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Эффективность анти-IL-5 терапии меполизумабом тяжёлой бронхиальной астмы и сопутствующих воспалительных заболеваний носа в реальной клинической практике

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АННОТАЦИЯ

Обоснование. Т2-воспаление лежит в основе неаллергической, эозинофильной тяжёлой бронхиальной астмы и хронического полипозного риносинусита. Существующие таргетные препараты, направленные против IL-5, могут улучшать клинико-функциональные показатели у пациентов с сочетанием тяжёлой астмы и хронического полипозного риносинусита.

Цель — оценить эффективность меполизумаба у пациентов с неаллергической тяжёлой бронхиальной астмой и сопутствующими воспалительными заболеваниями носа в реальной клинической практике.

Материалы и методы. Исследование проводилось без контрольной группы, методом сравнения связанных совокупностей (анализ «до-после») на основе Свердловского областного регистра взрослых пациентов с тяжёлой бронхиальной астмой и сопутствующими воспалительными заболеваниями носа. В качестве первичной конечной точки оценивали достижение контроля над астмой (опросник АСТ) и уменьшение доли пациентов с неконтролируемой тяжёлой астмой. Оценивали также количество обострений астмы, вызовов скорой медицинской помощи и госпитализаций, качество жизни по опроснику AQLQ, уровень эозинофилов периферической крови, функцию внешнего дыхания (объём форсированного выдоха за первую секунду, форсированную жизненную ёмкость лёгких, а также соотношение этих параметров). Динамика состояния пациентов с воспалительными заболеваниями носа оценивалась по опросникам SNOT-22 и ВАШ.

Результаты. За 12 мес терапии меполизумабом АСТ увеличился с 9 (Q1–Q3: 7–11) до 22 (Q1–Q3: 21–24) баллов (p <0,001). Доля пациентов с неконтролируемой астмой снизилась со 100 до 10% (p <0,001). Снизилось количество обострений астмы с 3,18±2,8 случая на пациента в год до 0 (p <0,001) и госпитализаций с 0,57±0,9 до 0 (p=0,007). Качество жизни по AQLQ повысилось с 3,48±1,05 (95% ДИ 2,73–4,24) до 5,59±0,88 (95% ДИ 4,96–6,22) баллов (p <0,001). Количество эозинофилов крови снизилось с 442 (Q1–Q3: 336–853) до 90 кл/мкл (Q1–Q3: 73–117) (p <0,001). Наблюдалось увеличение $ОФВ_1$ с 63,9±24,2% (95% ДИ 46,6–81,2) до 80,5±18,3% (95% ДИ 67,4–93,6) (p=0,015). По опроснику SNOT-22 получено снижение на 33 пункта — с 45±30 до 22±15 (p=0,006), по ВАШ — на 5 баллов: с 8 (Q1–Q3: 5–8) до 3 (Q1–Q3: 3–5) (p=0,017).

Заключение. По результатам исследования наблюдались улучшение контроля над астмой, уменьшение количества обострений бронхиальной астмы, улучшение качества жизни по AQLQ. Выявлено также статистически значимое снижение уровня эозинофилов в периферической крови и улучшение функции внешнего дыхания. Со стороны сопутствующих воспалительных заболеваний носа отмечалось существенное улучшение носового дыхания, подтверждаемое данными опросников SNOT-22 и ВАШ.

Ключевые слова: тяжёлая бронхиальная астма; хронический полипозный риносинусит; иммунобиологическая терапия; генно-инженерные биофармацевтические препараты; меполизумаб.

Как цитировать

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Efficacy of anti-IL-5 therapy with mepolizumab for severe bronchial asthma and concomitant inflammatory nasal diseases in real clinical practice

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ABSTRACT

BACKGROUND: T2 inflammation underlies nonallergic eosinophilic severe bronchial asthma and chronic rhinosinusitis with nasal polyposis. Existing targeted anti-IL-5 drugs can improve the clinical and functional parameters in patients with a combination of severe asthma and CRSwNP.

AIM: To evaluate mepolizumab efficacy in patients with nonallergic severe asthma and concomitant inflammatory nasal diseases in real clinical practice.

MATERIALS AND METHODS: The study was conducted without a control group, by comparing related populations (before–after analysis) and based on the Sverdlovsk regional register of adult patients with severe asthma and concomitant inflammatory nasal diseases. The primary endpoints were asthma control achievement (ACT questionnaire) and a decrease in the proportion of patients with uncontrolled severe asthma. The number of asthma exacerbations, emergency calls and hospitalizations, quality of life according to the AQLQ questionnaire, peripheral blood eosinophil level, and respiratory function (the volume of forced exhalation in the first second, the forced vital capacity of the lungs, as well as the ratio of these parameters) were also assessed. The dynamics of nasal symptoms was assessed using the SNOT-22 questionnaire and visual analog scale.

RESULTS: During 12 months of therapy with mepolizumab, the ACT score increased from 9 (Q1–Q3, 7–11) to 22 (Q1–Q3, 21–24) points (p <0.001). The proportion of patients with uncontrolled asthma decreased from 100% to 10% (p <0.001). The number of asthma exacerbations decreased from 3.18±2.8 per patient per year to 0 (p <0.001), and that of hospitalizations decreased from 0.57±0.9 per patient per year to 0 (p=0.007). The quality of life according to the AQLQ increased from 3.48±1.05 (95% CI, 2.73–4.24) to 5.59±0.88 points (95% CI, 4.96–6.22) (p <0.001). The number of blood eosinophils decreased from 442 (Q1–Q3, 336–853) to 90 (Q1–Q3, 73–117) cells/μL (p <0.001). There was increase in FEV_1 from 63.9%±24.2% (95% CI, 46.6–81.2) to 80.5%±18.3% (95% CI, 67.4–93.6) (p=0.015). Decreases in the SNOT-22 questionnaire score by 33 points, from 45±30 to 22±15 (p=0.006), and in the visual analog scale score by 5 points, from 8 (Q1–Q3, 5–8) to 3 (Q1–Q3, 3–5) (p=0.017), were also noted.

CONCLUSIONS: Based on the study results, there were asthma control improvement, a decrease in asthma exacerbations, and quality of life improvement according to the AQLQ. A statistically significant decrease in the number of peripheral blood eosinophils and respiratory function improvement were also revealed. In patients with concomitant inflammatory nasal diseases, significant improvement in nasal breathing was noted, which was confirmed by the scores of the SNOT-22 questionnaire and visual analog scale.

Keywords: severe bronchial asthma; chronic rhinosinusitis with nasal polyposis; targeted therapy; biologicals; mepolizumab.

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List of abbreviations

LTRA — leukotriene receptor antagonist
IDN — inflammatory diseases of the nose
LAMA — long-acting muscarinic antagonist
LABA — long-acting beta2-agonist
ICS — inhaled corticosteroids
INCS — intranasal corticosteriods
SABA — short-acting beta2-agonist
SCS — systemic corticosteroids
EMS — emergency medical services
SA — severe asthma
CRSwNP — chronic rhinosinusitis with nasal polyps
CRS — chronic rhinosinusitis
IL — interleukin

BACKGROUND

Severe asthma (SA) affects up to 10% of all asthma patients [1], accounts for significant expenses to healthcare systems owing to disability of patients and high-treatment costs. In 40% of these patients, SA is combined with chronic rhinosinusitis with nasal polyps (CRSwNP) [2–4], which significantly impairs patients' quality of life.

Since the underlying cause of SA combined with CRSwNP is type 2 inflammation, biologics that block interleukin (IL)-4, IL-5, and IL-13 are used to treat this condition. IL-5-blocking biologics include mepolizumab. The efficacy of mepolizumab in patients with SA was evaluated in large trials (randomized controlled or observational cohort studies that involved more than 300 patients) [3–8], meta-analyses [9], as well as real-life studies with up to 50 participants [10–14] that specifically included patients with SA and CRSwNP.

Omalizumab, the first biologic to treat SA, was registered in the Russian Federation in 2007. Mepolizumab was introduced in 2019 in the Sverdlovsk region.

The aim of this study is to evaluate the effectiveness of mepolizumab in patients with severe nonallergic (eosinophilic) asthma and concomitant inflammatory diseases of the nose (IDN) in clinical practice.

MATERIALS AND METHODS

Study design

An open, nonrandomized prospective study was conducted in clinical practice in real-life. The study was conducted without a control group by comparing associated populations (prepost analysis).

Eligibility criteria and conditions

The efficacy study of mepolizumab was based on the regional registry of adult patients (18 years of age and older) with SA and concomitant IDN. Registration of adult patients with SA has been conducted in the Sverdlovsk region since 2016. Upon inclusion of patients in the register, the diagnosis of SA was verified according to the following criteria of the American Thoracic Society and European Respiratory Society (ATS/ERS, 2014) [15] and its subsequent amendments [1, 16]: patients with uncontrolled asthma despite treatments of comorbidities and maximum adherence to optimized therapy (GINA steps 4 or 5), or patients who lost asthma control when they attempted to reduce therapy.

The selection of patients for the register was conducted on the basis of the Sverdlovsk Region Ministry of Health orders dated January 24, 2014 (No. 64-0) and January 23, 2015 (No. 73-o/17[1]) based on which it was possible to ungroup diagnostic related groups and decentralize the provision of high-tech medical care for patients with SA. Detailed description of the immunobiological therapy organization of SA in the Sverdlovsk region was published earlier by Beltyukov et al. [17].

Study duration

Owing to the fact that mepolizumab was registered in the Russian Federation in 2018, the analysis included patients (n=14) enrolled in the SA register from June 2019 to July 2021. Each patient underwent initial pretreatment assessments, and at the 4th (Month 4) and 12th (Month 12) months of therapy. Thus, at the time of data analysis (October 2021), 10 patients had completed the initial, Month 4, and Month 12 evaluation visits; four patients had only completed the initial and Month 4 evaluation visits.

Description of medical interventions

Upon inclusion of patients in the register, diagnosis of SA was verified, and phenotyping of the disease was conducted. Allergy history records, skin tests with allergens, determination of specific immunoglobulin E (IgE), total IgE, and peripheral blood eosinophilic levels were used for asthma phenotyping. The Phadiatop ImmunoCAP test (henceforth referred to as Phadiatop) was also performed.

The SA atopic phenotype was determined in patients with a combination of positive allergy history and positive skin

[1] Order of the Ministry of Health of Sverdlovsk Region and the Territorial Fund for Obligatory Medical Insurance of Sverdlovsk Region dated January 23, 2015 N 73-p/17 "On the formation and maintenance of territorial registers of patients with certain diseases requiring the use of expensive drugs." Access mode: http://docs.cntd.ru/document/561785169. Reference date 15.01.2022.

tests, or positive allergy history and at least one positive, clinically significant, specific IgE, or positive allergy history and a positive Phadiatop test.

The eosinophilic phenotype of SA was determined by negative allergy history, negative skin tests, negative specific IgE and Phadiatop tests, and blood eosinophil levels >150 cells/μl [1, 18].

Mixed SA phenotype was determined by a combination of allergic and non-allergic components. Allergic components were determined by a combination of positive allergy history and positive skin tests, or positive allergy history, and at least one positive, clinically significant specific IgE, or positive allergy history and a positive Phadiatop test. Non-allergic components were determined by the late onset of asthma combined with CRSwNP or chronic rhinosinusitis (CRS), and blood eosinophils levels ⩾330 cells/μL. There was also an assessment done on patient's hypersensitivity to aspirin, which in 100% of cases indicates the presence of non-allergic components. At the same time, the absence of hypersensitivity to aspirin does not exclude the non-allergic component.

The reason for inclusion of CRSwNP and CRS for non-allergic components of mixed SA was the frequency analysis of CRSwNP and CRS in the group of patients with non-allergic SA (J45.1, *n*=32), which demonstrated that 26 (81.3%) patients had CRS with/without polyps and no allergic rhinitis.

The reason for inclusion of blood eosinophilic levels >330 cells/μl in the criteria of non-allergic components of mixed SA was the receiver operating characteristic analysis of non-allergic asthma probability that dependent on the level of eosinophils in peripheral blood.

Allergic rhinitis was diagnosed on the basis of clinical and allergological assessments in accordance with clinical guidelines on allergic rhinitis validated in 2018 (and amended subsequently) [19, 20].

Diagnosis of CRSwNP and CRS without polyps was made on the basis of clinical data, including otorhinolaryngologist examination and a computed tomography scan of the paranasal sinuses.

Mepolizumab was prescribed subcutaneously at a dose of 100 mg once every 4 weeks in a clinical setting according to the instructions.

Primary outcome of the study

As the primary endpoint in the evaluating of the effectiveness of mepolizumab therapy, the achievement of asthma control (Asthma Control Test, ACT) and decrease in the proportion of patients with uncontrolled SA were assessed.

Additional study outcomes

Secondary endpoints were the number of asthma exacerbations, emergency medical service (EMS) calls and hospitalizations, the need for short-acting beta-agonists (SABA), volume of therapy, quality of life according to the Asthma Quality of Life Questionnaire (AQLQ), eosinophilic levels in peripheral blood, pulmonary functional tests — which included forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), as well as the ratio of these parameters (FEV1/FVC) — and safety assessments (adverse events). The dynamics of the patients' statuses with IDN was assessed based on a 22-item questionnaire Sinonasal Outcome Test (SNOT-22) and a visual analog scale (VAS).

Outcome registration methods

The level of asthma control was determined by the number of AST points: 5–19 points for uncontrolled asthma, 20–24 points for partially controlled asthma, and 25 for controlled asthma.

In addition to the ACT, patients completed the AQLQ, SNOT-22, and VAS questionnaires at each evaluation visit; then, they underwent clinical blood tests which involved eosinophilic counts and spirometry tests, and data were collected on the number of asthma exacerbations, EMS calls, hospitalizations, volume of therapy, and adverse events.

Ethical review

The creation of the SBA register and the management of patients based on its use were approved by the local ethics committee of the FSBEI HE Ural State Medical University of the Ministry of Health of the Russian Federation (Yekaterinburg, Russian Federation, Protocol No. 8 dated 10/25/2019). Upon inclusion in the register, all patients signed an informed consent for the use of their medical data for scientific purposes. This study will also be included in a doctoral thesis for a habilitation degree in Medicine, approved by the local ethics committee of the FSBEI HE Ural State Medical University of the Ministry of Health of the Russian Federation (Yekaterinburg, Russian Federation, protocol No. 8 of 11/20/2020). The study was conducted in accordance with the principles stated in the Declaration of Helsinki.

Statistical analysis

Statistical analysis was conducted using StatTech (version 2.4.8, LLC StatTech, City, Russian Federation). The sample size was not calculated because the study was conducted in real-life clinical practice based on a patient register.

Quantitative indicators were evaluated for compliance to normal distribution using the Shapiro–Wilk test (with <50 subjects). Quantitative indicators compliant to the normal distribution were described using arithmetic means (M), standard deviations, and 95% confidence interval limits (95% CI). In the case in which the distribution was not normal, quantitative data were described using the median (Me) and lower and upper quartiles (Q1–Q3).

Categorical data were described with absolute values and percentages.

For comparison of three or more related groups according to normally distributed quantitative traits, one-way repeated measurements analysis of variance was

used. Statistical significance of changes in the indicator over time was estimated using Pillai's Trace. Post-hoc analyses were performed using paired Student's t-test with Holm's correction.

The Wilcoxon test was used to compare non-normally distributed quantitative indicators in two related groups.

For comparison of three or more dependent populations, the distribution which differed from the normal one was determined based on the nonparametric Friedman test with post-hoc comparisons using the Wilcoxon's test with Holm's correction, and applied.

Comparison of binary indicators characterizing more than two related populations was performed using Cochran's Q-test. Post-hoc analysis was performed using the McNemar test with Holm's correction.

RESULTS

Objects (participants) of the study

As of October 2021, the registry included 14 patients with SA who had been receiving mepolizumab for at least 4 months. This group was dominated by women (78.6%) and the non-allergic asthma phenotype (85.7%) (Table 1). The mean age was 60 years (Q1–Q3: 54–67). The mean age at the time asthma was diagnosed was 42.5 years (Q1–Q3: 38–51.8). The diagnosis of asthma was identified at younger ages in patients without concomitant IDN. Concomitant IDNs were predominantly represented by chronic rhinosinusitis (71.4%): CRSwNP (*n*=9), CRSwNP + allergic rhinitis (*n*=1), and CRS without polyps (*n*=1) (see Table 1).

Hypersensitivity to nonsteroidal anti-inflammatory drugs was more frequently observed in the group of patients with CRSwNP (35.7%). Mean Phadiatop and total IgE values were 0.1 PAU/L (Q1–Q3: 0.02–0.84) and 91 IU/mL (Q1–Q3: 49.7–333) respectively.

Primary study results

The achievement of SA control was assessed using AST. Prepost analysis showed an increase in the number of points according to AST at the 4th month of therapy with the trend remaining the same up until the 12th month (p <0.001). Accordingly, the proportion of patients with uncontrolled asthma decreased from 100% initially to 40% at 4 months of therapy, and to 10% at 12 months (p <0.001) (Fig. 1).

Additional study results

With an increase in the proportion of patients with controlled asthma, the need for SABA decreased (p <0.001) (Fig. 2a).

Table 1. Characteristics of patients in the register with severe asthma and concomitant inflammatory nasal diseases who received mepolizumab

Indicators	Total *n*=14	AR *n*=1	CRSwNP *n*=9	AR + CRSwNP *n*=1	CRS without polyps *n*=1	No IDN *n*=2
Women, *n* (%)	11 (78.6)	1 (7.1)	7 (50)	1 (7.1)	1 (7.1)	1 (7.1)
Men, *n* (%)	3 (21.4)	0	1 (7.1)	1 (7.1)	0	1 (7.1)
Mean age, years, Me (Q1–Q3)	60 (54–67)	67	63 (59.5–67.3)	42.5 (42.3–42.8)	54	52.5 (45.8–59.3)
Mean age at diagnosis of asthma, years, Me (Q1–Q3)	42.5 (38–51.8)	55	47.5 (43.3–53.3)	36.5 (35.3–37.8)	38	19.5 (15.8–23.3)
Asthma phenotype J45.1, *n* (%)	12 (85.7)	0	9	1	1	2
Asthma phenotype J45.8, *n* (%)	2 (14.3)	1	0	0	0	0
BMI, kg/m^2, Me (Q1–Q3)	30.6 (28.2–32.2)	30.67	29.7 (27.9–32.4)	27.5 (25.3–29.7)	39.25	31.5 (31.0–31.9)
NSAIDS intolerance, *n* (%)	7 (50)	0	5 (35.7)	0	1 (7.1)	1 (7.1)
Smoking, *n* (%)	3 (21.4)	0	1	1	0	1
Total IgE, ME/л, Me (Q1–Q3)	91 (49.7–333)	-	-	-	-	-
Phadiatop, PAU/l, Me (Q1–Q3)	0.1 (0.02–0.84)	-	-	-	-	-

Note: AR — allergic rhinitis, CRSwNP — chronic rhinosinusitis with nasal polyps, CRS — chronic rhinosinusitis, IDN — inflammatory diseases of the nose, BMI — body mass index, NSAIDS — nonsteroidal anti-inflammatory drugs median, Me — median, IgE — immunoglobulin E, Q1–Q3 — lower and upper quartiles.

For each patient, we analyzed the numbers of asthma exacerbations, EMS calls, and hospitalizations for asthma 1 year before the start of targeted therapy. Exacerbation of asthma was defined as a decline in the patient's condition, requiring an increase in therapy volume (including nebulizer therapy, systemic corticosteroid therapy) and/or hospitalization. Of the 14 patients, only one patient had no asthma exacerbation in the year prior to targeted therapy. The average number of exacerbations was 3.18±2.8 per patient per year. After 4 months of mepolizumab therapy, only 3 out of 14 patients experienced one exacerbation (0.21±0.4 per patient per year). The rest of the patients had no exacerbations. In the period from 4 to 12 months of therapy, none of the patients suffered asthma exacerbations (p <0.001) (Fig. 3a). Prior to the initiation of mepolizumab therapy, five patients were hospitalized owing to asthma exacerbations. The average number of hospitalizations was 0.57±0.9 per patient per year. During the year after the start of mepolizumab therapy, there were no hospitalizations (p=0.007). The number of EMS calls for asthma exacerbations decreased, but the trend was statistically not significant (p=0.086).

The analysis revealed a statistically significant improvement in the quality of life according to the AQLQ (p <0.001) (Fig. 4a).

The dynamic trend study of peripheral blood eosinophil counts revealed a statistically significant decrease in eosinophils at the 4th and 12th months of therapy compared with the initial level (p <0.001) (Fig. 3b).

During the analysis of spirometry parameters, a statistically significant increase in FEV1 was noted from 63.9%±24.2% (95% confidence interval (CI) 46.6–81.2) to 80.5%±18.3% (95% CI 67.4–93.6); p=0.015 (Fig. 3c). No statistically significant changes in FVC and FEV1/FVC were detected.

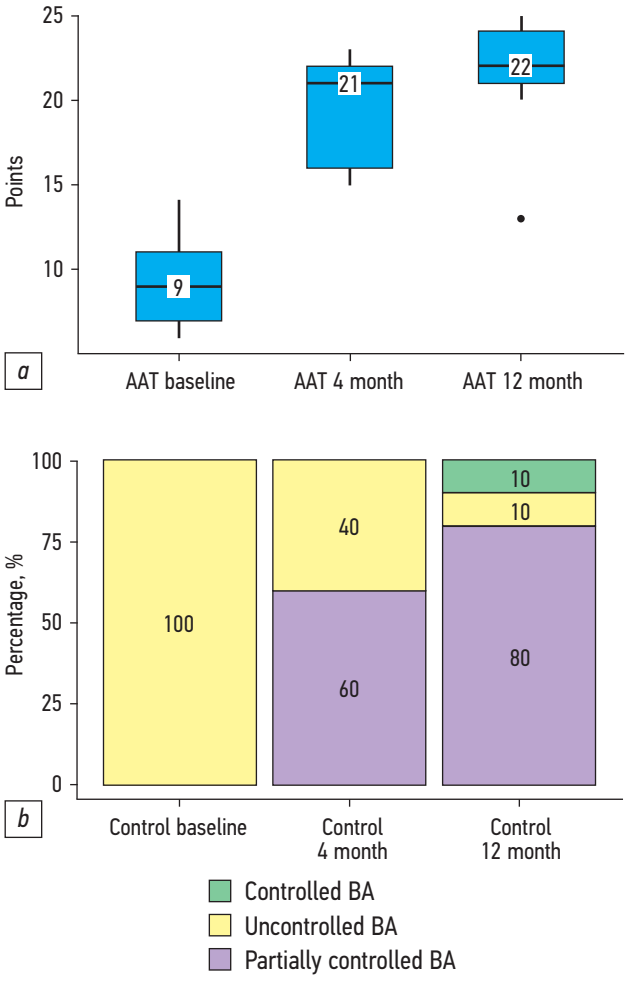

Fig. 1. Primary results of the study: *a* — changes of AAT scores (p_{total} <0.001; $p_{AAT\ baseline\ -\ AAT\ 4\ month}$ = 0.020; $p_{AAT\ baseline\ -\ AAT\ 12\ month}$ = 0.006); *b* — asthma control level trend (p_{total} <0.001; $p_{control\ baseline\ -\ control\ 4\ month}$ = 0.043; $p_{control\ baseline\ -\ control\ 12\ month}$ = 0.004).
Note: AAT — aspartate aminotransferase, BA — bronchial asthma.

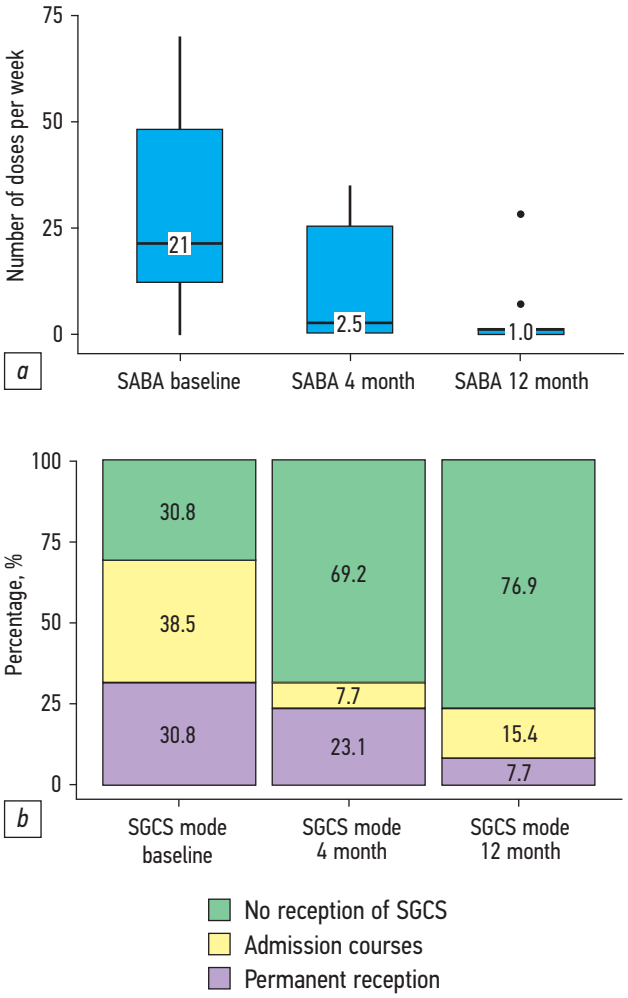

Fig. 2. Additional research results: *a* — trend of SABA demand (p_{total} <0.001; $p_{SABA\ baseline\ -\ SABA\ 4\ month}$ = 0.035; $p_{SABA\ baseline\ -\ SABA\ 12\ month}$ = 0.002); *b* — trend of use mode of systemic corticosteroids ($p_{SGCS\ mode\ baseline\ -\ SGCS\ mode\ 12\ month}$ = 0.032).
Note: SABA — short-acting β2-agonists, SGCS — systemic corticosteroids.

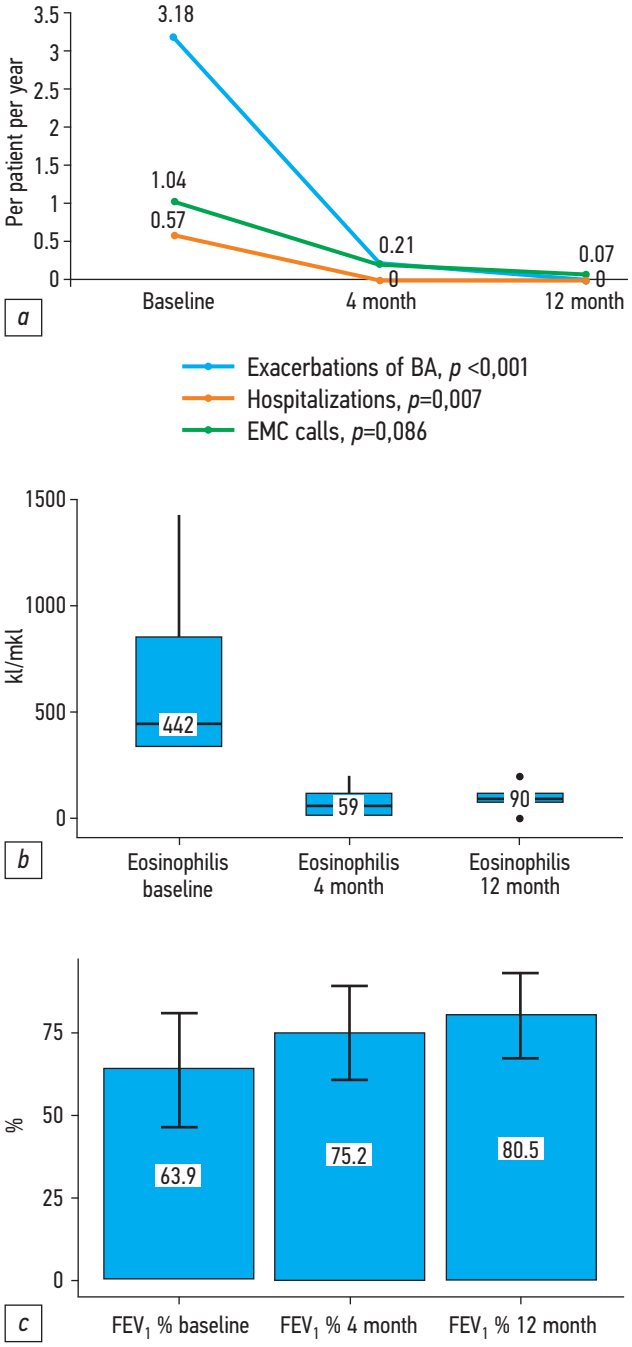

Fig. 3. Additional research results: *a* — asthma exacerbations trend, hospitalizations and emergency medicine services (EMS) calls due to asthma exacerbations; *b* — blood eosinophilic level trend (p_{total} <0.001; $p_{Eosinophils\ baseline\ -\ Eosinophils\ 4\ month}$ = 0.007; $p_{Eosinophils\ baseline\ -\ Eosinophils\ 12\ month}$ = 0.008); *c* — FEV_1 trend, % (p=0.015).

Note: BA — bronchial asthma; EMC — emergency medical care; FEV_1 — volume of forced exhalation in the first second.

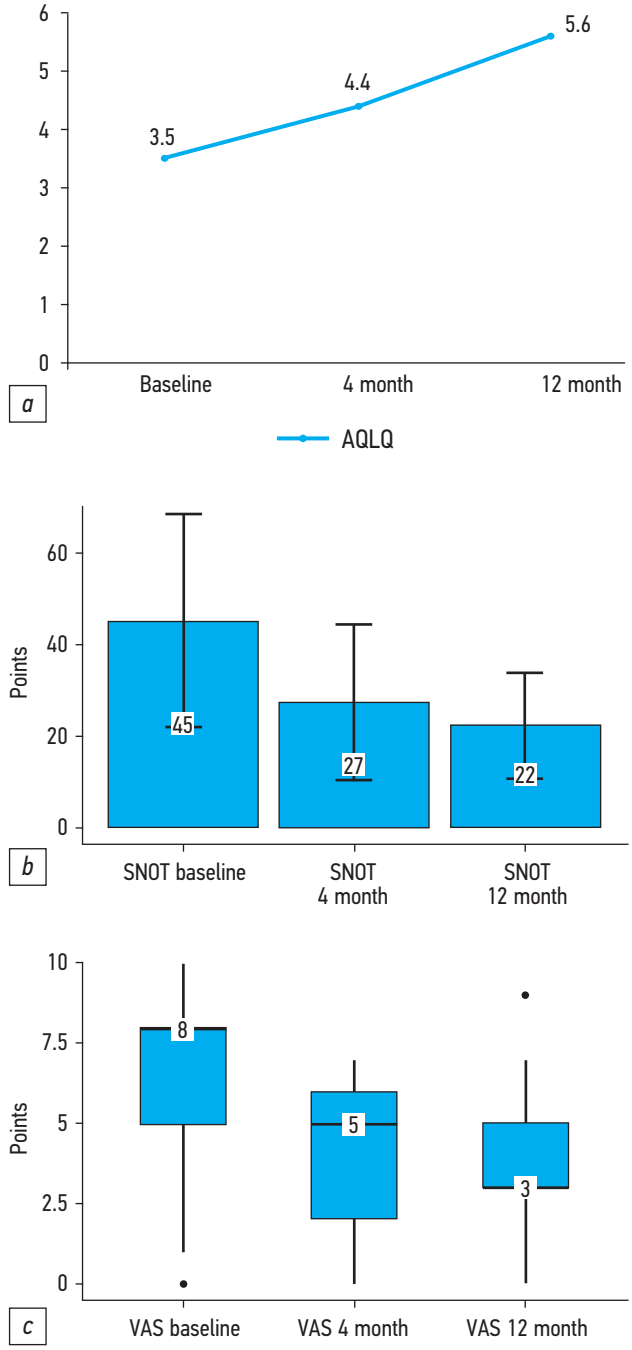

Fig. 4. Additional study results: *a* — trend of quality of life according to AQLQ (p_{total} <0.001; $p_{AQLQ\ 12\ month\ -\ AQLQ\ 4\ month}$ = 0.005; $p_{AQLQ\ 12\ month\ -\ AQLQ\ baseline}$ <0.001; $p_{AQLQ\ 4\ month\ -\ AQLQ\ baseline}$ = 0.005); *b* — trend of SNOT-22 scores (p_{total} = 0.006; $p_{SNOT\ 12\ month\ -\ SNOT\ baseline}$ = 0.037; $p_{SNOT\ 4\ month\ -\ SNOT\ baseline}$ = 0.037); *c* — VAS scores trend (p=0.017).

Assessment of nasal pathology over time was conducted using SNOT-22 and VAS. Prepost analysis revealed a significant decrease in SNOT-22 and VAS scores (p=0.006 and p=0.017, respectively), which indicated an improvement in nasal breathing function (Figs. 4b, 4c).

At the time of inclusion in the register, all patients received basic therapy equivalent to the 4th and 5th GINA steps. However, initially, only one patient received two-component therapy (ICS + LABA), four patients received five-component therapy, four patients received four-component therapy, and

five patients received three-component therapy (Table 2). By the 12th month of treatment with mepolizumab, there was a decrease in the number of patients who received 4–5 drugs, and an increase in the number of patients who received two- and three-component therapy. These small samples were not statistically processed.

In the analysis of inhaler therapy, the number of patients who received high doses of inhaled corticosteroids (ICS) decreased from 50% to 40%, but there were patients who switched to low doses of ICS (p=0.22) (Fig. 5). Before the onset of biological therapy, approximately 64% of patients received systemic corticosteroids (SCS): patients on permanent therapy and those on SCS courses during exacerbations were taken into account. By the 12th month of treatment with mepolizumab, the number of patients who required SCS decreased to 27.3% (p=0.115) (see Fig. 5). A decreasing trend in the proportion of patients who received antileukotriene drugs (LTRA) was observed. However, as in the case of long-acting muscarinic antagonists, there were no statistically significant changes in the administration of LTRA.

Statistically significant changes in the regimen of SCS administration were registered: three out of four patients managed to stop the continuous use of SCS by the 12th month of therapy. Three out of five patients stopped using SCS during exacerbations. In general, by the 12th month of therapy, 76.9% of patients did not use SCS (p=0.032) (Fig. 2b).

Table 2. Characteristics of basic therapy of patients with severe asthma who received mepolizumab

Basic asthma therapy		Initially n=14	Four months n=14	Twelve months n=10
Two-component	ICS + LABA	1	3	4
	ICS + LABA + LTRA	2	2	2
Three-component	ICS + LABA + LAMA	1	4	2
	ICS + LABA + SCS	2	1	1
	ICS + LABA + LTRA + LAMA	0	1	0
Four-component	ICS + LABA + LTRA + SCS	2	1	0
	ICS + LABA + LAMA + SCS	2	1	0
Five-component	ICS + LABA + LAMA + LTRA + SCS	4	1	1

Note: ICS — inhaled corticosteroids, LABA — long-acting β2-agonists, LTRA–leukotriene receptor antagonists, LAMA–long-acting muscarinic antagonists, SCS — systemic corticosteroids.

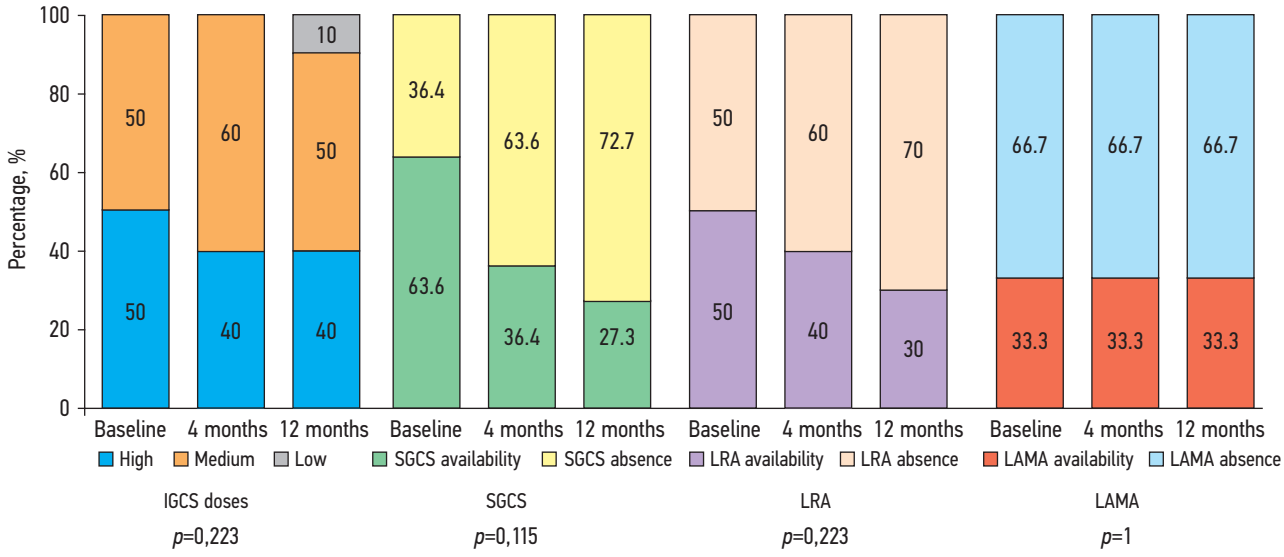

Fig. 5. Trend of basic therapy volume in patients with severe asthma receiving mepolizumab.
Note: IGCS — inhaled glucocorticosteroids, SGCS — systemic corticosteroids, LRA — leukotriene receptor antagonist, LAMA — long-acting muscarinic antagonist.

Adverse events

In four (28.6%) out of 14 patients, one adverse event was observed after the administration of mepolizumab (weakness, dizziness, fever, rash). No combined effects were observed. All events were of mild severity, did not require additional therapy, and did not lead to refusal of treatment. Undesirable effects stopped on their own within a few hours to a day after the onset.

DISCUSSION

Summary of the primary study results

Following 12 months of mepolizumab use among patients with severe asthma and IDN, it became possible to reduce the proportion of patients with uncontrolled asthma from 100% at baseline to 10% at 12 months (p <0.001). An increase in the disease control rate was associated with a decrease in the exacerbation frequency, EMS calls and hospitalizations, improvement in the quality of life, and respiratory function, and decrease in nasal symptoms.

Discussion of the primary study results

The majority of our samples from the register were mainly from women (78.6%). In large studies with more than 300 patients, women were the majority (proportions ranged from 58 to 62%) [4, 8, 9]. In studies with small samples (up to 50 patients) there was no clear gender prevalence: in some of these samples men were the majority (54%–55%) [10, 13], but in others, women were the majority (70%–81%) [11, 14].

It should be noted that nondomestic studies of mepolizumab effectiveness included patients with severe eosinophilic asthma caused by both non-allergic and allergic components. Investigators pointed to sensitization (positive skin tests and/or sIgE) in 70%–97.3% [4, 8, 11, 12] or atopic comorbidities in 37%–64% of enrolled patients (including respiratory allergy, hay fever, or atopic dermatitis) [2, 4, 10]. We selected patients who were primarily associated with non-allergic mechanisms for mepolizumab treatments. Only two (14.3%) patients had allergic rhinitis and pollen sensitization that cannot constitute the predominant component in severe, year-round manifestations of asthma.

The age at which asthma was diagnosed in our patients was 42.5 years. This is above the age registered in other studies. For example, Yilmaz et al. [14] reported the asthma onset at 15 years of age, while Harvey et al. [8] at the age of 26. In 64% of patients included in randomized controlled trials (RCTs) MENSA and MUSCA, asthma was diagnosed before the age of 40, and in 36% of the patients with ages >40 years [9]. This difference in nondomestic studies may be conditioned by the inclusion of patients with severe allergic asthma characterized by an earlier onset. This is also the reason for higher values of total IgE levels (137.5–485 IU/ml) [8, 10, 11] compared with the data in our study (91 IU/ml; Q1–Q3: 49.7–333).

In most studies, the average age of patients was in the range of 50.4–56.3 years [4, 9–13], average body mass index (BMI) was in the range of 22.8–28.7 kg/m^2 [4, 10–12], and 35.5%–45.8% of patients suffered from obesity [8, 12]. In general, patients in our sample were older than 60 years (Q1–Q3: 54–67), with higher BMI values (30.6 kg/m^2; Q1–Q3: 28.2–32.2). Obesity in our study was observed in nine (64.3%) patients out of 14. The research study conducted by Harvey et al. [8] also included older patients (59.6 (Q1–Q3: 49.9–68.3) years) with higher BMI values (29.5 kg/m^2 (25.3–34.5)).

In a small number of studies in real-life clinical practice, hypersensitivity to aspirin was variable, and yielded the following outcomes: 10% [10], 63% [14], and 100% [13].

CRSwNP occurred in patients with SA in 38%–42.6% of cases according to the scientific literature [2–4]. Individual data on allergic rhinitis are rare. In patients selected by us for mepolizumab treatment, CRSwNP and CRS without polyps were accompanied by SA in 71.4% of cases. Allergic rhinitis was also identified (n=1), and only 2 (14.3%) out of 14 patients did not have IDN.

Control assessments

Only 30% of patients had good asthma control at baseline as described by the meta-analysis of two RCTs [9]. In large studies, changes in level control were registered using the Asthma Control Questionnaire (ACQ). The results showed a significant decrease in the number of points (increase in asthma control) in all analyzed research publications [4, 8, 9]. In a small number of studies, control was assessed using AST [10–12, 14]. This selection of questionnaires was determined based on the fact that ACQ was convenient for RCTs, while AST is more suitable for routine practice [21]. Initially, in our study, patients had lower mean AST scores equal to nine points (Q1–Q3: 7–11) compared with other studies which registered ACT scores in the range of 11.9–15.2 points [10–12, 14]. This difference is likely due by the fact that in our group of patients with SA, non-allergic eosinophilic asthma that is more severe than allergic asthma dominated. At the same time, 100% of patients had uncontrolled asthma. However, by the 12th month of mepolizumab therapy, we recorded an increase in AST scores of up to 22 points (Q1–Q3: 21–24), which did not contradict the results of other researchers — 19.5–22.3 points [10–12], and achieved an increase in proportion of controlled asthma (AST 20–25) to 90%.

In the considered studies [3–9, 10–14], there was no decrease in the use of SABA during effective targeted therapy, while it is recognized to be one of the indicators of improved disease control. In our study, the use of SABA decreased on average from 21 doses per week (Q1–Q3: 12.2–48.1) to one dose per week (Q1–Q3: 0–1).

Exacerbations

Before the mepolizumab prescription, the number of exacerbations was 4.63–6.0 per patient per year according to different authors [2, 4, 10–12], which is higher than our

results (3.18±2.8 exacerbations per patient per year). Possible reasons for this controversy are the underdiagnosis of asthma exacerbations and the lack of medical help-seeking. However, a statistically significant decrease (which reached zero) in the number of SA exacerbations, including those who required hospitalization by the 12th month of mepolizumab therapy corresponded to global indicator values in the range of 0–2.9 per patient per year according to our study [2, 4, 10–12]. Decrease in EMS calls was not statistically significant due to the small sample size.

Quality of life

MENSA and MUSCA RCTs used St. George's Respiratory Questionnaire for patients with respiratory diseases [6, 7]. In a number of studies, the quality of life was assessed using AQLQ [8, 22, 23]. At the 6th month of mepolizumab therapy, the total AQLQ scores increased by 1.24 [22] and by 1.6 [8] points. Haldar et al. [23] described an increase in the scores by 0.55 by the 12th month of therapy. We registered an increase of 2.1 points after one year of treatment with mepolizumab.

Eosinophils

The mechanism of mepolizumab action involves blocking IL-5, which leads to decreased levels of peripheral blood eosinophils. We observeda significant decrease in eosinophils from 442 (Q1–Q3: 336–853) to 90 cells/μL (Q1–Q3: 73–117) by the 12th month of mepolizumab therapy. This effect was observed in all ongoing studies [2, 4, 8, 10–14, 24]. At the same time, the initial eosinophilic levels were higher in studies that specifically recruited patients with SA and CRSwNP (864–1393 cells/mcL) [10, 11, 14, 24] compared with those that included samples of patients with SA alone (370–791 cells/mcL) [10, 11, 14, 24]. μl) [2, 4, 8, 12]. The level of eosinophils decreased to 49.5–177 cells/μl after 1 year of mepolizumab use [2, 4, 8, 10–14, 24].

FEV_1

Improvement in respiratory function also took place in all studies. Indeed, some authors registered an increase in FEV_1 from 63%–71.4% initially to 70%–84.6% in the 12th month of therapy [2, 12–14], which corresponds to our results. We did not obtain statistically significant changes in FVC and FEV_1/FVC, probably due to the insufficient number of observations.

SNOT-22

When assessing the changes in nasal condition, we registered a significant decrease of 33 points on SNOT-22, which corresponds to the minimum significant difference of 8.9 points identified during the questionnaire validation [25]. Nasal condition improvement in patients with SA who received mepolizumab has also been observed by other investigators. For example, Kurosawa et al. [13] registered a statistically significant decrease of 18 points on SNOT-22, while Detoraki et al. [10] registered a decrease by 21.8 points.

Volume of therapy

Upon analyzing the volume of basic therapy for SA, we registered a decreasing trend in the number of patients who received four and five drugs. As soon as the 4th month of mepolizumab treatment was reached, most patients switched to the use of two or three basic therapy drugs. Small sample sizes did not allow us to conclude on the statistical significance of these changes.

According to various researchers, "steroid addiction" among patients with SA ranges from 47% to 92.8% [2, 8, 12]. When mepolizumab was prescribed, the number of patients who required permanent TCS decreased by 43%–51.7% a year [2, 4, 11, 12]. In our study, 30.8% of patients took TCS on a continuous basis, and another 38.5% of patients required the prescription of TCS during exacerbations. By the 12th month of therapy, the number of patients on continuous TCS therapy decreased by 23.1%, and the number of patients who required TCS during asthma exacerbation decreased by the same amount.

Study limitations

When we planned and conducted the study, the sample sizes required to achieve the required statistical power were not calculated. Therefore, participants' samples collected during the study could not be considered sufficiently representative. This did not allow the extrapolation of the results and their interpretation to the general population of similar patients. Study limitations are also associated with the absence of the control group and the small sample sizes, which are attributed to the fact that the study was conducted in real-life clinical practice. We did not assess polyp sizes visually.

CONCLUSION

Following one year of mepolizumab treatment in patients with SA and concomitant IDN, there was a significant improvement in asthma control, a decrease in the number of asthma exacerbations, a decrease in the need for emergency drugs, a decrease in the proportion of patients who required SCS, and an improvement in the quality of life according to AQLQ. A statistically significant decrease in the peripheral blood eosinophilic levels and an improvement in respiratory function were also registered. With regard to concomitant IDN, there was a significant improvement in nasal breathing, as confirmed by SNOT-22 and VAS data.

ADDITIONAL INFORMATION

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organization and design of the study, editing of the text of the article; D.V. Kiseleva — data collection, writing of the text of the article. 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.

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