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Biological therapy of severe bronchial asthma

Iryna Melnychaiko*

Postgraduate Student
I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine
46001, 1 Maidan Voli, Ternopil, Ukraine
https://orcid.org/0009-0007-2136-2675

Serhiy Andreychyn

Doctor of Medical Sciences, Head of the Department
I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine
46001, 1 Maidan Voli, Ternopil, Ukraine
https://orcid.org/0000-0001-6754-0026

Abstract. Bronchial asthma is a major public health problem in the world. A considerable proportion of patients suffer from severe asthma, which is manifested by a decrease in the quality of life, an increase in the frequency of exacerbations, hospitalisations, and mortality. The ineffectiveness of conventional therapy in such patients contributes to the development of biological treatment methods with higher specificity, aimed at the pathogenetic links of the disease. The purpose of the study was to analyse the effectiveness of the treatment of severe bronchial asthma with monoclonal antibodies based on literature data. The study examines publications over the past 5 years that are available on the Internet. The following terms were used for the search: monoclonal antibodies, endotype, phenotype. Five monoclonal antibody biological agents targeting IgE, IL-5, IL-4, and IL-13, which are approved for use in patients with severe asthma, were analysed: omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab. The use of these medications has led to progress in the treatment of bronchial asthma. It was found that determining disease endotypes based on the assessment of biomarkers such as eosinophil count in blood and sputum, fractional exhaled nitric oxide, and serum periostin contributes to the greater effectiveness of biological therapy. It was investigated that monoclonal antibody treatment improves lung function, reduces exacerbation frequency, and decreases the need for additional medications. Many other biological agents, particularly those targeting key cytokines, are in the clinical development stage. Approved monoclonal antibodies targeting IgE, IL-5, and IL-4/IL-13 demonstrate high efficacy in the treatment of severe bronchial asthma. The use of these agents in patients with severe asthma and high Th2 levels considerably improves lung function, symptom control, and reduces the frequency of disease exacerbations

Keywords: biological agents; monoclonal antibodies; endotype; phenotype; biomarkers

INTRODUCTION

Bronchial asthma (BA) is one of the current healthcare challenges worldwide due to the prevalence of this disease and its negative impact on the quality of life of people of all ages in all parts of the world. BA is a frequent cause of temporary work disability and impairment at any age. Despite the available treatment methods, severe bronchial asthma remains a problem for many patients who do not experience sufficient relief from symptoms. Biological therapy, which utilises specific agents to modulate the immune response, shows potential for improving disease control and enhancing the quality of life for patients.

According to the Global Initiative for Asthma (GINA) in 2022, it affected 262 million people. The main goal of modern treatment of asthma patients is to achieve and maintain complete control over the symptoms for a long time, minimising the risks of future exacerbations, fixed bronchial obstruction, and undesirable side effects [1, 2]. In the majority of patients, high control of the disease can

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*Corresponding author

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be achieved using standard inhalation treatment methods. However, up to 10% of patients suffer from severe asthma, which is characterised by a decrease in quality of life, increased frequency of exacerbations, hospitalisations, and mortality [3].

I. Sulaiman *et al.* [4] note that unsatisfactory control of the disease is due to non-compliance with the prescribed treatment and incorrect technique of using a pocket inhaler. However, other studies indicate that many patients have daily symptoms and frequent exacerbations, despite maximum inhaled glucocorticosteroid (IGCS) therapy and high adherence to treatment. They often require maintenance therapy with systemic glucocorticosteroids (SGS) to avoid life-threatening conditions [5]. Although SGS remain important for exacerbation treatment, several studies highlight that their repeated or continuous use is associated with an increased risk of osteoporosis, infections, and type 2 diabetes. The use of SGS in patients with BA is more frequently linked to kidney function impairment, sleep apnea, and weight gain. It has also been established that the use of these drugs in the treatment of BA leads to an increase in the use of health system resources in the future. For these reasons, the priority is to reduce the use of SGS in such patients [6-8].

A. Rask-Andersen *et al.* [9] investigated the negative effects of BA on emotional and mental health. Insomnia symptoms in asthma have been found to be associated with poor disease control and exposure to characteristic comorbidities such as chronic rhinosinusitis, gastroesophageal reflux, obesity, anxiety, and depression. Other studies show that the disease complicates the family and work life of patients. BA symptoms have been shown to negatively affect daily physical activity and limit social opportunities [10-12]. The ineffectiveness of step-by-step treatment approaches in such patients indicates the heterogeneity of severe asthma and requires alternative methods of therapy with higher specificity aimed at the pathogenetic links of the disease. W.W. Busse [13] notes that advances in understanding the etiopathological mechanisms of various phenotypes and endotypes of severe asthma have contributed to the development of new biological treatments and personalised therapies for this group of patients.

The purpose of the study was to analyse and compare the effectiveness of the treatment of severe BA with monoclonal antibody preparations based on literature data.

PHENOTYPING AND DETERMINATION OF ENDOTYPES IN THE TREATMENT OF SEVERE BA

Recently, the use of biological therapy has led to progress in the treatment of BA. The advantage of this method is its selective effect on the immune system without considerable systemic effects on the body [13]. The use of biological methods in the treatment of severe BA that is resistant to standard therapy requires the use of phenotyping and determination of disease endotypes [14, 15]. The concept of "phenotype" characterises the clinical manifestations of the disease without considering the pathophysiological mechanisms. Severe asthma includes several clinical phenotypes that differ in the age of onset, presence or absence of other allergic conditions, degree of airflow limitation, frequency of exacerbations, and response to treatment [16].

The establishment of the BA endotype is based on the cellular and molecular mechanisms of airway inflammation, considering biomarkers. Their determination and dynamic assessment contribute to a better understanding of the pathological process, allow for individualised patient treatment, and help predict the course of the disease and response to therapy [17]. There are two main endotypes of BA: with high and low levels of T helper 2 (Th2) [18].

Asthma with a high Th2 level is characterised by eosinophilic airway inflammation with the secretion of interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13) and is determined using the following biomarkers: eosinophil count in blood and sputum, fractional exhaled nitric oxide (FeNO), and serum periostin [17]. M.R. Edwards *et al*. [18] found that patients with this endotype are more likely to develop virus-induced exacerbations of BA. Recent data indicate that this susceptibility to viruses may be secondary to insufficient interferon production. Approximately 50% of mild to moderate asthma and a large proportion of severe asthma cases have been shown to be characterised by inflammation with high Th2 levels [19]. Depending on the age of onset of the disease, the presence or absence of other allergic conditions, and additional clinical characteristics, the following asthma phenotypes belonging to this endotype are distinguished: allergic asthma, late-onset asthma, and aspirin-induced respiratory disease [20].

Allergic BA is characterised by early onset, positive skin allergy tests, and elevated IgE levels in the blood. It is important to note that only the presence of elevated total or specific IgE is a biomarker for this asthma phenotype, as allergy skin tests can be positive in 50% of the general population [21].

The main characteristics of late-onset asthma include significant blood and sputum eosinophilia, resistance to treatment with inhaled and systemic corticosteroids, frequent exacerbations, and a severe clinical course with fixed airflow obstruction. The vast majority of these patients have comorbid chronic rhinosinusitis, which usually precedes the development of BA. High FeNO levels and normal or elevated serum total IgE levels are also detected in these individuals. Determination of this phenotype may be an indication of an earlier escalation of therapy [22].

Aspirin-exacerbated respiratory disease (AERD) is caused by non-allergic hypersensitivity to nonsteroidal anti-inflammatory drugs such as aspirin, which inhibit cyclooxygenase, a synthetic enzyme of prostaglandins. The most important clinical characteristic of AERD is eosinophilic rhinosinusitis with nasal polyps, which often leads to hyposmia. The majority of patients with this phenotype suffer from a severe disease course, and they typically develop persistent airflow obstruction that minimally improves after inhalation of β2-agonists. Only 10% of people with aspirin-induced asthma have mild symptoms [23].

The low Th2 asthma endotype is characterised by neutrophilic and paucigranulocytic inflammation. Unlike eosinophilic asthma, the specific biomarkers for neutrophil asthma that would help determine it have not yet been clearly defined. As noted by A. Matucci *et al.* [24], sputum neutrophils can serve as the only biomarker of this endotype. The mechanisms underlying neutrophilic airway inflammation are still understudied. Severe neutrophilic asthma has been linked to chronic infection caused by

atypical bacteria, obesity, smoking, and smooth muscle abnormalities. BA with low Th2 levels includes the following phenotypes: non-allergic asthma and asthma associated with obesity [25].

The main signs of non-allergic asthma are the absence of allergic sensitisation, detection of neutrophils in sputum, and onset in adulthood. This phenotype is found in 10-33% of patients with BA, is more common in women, and has a later onset than allergic BA. In many cases, non-allergic asthma is more severe than allergic asthma and may be less susceptible to standard therapy [26].

The pathophysiological mechanisms of BA associated with obesity are complex and multifaceted, but most studies suggest non-eosinophilic inflammatory changes at the molecular level. This phenotype is characterised by both early and late onset and severity of clinical symptoms with moderately preserved lung function [27]. These patients have worse asthma control, lower quality of life, and resistance to IGCS therapy. The mechanisms of the inadequate response to standard therapy are associated with increased production of inflammatory cytokines in obesity [28].

Assessing clinical symptoms, disease severity, determining biomarkers, and establishing phenotypes help select the most appropriate biologic agent for individualised treatment in each patient.

BIOLOGICAL PREPARATIONS AND THEIR MAIN CHARAC-TERISTICS

Five biologic therapy drugs belonging to different monoclonal antibody groups are officially approved for use in patients with severe asthma: omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab [29].

Omalizumab was the first biologic therapy drug approved for asthma treatment, receiving approval for use in the United States in 2003 and in European countries in 2005. It is a representative of humanised anti-IgE monoclonal antibodies. Its action aims to block and neutralise IgE in the blood, thus preventing the activation of mast cells, the release of pro-inflammatory cytokines and leukotrienes, and the development of eosinophilic inflammation [30]. Omalizumab is approved for subcutaneous administration to individuals over 6 years of age who have been diagnosed with severe allergic asthma, the symptoms of which are not controlled by IGCS. S. Rojo-Tolosa *et al*. note that a pronounced clinical effect of anti-IgE monoclonal antibodies is observed in patients with high levels of FeNO, peripheral blood eosinophils, and periostin [31]. Clinical studies have shown that the use of omalizumab improves lung function and reduces the need for additional medications. Moreover, when combined with inhaled corticosteroid and long-acting beta-agonist therapy, omalizumab reduces the frequency of exacerbations by 25% [32]. A revolution in the treatment of severe eosinophilic BA was caused by the use of monoclonal antibodies to block IL-5, which is responsible for cell differentiation, maturation, and activation of eosinophils [33].

Mepolizumab is a humanised anti-IL-5 monoclonal antibody of the IgG1/κ isotype. Studies have shown that its use in BA patients with eosinophilia notably reduces the eosinophil count in the blood, bronchoalveolar lavage fluid, and bone marrow, and reduces the frequency of exacerbations and the use of SGS in these individuals by approximately 50%. Therapy with this drug has been shown to improve patients' quality of life and control of disease symptoms [34].

Another biological agent targeting IL-5 is reslizumab, a humanised monoclonal antibody of murine origin. Its clinical effects have been demonstrated in several randomised trials. The impact of this medication on reducing eosinophil counts in sputum, improving lung function, and increasing forced expiratory volume in 1 second (FEV1) has been examined in patients with severe refractory eosinophilic asthma, particularly with late-onset disease [35].

Benralizumab – another anti-IL-5 monoclonal antibody that induces eosinophil apoptosis through antibody-dependent cellular cytotoxicity, leading to deeper and faster eosinophil depletion. This agent is approved as an add-on therapy for inadequately controlled severe asthma with eosinophilia in patients aged 12 and older [36]. Overall, studies on IL-5-targeted monoclonal antibodies demonstrate clinical improvement in over half of patients with refractory asthma and eosinophilia. Recent data have shown better efficacy of benralizumab in patients previously treated with omalizumab and mepolizumab, attributed to its unique mechanism of action compared to other anti-IL-5 agents [37, 38]. Key components of BA pathogenesis are also IL-4 and IL-13, which regulate cell proliferation, apoptosis, and expression of lymphocytes, macrophages, fibroblasts, epithelial and endothelial cells, and are involved in the regulation of Th2 functions and the synthesis of IgE with B lymphocytes [39].

Dupilumab, a human monoclonal antibody, specifically recognises and blocks the α-subunit of the IL-4 receptor, thus suppressing the biological activity of both IL-4 and IL-13. Treatment with dupilumab without maintenance therapy provides long-term symptom control, significant improvement in lung function, and reduction in Th2-related biomarkers [40]. Significant reduction in sinusitis symptoms and improvement in olfaction have been observed with the use of this medication in patients with aspirin-exacerbated asthma [41].

In addition to these agents already available in clinical practice, many other biological therapies are in various stages of clinical development. One area of the studies focuses on alarmins, key cytokines involved in the mechanisms of airway inflammation in asthma, such as thymic stromal lymphopoietin (TSLP), IL-33, and IL-25. These molecules are released by the respiratory tract epithelium against the harmful effects of microbes, pollutants, allergens, and cigarette smoke. Studies are being conducted that evaluate various drugs targeting these cytokines [42].

Tezepelumab is a monoclonal antibody that targets TSLP, an epithelial alarmin that plays a significant role in asthma pathogenesis. In the presence of tezepelumab, TSLP is unable to bind to its receptor. A number of studies have clearly shown that patients with severe uncontrolled BA treated with tezepelumab experienced a reduction in the frequency of exacerbations, increased asthma control, improved lung function, and health-related quality of life. Regarding the safety profile of this medication, no anaphylactic reactions associated with tezepelumab or the development of neutralising antibodies have been reported [43, 44].

Ipetekimab is a monoclonal antibody targeting IL-33, which leads to the activation of the high Th2 inflammatory

pathway in asthma. Phase 2 trials of this biological agent are ongoing, but preliminary results have shown a reduction in blood eosinophils in patients with severe asthma [45].

As for potential molecular targets in the biological treatment of low Th2 asthma, current research focuses on the pathogenic link connecting IL-1β, IL-23, and IL-17. Medications such as canakinumab, secukinumab, and brodalumab are under investigation in clinical trials [46].

Canakinumab is a humanised monoclonal antibody that can induce prolonged and selective blockade of IL-1β, thereby interrupting the inflammatory cascade in certain autoimmune diseases. A randomised double-blind clinical study evaluating the safety and tolerability of canakinumab in patients with mild allergic asthma, assessing its anti-inflammatory action on the late asthmatic response after allergen inhalation, showed symptom improvement compared to the pre-treatment state [47]. Despite these encouraging findings, there are no further studies of this asthma medication. Secukinumab is a monoclonal antibody targeting IL-17A, which has demonstrated symptom reduction in other diseases such as psoriasis and rheumatoid arthritis. Phase II clinical trials involving patients with uncontrolled asthma have been completed, but results are not yet available. Brodalumab, a monoclonal antibody drug directed against IL-17RA, has also recently been tested in Phase II clinical trials for patients with moderate to severe asthma. The results showed no differences in the dynamics of asthma control between those who received brodalumab and those who received placebo, but there was a clinically significant improvement in lung function [48].

These data indicate that advances in understanding the pathophysiological mechanisms underlying different asthma phenotypes and endotypes have contributed to the development of effective monoclonal antibody therapies. The practical application of phenotyping and biomarker identification allows for individualised treatment of patients and improves therapy response.

CONCLUSIONS

In most patients, asthma control can be achieved with standard therapy. However, some individuals experience severe and persistent symptoms despite appropriate treatment. Recent clinical discoveries in the pathogenesis of asthma and the application of phenotyping and endotyping allow for personalised therapy in individuals with severe asthma, selecting the most suitable biological agent for treatment. Phenotyping based on disease severity and other clinical characteristics, along with the assessment of biomarkers such as blood and sputum eosinophil counts, fractional exhaled nitric oxide (FeNO) levels, and serum periostin, contribute to the improved effectiveness of biological therapy and help choose the appropriate medication for each patient.

Approved biological therapies such as omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab demonstrate high efficacy in the treatment of severe asthma. Overall, studies on anti-IgE, anti-IL-5, and anti-IL-4/IL-13 monoclonal antibodies show clinical improvement in the majority of patients, reducing symptoms and positively impacting functional indicators. The use of anti-IgE monoclonal antibodies in individuals with high levels of FeNO and peripheral blood eosinophils improves lung function and reduces the need for additional medications. The application of anti-IL-5 monoclonal antibodies in patients with severe asthma and high Th2 levels significantly enhances symptom control, reducing the frequency and severity of exacerbations. The use of anti-IL-4/IL-13 monoclonal antibodies without maintenance therapy provides long-term symptom control and decreases biomarker levels.

In addition to the medications approved for use in clinical practice, many other biological agents targeting cytokines such as IL-1β, IL-23, and IL-17 are under investigation and demonstrate symptom reduction and improved asthma control. Patients with severe asthma and low Th2 levels lack the advantage of biological therapy due to the absence of approved agents for such individuals. Therefore, there remains a need for further research to develop new biological treatment methods to enhance therapy for all types of severe asthma.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Біологічна терапія важкої бронхіальної астми

Ірина Ярославівна Мельничайко
Аспірант
Тернопільський національний медичний університет імені І. Я. Горбачевського МОЗ України
46001, майдан Волі, 1, м. Тернопіль, Україна
https://orcid.org/0009-0007-2136-2675
Сергій Михайлович Андрейчин
Доктор медичних наук, завідувач кафедри
Тернопільський національний медичний університет імені І. Я. Горбачевського МОЗ України
46001, майдан Волі, 1, м. Тернопіль, Україна
https://orcid.org/0000-0001-6754-0026

Анотація. Бронхіальна астма є важливою проблемою охорони здоров'я в світі. Значна частка хворих страждають від важкої астми, яка проявляється значним зниженням якості життя, збільшенням частоти загострень, госпіталізацій та смертності. Неефективність стандартної терапії у таких хворих сприяє розробці біологічних методів лікування з більш високою специфічністю, спрямованих на патогенетичні ланки захворювання. Метою дослідження було проаналізувати ефективність лікування важкої бронхіальної астми моноклональними антитілами на основі даних літератури. У дослідженні опрацьовано наукові публікації за останні 5 років, які доступні у мережі «Інтернет». Для пошуку було використано терміни англійською мовою: monoclonal antibodies, endotype, phenotype. Було проаналізовано п'ять біологічних препаратів моноклональних антитіл, спрямованих на IgE, ІЛ-5, ІЛ-4 та ІЛ-13, які дозволені для використання пацієнтам із важкою астмою: омалізумаб, меполізумаб, реслізумаб, енралізумаб та дупілумаб, застосування яких зумовило прогрес у лікуванні бронхіальної астми. Виявлено, що більшій ефективності біологічної терапії сприяє визначення ендотипів захворювання, що базується на оцінці таких біомаркерів, як: кількість еозинофілів в крові та харкотинні, фракція оксиду азоту у видихуваному повітрі та сироватковий періостин. Було досліджено, що лікування моноклональними антитілами покращує функцію легень, знижує частоту загострень та зменшує потребу в додаткових лікарських засобах. Встановлено, що багато інших біологічних препаратів, зокрема спрямованих на ключові цитокіни, знаходяться на стадії клінічної розробки. Схвалені до використання в світі, анти-IgE, анти-ІЛ-5, анти-ІЛ-4/ІЛ-13 моноклональні антитіла показують високу ефективність у лікуванні важкої бронхіальної астми. Застосування цих препаратів у пацієнтів з важкою астмою та високим рівнем Th2 значно покращує функцію легень, контроль над симптомами та знижує частоту загострень захворювання

Ключові слова: біологічні препарати; моноклональні антитіла; ендотип; фенотип; біомаркери