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Biological treatment options for severe asthma in Poland

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Abstract

Intruduction and purpose: Patients with severe asthma account for approximately 3% to 10% of all asthma patients. They have higher hospital utilization rates and treatment costs than patients with non-severe asthma. Previously, treatment options for these patients were limited due to unacceptable side effects. However, the advent of biologic therapies has provided promising targeted therapy for these patients.

State of knowledge: Biologic therapies target inflammatory modulators that play a key role in the pathogenesis of asthma, particularly in patients with high T2 cells. These therapies have shown promising results in reducing asthma symptoms, improving lung function, decreasing the use of oral corticosteroids, and enhancing patients' quality of life.

Conclusions: This article reviews the mechanism of action, efficacy, and indications of currently approved biologic drugs available in Poland, as well as potential therapeutic targets for the future.

Keywords: severe asthma; asthma treatments; biologics; monoclonal antibodies

1.Introduction

Asthma is a chronic inflammatory disease of the lower airways that is heterogeneous in nature. Its symptoms, which include coughing, wheezing, shortness of breath, and chest tightness, can vary over time due to varying degrees of bronchial obstruction [1]. Patient education is crucial in the traditional approach to asthma management, as it enables better understanding of the disease and self-management of its progression. This includes recognizing and avoiding asthma triggers such as allergens, cigarette smoke, and air pollution [2]. Most patients achieve adequate symptom control with modern inhaled medications, namely inhaled corticosteroids (ICS) and long-acting beta-agonists (LABAs). However, a small percentage of patients, approximately 3-10%, suffer from severe, refractory asthma with limited therapeutic options [1,3]. These options include recently developed biologic drugs such as omalizumab, mepolizumab, benralizumab, dupilumab, and tezepelumab. Biologic therapies should be considered for patients with severe asthma who do not achieve adequate disease control despite high doses of ICS and LABAs. It is important to note that not all patients with severe refractory asthma are eligible for biologic treatment [1, 4, 5]. According to current clinical guidelines, biologic therapy should be used as an additional treatment option.

For patients with severe asthma who continue to experience exacerbations and have uncontrolled disease despite optimal standard therapy, biologic therapy may be considered after a thorough clinical evaluation that takes into account specific phenotypic and endotypic features of the disease [6].

2. Types of asthma

Asthma is a heterogeneous disease that requires identification of its various endophenotypes. Due to the role of T-cells in the pathomechanism of asthma, it can be classified into two main types: Type 2 - high asthma, which is further divided into allergic eosinophilic and non-allergic eosinophilic/neutrophilic, and Type 2 - low level asthma, which is also divided into subtypes such as mixed granulocytic and poor granulocytic asthma [7, 8]. Recently published data indicate that approximately 50% of asthma cases are eosinophilic asthma [9].

2.1. Type 2 - high asthma

High T2 asthma comprises both allergic and non-allergic eosinophilic asthma. Allergic asthma is influenced by IgE-dependent processes, while non-allergic asthma may be predominantly influenced by T2 cytokine inflammation [10]. In T2-high asthma, inhaled allergens, microorganisms, and pollutants interact with the airway epithelium, leading to the activation of mediators such as thymic stromal lymphopoietin, interleukin (IL)-25, and IL-33. This process results in the activation of IL-4, IL-5, and IL-13. IL-5 is a crucial cytokine for eosinophil recruitment, maturation, and survival, while IL-4 and IL-13 increase the number of adhesion receptors in the vascular endothelium, facilitating eosinophil penetration into the tissue. Chemokines recruit eosinophils across the pulmonary mucosa through the activation of the prostaglandin D2 type 2 receptor, which is expressed in T2 lymphocytes, innate lymphoid cells type 2 (ILC2), and mast cells. Recruited eosinophils damage the bronchial epithelium and cause bronchial obstruction through the secretion of leukotrienes. Additionally, IL-4 enables the production of IgE in B cells. IgE binds to mast cells, inducing cell degeneration and securing eicosanoids and cytokines, which activate airway inflammation, epithelial cells, mucosal glands, and airway smooth muscles. IL-13 is also involved in airway smooth muscle hypersensitivity and excessive mucus secretion [11-13]. Serum IgE, sputum eosinophil counts, blood eosinophil counts, serum FeNO, and periostin are biomarkers that are important in predicting the response to biologic drugs for T2 inflammation [14].

2.2. Type 2 - low level asthma

T2-low asthma comprises neutrophilic, paucigranulocytic, or mixed asthma, whose pathophysiology is less understood than that of T2-high asthma. This type of asthma activates both T helper (Th) 1 cells and Th17 cells. Patients with moderate to severe asthma have been found to have high levels of IL-17A mRNA [15-17]. They are generally less sensitive to corticosteroids, less prone to allergies, and older at diagnosis than patients with other endotypes. The development of drugs to treat T2-low asthma has not made significant progress, and no biologic drugs have yet been approved. Some studies have described the effects of bronchial thermoplasty and azithromycin treatment [18-19].

3. Pre-qualification for biological treatment of asthma

Biologic drug therapy may be considered for patients with type 2 inflammation. Thus, it is of the utmost importance to accurately diagnose asthma and determine the phenotype and endotype of the disease in initial qualification for biologic treatment [20].

Difficult-to-treat asthma is diagnosed when a patient's asthma cannot be controlled despite the use of high doses of GCS with additional control medication. The first step in distinguishing difficult-to-treat asthma from severe asthma is to determine whether the observed symptoms are related to asthma. Patient history is crucial in assessing reversible bronchospasm. Spirometry and regular peak expiratory flow (PEF) measurements are used for this purpose. It is also important to check for factors that may contribute to inadequate disease control, such as improper inhalation technique, noncompliance, and abuse of short-acting beta-agonists (SABA) medications. Evaluation of associated conditions, such as gastroesophageal reflux disease (GERD), chronic rhinosinusitis, anxiety syndromes, depression, obesity, lack of fitness, and chronic obstructive pulmonary disease (COPD), is also recommended. Additionally, modifiable risk factors, such as exposure to allergens that sensitize the patient or cigarette smoke, should be considered. It is important to note that certain medications, especially beta-blockers and nonsteroidal anti-inflammatory drugs (NSAIDs), as well as socioeconomic conditions or drug side effects, can also impact asthma control. The third step in optimizing therapy involves educating the patient, removing

modifiable factors, properly treating chronic conditions, and modifying anti-asthma therapy. Consider incorporating a previously unused disease-controlling drug such as a LABA, long-acting muscarinic antagonists (LAMA), or leukotriene receptor antagonists (LTRA), or using a systemic steroid. After 3-6 months evaluate the response to the treatment by assessing symptom frequency, SABA consumption, nocturnal awakenings, ability to exercise, and number of exacerbations if asthma control is achieved, the next step is to attempt to reduce drug doses. If treatment modification leads to relapse or exacerbation, severe asthma should be diagnosed. Severe asthma should also be diagnosed if a satisfactory effect is not achieved after 3-6 months. At this stage, the patient should be referred to a specialized center where the disease phenotype can be diagnosed and treated [20].

4. Biological Treatment Options for Asthma

The Drug Program is a health benefit that is free of charge for patients in Poland. Its purpose is to increase patients' access to new and innovative drug therapies. To be eligible for treatment under the program, patients must meet specific criteria. This requirement is necessary because the program provides treatment with innovative and expensive active substances that are not covered by other guaranteed benefits. However, eligibility criteria for drug programs often have more restrictive requirements than the recommendations of scientific societies and the characteristics of medicinal products. This can result in a limited number of patients receiving treatment, as is the case with the asthma treatment program in Poland [21].

Currently, the Polish drug program 'Treatment of patients with severe asthma' reimburses five active substances. When the B.44 drug program was introduced in November 2012, only one substance, omalizumab (Xolair), was available. Mepolizumab (Nucala) was introduced in November 2017, followed by benralizumab (Fasenra) in November 2019. Dupilumab (Dupixent) became available in May 2022, and tezepelumab (Tezspire) was introduced in April 2024 [21].

4.1. Omalizumab

It was the first biologic drug approved for asthma treatment in the United States and the European Union. Omalizumab is a humanized monoclonal antibody that targets IgE, which is essential in the inflammatory cascade of allergic asthma. About 70% of asthma cases are allergic asthma, where IgE plays a crucial role in the inflammatory process [22-23]. B cells produce IgE in response to allergen-induced activation of the cellular immune response. Omalizumab inhibits the allergic response by preventing IgE from binding to the high affinity receptor (FcεRI) present on mast cells and basophils, which suppresses the release of pro-inflammatory mediators [24-25]. Additionally, it reduces inflammation by decreasing IgE receptor expression on mast cells [25].

In Poland, Omalizumab treatment is indicated for patients over 6 years of age with severe, uncontrolled allergic bronchial asthma and confirmed allergy to perennial allergens through skin prick tests or specific IgE tests. It is used in combination with other asthma-controlling drugs, including high doses of ICS and LABA. This text describes the qualification criteria for adults and children aged 12 years and over who use leukotriene modifiers or long-acting muscarinic receptor blockers chronically and have experienced two or more exacerbations requiring systemic glucocorticoids or an increase in their dose in the year prior. Children aged 6-11 years must have two or more exacerbation episodes per year, but treatment with oral corticosteroids (OCS) is not mandatory. An additional criterion for diagnosis is the total IgE concentration in serum, which should be between 30-1500 IU/ml. However, if the total sIgE concentration does not exceed 76 IU/ml, it is necessary to establish clear in vitro reactivity to year-round allergens. Additionally, the patient must meet at least two of the following criteria:

1)exhibit symptoms of uncontrolled asthma (as indicated by an ACQ asthma control questionnaire score of >1.5 points),

2)experience a decrease in quality of life due to asthma (with a mean score of <5.0 points on the mini-AQLQ asthma quality of life test),

3) have had a life-threatening asthma attack in the past,

4) have been hospitalized in the past 12 months due to an asthma exacerbation or

5) persistent airway obstruction is defined as having a FEV1 less than 80% of the normal value or a diurnal variation in PEF greater than 30%.

The criteria for severe asthma include: a decrease in quality of life due to asthma (indicated by an average score of less than 5.0 points on the miniAQLQ quality of life control test for asthma patients aged 12 years and older, or less than 5.0 points on the PAQLQ for children aged 6-11 years); 3) a history of life-threatening asthma attacks; and 4) hospitalization within the last 12 months due to asthma exacerbation.

Persistent airway obstruction is defined as a forced expiratory volume in one second (FEV1) of less than 80% of the predicted value or a daily variability of PEF greater than 30%.

The remaining criteria pertain to body weight (20-150 kg) and the exclusion of causes other than the body's reaction to year-round inhalant allergens causing severe asthma.

Omalizumab is administered at a dose of 75 to 600 mg in 1 to 4 injections, with a maximum recommended dose of 600 mg every 2 weeks. The dosage schedule should be determined based on the patient's body weight (kg) and the initial IgE concentration (IU/ml), which is determined before the start of treatment. The dosage tables included in the current Summary of Product Characteristics should be consulted for detailed information [26].

4.2. Mepolizumab and benralizumab

IL-5 is a cytokine that plays a significant role in eosinophil recruitment, activation, and survival. Anti-IL-5 biologics inhibit this pathway, thereby reducing eosinophilic airway inflammation [27]. Mepolizumab and benralizumab are monoclonal antibodies that bind and inhibit IL-5, preventing it from binding to its receptor on eosinophils and reducing eosinophilic inflammation [28].

Benralizumab binds to the α subunit of the IL-5 receptor on eosinophils and basophils, preventing IL-5 binding and subsequent eosinophil recruitment and activation.

Additionally, afucosylation of the benralizumab monoclonal antibody enhances its ability to bind to FcγRIIIa on natural killer cells, causing aggregation around eosinophils. This

results in antibody-directed cellular cytotoxicity and apoptosis of eosinophils, followed by phagocytosis by macrophages [28].

Both drugs can be administered to patients over the age of 18 with severe, refractory eosinophilic asthma. This type of asthma can be diagnosed in patients whose blood eosinophil count remained at a level of ≥350 cells/µl during the qualifying visit or in the 12 months preceding the patient's qualification to participate in the program. Or ≥150 cells/µl, if systematically, for a period of 6 months before qualification, due to lack of asthma control, it was necessary to take systemic steroids at a dose of ≥5 mg daily and the cumulative annual dose of OCS is ≥1.0 g (calculated as prednisone). In addition, patients who are eligible for traditional treatment must use high doses of ICS in combination with another asthma control drug (LABA, LTRA, LAMA) and have had two or more episodes of exacerbations in the last year that required the use of systemic glucocorticosteroids or an increase in their dose for a period longer than three days in individuals who use them chronically.

Additionally, for a patient to be eligible for this treatment (similar to omalizumab), they must meet at least two of the following criteria:

1) Exhibit symptoms of uncontrolled asthma (as indicated by an ACQ Asthma Control Questionnaire score of >1.5 points),

2) Experience a decrease in quality of life due to asthma (with an average score of <5.0 points on the mini-AQLQ quality of life control test for asthma patients),

3) Have had a life-threatening asthma attack in the past,

4) Have been hospitalized in the last 12 months due to asthma exacerbation orpersistent airway obstruction should be diagnosed when FEV1 is less than 80% of the predicted value or when there is a daily variability of PEF greater than 30%.

Additionally, during qualification, it is important to exclude other hypereosinophilia syndromes, clinically significant lung diseases, and parasitic infections based on stool examination.

Mepolizumab is administered subcutaneously at a dose of 100 mg every 4 weeks. Benralizumab is recommended to be administered subcutaneously at a dose of 30 mg every 4 weeks for the first three doses, followed by every 8 weeks thereafter [26].

4.3. Dupilumab

Dupilumab is a monoclonal antibody that targets the IL-4α receptor, blocking signaling of both IL-4 and IL-13. These cytokines promote the production of IgE and the recruitment of inflammatory cells, as well as stimulating goblet cell hyperplasia and modulating airway hyperresponsiveness and airway remodeling [29]. Two patient profiles are eligible for dupilumab treatment. The first group consists of patients over 18 years of age with severe, treatment-resistant asthma with type 2 inflammation characterized by a blood eosinophil count of ≥350 cells/µl at the qualifying visit or during the 12 months preceding the patient's qualification to participate in the program or ≥150 cells/µl if, due to lack of asthma control, it was necessary to take systemic steroids at a dose of ≥5 mg daily for a period of 6 months before qualification, and the cumulative annual dose of OCS is ≥1,0 (calculated as prednisone), requiring the use of high doses ICS in combination with another asthma control drug (LABA, LTRA, LAMA) who have had two or more episodes of exacerbation requiring the use of systemic glucocorticoids or an increase in their dose for a period in the last year longer than three days in people who use them chronically.

Additionally, for a patient to be eligible for this treatment, they must meet at least two of the following criteria:

1) exhibit symptoms of uncontrolled asthma (as indicated by an ACQ Asthma Control Questionnaire score of >1.5 points),

2) experience a decrease in quality of life due to asthma (with an average score of <5.0 points on the mini-AQLQ quality of life control test for asthma patients),

3) have had a life-threatening asthma attack in the past,

4) have been hospitalized in the last 12 months due to asthma exacerbation or

5) persistent airway obstruction should be diagnosed when the FEV1 is less than 80% of the predicted value or when there is a daily variability of PEF greater than 30%.

Additionally, during qualification, it is important to exclude other hypereosinophilia syndromes, clinically significant lung diseases, and parasitic infections based on stool examination.

The second group of patients consists of those over 12 years of age with severe, uncontrolled asthma and type 2 inflammation, characterized by a blood eosinophil count of ≥150 cells/microliter at the qualifying visit or during the 12 months preceding qualification for the program, and confirmed year-round allergy to allergens by skin prick tests or specific IgE tests, Requires the use of high doses of ICS in combination with another asthma controller (LABA, LTRA, LAMA) who has had two or more episodes of exacerbations requiring the use of systemic glucocorticosteroids or an increase in their dose for a period of more than three days in people who use them chronically.

Both drugs can be administered to patients over the age of 18 with severe, refractory eosinophilic asthma. This type of asthma can be diagnosed in patients whose blood eosinophil count remained at a level of ≥350 cells/μl during the qualifying visit or in the 12 months preceding the patient's qualification to participate in the program.

An additional criterion is a serum total IgE concentration of 30-1500 IU/ml.

Additionally, for a patient to be eligible for biologic drugs, they must meet at least two of the following criteria:

1) exhibit symptoms of uncontrolled asthma (as indicated by an ACQ asthma control questionnaire score of >1.5 points),

2)experience a decrease in quality of life due to asthma (with a mean score of <5.0 points on the mini-AQLQ asthma quality of life test),

3) have had a life-threatening asthma attack in the past,

4) have been hospitalized in the past 12 months due to an asthma exacerbation or

5) persistent airway obstruction is defined as having a FEV1less than 80% of the normal value or a diurnal variation in PEF greater than 30%.

Additionally, during the patient's qualification, other causes of severe asthma, aside from the body's reaction to year-round inhalant allergens and parasitic infection, should be ruled out based on a stool examination.

Dupilumab should be administered according to the dosage specified in the current Summary of Product Characteristics as of the date of the decision [26].

4.4. Tezepelumab

Tezepelumab is a first-in-class human monoclonal antibody that binds to TSLP (thymic stromal lymphopoietin), inhibiting its interaction with the TSLP receptor complex. TSLP is overexpressed in the airways of severe asthmatics and is an upstream cytokine that orchestrates inflammatory responses in asthma by binding to a high-affinity heteromeric receptor complex consisting of TSLPR and IL-7Rα [30].

The documentation of TSLP polymorphisms with airway hyperresponsiveness, IgE, eosinophilia, and asthma is well-established. TSLP has been implicated in the pathophysiology of asthma [30].

Eligible patients are individuals who are 12 years of age or older have severe, refractory asthma. This is defined as the need for high doses of inhaled corticosteroids in combination with another asthma-controlling drug, such as a LABA, LTRA or LAMA. The study includes individuals who have experienced two or more exacerbation episodes in the past year requiring systemic corticosteroids, or an increase in the dose of corticosteroids for more than three days in those who use them chronically.

Additionally, for a patient to be eligible for biologic drugs, they must meet at least two of the following criteria:

1)exhibit symptoms of uncontrolled asthma (as indicated by an ACQ asthma control questionnaire score of >1.5 points),

2)experience a decrease in quality of life due to asthma (with a mean score of <5.0 points on the mini-AQLQ asthma quality of life test),

3) have had a life-threatening asthma attack in the past,

4) have been hospitalized in the past 12 months due to an asthma exacerbation or

5) persistent airway obstruction is defined as having a FEV1 less than 80% of the normal value or a diurnal variation in PEF greater than 30%.

Additionally, during patient qualification based on stool examination, other clinically significant lung diseases and parasitic infections should be ruled out.

Tezepelumab should be administered according to the dosage specified in the current Summary of Product Characteristics as of the decision [26].

Criteria that patients must meet to qualify for the above-mentioned drugs include:

- not smoking,

- the absence of significant comorbidities that would contraindicate therapy as determined by the treating physician based on the current SmPC,

- no contraindications to the use of the drug according to the current SmPC,

- exclusion of pregnancy or lactation period.

When considering biologic treatment for severe asthma in patients who are already receiving immunosuppressants, anticancer drugs, or other biologics, the treating physician should carefully evaluate the risks and benefits of such treatment. It is recommended that patients do not receive any other biologic drugs to treat asthma until at least 2 months after the end of therapy.

Patients should be monitored for at least 2 hours after the initial administration of each drug. If the patient tolerated the first drug administration well, and subsequent administrations (second, third, and fourth) were also well-tolerated, they should be observed for 30 minutes. If both the doctor and patient agree, treatment can be continued at home [26].

For the population with severe asthma in Poland, the availability of innovative medicines is insufficient. According to data from the National Health Fund's database, approximately 2 million people in Poland suffer from asthma, with 5% experiencing a severe course of the disease. Only 2,500 people were enrolled in the B.44 drug program in 2022, despite 32,000-38,000 people with severe uncontrolled asthma being eligible for biologic therapies [21].

Additionally, the drug reslizumab is not reimbursed in Poland [21].

5. Future potential biological drugs for treating asthma.

With a deeper comprehension of the immunopathogenesis of asthma, researchers have identified additional inflammatory pathways as therapeutic targets, leading to the development of new biologic drugs. Currently, all FDA-approved biologic drugs target

downstream T2 inflammatory pathways. However, investigations are underway to target earlier T2 inflammatory pathways, such as IL-25, IL-33, and TSLP. Biologic drugs and small-molecule antagonists that target kinases, such as Janus kinase pathways, downstream of these T2 cytokines are also under development [31]. Researchers are also evaluating alternative delivery methods for biologic therapies beyond subcutaneous or intravenous delivery. It is worth noting that plasma concentrations of biologic drugs after intravenous administration are much higher than BAL concentrations [32]. Researchers are investigating nebulized biologic therapy to increase drug concentrations in the terminal bronchi while reducing systemic toxicity. A recent animal study evaluated the use of a nebulizer to deliver anti-IL-13 mAb fragments to terminal bronchioles, which showed a reduction in allergic airway response and was well tolerated [33-34].

6. Conclusions

For asthma patients, biological treatment is often the only option to improve their quality of life and alleviate disease symptoms. Patients treated with OCS require significantly less medication to control the disease, which improves their condition and reduces the number of complications. Additionally, lung function parameters significantly improve.

Biological therapies are available for patients suffering from asthma in Poland under a therapeutic program for the treatment of severe asthma. Eligibility for this program is determined by a specialist allergist or pulmonologist affiliated with a center contracted to provide this service, following the criteria specified in the announcement by the Minister of Health regarding the list of reimbursed drugs. According to the current provisions of the therapeutic program, only beneficiaries diagnosed with severe asthma qualify for biological treatments. The selection of the specific drug depends on the phenotype and endotype of the disease and should be preceded by comprehensive differential diagnostics, in accordance with the recommendations provided by GINA as presented above.

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Authors' contribution

Conceptualization: Klaudia Wilk-Trytko, Maciej Superson; Methodology: Katarzyna Szmyt, Sylwia Samojedny; Validation: Katarzyna Szymańska, Kamil Walczak; Formal Analysis: Julia Krasnoborska, Julia Zarębska; Research: Klaudia Wilk-Trytko, Katarzyna Szmyt, Maciej Superson; Resources: Sylwia Samojedny, Julia Zarębska; Writing - Original Draft Preperation: Julia Krasnoborska, Katarzyna Szymańska, Kamil Walczak; Writing - Review & Editing: Klaudia Wilk-Trytko, Katarzyna Szmyt, Maciej Superson, Sylwia Samojedny

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