DOI: 10.20514/2226-6704-2024-14-1-15-22
УДК [616.248-06:616.23-002]-085.234
EDN: BCAMYY

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ЭФФЕКТИВНОСТЬ МЕПОЛИЗУМАБА В ЛЕЧЕНИИ ТЯЖЕЛОЙ АСТМЫ СО СМЕШАННЫМ ГРАНУЛОЦИТАРНЫМ ПАТТЕРНОМ ВОСПАЛЕНИЯ ДЫХАТЕЛЬНЫХ ПУТЕЙ (ОПИСАНИЕ КЛИНИЧЕСКИХ СЛУЧАЕВ)

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Efficacy of Mepolizumab in the Treatment of Severe Asthma with a Mixed Granulocytic Pattern of Airway Inflammation (Case Report)

Резюме

В данной статье представлено описание двух клинических наблюдений применения меполизумаба у пациентов с тяжелой неконтролируемой астмой со смешанным гранулоцитарным паттерном воспаления в бронхах на фоне коморбидной патологии.

Смешанная гранулоцитарная форма тяжелой бронхиальной астмы характеризуется сочетанием в себе признаков как Т2-эндотипа, так и не-Т2-эндотипа. Наиболее часто смешанный гранулоцитарный паттерн тяжелой астмы встречается при коморбидной патологии, в частности, при ее сочетании с хронической обструктивной болезнью легких или бронхоэктазами.

В представленных наблюдениях оба пациента отличались наличием стажа курения, поздней манифестацией астмы с развитием центрилобулярной эмфиземы, необратимым снижением отношения $ОФВ_1$/ФЖЕЛ в рамках формирования хронической обструктивной болезни легких. Особенностью одного из случаев стало наличие у пациента цилиндрических бронхоэктазов обоих легких. Выбор меполизумаба в качестве дополнительного агента поддерживающей терапии на ступени 5 GINA в обоих случаях был обоснован неконтролируемым течением астмы, несмотря на применение высокой дозы ингаляционных глюкокортикостероидов в сочетании с другими базисными препаратами и потребность в применении системных глюкокортикостероидах >50 % времени в году, историей повторяющихся обострений в предшествующие 12 месяцев, наличием персистирующей эозинофилии крови (>150 клеток/мкл), а также сочетанием бронхиальной астмы с полипозным риносинуситом у одного из пациентов.

В целом применение меполизумаба в дозе 100 мг каждые четыре недели подкожно в дополнение к регулярной максимальной оптимизированной поддерживающей терапии характеризовалось быстрой, значимой и устойчивой эффективностью, которая выражалась в раннем достижении контроля астмы в течение первых 16 недель от начала терапии.

Ключевые слова: *тяжелая бронхиальная астма, меполизумаб, таргетная терапия, ХОБЛ, бронхоэктазы, смешанный гранулоцитарный паттерн воспаления*

Конфликт интересов

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

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Источники финансирования
Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 21.08.2023 г.
Принята к публикации 25.01.2024 г.

Для цитирования: Губарева А.М., Федосенко С.В., Винокурова Д.А. и др. ЭФФЕКТИВНОСТЬ МЕПОЛИЗУМАБА В ЛЕЧЕНИИ ТЯЖЕЛОЙ АСТМЫ СО СМЕШАННЫМ ГРАНУЛОЦИТАРНЫМ ПАТТЕРНОМ ВОСПАЛЕНИЯ ДЫХАТЕЛЬНЫХ ПУТЕЙ (ОПИСАНИЕ КЛИНИЧЕСКИХ СЛУЧАЕВ). Архивъ внутренней медицины. 2024; 14(1): 15-22. DOI: 10.20514/2226-6704-2024-14-1-15-22. EDN: BCAMYY

Abstract
This article describes two clinical observations of the use of mepolizumab in patients with severe uncontrolled asthma with a mixed granulocytic pattern of inflammation in the bronchi and comorbid pathology.
The mixed granulocytic form of severe asthma is characterized by a combination of T2 endotype and non-T2 endotype. The most common mixed granulocytic pattern of severe asthma occurs in comorbid pathology, in particular, when it is combined with chronic obstructive pulmonary disease (COPD) or bronchiectasis.
In the presented observations, both patients had an experience of smoking, a late manifestation of bronchial asthma with the development of centrilobular emphysema and an irreversible decrease in the FEV/FVC ratio as part of the development of COPD. A feature of one of the cases was the presence of cylindrical bronchiectasis in both lungs. The choice of mepolizumab as an additional maintenance agent at GINA stage 5 in both cases was justified by the uncontrolled course of asthma despite the use of a high dose of glucocorticosteroids in combination with other basic drugs and the need for the use of systemic corticosteroids > 50 % of the time per year, a history of recurrent exacerbations in previous 12 months, the presence of persistent blood eosinophilia (>150 cells/μl), as well as a combination of asthma with polypous rhinosinusitis in one of the patients.
Overall, the use of mepolizumab 100 mg subcutaneously every four weeks in addition to regular maximum optimized maintenance therapy was characterized by rapid, significant and sustained efficacy, which was expressed in early achievement of asthma control within the first 16 weeks of therapy.

Key words: *severe asthma, mepolizumab, targeted therapy, COPD, bronchiectasis, mixed granulocytic type of inflammation*

Conflict of interests
The authors declare no conflict of interests

Sources of funding
The authors declare no funding for this study

Article received on 21.08.2023
Accepted for publication on 25.01.2024

For citation: Gubareva A.M., Fedosenko S.V., Vinokurova D.A. et al. Efficacy of Mepolizumab in the Treatment of Severe Asthma with a Mixed Granulocytic Pattern of Airway Inflammation (Case Report). The Russian Archives of Internal Medicine. 2024; 14(1): 15-22. DOI: 10.20514/2226-6704-2024-14-1-15-22. EDN: BCAMYY

BA — bronchial asthma, GCS — glucocorticosteroids, GEBD — genetically engineered biologic drugs, LABA — long-lasting beta-2 agonists, iGCS — inhaled glucocorticosteroids, thoracic CT — computer tomography of thoracic organs, FEV_1 — forced expiratory volume over the first second, PFT — pulmonary function test, FLC — functional lung capacity, COPD — chronic obstructive pulmonary disease, тACQ-5 — Asthma Control Questionnaire–5, ACT — Asthma Control Test, GINA — Global Initiative for Asthma, IgE — immunoglobulin E, mMRC — Modified Medical Research Council

Introduction

Severe bronchial asthma with a mixed granulocytic inflammation pattern combines signs both of T2 endotypes and non-T2-endotypes, with a concurrent high neutrophil and eosinophil count in induced sputum or bronchoalveolar lavage samples [1]. According to various sources, the incidence of this variant of inflammation in asthmatic patients is 3 % (with eosinophils of ≥ 3 % and neutrophils of ≥ 76 % in induced sputum) to 22 % (with eosinophils of ≥ 2 % and neutrophils of ≥ 50 % in induced sputum) [2]. The mixed granulocytic inflammation pattern is most common in smokers, in comorbidities, in particular in bronchial asthma with chronic obstructive pulmonary disease (COPD) or bronchiectasis [1].

Bronchial asthma, COPD and bronchiectasis are common conditions; their combination makes patient curation very challenging and a risk of an uncontrolled disease significantly higher; response to conventional maintenance therapy deteriorates, necessitating an increase in the dose of inhaled glucocorticosteroids (iGCS), administration of additional long-lasting beta-2 agonists (LABA) and long-lasting M3-cholinoblockers; often, systemic glucocorticosteroids (GCS) are required; infection-dependent exacerbations and associated antibiotic therapy and hospitalisation become more common [3].

In accordance with the staggered approach, patients with severe bronchial asthma may have genetically engineered biologic drugs (GEBD) prescribed, including mepolizumab, a humanised monoclonal antibody with high affinity to interleukin-5. In clinical trials, COPD and bronchiectatic disease are often non-inclusion criteria; therefore, limited data are available on the efficacy of target therapy in patients with this comorbidity.

In 2017, the results of two randomised double-blind trials (METPEX and METREO) were published; they compared the 52-week efficacy of mepolizumab and placebo in COPD patients who had moderate and severe exacerbations during the previous year while taking triple maintenance therapy. The use of mepolizumab at a dose of 100 mg as an adjuvant therapy to the conventional

baseline therapy was associated with a lower rate of exacerbations during the year [4].

In 2021, Crimi C. et al. presented the results of a single-center retrospective study in patients with severe bronchial asthma (BA) and bronchiectasis. The authors concluded that the use of mepolizumab as an adjuvant to the maintenance therapy improved asthma control, reduced the number of exacerbations during the year, and reduced the need for systemic glucocorticosteroids [5].

This article describes clinical cases illustrating management of patients with a mixed granulocytic inflammation at the Intermediate Therapeutic Clinic of the Federal State Budgetary Educational Institution of Higher Education Siberian State Medical University of the Ministry of Health of Russia (Tomsk), with long-lasting continuous therapy with mepolizumab at a dose of 100 mg every four weeks (q4w).

Patients in both clinical cases provided their written consent, with their personal data being presented anonymized.

Case Study No. 1

Severe bronchial asthma, recurrent rhinosinusitis polyposa and COPD in a patient with a long-lasting history of smoking and a mixed granulocytic inflammation of upper respiratory tract

Male patient M., 70 years old; in June 2021, he was referred by a pulmonologist, complaining of attack-like cough with viscous white-yellowish sputum; mixed-pattern shortness of breath while walking (mMRC score: two points), worsening when the patient walks uphill or climbs 1–2 flights of stairs; episodes of expiratory suffocation, mostly spontaneous in the evening and predawn time, as well as outside in cold weather. To relieve the symptoms, the patient used medications containing short-lasting beta-2-agonists (salbutamol, fenoterol/ipratropium bromide) up to 3–4 times during the day and at night.

Past medical history and current therapy

The patient is followed up by a pulmonologist for the underlying comorbidity, comprising two conflicting conditions.

In 2014, the patient was diagnosed with bronchial asthma; however, typical respiratory symptoms (respiratory discomfort, expiratory dyspnoea with intense exercises) were noted in 2008. When the condition was diagnosed, the patient was 57 years old (late-onset asthma). Also, in 2014 an entry was made in the medical record about chronic obstructive pulmonary disease with predominant emphysematous phenotype, diagnosed with due account of a long history of smoking and typical changes seen on CT scans (bilateral centrilobular, mostly supralobar emphysema, trapped air and hyperinflation) and respirometry results (persistent obstructive changes in pulmonary function tests (PFT) with a stable reduction in the post-bronchodilatatory ratio of forced expiratory volume over first second (FEV_1) and functional lung capacity (FLC) to < 0.7, despite a multi-component inhalation therapy).

Immediately after diagnosis confirmation, BA severity was assessed as moderate in accordance with the current recommendations of the Global Initiative for Asthma (GINA); thus, in 2014–2017, the patient was constantly using a fixed combination of a low-dose iGCS (fluticasone propionate 500 μg/day) and LABA (salmeterol 100 μg/day). In 2018, when asthma was no longer controlled, the dose of fluticasone propionate was increased to 1,000 μg/day, the condition was still uncontrolled and pulmonary function tests were below normal values. As a result, from January 2019 and up to the target therapy initiation, the patient had been constantly using a fixed dose of budesonide/formoterol at a dose of 640/18 μg/day (metered-dose powder inhaler), as well 5 μg of tiotropium bromide for inhalation (Respimat delivery system) and 10 mg of oral monteleukast before bed. Transition to the three-component inhalation therapy with medium doses of iCGS, LABA and long-lasting anticholinergic product combined with an oral leukotriene receptor antagonist initially improved the clinical condition of the patient; however, starting from September 2019, the patient was unable to control the disease. Over the past two years, asthma relapses were recorded (up to 6–8 episodes a year) and the patient needed broncholytic nebulizer therapy and an increase in the daily GCS doses: addition of a nebulized budesonide suspension and/or a short (5–7 days) course of prednisolone at a dose of 90 mg/day with aminophylline solution 4 times over 12 months, which preceded the GEBD therapy initiation. The last course of infusion therapy with systemic GCSs because of asthma and COPD relapse caused by an acute viral infection was recorded in May 2021.

The nature of upper respiratory tract involvement

The patient has had rhinosinusitis polyposa since 1996. Surgery to remove sinonasal polypous vegetation from the nasal cavity and paranasal sinuses was performed in 1996, 1999, 2013, 2017, and March 2021. Upon admission for GEBD therapy initiation, the patient was taking mometasone furoate, an intranasal GCS, at a dose of 200 μg/day; however, the patient complained of nasal airflow obstruction and small amount of pale nasal discharges.

History of allergies is unremarkable: there is no solid evidence of bronchial asthma or allergies in close relatives. During a detailed interview, review of the patient's medical record and taking into account an Immunocap test of allergen-specific immunoglobulin E (IgE) concentrations (June 2021), no data were found to confirm allergic hypersensitivity to the main (domestic,

fungal, pollen, epidermal) airborne allergens, pharmaceutical anaphylaxis or individual hypersensitivity reactions to any medicines, including non-steroidal anti-inflammatory drugs.

History of smoking

The patient is a former smoker who used to smoke 10–20 cigarettes a day for 45 years. The minimum and the maximum smoking rates were 22.5 pack/years and 45 pack/years, respectively. The patient quit smoking in 2014.

Physical examination

Height: 165 cm, weight: 60 kg, body mass index: 22.33 kg/m^2, normosthenic composition. Condition is rather satisfactory.

Chest is normal, painless on palpation. Percussion sound is slightly hyperresonant, similar above symmetric lung sections. Auscultatory breathing is harsh, with individual dry rales above the middle section of the lungs. Respiratory rate is 16 per minute. Peripheral oxygenation is 98 %.

Cardiac sounds are clear, rhythmic, with loud second heart sound above aorta. No pathologic heart murmurs. Heart rate is 70 bpm. Blood pressure is 124/76 mm Hg.

Other organs and systems are unremarkable.

Laboratory and instrumental examination results supporting the diagnosis and selected therapy strategy

A mixed nature of granulocytic inflammation in the respiratory tract in this patient is confirmed by cytological examination of bronchoalveolar lavage fluid in February 2019 (eosinophils 40 % and neutrophils 50 % of the cellular composition), induced sputum in July 2020 (eosinophils 18 % and neutrophils 60 % of the cellular composition) and in March 2021 (eosinophils 22 % and neutrophils 68 % of the cellular composition).

When the patient was hospitalised in July 2021, the anti-T2-cytokine therapy was favoured due to the blood eosinophil level (4.5 % of WBC count and 390 cell/μL) and the total immunoglobulin E level (177 IU/mL).

Of note, when the target therapy was initiated, the patient demonstrated significantly reduced FLC values. In July 2021, baseline FEV1 was 1.51 L (59.5 % of the normal value) and 1.64 L (64.5 % of the normal value) before and after salbutamol test, respectively; post-bronchodilatatory lung capacity was 94 % and FLC was 104 % of the normal values, with FEV1/FLC being 0.52. A β2-adrenoceptor agonist test gave positive results: FEV1 increased by 34 % and 470 mL.

Examinations of other systems of organs, including ECG and EchoCG, thoracic CT and referral to rule out systemic eosinophilia (for instance, eosinophilic granulomatosis with polyangitis), did not reveal any other significant pathologies which could affect the management of the patient.

Therefore, based on the complaints, medical record, examination and test results, the underlying comorbidity has been updated: bronchial asthma, T2-endotype, non-allergic, eosinophilic phenotype, severe (GINA stage 5) uncontrolled disease with a high risk of relapses; chronic obstructive pulmonary disease, mostly emphysematous phenotype, GOLD 2 obstruction, with marked symptoms (mMRC: 2 points) and frequent relapses, group D (clinical guidelines of the Ministry of Health of Russia, 2021); other diseases: recurrent rhinosinusitis polyposa (surgery in 2012, 2013, 2017, and March 2021).

Since the optimised multicomponent baseline therapy, including iGCS with the need for frequent courses of prednisolone due to asthma relapses, was inefficient, taking into account persistent blood and respiratory eosinophilia, as well as lack of clinically significant allergic hypersensitivity, regular target therapy with mepolizumab 100 mg q4w SC was initiated in July 2021.

Further follow-up during mepolizumab therapy demonstrated significant improvements. Early efficiency of the target therapy noted just four weeks after the first injection was seen as the absence of shortness of breath during physical exercises, absence of episodes of suffocation, and no need for rescue medications. The patient, however, still had a cough with a small amount of clear sputum. By the time of the initial GINA-recommended assessment (16 weeks), the patient noted improvement: fewer episodes of cough (a cough with a small amount of white sputum, characterised by the patient as "minor", was uncommon), relief of shortness of breath: shortness of breath appeared only with moderate activities (normal walking) — two points on the mMRC (Modified Medical Research Council) scale. Also, the patient noted absence of episodes of suffocation and need for rescue medications. Objective improvement in asthma control was recorded (Asthma Control Questionnaire–5 (ACQ-5) reduction from 1.5 to 0.8 points).

One year after therapy initiation, the patient does not have any major complaints; Asthma Control Test (ACT) was 23 points (well-controlled), ACQ-5 – 0.2 points (well-controlled).

Respirometry results obtained with the use of the target therapy demonstrated an increase in pre-FEV1 from 1.51 L (59.5 % of the normal value) at baseline to 1.92 L (77.7 % of the normal value) 12 month after GEBD therapy initiation. An absolute increase in FEV1 was 300 mL after a year of therapy, meaning significant response to the therapy.

Over two years of continuous mepolizumab therapy, there were no asthma and COPD relapses and no need for systemic GCS.

Also, rhinosinusitis polyposa improvement was noted with GEBD therapy. The patient noted better nasal airflow; nasal discharges disappeared after 16 weeks of therapy. No rhinosinusitis relapses were recorded over 24 weeks of therapy.

Table 1. Control of asthma, severity of shortness of breath and respiratory function (clinical observation No. 1)

Parameter	Initial results	16 weeks of mepolizumab therapy	12 months mepolizumab therapy	24 months mepolizumab therapy
Pre-FEV1, l	1,51	1,81	1,92	1,81
Pre-FEV1 % predicted value	59,5	71	77,7	71,6
Post-FEV1, l	1,64	1,82	2,06	1,82
Post-FEV1 % predicted value	64,5	71,5	80,8	79,4
Post-FEV1/FVC	0,51	0,57	0,56	0,54
mMRC, points	3	2	0	0
ACT, points	17	17	23	25
ACQ-5, points	1,5	0,8	0,2	0,2
Blood eosinophils, cells/μl	390	50	52	50

Note: FEV1 — forced expiratory volume in the first second; FVC — forced vital capacity; pre-FEV1 — forced expiratory volume in the first second pre-bronchodilator; post-FEV1 — forced expiratory volume in the first second post-bronchodilator; ACT — asthma control test; ACQ-5 — Asthma Control Questionnaire–5; mMRC — Modified Medical Research Council

Changes in scores of the asthma control and dyspnoea severity questionnaire, as well as changes in peripheral blood eosinophils and PFT values, are presented in Table 1.

Case Study No. 2

Severe bronchial asthma with bronchiectasis in a patient with a mid-lasting history of smoking and a mixed granulocytic inflammation of upper respiratory tract

Male patient P., 48 years old; in September 2021, he was referred by a pulmonologist, complaining of spontaneous day-time episodes of suffocation and suffocation after moderate physical activity (up to four times a week) and night suffocation 1–2 times a week; need in salbutamol to relieve shortness of breath (up to 2–4 times a week); expiratory suffocation when the patient walks uphill or climbs 1–2 flights of stairs (mMRC score: 3 points); wheezing; attack-like cough with a small amount of viscous yellow-greenish sputum.

Past medical history and current therapy

BA was diagnosed in 2001 (the patient was 28 years old). Once the diagnosis was made, a therapy was initiated: a fixed combination of mid-dose iGCS (budesonid 640 μg/day) and LABA (formoterol 18 μg/day) as a metered-dose powder inhaler. The patient was undergoing this therapy in 2001–2021. Also, during the past two years, the patient had occasional short-term (1–2 months) courses of tiotropium bromide (Respimat delivery system) at a dose of 5 μg/day and monteleukast 10 μg/day.

In 2020–2021, the patient noted stable worsening in his asthma: worse shortness of breath, more episodes of suffocation and the need to use rescue medications up to 4–6 times daily, more severe cough with more sputum, very often it was very viscous and yellow-greenish. Exacerbations occurred up to 6 times a year, and GCSs were required.

In July 2021, a pulmonologist corrected the therapy and recommended daily use of vilanterol/fluticasone furoate at a dose of 22/184 μg in the evening, tiotropium bromide for inhalation (Respimat delivery system) at a dose of 5 μg in the morning and monteleukast 10 μg before bed. With the corrected therapy, in August 2021 the patient experienced another (a third within 12 months) BA relapse, which required a course of nebulizer therapy (budesonide 2,000 μg/day, fenoterol/ipratropium bromide solution for inhalation) and oral prednisolone (30 mg for 7 days, then the dose was reduced to 5 mg and daily systemic GCS at a mentioned dose). Also, since the patient had large amounts of green sputum, clarithromycin 1,000 mg daily was added for 7 days.

History of allergies

According to the patient, his grandmother and father have asthma. In 2015, a skin allergen test revealed hypersensitivity to domestic dust, and allergen-specific therapy was initiated, which was later interrupted because of uncontrolled asthma. Since childhood, the patient has been suffering from all-year-round nasal allergy; in addition to domestic dust, he is sensitive to cats, library dust (itchy eyes, eye tearing), episodes of suffocation during finishing works. He has a history of itchy skin when taking bicillin.

History of smoking

The patient confirmed short periods of episodic smoking for 20 years. An approximate smoking rate is no more than 10 packs/year. When the target therapy was started, the patient was a non-smoker.

Physical examination

Height: 182 cm, weight: 79 kg, body mass index: 23.9 kg/m^2, normosthenic composition. Condition is rather satisfactory. Chest is normal, painless on palpation. Percussion sound comes from lungs, similar above symmetric lung sections. Auscultatory breathing is harsh, with multiple dry rales above the middle and lower section of the lungs. Respiratory rate is 19 per minute. Peripheral oxygenation is 96 %. Cardiac sounds are clear, rhythmic. No pathologic heart murmurs. Heart rate is 76 bpm. Blood pressure is 138/88 mm Hg. Other organs and systems are unremarkable.

Key laboratory and instrumental examination results supporting the diagnosis and selected therapy strategy

For a considerable period of time before GEBD therapy initiation, patient's peripheral blood tests revealed persistent high eosinophil count ≥ 150 cell/μL. When GEBD therapy was initiated, blood eosinophils were 2.8 % and 242 cell/μL. Of note, this patient was taking prednisolone 5 mg daily. Total IgE on August 3, 2021 was 227 IU/mL. However, allergen-specific EIA IgE test (main allergens — domestic, fungal, pollen, epidermal) dated August 3, 2021 demonstrated a negative result, thus ruling out *Alternaria tenuis*; also, allergen-specific IgE to it was clinically normal (0.111 kU/L).

In 2018, during one of the asthma relapses caused by a respiratory infection with long-lasting cough and purulent sputum, chest CT demonstrated cylindrical bronchiectasis in individual segmental and subsegmental bronchi in both lungs. Cytological examination of sputum revealed a combination of high eosinophil (8 % of the cellular composition) and neutrophil counts (82 % of cells). When the target therapy was initiated (August 2021), thoracic CT demonstrated bronchial wall induration, cylindrical dilation of individual segmental and subsegmental bronchi (cylindrical bronchiectasis), with small bands and adhesions in subpleural sections of the apex of lung, as well small apical overlaps on both sides.

In addition to clear clinical signs of uncontrolled asthma with frequent relapses, probably associated with an infectious trigger (bacterial contamination of the respiratory tract), this patient had impaired PFTs. Spirography results dated August 2021 demonstrated pre-FEV1 of 67 % and 78 % of the normal value before and after salbutamol 400 μg, respectively (an increase in FEV_1 was 16.35 % and 610 mL); the post-FLC value was 100 % of the normal value, while the post-FEV_1/FLC ratio was 0.63.

Based on the patient's complaints, past medical records and examination results, the following condition was diagnosed: a mixed-type bronchial asthma, eosinophilic phenotype, severe (GINA stage 5) uncontrolled disease with a high risk of infection-dependent relapses. Comorbidities: cylindrical bronchiectasis in individual segmental and subsegmental bronchi in both lungs. Moderate persistent nasal allergy caused by domestic and epidermal allergens.

Since despite the optimal baseline therapy including a fixed combination of high doses of iGCS/LABA, long-lasting M-cholinoblocker, leukotriene receptor antagonis and systemic GCSs at a dose of 5 mg (prednisolone), the patient could not achieve stable asthma control (ACT: 9 points, ACQ-5: 3.6 points), the medical panel decided to initiate the target therapy with mepolizumab, an anti-interleukin-5 GEBD, at a dose of 100 mg q4w SC from September 2021.

Further follow-up during mepolizumab therapy demonstrated significant improvements. Early efficiency of the target therapy noted just four weeks after the initiation of the therapy was seen as withdrawal from prednisolone, absence of episodes of suffocation at night, improvement in shortness of breath, absence of wheezing, and smaller amounts of discharges with cough.

Table 2. *Control of asthma, severity of shortness of breath and respiratory function (clinical observation No. 2)*

Parameter	Initial results	16 weeks of mepolizumab therapy	12 months mepolizumab therapy	24 months mepolizumab therapy
Pre-FEV_1, l	2,57	3,27	3,11	3,17
Pre-FEV_1 % predicted value	67	83,5	79	81,7
Post-FEV_1, l	2,73	3,3	3,04	3,2
Post-FEV_1 % predicted value	78	84,4	78	82,3
Post-FEV_1/FVC	0,63	0,64	0,57	0,6
mMRC, points	3	2	0	0
ACT, points	9	25	25	25
ACQ-5, points	3,6	0,4	0,4	0,4
Blood eosinophils, cells/μl	241	47	70	32

Note: FEV1 — forced expiratory volume in the first second; FVC — forced vital capacity; pre-FEV1 — forced expiratory volume in the first second pre-bronchodilator; post-FEV1 — forced expiratory volume in the first second post-bronchodilator; ACT — asthma control test; ACQ-5 — Asthma Control Questionnaire–5; mMRC — Modified Medical Research Council

By the time of the initial GINA-recommended assessment (16 weeks), the patient noted improvement: no episodes of suffocation and no need in rescue medications, significantly reduced number of episodes of cough (cough was uncommon, without sputum), improvements in shortness of breath (only with moderate physical activity). Objective evidence of asthma control (ACT = 25 points, ACQ-5 = 0.4 points). During the year after therapy initiation, the patient does not have any major complaints; his asthma is well-controlled without new relapses.

Respirometry results obtained with the use of the target therapy with mepolizumab demonstrated an increase in pre-FEV_1 value from 67 % of the normal value (at the moment of therapy initiation) to 81.7 % of the normal value (24 months of therapy). An absolute increase in FEV_1 over the first 12 months of therapy was 540 mL and over 24 months of therapy — 600 mL, meaning significant response to the therapy. Normalised FEV_1/FLC ratio with the use of the target therapy with mepolizumab (post-FEV_1/FLC > 0.7) is also worth mentioning.

Changes in scores of the asthma control and dyspnoea severity questionnaire, as well as changes in peripheral blood eosinophils and PFT values, are presented in Table 2.

Discussion

Severe bronchial asthma with a mixed granulocytic inflammation pattern and a history of smoking in a combination with such comorbidity as chronic obstructive pulmonary disease and bronchiectasis, is associated with bacterial contamination. In turn, it increases the risk of an uncontrolled disease with a worse response to conventional maintenance therapy, necessitating an increase in the dose of inhaled GCSs, additional long-lasting beta-2 agonists and long-lasting M3-cholinoblockers; often, systemic GCSs are required; infection-dependent exacerbations and associated antibiotic therapy and hospitalisation become more common [3].

Currently, in accordance with the staggered approach, patients with severe bronchial asthma have GEBDs prescribed, including those binding to the key driver of interleukin-5. Given the pathogenetic interconnection of neutrophil and eosinophil inflammation patterns in this group of comorbid patients, reduction of the number of recruited eosinophils in the area of inflammation can have positive effect on the activity of associated neutrophil inflammation.

Currently available trials to study the use of mepolizumab in patients with a mixed granulocytic pattern in severe uncontrolled bronchial asthma with COPD and bronchiectasis demonstrate high efficacy of the target genetically engineered therapy, namely: improved asthma control and patients' quality of life, reduced number of relapses per year, and reduced need in systemic glucocorticosteroids [4, 5].

These clinical cases demonstrate the efficacy of mepolizumab in patients with a mixed granulocytic phenotype of BA in combination with a comorbidity (COPD, bronchiectasis).

Conclusion

The use of mepolizumab at a dose of 100 mg every four weeks subcutaneously as adjuvant therapy to the optimised maintenance therapy (GINA stage 5) demonstrated high efficiency in the management of severe BA with a mixed granulocytic bronchial inflammation with a history of smoking and comorbidities (COPD, bronchiectasis). Therapy efficacy was seen as early (within 16 weeks after therapy initiation) and steady asthma control, no need to take systemic GCSs, absence of BA exacerbations during at least 24 months of follow-up, and marked improvement in PFT values.

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