Alergologia Polska – Polish Journal of Allergology 2020; 7, 2: 98–105
DOI: https://doi.org/10.5114/pja.2020.96130
Otrzymano: 4.02.2020, **zaakceptowano:** 20.04.2020.

Alergologia POLSKA
Polish Journal of Allergology

REVIEW PAPER/*PRACA POGLĄDOWA*

A summary of novel biologics for asthma treatment

Podsumowanie dotyczące nowych leków biologicznych w leczeniu astmy

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ABSTRACT

Over 235 million people struggle with asthma. Many patients suffering from a severe type of asthma have a problem with disease control. In this case, basic treatment like high-dose inhaled corticosteroids may not have a suitable effect. With the present level of knowledge about phenotypes and endotypes of asthma, there is a way to customise a more personalised and effective type of medication for every patient. Omalizumab was the first novel type of therapy, and almost 20 years since its approval, it is still one of the most commonly prescribed biologics for asthma treatment. Now, new types of innovating biologics are being invented. This overview presents drugs that are being investigated for treatment or have already been approved.

KEY WORDS

asthma, biologics, interleukins.

STRESZCZENIE

Obecnie na świecie ponad 235 milionów ludzi zmaga się z astmą. Wielu pacjentów cierpiących na jej ciężką postać ma trudności z kontrolą choroby, a klasyczne leczenie astmy, takie jak podawanie wysokich dawek wziewnych glikokortykosteroidów, nie przynosi odpowiedniego efektu. Dzięki coraz większej wiedzy na temat występujących fenotypów i endotypów astmy możliwe jest dostosowanie leczenia w sposób bardziej spersonalizowany i co za tym idzie – skuteczniejszy. Omalizumab jako pierwsza nowatorska terapia astmy, mimo że jest dostępna od prawie 20 lat, nadal jest stosowana. Poniższy artykuł przedstawia przegląd obecnie badanych lub już zatwierdzonych leków biologicznych jako nowych rodzajów innowacyjnego leczenia astmy.

SŁOWA KLUCZOWE

astma, leki biologiczne, interleukiny.

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INTRODUCTION

ASTHMA

Asthma is a disease that can affect everyone at all ages, ranging from 20% of children aged 6–7 years with severe episodes of wheezing, to adults with a global incidence of 1% to 21% [1]. Bronchial asthma is a heterogeneous disease with symptoms characterised by chronic airway inflammation. The most characteristic symptoms are shortness of breath, dyspnoea, wheezing, coughing, and chest tightness. With time, untreated asthma may lead to progressive airway remodelling, which can cause airflow obstruction [2, 3].

The main factors causing asthma are allergens, both those indoors (dust, domestic pollution, or the presence of pets) as well as those outsides (pollen, mould, mites), but there are other environmental and individual factors that can trigger asthma (Figure 1) [4].

Allergic asthma has a Th2 profile of chronic lower respiratory tract infection, in which, by tilting the balance towards CD4 + lymphocytes having the Th2 phenotype, bronchial epithelium produces cytokines of this profile, which is characteristic of type I hypersensitivity. The main reaction in allergic asthma is antigen (allergen) attachment to IgE connected with the high-affinity receptor for immunoglobulin E (FcεRI) on mast cells and basophils. After this connection, all kinds of mediators are released, which results in bronchial obstruction (narrowing of the lumen of their vessels) inflammation (Figure 2). Also characteristic are goblet cell hyperplasia within the bronchi, thickening of the basement membrane, increased number of mucous glands, hypertrophy of the muscle membrane, and exfoliation of the bronchial epithelium and its defragmentation [5–7].

ASTHMA PHENOTYPES AND ENDOTYPES

For a long time, asthma was treated universally for all patients, and omalizumab, targeting IgE antibodies, was the only treatment for severe allergic asthma. Now, thanks to biology methods, we can understand the asthma pathophysiology more precise and treat it more reasonably. Thanks to of epigenomics, genomics, transcriptomics, proteomics, and metabolomics, biological profiles of asthma have been selected.

There are many ways to categorise phenotypic asthma. The main features guiding the division into categories are age at onset, symptom triggers, disease severity, airflow obstruction, inflammatory patterns, exacerbations, and gender. The biggest problem with this approach of categorising the phenotypes is that sections overlap or do not distinguish the groups. Modern approaches have used a methodology of systems biology, which solves the problem of preconceived biases. Thanks to algorithms in a cluster analysis, multiple components that interact with each other in large cohorts can describe or predict clinical phenotypes, as well as molecular mechanisms, of asthma. The three most efficient programs are the Severe Asthma Research Program (SARP), Airways Disease Endotyping for Personalised Therapeutics (ADEPT), and the

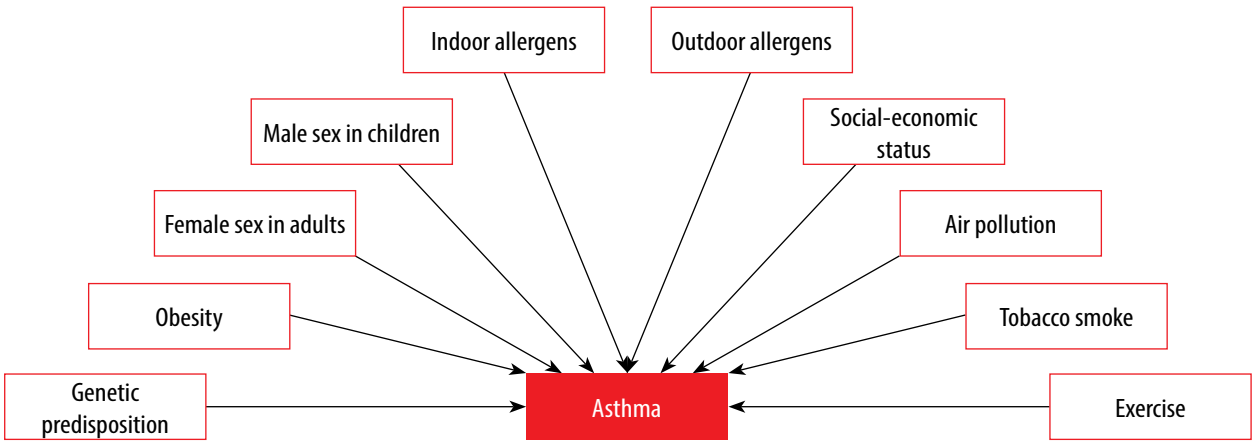

FIGURE 1. The most common asthma triggers

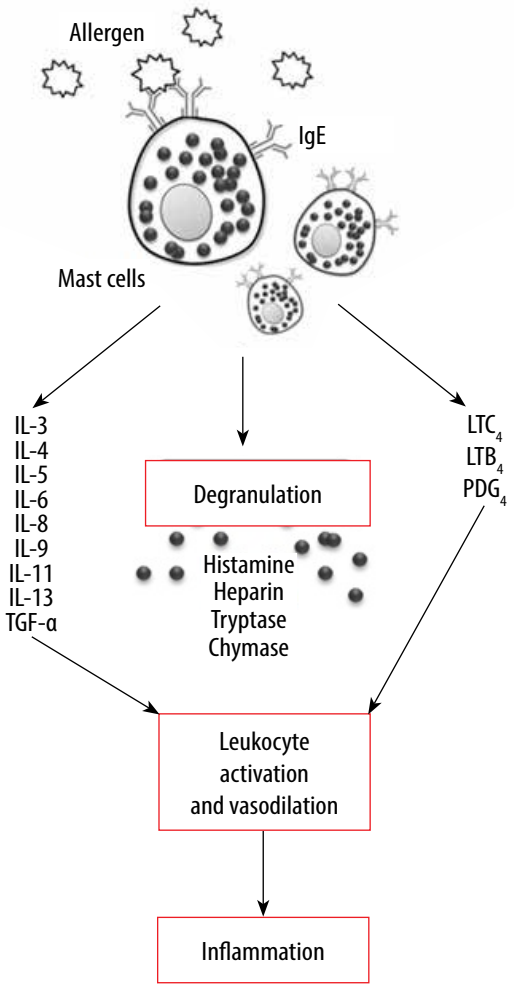

FIGURE 2. The role of mast cells in allergic inflammation [8]

Unbiased Biomarkers for the Prediction of Respiratory Disease Outcome (U-BIOPRED). After comparing these programs, two major groups were structured: T2-high and non-T2-high groups [8, 9].

We can define endotype by pathophysiologic mechanisms that underlie the phenotype (or phenotypes). Asthma endotypes describe these pathophysiologic, molecular mechanisms. Based on those mechanisms, we classify asthma endotypes on T helper type 2 cell high (Th2-high) and low (Th2-low).

In the Th2-high subtype, the high level of eosinophil is present. This subtype can be early onset with allergic sensitisation and responsiveness to inhaled corticosteroids, late-onset with an absence of allergic sensitisation and lack of responsiveness to corticosteroids, or aspirin-exacerbated respiratory disease (AERD), which is present mostly in adults. For now, the most validated method to confirm the Th2-high endotype is by sputum cytometry. Thanks to this method, four inflammatory patterns can be detected based on the granulocytes in the patient's sputum – paucigranulocytic, eosinophilic, neutrophilic, and mixed-granulocytic (neutrophils and eosinophils). Most of the new biologic drugs have Th2 cytokine (IL-3, IL-4, IL-5, IL-9, IL-13) pathways as a target.

TABLE 1. Biologics used for asthma treatment

Name of the drug	Target	Approved or investigational
Omalizumab	IgE	Approved
Lebrikizumab	IL-13	Investigational
Tralokinumab	IL-13	Investigational
Pitrakinra	IL-4/IL-13	Investigational
Dupilumab	IL-4/IL-13	Approved
Mepolizumab	IL-5	Approved
Reslizumab	IL-5	Approved
Benralizumab	IL-5	Approved
Secukinumab	IL-17	Investigational
Brodalumab	IL-17	Investigational
DNAzyme hgd40	GATA-3 mRNA	Investigational
QAW039	DP2	Recently rejected
Tezepelumab	TSLP	Investigational
SCH-527123	CXCR2	Investigational
Imatinib	KIT	Approved

*Biologics being investigated in the treatment of asthma but approved in other diseases.

In the Th2-low subtype, we can observe neutrophilic or paucigranulocytic inflammation of the airway. This subtype may contain the following elements: 1) asthma and chronic obstructive pulmonary disease overlap syndrome (ACO) which is late-onset and characterized by neutrophilic inflammation; 2) paucigranulocytic asthma associated with smooth muscle; 3) obesity-related asthma, mostly late-onset; 4) smoking-related asthma, mostly adult-onset [9–11].

BASIC TREATMENT

Asthma is an incurable disease that can be treated symptomatically. The basis of treatment, besides determining risk factors and factors provoking the patient, is pharmacotherapy. Asthma pharmacotherapy is based on inflammation treatment and minimising symptoms of the disease. There are two main types of classic medication. The first type is focused on controlling the symptoms and anti-inflammation functionality. Corticosteroids are the most commonly used drugs of this type, mainly by inhalation (ICS). The second type is most commonly sympto-

matic drugs with a relaxant and bronchoprotective effect, such as β_2-mimetics. More complex therapy that can be used to treat asthma utilises leukotriene receptor antagonists (LTRAs), which show weaker anti-inflammation functionality than ICS, but reduce the severity of symptoms and the frequency of exacerbations while improving lung function. These medications have been used for all types of asthma for decades. Now, as our knowledge has grown, we can use biologic treatment that can help more precisely [12, 13] (Table 1).

BIOLOGIC THERAPY

Biologic drugs can be used for the treatment of many diseases and conditions, including asthma. Thanks to this type of treatment we can target the element of interest in asthma to create more effective treatment. The development of biologics that target specific factors of inflammation have shown promise in achieving asthma control in patients. Biologic therapy is a promising concept to treat asthma, and drug development innovation is needed to achieve good results [14].

BIOLOGICS TARGETING SPECIFIC INTERLEUKINS

Interleukins 4 and 13

Interleukin 4 is a cytokine produced by Th2 lymphocytes, mast cells, and basophils. IL-4 has many important proinflammatory functions. The functions include stimulating B lymphocytes to switch antibody class production towards IgE. These are crucial for mast cell activation, resulting in immediate allergic reactions. IL-4 also induces mucin gene expression, thus increasing the secretion of mucus. Another important activity of the cytokine is directing the migration of immune system cells like T lymphocytes and monocytes into the inflammatory site. All of the functions together make IL-4 an important factor in the development of asthma. Consequently, the cytokine is also a good target for biological therapies [15]. Biologic treatment targeting IL-4 includes drugs like pitrakinra and dupilumab. Both of the substances, in addition to IL-4, also target IL-13 [16, 17].

Interleukin 13 is another cytokine involved in the pathogenesis of asthma. Similar to IL-4, IL-13 induces the antibody class switching in favour of IgE. The cytokine also increases mucin secretion and its activity may result in the airway hyper-reactivity, which are both important in the development of respiratory disorders [16, 17]. Studies that focused particularly on IL-13 proved that it is crucial to trigger many symptoms of allergic asthma without the need to cooperate with other Th2 cytokines [18].

In addition to pitrakinra and dupilumab targeting both IL-13 and IL-4, there are still some biologics dedicated exclusively to IL-13. These include lebrikizumab and tralokinumab. IL-4 and IL-13 function through the IL-4 alpha receptor subunit. Both pitrakinra and dupilumab focus on inhibiting the activity of the receptor, thus blocking the signalling pathway of these cytokines. However, there is a difference between these two drugs regarding the routes of administration. Pitrakinra is a mutein, which can be inhaled, whereas dupilumab is an injectable antibody [19, 20]. Lebrikizumab and tralokinumab are monoclonal antibodies able to recognise and neutralise the activity of IL-13. Both drugs are still being investigated to determine their efficacy; however, the prognosis is good [21, 22].

Interleukin 5

Interleukin 5 is produced by T lymphocytes, mast cells, and eosinophils. It is a proinflammatory cytokine selective for basophils and eosinophils, which are the main effectors in allergic reactions. Interleukin 5 is associated with growth, differentiation, migration, and activation of eosinophils. During contact with an allergen, eosinophils are able to infiltrate the airways. Then they are activated by IL-5, which promotes eosinophil recruitment and survival. Interleukin 5 was observed only in the bronchoalveolar lavage fluid of asthmatic patients who had late-phase antigen response. Because of the fact that eosinophils are one of the most important cells in asthma development, preventing their activation by targeting interleukin 5 and its receptor could help reduce asthma symptoms [23, 24].

There are three approved biologic drugs for asthma targeting interleukin 5: mepolizumab, reslizumab, and benralizumab. They all are monoclonal antibodies. Mepolizumab and reslizumab neutralise circulating interleukin 5 and prevent its binding to neutrophils. Benralizumab, on the other hand, targets IL-5 receptor α (IL-5Rα), and the result is the same as during treatment with mepolizumab and reslizumab. All three drugs are used to decrease eosinophilic inflammation among asthma patients [23].

Interleukin 17

Interleukin 17 is produced by CD4-positive T cells called Th17 cells. Th17 cells take part in an unusual pathway during an allergic reaction because primary effector cells are neutrophils. IL-17 is associated with neutrophilic asthma – patients with this type of asthma are usually resistant to inhaled steroids. This cytokine contributes to increasing airway inflammation during an allergic response.

Inhibiting IL-17 activity seems to be a promising way to improve asthma patients' lung conditions and to partially decrease asthma symptoms [23, 25].

Currently, on the market there are two FDA-approved biologic drugs targeting IL-17: secukinumab and brodalumab. Both are monoclonal antibodies, but secukinumab targets circulating IL-17, while brodalumab targets interleukin 17 receptor A (IL-17RA). So far, secukinumab is used in IL-17-mediated diseases treatment, mostly psoriasis, and brodalumab is under investigation as an approach in the treatment of psoriasis and asthma [23, 26].

BIOLOGICS NOT TARGETING INTERLEUKINS

QAW039, target: DP2

Prostaglandin D2 receptor (DP2) is a receptor for prostaglandin D2 (PGD2). In asthma patients, after exposure to allergens, mast cells and antigen-presenting cells are activated. As a response, they start producing prostaglandin D2 and expressing DP2. PGD2 binds to its receptor, which becomes activated. It contributes to the contraction of smooth muscles, vasodilation, and vascular leak. DP2 is also expressed by human dendritic cells, Th2 cells, eosinophils, basophils, and macrophages. Its activity can cause chemotaxis and activation of enumerated cells. Moreover, DP2 intensifies cellular responses to other mediators released during an allergic reaction, such as histamine [27, 28]. QAW039 reversibly binds to the prostaglandin D2 receptor. During an allergic reaction, it prevents prostaglandin D2 binding to DP2. Thereby, QAW039 reduces smooth muscle contraction in the upper respiratory tract after contact with allergens and eases respiratory gas exchange [29–31].

Employment of QAW039 in asthma patients has been assessed in eight clinical studies. Gonem *et al.* evaluated the effectiveness of QAW039 in patients with persistent eosinophilic asthma in a single-centre, randomised, double-blind, parallel-group, placebo-controlled trial that lasted 12 weeks. They compared placebo and QAW039 groups and observed that QAW039 reduces inflammation of the upper respiratory tract and is well tolerated by patients with persistent asthma. Other clinical studies (phase 2) conducted by White *et al.* show that QAW039 in asthma treatment reduces airway smooth muscle mass, promotes repair of epithelium, and reduces airway inflammation. These results indicate that QAW039 might improve lung function and moderate asthma symptoms. Therefore, QAW039 seems to be a potential control medication for asthma patients [32, 33].

DNAzyme hgd40, target: GATA-3 DNAzyme

Gata3 binding protein is a zinc finger transcription factor that belongs to the GATA family. The proteins recognise and bind to the "GATA" DNA sequences in particular gene promoters. Consequently, the genes are activated or repressed [34, 35].

GATA3 is necessary for the differentiation and activation of Th2 cells. Activated Th2 cells release cytokines such as IL-4, IL-5, IL-9, and IL-13. These cytokines stimulate B-cells to produce IgE, which subsequently binds to mast cells. The cells promptly release mediators leading to the contraction of smooth muscles, resulting in airway narrowing along with vascular leakage. Production of Th2 cytokines also leads to local allergic inflammation by recruiting eosinophils and lymphocytes. This indicates the importance of GATA3 activity in immunological processes initiating asthma [36].

GATA3 overexpression is found in lung biopsies taken from patients suffering from severe asthma. Because GATA3 is expressed intracellularly, specific GATA3 DNAzyme has been developed with the ability to penetrate through the cell membrane *in vivo* [37]. DNAzymes are short, catalytically active molecules, which are able to cleave sequence-specific RNAs [38]. DNAzyme hgd40 is made up of 34 bases. It contains two binding domains on both 3' and 5' regions that are highly specific for the mRNA of GATA3. The catalytic domain of the molecule is placed internally, which is responsible for cleaving the targeted mRNA [37].

The efficacy of DNAzyme hgd40 has been assessed in a phase 2a trial (randomised, double-blind, placebo-controlled). Both the drug and the placebo were administered by inhalation. During the trial, it was found that the asthmatic responses were attenuated significantly after the treatment (28 days) with DNAzyme hgd40. This included the impairment of allergen-induced increasement of sputum eosinophilia, but the change was non-significant (p = 0.06). A significant difference (p = 0.05) was observed in the levels of blood IL-5, which is one of the Th2 cytokines that are important in the pathogenesis of asthma. In subjects receiving DNAzyme hgd40, IL-5 levels were lower when compared to the placebo group.

There were no noticeable differences in adverse effects between the placebo and the DNAzyme hgd40 groups. The most commonly observed adverse events were headache, sciatica, infections with herpes simplex, and nasopharyngitis [37]. DNAzyme hgd40 might be a novel biologic that is able to benefit patients suffering from severe asthma; however, further research is needed to confirm its effectiveness [37].

Tezepelumab, target: TSLP

There are many factors in the pathogenesis of asthma, and one of them is cytokine thymic stromal lymphopoietin (TSLP). A high concentration of TSLP was found in the lungs of asthma patients, which can be indicative of the importance of TSLP in asthma pathogenesis. This cytokine is produced by many types of cells in the human body as well as by cells associated with asthma: basophils, mast cells, and dendritic cells. The activity of TSLP contributes to the expansion of inflammation mainly by increasing cytokine production and suppressing the development of Treg cells. Among asthma patients, the production of TSLP leads to exacerbation of asthma symptoms and increased sensitivity of lungs to allergens [39].

Tezepelumab is an IgG_2 human monoclonal antibody used to treat asthma and atopic dermatitis. The variable heavy chain domain of tezepelumab recognises the TSLP molecule, subsequently binding to its critical region. Consequently, TSLP is unable to bind to its receptor, and the molecule's activity is impaired. This results in inhibition of the airway inflammation [40, 41].

The efficacy of tezepelumab has been assessed in a phase II and III trial (randomised, double-blind, placebo-controlled). The study showed that tezepelumab successfully reduced the number of eosinophils in blood and sputum. In addition, the drug lowered levels of other biomarkers (serum IgE, FeNO) and improved ACQ-6 along with AOLQ scores (questionnaires for asthma patients describing their quality of life). These results indicate the possible effect of the drug on IL-4, IL-5, and IL-13 pathways, which are important in asthma pathogenesis. Furthermore, tezepelumab also reduced the late asthmatic response following allergen exposure [40].

However, three very serious adverse effects were observed during the trial in two patients. The first patient suffered from pneumonia and stroke, and the second one was diagnosed with Guillain-Barrè syndrome [40]. Nonetheless, tezepelumab is effective in reducing symptoms in both eosinophilic and non-eosinophilic asthma patients, in whom TSLP mediation is observed. Currently, more studies are still evaluating the safety of the drug [40].

SCH-527123, target: CXCR2 – interleukin 8 receptor β

CXCR2 is a receptor for interleukin 8 (IL-8), which binds to it with high affinity. Interleukin 8 has two main functions. Firstly, it stimulates the migration of neutrophils and other granulocytes into the site of inflammation. Secondly, it induces phagocytosis after the migration. The accumulation of neutrophils is linked to chronic airway narrowing in patients with asthma [42]. It is not known whether neutrophils contribute to reduced control and severity in asthma patients. Currently, it is being investigated whether CXCR2 antagonists could be useful in the treatment of severe asthma [43].

Holz *et al.* conducted a trial verifying the efficacy of SCH-527123 in healthy subjects with ozone-induced neutrophilia. During the research, the drug was shown to suppress the migration of neutrophils, thus inhibiting excessive neutrophilic inflammation of the airways. However, during the trial, some patients experienced mild adverse effects. The most common events included neutropaenia and headaches. These findings suggest that SCH-527123 may be a novel biologic able to improve the quality of life of patients suffering from asthma [44].

Imatinib, target: KIT – mast/stem cell growth factor receptor

The target of imatinib is a receptor called KIT (or CD117). It is located on the surface of haematopoietic mast cells and is a receptor for a stem cell factor. Its activation leads to cell proliferation, differentiation, and promotion of cell survival. The presence of KIT receptors provides normal development and survival of mast cells. Because mast cells play a key role in asthma pathogenesis, there is an approach of blocking KIT receptors so that mast cells cannot develop as they would in natural conditions [45].

Imatinib is an inhibitor of the KIT receptor; during imatinib treatment mast cells are partly undeveloped, and during contact with an allergen, inflammation of the upper airways is decreased because of the lower count of mast cells and lower responsiveness to allergens [45].

In 2017 a clinical study of imatinib use in asthma individuals was completed. The results indicated that imatinib improves lung condition among asthma patients, decreases hypersensitivity to allergens, and decreases the number of mast cells. Imatinib turned out to be an effective medicine in asthma control [46]. However, a number of adverse effects were observed during the trial. Imatinib intake was connected with a higher probability of muscle cramps occurrence and metabolic abnormalities [45].

SUMMARY

The number of biologic therapies for patients suffering from severe asthma is still expanding. Biologic drugs are being eagerly developed due to their unique properties and high efficacy. They are used to block spe-

cific receptors or activity of other important molecules in the pathogenesis of asthma, without interfering with undesirable pathways. In addition, biologics mostly have a longer duration of action when compared to standard methods of treatment like glucocorticoids. Although very promising, biologic therapies are still associated with a high cost, which may not be affordable for everyone. In addition, they are usually connected with some adverse effects, which are specific for each medicine.

ACKNOWLEDGMENTS

All authors contributed equally to this work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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