsk region. The organization and functioning of the SBA register are described comprehensively in a previously published paper [5].

Inclusion criteria: patients from the regional SBA register with concomitant CIDN who were prescribed dupilumab as part of step 5 of asthma management. CIDN included allergic rhinitis (AR), CRS, and CRS with nasal polyps (CRSwNP).

Exclusion criteria: patients from the regional SBA register who were prescribed any other targeted drugs and patients aged <18 years.

Study duration

From February 2020 to July 2022, the register included 37 patients who were prescribed dupilumab. In this study, the maximum follow-up period for each patient was 12 months.

Description of medical intervention

The diagnosis of patients included in the register had been confirmed, and SBA phenotyping before the targeted therapy was prescribed. According to the International Classification of Diseases, 10th Revision (ICD-10), patients were classified as groups with allergic asthma (J45.0), non-allergic asthma (J45.1), and mixed asthma (J45.8). SBA phenotyping was described in detail in our previous paper [6].

AR was diagnosed in accordance with the clinical practice guidelines for the management of this disease, approved in 2018, and subsequently amended [7, 8].

CRSwNP and CRS without polyps were diagnosed based on the history, clinical presentation (symptoms for ⩾6 months: persistent nasal congestion and nasal obstruction, possible anosmia, and scanty nasal discharge), taking into account consultation of an ENT specialist and the results of computed tomography of the paranasal sinuses.

Dupilumab was prescribed to patients with allergic, non-allergic, and mixed asthma according to the instructions for use (starting dose of 600 mg, then 300 mg subcutaneously once every 2 weeks).

To assess the dynamics of patients' condition and the safety of the therapy, the following control points were

established: baseline visit, month 4 visit, and month 12 visit. At the time of data analysis (October 2022), of 37 patients, 34 completed month 4 visit and 20 completed month 12 visit.

Primary outcome

The primary efficacy endpoint of dupilumab therapy was the change in the mean Asthma Control Test (ACT) score and the increase in the proportion of patients with partially and fully controlled SBA.

Secondary outcomes

The study also assessed the dynamics of SBA exacerbations, number of hospitalizations due to asthma exacerbations, emergency calls per patient per year before the start of biological therapy and during the year of dupilumab treatment, changes in the amount of pharmacotherapy (need for short-acting bronchodilators and proportion of patients requiring systemic corticosteroids). Changes in the quality of life of patients with SBA were assessed using the Asthma Quality of Life Questionnaire (AQLQ). Spirometry (forced expiratory volume in 1 s, FEV_1) and blood eosinophil counts were analyzed in dynamics. The dynamics of nasal symptoms was recorded using the Sinonasal Outcome Test (SNOT-22) questionnaire and the visual analog scale (VAS). Adverse events were monitored.

Subgroup analysis

The study also formed subgroups of patients based on CIDN phenotypes: patients with CRSwNP, CRS (without polyps), AR, AR + CRSwNP, and without nasal diseases. In subgroups, a comparative analysis of the mean score in the ACT was carried out before the start of biological therapy and at month 4 or 12 of therapy.

The dependence of changes over time in the mean score in ACT and FEV_1 (%) on the baseline peripheral blood eosinophil count and at month 12 of dupilumab therapy was also assessed, which formed the subgroups of patients with a baseline eosinophil count: subgroup 1 (<300 cells/μL) and subgroup 2 (≥300 cells/μL).

Outcome registration methods

At control points, patients reported information about asthma exacerbations and episodes of seeking medical attention because of exacerbations. Information about the therapy used and side effects of drugs was collected from patients. A general blood test with white blood cell differential was performed, and external respiration function was assessed. Patients completed questionnaires on asthma control (ACT), quality of life (AQLQ), and nasal symptoms (SNOT-22 and VAS).

Ethical aspects

The study was approved by the Local Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education Ural State Medical University of the Ministry of Health of Russia (Ekaterinburg, Russia, Meeting Minutes No. 8 of November 20, 2020). All patients signed the informed consent form when included in the SBA register, including the use of examination and observation results for scientific purposes. The study observed the principles of the Declaration of Helsinki.

Statistical analysis

Since the study was conducted in real-world clinical practice, the sample size was not pre-calculated. StatTech v. 2.8.8 (OOO Stattech, Russia) was used for the statistical analysis. Significance level was set at p <0.05.

The Shapiro–Wilk test was used to assess the normality of distribution of quantitative parameters. Normally distributed quantitative parameters are presented as arithmetic means and standard deviations (M±SD) with 95% confidence interval limits (95% CI). The median with quartiles was used to describe non-normally distributed quantitative data (Me; Q1–Q3). Categorical parameters were indicated as absolute values and percentages. The Mann–Whitney U-test was used to compare two groups of quantitative parameters with non-normal distribution. In two linked samples with non-normally distributed quantitative parameters, the comparison was performed using the Wilcoxon test. In non-normally distributed quantitative parameters, the Kruskal–Wallis test was used to compare three or more groups. Post hoc comparisons were performed using Dunn's test with Holm's correction. One-way analysis of variance (ANOVA) and Tukey's test for post hoc analysis were used to compare scores in ≥3 groups, assuming a normal data distribution. Percentages in the analysis of multi-way contingency table were compared using Pearson's chi-square test. One-way ANOVA and paired Student's t-test with Holm's correction for post hoc comparisons were used to compare scores in related groups with a normal distribution. By using Pillai's trace test, we assessed the statistical significance of changes in parameters over time. The nonparametric Friedman test was used to compare ≥3 dependent samples with non-normal distribution. Post hoc analysis was performed using the Conover–Iman test with Holm's correction.

RESULTS

Study population

In the registry, female patients comprised 81.1% of patients receiving dupilumab, 54.1% had non-allergic eosinophilic SBA, 19 (52.8%) had CRSwNP, 16 (43.2%) had AR, and 7 (19.4%) had CRS. Combinations of CIDN are presented in Table 1, and 4 (10.8%) patients did not have concomitant CIDN. Intolerance to NSAIDs was more common in patients with CRSwNP (patients with CRSwNP, n=6; patients with AR+CRSwNP, n=5). A significant increase in total IgE was observed in patients with AR, which can be explained by the presence of concomitant atopic dermatitis. An increase

Table 1. Characteristics of comorbid patients receiving dupilumab from the register

Parameters	Total *n*=37	AR *n*=7	CRSwNP *n*=10	AR+CRSwNP *n*=9	CRS without polyps *n*=7	W/o CIDN *n*=4
Women, *n* (%)	30 (81.1)	5 (13.5)	8 (21.6)	7 (18.9)	7 (18.9)	3 (8.1)
Men, *n* (%)	7 (18.9)	2 (5.4)	2 (5.4)	2 (5.4)	0	1 (2.7)
Mean age, years, Me (Q1–Q3)	52.0 (42.2–59.8)	39.0 (35.5–52.0)	51.5 (39.0–62.0)	53.0 (48.0–65.0)	55.0 (50.5–58.5)	46.5 (41.5–53.5)
Mean age at diagnosis of asthma, years, Me (Q1–Q3)	37.0 (29.5–44.5)	36.0 (6.0–42.0)	38.0 (34.0–38.0)	37.0 (23.0–41.0)	46.0 (32.0–48.5)	33.0 (29.0–37.5)
BA phenotype J45.0, *n* (%)	7 (18.9)	4	0	2	0	1
BA phenotype J45.1, *n* (%)	20 (54.1)	0	9	1	7	3
BA phenotype J45.8, *n* (%)	10 (27.0)	3	1	6	0	0
Body mass index (kg/m^2), Me (Q1–Q3)	26.1 (23.5–31.6)	25.3 (24.2–29.7)	27.8 (23.9–34.5)	23.4 (20.6–25.4)	32.1 (28.8–33.8)	28.6 (24.4–31.5)
Intolerance to NSAIDs, *n* (%)	16 (43.2)	0	6 (16.2)	5 (13.5)	4 (10.8)	1 (2.7)
Smoking, *n* (%)	4 (10.8)	2	2	0	0	0
Atopic dermatitis, *n* (%)	6 (16.2)	5	0	1	0	0
Total IgE, IU/L, Me (Q1–Q3)	158.3 (84.1–1020.0)	1843.5 (1020.0–8113.0)	94.1 (75.6–428.0)	191.6 (115.0–341.0)	115.1 (56.7–145.7)	302.8 (163.8–736.4)
Phadiatop, PAU/L, Me (Q1–Q3)	0.4 (0.1–9.3)	8.37 (3.45–39.5)	0.1 (0.03–0.83)	7.1 (4.3–10.8)	0.02 (0.01–0.02)	0.07 (0.05–29.7)

Note: AR, allergic rhinitis; BA, bronchial asthma; CRSwNP, chronic rhinosinusitis with nasal polyps; CRS, chronic rhinosinusitis; CIDN, chronic inflammatory diseases of the nose; NSAIDs, non-steroid anti-inflammatory drugs.

in Phadiatop to 8.37 (3.45–39.5) and 7.1 (4.3–10.8) PAU/L* (*Phadia arbitrary units, measurements developed by Pharmacia Diagnostics) in patients with AR and AR+CRSwNP, respectively, was found (Table 1).

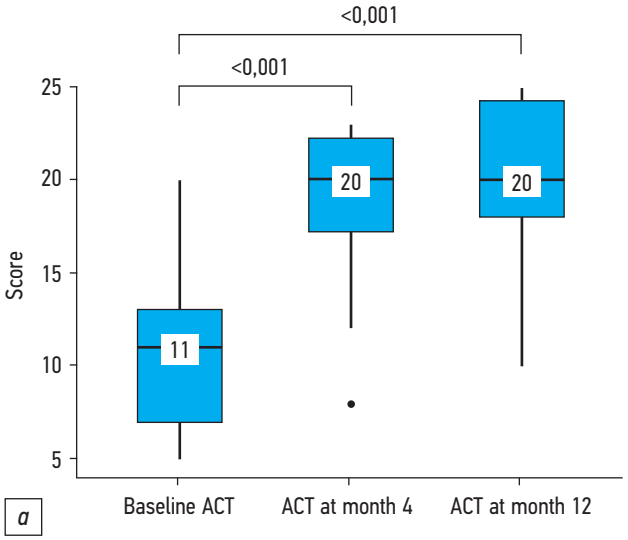
Key study findings

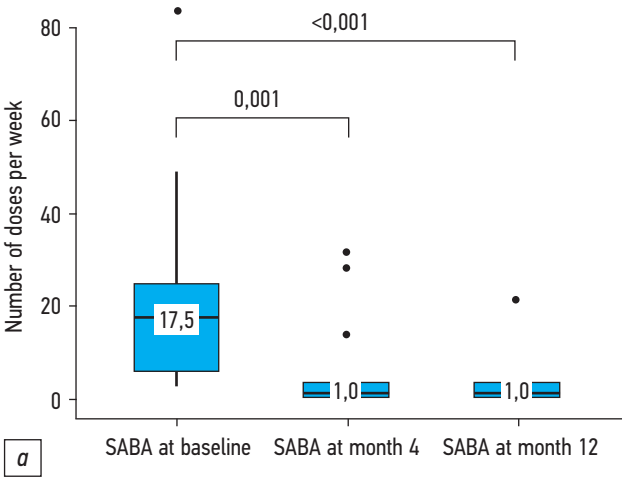
The ACT questionnaire revealed the SBA control level. Data from 19 patients on 12-month dupilumab therapy were available for analysis. Linked sample analysis revealed an increase in the mean ACT score after 4 months of therapy (p <0.001). By month 12 of therapy, the trend persisted (p <0.001) (Fig. 1a). Before the start of therapy, asthma symptoms were poorly controlled in all patients (ACT ⩽19 points). During dupilumab therapy, the proportion of patients with ACT scores ⩾20 increased. By month 4 of therapy, 52.6% of patients had partially controlled SBA (ACT 20–24 points). The proportion of patients with poorly controlled asthma also decreased from 100% before therapy to 42.1% at 1 year of therapy (p <0.001). By month 12 of therapy, 57.9% of the patients scored ⩾20 points in the ACT, including 4 (21.1%) patients with well-controlled asthma (ACT of 25 points) (Fig. 1, *b*).

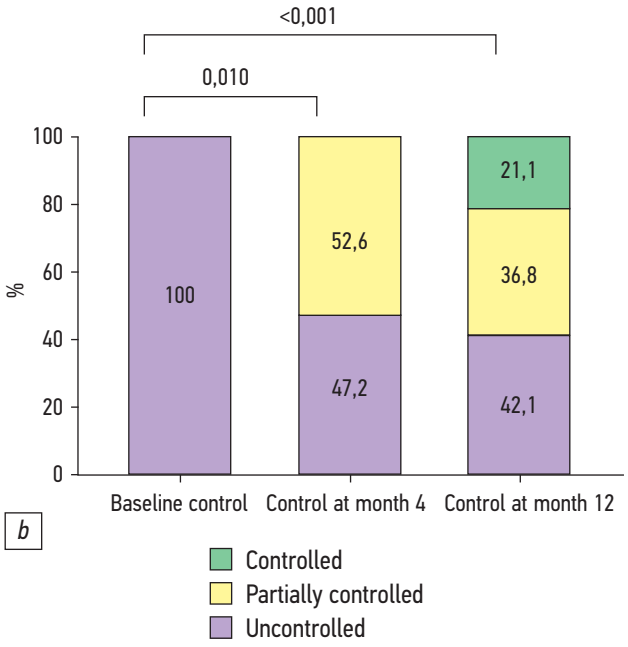
Additional study results

As disease control improved, the number of used short-acting beta-agonist doses decreased from 17.5 doses per week (Q1–Q3: 5.8–24.5) at baseline to 1 dose per week per patient (Q1–Q3: 0.0–2.2) at month 12 of dupilumab therapy (p <0.001) (Fig. 2, *a*). During dupilumab therapy, the number of patients receiving systemic corticosteroids (sCCs) also decreased from 68.5% (n=13) at baseline to 10.5% (n=2) at month 4 of therapy (p <0.001) with maintained trends until month 12 of therapy (Fig. 2, *b*).

Improvement in SBA control was accompanied by a statistically significant decrease in the number of asthma exacerbations from 2.19±1.83 per patient per year at baseline to 0.22±0.55 per patient at month 12 of dupilumab therapy (p <0.001) (Fig. 3). Accordingly, the use of healthcare resources (hospitalizations and emergency calls due to SBA exacerbations) decreased. Before the initiation of dupilumab therapy, 12 patients were hospitalized for exacerbations of bronchial asthma, of which seven had repeated hospitalizations over the year. The mean number of hospitalizations was 1.0±1.27 per patient per year. During the 12-month dupilumab therapy, three hospitalizations were reported during the first 4 months of observation and 3 hospitalizations during months 4–12 of observation (the mean number of hospitalizations was 0.11±0.47 and 0.17±0.51, respectively; p <0.001). A downward trend in emergency calls because of SBA exacerbations was observed, but was not statistically significant (p=0.205).







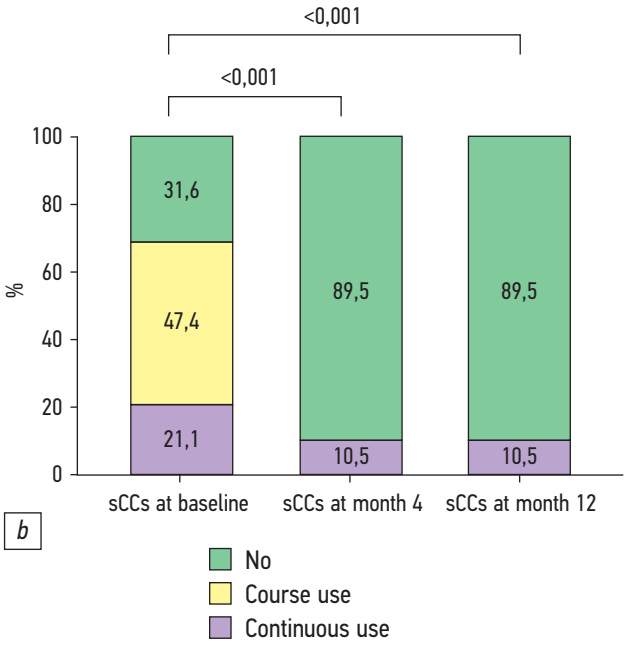


Fig. 1. Level of control of severe bronchial asthma in patients from the registry according to the ACT questionnaire: *a*, dynamics of ACT scores (p_{total} <0.001); *b*, asthma control in patients on 12-month dupilumab therapy (p_{total} <0.001).

Fig. 2. Need for anti-inflammatory drugs in patients from the register with >12 months of dupilumab therapy: *a*, beta2-adrenergic agonists (p_{total} <0.001); *b*, systemic corticosteroids (p_{total} <0.001).

The dynamics of the AQLQ scores indicated an increase in the quality of life (p <0.001): initially, the mean score was 2.91 (Q1–Q3: 2.43–3.86); at month 4 of therapy, it was 5.39 (Q1–Q3: 4.14–5.91), and at month 12, it was 5.89 (Q1–Q3: 4.70–6.59).

FEV_1 was used to assess the dynamics of external respiration function. Its value was 55.4%±16.7 (95% CI 47.1–63.7) and significantly increased to 81.5%±19.1 at month 12 of therapy (95% CI 72.0—91.0) (p <0.001; Fig. 4).

During the dupilumab therapy, eosinophils in the peripheral blood increased from 460 cells/μL (Q1–Q3: 306–706) at baseline to 522 cells/μL (Q1–Q3: 257–880) at month 12 of therapy (p=0.504; Fig. 5).

Biological therapy resulted in a decrease in nasal symptoms, which was confirmed by a significant decrease in the SNOT-22 and VAS scores from month 4 to month 12 of therapy (p <0.001 and p <0.001, respectively, Fig. 6).

Subgroup analysis

No statistically significant differences were recorded before the start of biological therapy when comparing the mean ACT scores in subgroups formed by CIDN phenotypes (p=0.521). By month 4 of dupilumab therapy, a statistically significant difference was found (p=0.003): asthma control was significantly better in patients with CRSwNP and

AR+CRSwNP than in patients with concomitant CRS without polyps (p=0.002 and p=0.010, respectively; Fig. 7). By month 12 of treatment, the trend persisted; however, given the small number of patients in the subgroups, assessing statistical significance was impossible.

The analysis of the efficacy of dupilumab therapy based on the baseline level of peripheral blood eosinophils revealed no differences between subgroups 1 and 2 before therapy in the ACT score, 10 (Q1–Q3: 6–13) and 11 (Q1–Q3: 7–12), respectively (p=0.667) and FEV_1, 53.00 (Q1–Q3: 50.75–63.75) and 57.00 (41.50–66.50), respectively (p=0.832). The ACT score increased to 18 (Q1–Q3: 16–19) and FEV1 to 64.50 (Q1–Q3: 51.50–81.75) in subgroup 1 (<300 cells/μL) at month 12 of therapy. The changes were not statistically significant (p=0.125 and p=1.000, respectively). The ACT score statistically significantly increased to 22 (Q1–Q3: 19–25) and FEV_1 to 86.00 (Q1–Q3: 69.25–98.00) in subgroup 2 (⩾300 cells/μL) (p <0.001; Fig. 8).

Adverse events

The following adverse events were recorded during dupilumab therapy: pain at the injection site (n=5), increased blood pressure (n=1), headache (n=2), weakness (n=1), and lacrimation (n=1). All adverse events were mild, did not require drug cessation, and resolved on their own or with drug therapy (antihypertensive drugs and cromoglicic acid eye drops).

DISCUSSION

Dupilumab therapy in patients with SBA and concomitant CIDN for 12 months increased the proportion of patients with partially and fully controlled asthma from 0% at baseline to 57.9% (p <0.001). The improvement in clinical and functional parameters was accompanied by a decrease in the asthma exacerbation rate and the use of healthcare resources, improvement of the quality of life, and improvement of nasal breathing. These results supplement studies of the efficacy of dupilumab in patients with SBA using data from real-world clinical practice on the effect of the drug on comorbidities of the nose and paranasal sinuses.

Evidence for the efficacy and safety of dupilumab has been obtained from phase II and III randomized trials [9–14]. Women were also predominant participants of these studies (51%–62.9%); however, they included patients from the age of 12 years, and the mean age of the patients was lower (47.9–52 years). For the primary endpoints in the QUEST study, the reduction in the frequency of severe asthma exacerbations and the increase in FEV_1 was statistically significantly higher in the active treatment groups (200 or 300 mg dupilumab subcutaneously every 2 weeks) regardless of the baseline level of biomarkers [11]. In the subsequent VENTURE study, dupilumab generally reduced the number of asthma exacerbations compared with placebo by 59% with a reduction in the dose of oral sCCs; the effect was better in the subgroup

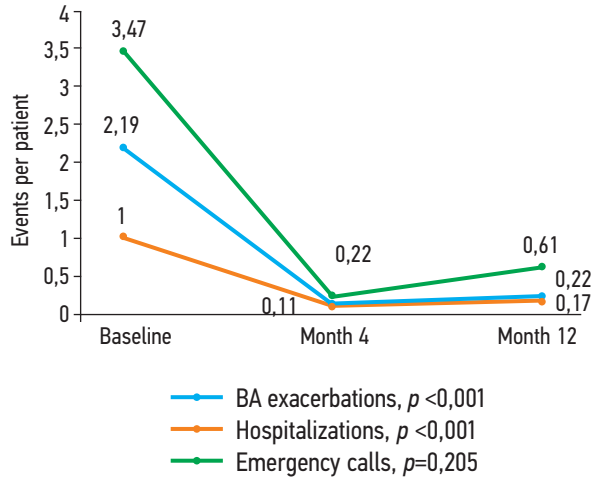


Fig. 3. Emergency calls, hospitalizations, and asthma exacerbations in patients with over 12 months of dupilumab therapy. BA, bronchial asthma.

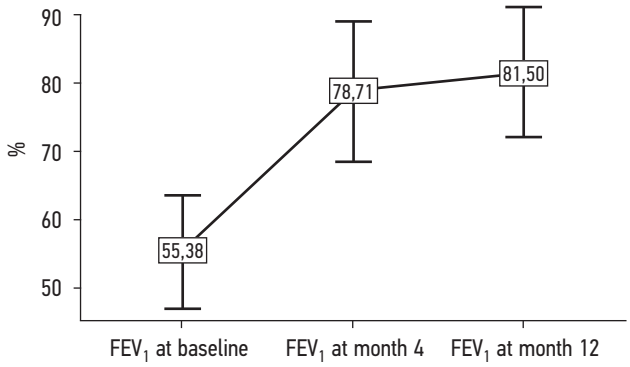


Fig. 4. Dynamics of the forced expiratory volume in 1 second (FEV_1 level, %) in patients with over 12 months of dupilumab therapy (p <0,001).

with a baseline eosinophil level of ⩾300 cells/μL than in the subgroup with <300 cells/μL; however, the difference was not statistically (71% and 60%, respectively) [13]. Corren et al. [12] also showed that the effect of dupilumab (exacerbation rate, increase in FEV_1, and improvement in ACQ control) was not dependent on the signs of allergic asthma. In the VENTURE study, 52% of patients discontinued corticosteroids by week 24 of dupilumab therapy, whereas in the placebo group, glucocorticoid withdrawal was registered in 29% of patients, which could be associated with an increase in adherence to treatment. Therefore, investigation of how drugs work in real-world practice, excluding the "ideal" conditions of large randomized trials, may yield different results.

In contrast to the VENTURE study, we obtained a more significant response to dupilumab in terms of respiratory function and ACT score in patients with baseline eosinophil count of ⩾300 cells/μL vs. patients with baseline eosinophil count of <300 cells/μL. We found three real-world studies on the efficacy of dupilumab. Carpagnano et al. [15] used

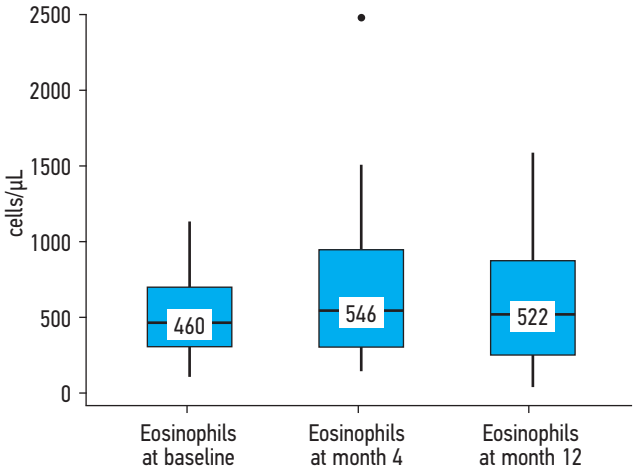


Fig. 5. Dynamics of blood eosinophil levels in patients over 12 months of dupilumab therapy (p=0.504).

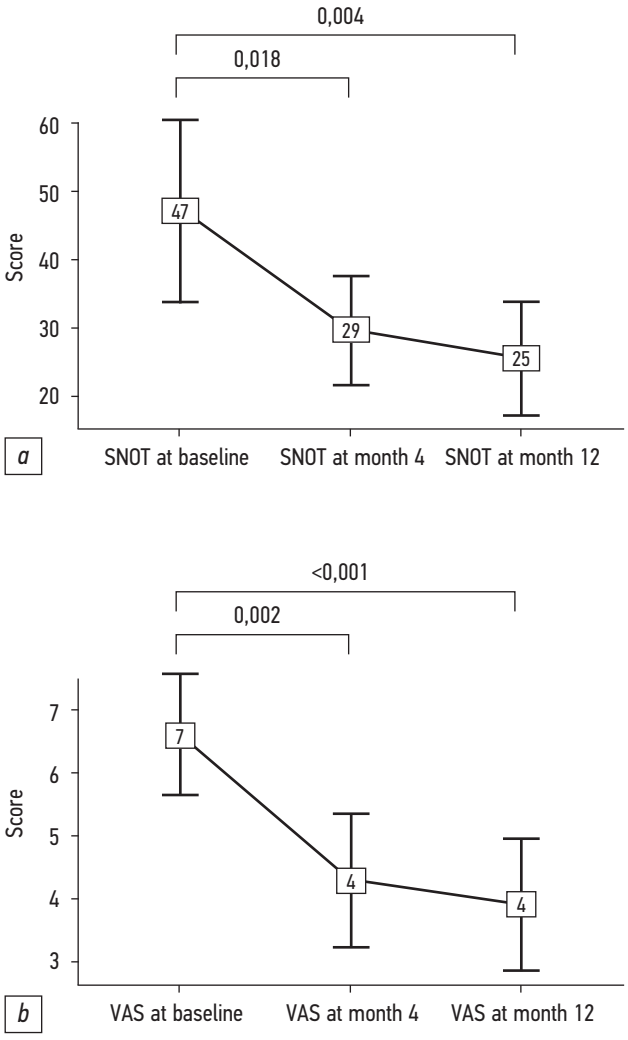


Fig. 6. Dynamics of sinonasal symptoms in patients with over 12 months of dupilumab therapy: *a*, according to the SNOT-22 questionnaire (p_{total} <0.001); *b*, according to VAS scores (p_{total} <0.001).

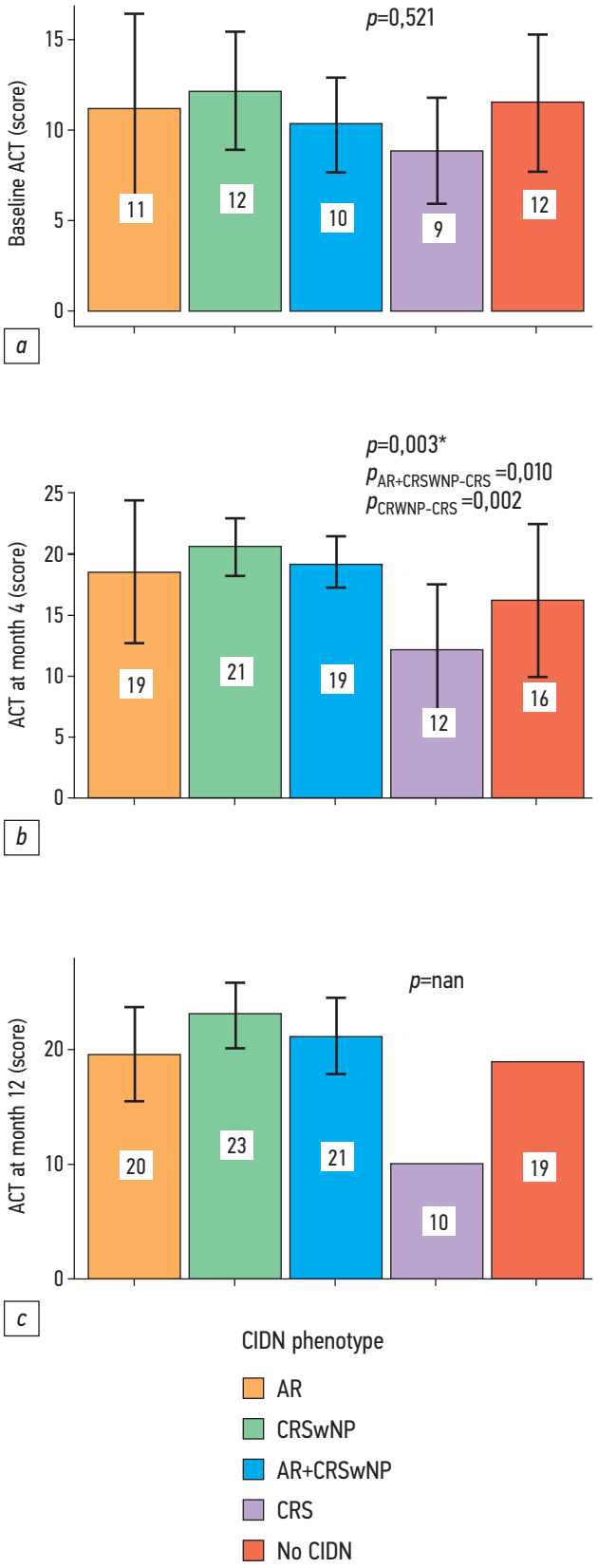


Fig. 7. Dynamics of ACT questionnaire scores before the start of biological therapy (*a*), at month 4 (*b*; * statistically significant difference), and at month 12 (*c*) of dupilumab therapy. AR, allergic rhinitis; CRSwNP, chronic rhinosinusitis with nasal polyps; CRS, chronic rhinosinusitis; CIDN, chronic inflammatory diseases of the nose.

peripheral blood eosinophil levels >300 cells/μl and/or FeNO >25 ppb as the criteria for selecting patients (*n*=12) for the study and obtained a statistically significant increase in ACT scores at month 3 of therapy (at baseline 13, 25±4.65; at month 3, 19.17±4.45; p <0.01), increase in FEV_1 (at baseline, 62.58%±15.73%; at month 3, 71.00%±13.11%; p <0.01). Dupin et al. [16] analyzed 64 patients, of which 53.1% were women and 30% had CRSwNP. The eosinophil levels in the peripheral blood and total IgE level did not affect the effectiveness of dupilumab (ACT score dynamics, exacerbation rate and frequency of hospitalizations, use of sCCs, and FEV_1). Patients with CRSwNP had higher FEV_1 values after 12 months of dupilumab therapy than patients with CRS without polyps: 2.4 [Q1–Q3: 1.75–3.09] and 1.81 [Q1–Q3: 1.13–2.50], respectively (p=0.0321). As in our study, patients experienced a rapid increase in FEV_1 by month 3 of therapy and then stabilization until month 12 [16]. Mümmler et al. [17] analyzed the outcomes of dupilumab therapy in 38 patients and showed improvements in ACT and FEV_1, decrease in FeNO, decrease in the exacerbation rate, and need for corticosteroids. Higher response rates have been reported in patients with baseline FeNO of >25 ppb.

Study limitations

The sample size was not previously calculated. The sample size (*n*=37) was small because the study was conducted in routine clinical practice, and this does not allow the extrapolation of the results to the general population. Moreover, the study had no control group.

CONCLUSION

In real-world clinical practice settings, 1 year of anti-IL-4,13 therapy with dupilumab for SBA in patients with concomitant CIDN improved asthma control. The improvement in clinical and functional parameters was accompanied by a decrease in the asthma exacerbation rate and use of healthcare resources, and improvement in nasal breathing and accordingly the quality of life. We obtained a more significant response to dupilumab in terms of respiratory function and ACT score in patients with baseline eosinophilia ⩾300 cells/μL compared with patients with baseline eosinophil count of <300 cells/μL. Patients with concomitant CIDN had decreased nasal symptoms. Patients with SBA and comorbid AR+CRSwNP or CRSwNP respond better to dupilumab therapy than patients with concomitant CRS without polyps.

ADDITIONAL INFORMATION

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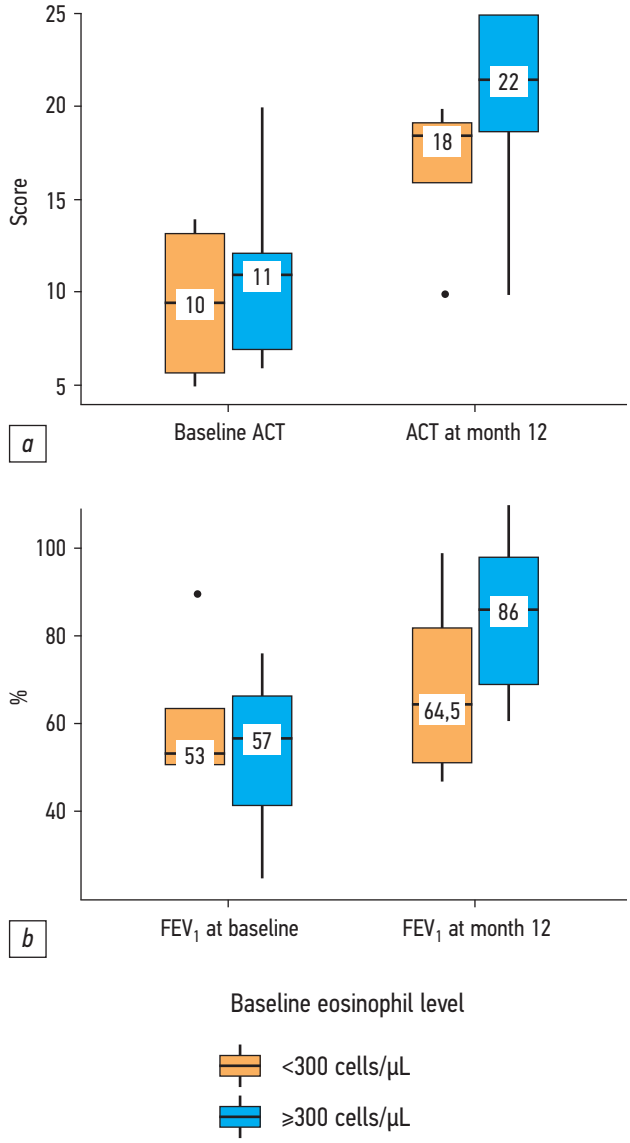

Fig. 8. Dynamics of ACT questionnaire scores (*a*) and FEV1 (*b*) at month 12 of dupilumab therapy. FEV_1, forced expiratory volume in 1 second.

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

Authors' contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work. V.V. Naumova — design of the study, collection, processing and analysis of the obtained data and literary sources, writing the text of the article; D.V. Kiseleva — collection, processing and analysis of the obtained data, writing and editing the text of the article; E.K. Beltyukov — concept, organization and design of the study, editing the text of the article; Ya.R. Starikova — analysis of literary sources, work with graphic material.

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