Chapter

Asthma Phenotypes and Current Biological Treatments

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Abstract

Asthma is a heterogeneous disease characterized by bronchial hyperreactivity, chronic airway inflammation, and reversible airflow obstruction, and it affects individuals in all age groups. In recent years, the concept of intrinsic and extrinsic asthma as per the former classification has been replaced by endotypic and phenotypic definitions. However, the two main asthma endotypes described and have simplified its classification. These endotypes, "Th2-high" and "Th2-low", are based on various measurements obtained for different biological materials, including blood, bronchial and sputum samples. The definitions of asthma is useful for targeted and individualized treatments, estimating the treatment response and prognosis. In the field of respiratory medicine, biological drugs (BDs) have shown rapid evolution and positive developments in the last 10 years, particularly for the treatment of asthma, interstitial lung disease, and lung cancer. However, because of the increasing number of BDs and associated studies, it has become very difficult to update treatment guidelines on a regular basis. BDs are used for patients with difficult-to-treat, moderate to severe, and/or uncontrolled allergic asthma. Here we present a review of current asthma phenotypes and the role, efficacy, and side effects of BDs used for the treatment of these conditions.

Keywords: Asthma, phenotype, endotype, biological treatment, biologics

1. Introduction

Asthma is a heterogeneous disease characterized by bronchial hyperreactivity, chronic airway inflammation, and reversible airflow obstruction, and it affects individuals in all age groups [1]. In recent years, studies on endotype and phenotype have intensified, and many different types have been identified. Symptom control is generally achieved with the use of inhaled corticosteroids (ICSs), although biological drugs (BDs) are used for patients with difficult-to-treat, moderate to severe, and/or uncontrolled allergic asthma [1], as these patient groups largely benefit from BD therapies. BDs, also known as biologics, encompass a number of agents that are rapidly growing and expanding their range of use. These drugs generally act on cell surface receptors or by interacting with a specific cytokine and are produced either directly from living sources (animal, human or microorganism) or by synthesizing from different cell cultures [2]. Currently, they are widely used in the fields of oncology, rheumatology, dermatology, and organ transplantation, and their indications include organ-specific cancers, psoriasis, rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, chronic urticaria, multiple sclerosis, and transplants [3]. In the field of respiratory medicine, biologics have shown rapid

evolution and positive developments in the last 10 years, particularly for the treatment of severe uncontrolled asthma, interstitial lung disease, and lung cancer. In this review, we will evaluate the current updates of asthma phenotypes and the role, efficacy, and side effects of BDs used for the treatment of these conditions.

2. Endotypes and phenotypes of asthma

The concept of intrinsic and extrinsic asthma as per the former classification has been replaced by endotypic and phenotypic definitions. However, a lack of clear classification system leads to a confusion and limitation in treatment. The current Global Initiative for Asthma (GINA) 2020 guideline mentions phenotypic differences in allergic asthma, nonallergic asthma, late-onset asthma, asthma with fixed airflow limitation, and asthma with obesity [1]. Although this guideline does not provide much details on asthma phenotyping, it mentions that further studies are necessary. Following the introduction of the phenotype concept, in 2006 Simpson et al. [4] conducted a study to fully characterize asthma based on the airway inflammatory type. The authors performed induced sputum analysis and divided the patients into the following four subgroups according to the dominant inflammatory cell type: a. neutrophilic, where neutrophils are >61% and the total cell count is >10 million cells/g; b. eosinophilic, where eosinophils are >1.9–3%; c. mixed granulocytic, where there is an increase in both neutrophils and eosinophils; and d. paucigranulocytic, where both neutrophils and eosinophils are within the normal range [4]. It is known that this classification of airway inflammation in asthma is important in predicting the clinical significance and response to BDs. Moreover, the authors reported that the rate of eosinophils in induced sputum is homogeneous and reproducible for eosinophilic asthma and heterogeneous for the other non-eosinophilic types of disease, and that further classification can be based on the presence of neutrophils [4].

However, a study involving 726 patients from the Severe Asthma Research Program (SARP) cohort was performed, and five main groups were identified [5] as follows: group 1, early-onset atopic asthma, control with two or fewer controlling drugs, normal lung function; group 2, early-onset atopic asthma, preserved lung function [65%; forced expiratory volume in 1 s (FEV1), >80% predicted], control with three or more controlling drugs (29% patients); group 3, late-onset nonatopic asthma, moderate decrease in FEV1, frequent oral corticosteroid (OCS) and ICS use for the treatment of exacerbations; group 4, early-onset atopic asthma with severely compromised pulmonary function (57% of the mean FEV1); and group 5, late-onset asthma, most severe airflow limitation (43% of the mean FEV1), less atopic patients with varying degrees of susceptibility to bronchodilator therapy. Then, subgroup analysis was performed as an extension of the same study, and the importance of eosinophil (≥2%) and neutrophil (≥40%) percentages in the sputum was emphasized [6]. From these findings, it was understood that asthma is a very heterogeneous disease with inflammatory and noninflammatory mechanisms. Considering the role of Type 2 T-helper cell (Th2) lymphocytes in eosinophilic airway inflammation, clinical studies have been inclined toward this topic. However, the two main asthma endotypes described in recent years have simplified its classification [7–9]. These endotypes, “Th2-high” and “Th2-low”, are based on various measurements obtained for different biological materials, including blood, and bronchial, and sputum samples [10]. The Th2-high type is generally characterized by increased eosinophils in the patient’s sputum and respiratory tract, while the Th2-low type is characterized by increased neutrophils or by the presence of a paucigranulocytic pattern [10]. The Th2-high patient group can be identified by

some biomarkers, particularly an elevated blood eosinophil count of >300 cells/mL, and these patients have shown a good response to treatment with BDs [10]. There are no defined biomarkers for the Th2-low endotype, so this phenotype is often identified by the absence of Th2-high biomarkers. Moreover, these patients do not respond well to steroids [10].

Currently, the serum immunglobulin (Ig)-E concentration and the number of peripheral blood eosinophilis are generally used to determine the response of patients with BD treatment [7, 9]. A combination of Th2 biomarkers such as interleukin (IL)-4, IL-5, and IL-13 is also considered to be a credible predictor of peripheral blood eosinophilia and eosinophilic inflammation [11]. Several other biomarkers that can be used include the following: **a.)** periostin, which plays a role in late-onset asthma and determines eosinophilic inflammation; **b.)** eotaxin-2, which determines eosinophilic inflammation; **c.)** L-arginine and leptin, which are associated with obesity-related asthma; **d.)** Chlamydia pneumonia antibodies (IgG, IgA, and IgE), which are associated with severe and obstructive asthma; **e.)** *Staphylococcus aureus* enterotoxin-IgE, which is associated with severe asthma, hospitalizations, OCS use, and lower FEV1; and f.) thymic stromal lymphopoietin (TSLP), which may play a role in sputum eosinophil elevation in smokers with asthma, thus helping in identification of this patient group [12]. Other investigations that help to improve endotyping include the measurements of the fraction of exhaled nitric oxide (FeNO) and skin prick tests [7]. The levels of allergen-specific antibodies may be considered clinically important in patients with asthma and atopy even if they are not used for endotyping. The World Asthma Phenotypes (WASP) study was initiated in 2016 and conducted in five countries; the results are awaited [13]. The aim of this study was to evaluate and compare detailed biomarker and clinical information, the distribution of disease phenotypes, and the risk factors and characteristics for each phenotype, including clinical severity.

In summary, the definition of asthma phenotypes and endotypes is useful for estimating the treatment response and prognosis. This approach has resulted in targeted and individualized treatments for patients (**Figure 1**).

2.1 Th2-high endotype

The asthma phenotypes that can be included in this group include aspirin-associated asthma, allergic bronchopulmonary mycosis (ABPM), early-onset (preschool wheezer) asthma, adult-onset asthma, late-onset severe hypereosinophilic asthma, and IgE-mediated occupational asthma (**Table 1**). These phenotypes can be classified under the Th2-high endotype because of the presence of significant allergic symptoms and eosinophilic inflammation.

Patients with aspirin-related or aspirin-sensitive asthma often present at polyclinics with nasal polyposis and severe rhinosinusitis [7]. The most important biomarkers are urinary leukotriene and blood eosinophils, although periostin may also be elevated [14]. The ABPM phenotype includes patients with adult-onset, severe asthma attacks and increased mucus production [7], and blood eosinophil counts, high IgE levels, high FeNO values, allergen-specific IgE, and skin prick tests can be used for identification [14]. Preschool wheezers are children with a family history of asthma who experience more than three episodes per year and often exhibit blood eosinophilia (>4%) and aeroallergen-specific IgE positivity [14]. The adult-onset allergic asthma phenotype includes patients having asthma since childhood, with symptoms of allergen-related rhinitis, positive skin prick tests, high IgE levels, and high FeNO values [7, 14]. The severe late-onset hypereosinophilic asthma phenotype includes nonatopic patients with severe exacerbations and peripheral blood eosinophilia [7, 14]. Patients with IgE-mediated occupational asthma, wherein asthma symptoms develop after the start of a new occupation or job, may also be included in

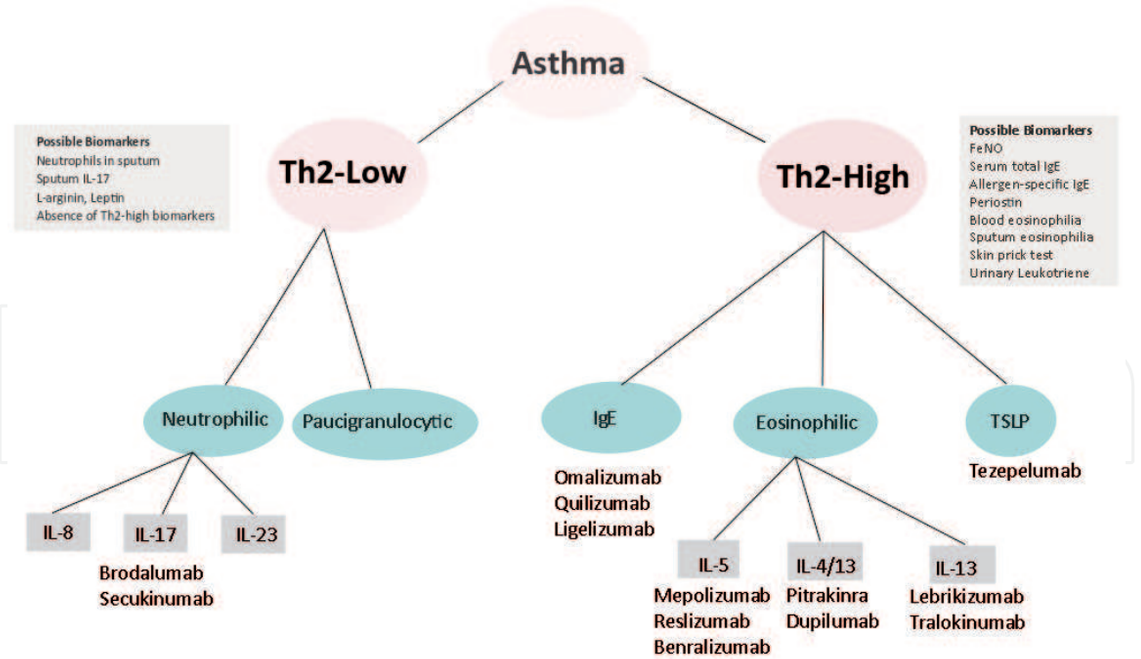

Figure 1.
Asthma phenotypes and current targets for biological treatment. Th2, T-helper type 2 cell; IL, interleukin; IgE, immunoglobulin E; TSLP, tymic stromal lymphopoietin; ACO, Asthma COPD overlap.

Phenotype	Clinical presentation	Biomarkers
Aspirin-Associated [7, 14]	Nasal polyposis, rhinosinusitis, adult onset,. **Therapy:** 5-LO or LTRA inhibitors	Urinary Leukotriene, increased periostin levels
Allergic Bronchopulmonary Mycosis [7, 14]	Mucus production, severe, adult onset, less reversibility, poor prognosis, **Therapy:** GKs, antifungals and biologics	High FeNO, High serum total IgE, High Aspergillus IgE, Positive Aspergillus skin testing.
Early Onset (preschool Wheezer) [14]	>3 episodes per year, early onset, history of asthma in parents **Therapy:** Daily inhaled GKs, LTRA, biologics	High FeNO, periostin, High IgE and Aeroallergen-specific IgE Eosinophils (often >4%) Positive Skin Pricktest,
Adult Onset [8]	Allergen associated symptoms/allergic rhinitis **Therapy:** GKs and biologics	High FeNO and total IgE, Positive Skin Pricktest,
Late Onset, severe and hypereosinophilic [7, 14]	Severe Exacerbations, non-atopic, GK-sensitive and often oral Gkk-dependent. **Therapy:** GKs and Anti-IL-5	High FeNO and eotaxins High Blood and Sputum Eosinophils,
Occupational, (IgE mediated) [15]	Asthmatic symptoms after onset new work **Therapy:** removal from exposure to the sensitizing agent	High FeNO, High IgE and allergen-specific IgE, sputum eosinophilia, Specific inhalation challenge, Peak expiratory flow

5-LO, 5-lipoxygenase; LT, leukotriene recepter antagonist; GK, Glucocorticoid; IgE,Immunglobulin E; FeNO, Fraction of exhaled nitric oxide in ppb; IL, Interleukin.

Table 1.
Possible Th2-high Endotypes of asthma.

this group. Specific inhalation challenge and peak expiratory flow measurement are required to diagnose these patients, along with high IgE levels, high allergen-specific IgE levels, high FeNO values, and sputum eosinophilia [15].

2.2 Th2-low endotype

This group includes asthma-COPD overlap (ACO; fixed obstruction) syndrome, late-onset nonatopic asthma, steroid-resistant or neutrophilic asthma, obesity related asthma, perimenstrual asthma, and non-IgE-mediated occupational asthma. Phenotypes induced by external factors, including exercise-induced asthma, cold-induced or cross-country skiers asthma, stress-induced asthma, and psychological asthma, may also be included in this group (**Table 2**). However, this classification needs to be improved by further research.

According to the current GINA guideline, the term ACOS is used for patients with chronic respiratory symptoms, exposure to a risk factor such as smoking, and a postbronchodilatator FEV1/forced vital capacity (FVC) of <0.7 [1]. Although the latter is not a well-known biomarker, the condition can be easily identified by using a questionnaire [1]. Late-onset nonatopic asthma generally affects women and adults.

Phenotype	Clinical presentation	Biomarkers
ACO or Fixed Obstruktion [1]	Chronic respiratory symptoms, exposure to a risk factor such as smoking, and post-bronchodilatator FEV1/FVC <0.7 Therapy: LABA + LAMA	—
Late Onset non-atopic [12, 16]	Particularly women, some adults, **Therapy:** require higher dose of ICS, relatively refractory to GKs	Absence of increase in sputum eosinophil count or FeNO
Poorly steroid responsive (neutrophilic) [7, 8]	Adult onset, low FEV1 and more Airtrapping, severe. **Therapy:** Macrolide, IL-17 antagonist	>76% neutrophils in sputum, IL-17
Obesity Related [12]	Often seen in obese women, less atopic, **Therapy:** Weight control	L-Arginin, Leptin
Pre- or perimenstrual [1]	A longer duration of Asthma, worsen in premenstrual phase, often dysmenorrhoe	—
Occupational (non-IgE mediated) [16]	Irritant-induced symptoms, poor prognosis, develops after acute high exposure to vapor, gas, fume, or smoke	Specific inhalation challenge. Peak expiratory flow
Asthma triggered by external factors		
Cold-Induced or Cross-Country Skiers [14]	Common upper respiratory tract infection, related to exercise and cold, poorly GKK respond **Therapy:** reducing cold exposure and training intensity	Normal FeNO, Normal blood eosinophil count, increased LT-E4 in urine
Exercise-Induced [17]	Develops due to increased catecholamines during exercise, resulting in increased airway resistance	—
Stress-Induced or Psychological [18]	After psychological stress, develop with the release of stress hormones	—

*ACO, Asthma-COPD-Overlap; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroids; FEV_1, forced expiratory volume in 1 s; FVC, orced vital capacity; See **Table 1** legend for expansion of other abbreviation.*

Table 2.
Possible Th2-low Endotypes of asthma.

Patients do not respond well to glucocorticoids and require high-dose ICSs [12]. This phenotype is similar to the obesity-associated phenotype. Although there is no biomarker, the absence of an increase in the sputum eosinophil count or FeNO is considered an indicator [16]. Patients with steroid-resistant asthma do not respond well to glucocorticosteroids and are mostly adults. Their FEV1 is considerably lower, with more air trapping, and there is an increased association with respiratory infections, obesity, smoking, and air pollution [8]. Increased sputum neutrophil counts and IL-17 levels can be used as biomarkers [7, 8]. Obesity-related asthma is thought to occur because of high-fat diet-related systemic inflammation, and L-arginine and leptin can be used as biomarkers [12]. Premenstrual or catamenial asthma is characterized by the deterioration of asthma symptoms in the premenstrual phase, and the role of hormone levels and systemic inflammation in these patients remains unknown [1]. Asthma in cross-country skiers or cold-induced asthma is characterized by mild to moderate symptoms and often triggered by exercise and cold. It is also associated with respiratory tract infection [14, 17]. Increased leukotriene (LT) E4 in urine may be used as a biomarker [14]. Exercise-induced asthma develops because of increased catecholamines during exercise, resulting in increased airway resistance [17]. Histamine and prostaglandin release reportedly play a role [17], but there is no specific biomarker. In asthma induced by stress or psychological factors, central nervous system activation by psychological stress, followed by the release of stress hormones (glucocorticoids, epinephrine, and norepinephrine) and immunological changes, may cause asthma exacerbation [18]. Although there is evidence regarding the critical role of psychological stress in the development and exacerbation of allergic asthma, this phenotype requires further research [18].

3. Asthma treatment and targets for biological drugs

A personalized approach with specific and targeted therapies for the cytokines constituting the inflammation cascade are of great benefit in the treatment of asthma, particularly the difficult-to-treat phenotypes [1, 14]. The pathophysiology of asthma has conventionally been mediated by Th2 lymphocytes, which induce the stimulation of eosinophils by IL-3, IL-5, and granulocyte–macrophage colony-stimulating factor (GM-CSF); basophils by IL-3; and mast cells by IL-4 and IL-9; alternatively, they cause direct mucosal damage via IL-4/IL-13 after antigen presentation [7–9]. Both IL-4 and IL-13 play a role in the activation of eosinophils, IgE synthesis, and, consequently, mucus secretion and airway remodeling [10]. However, they share the same receptor and signal pathways. All these cytokines also stimulate B-cells, causing the release of IgE. Currently approved targets for BD treatment in asthma include IgE, IL-4/IL-13, and IL-5, with uncontrolled or difficult-to-treat asthma requiring step 4 treatment as per the GINA guideline being the main indication [1]. In this group of patients, symptom control cannot be achieved despite maximum treatment [long-acting beta agonists (LABAs), tiotropium, high-dose ICSs, leukotriene antagonists, or theophylline with OCSs].

4. Classification for biologics

Biologics are divided into three common classes: monoclonal antibodies (mAbs), fusion proteins, and cytokines [2]. These drugs may be fully humanized mAbs or chimeric (human + murine mix) or fully murine/mouse antibodies [2, 19]. Diverse side effects with varying severities have been reported according to the level of humanization [3, 19]. Widely accepted nomenclature systems for biologics include the

USAN (the United States' Adopted Names) and INN (World Health Organization's International Nonproprietary Names) [2, 20]. Currently approved mAbs target IgE antibodies, cell surface molecules, soluble mediators, cytokines, viral proteins, and tumor antigens [2, 20]. Examples of these drugs include omalizumab (anti-IgE), rituximab (anti-CD20), infliximab [anti-tumor necrosis factor alpha (TNFα)], mepolizumab (anti-IL-5), and cetuximab (anti-epidermal growth factor receptor). Examples for fusion proteins; etanercept (anti-TNFα-RII), anakinra (anti-IL-1 receptor), and ritanercept (anti-IL-1β) are examples. The cytokine group includes recombinant cytokines such as interferon-α, interferon-β, GM-CSF, and IL-2.

5. Overview of biologics used for asthma treatment

Biologics have been used for the treatment of asthma since 2003. In the United States, omalizumab was the first drug approved for the treatment of severe and uncontrolled asthma [20]. Subsequently, several drugs targeting IgE, IL-5, IL-4, IL-5, IL-9, IL-13, IL-17, and TSLP were developed for the treatment of this patient group (**Table 3**). Details about these drugs are provided below.

5.1 Anti-IgE

a. **Omalizumab** (Xolair®) is a humanized mAb and the first drug to be approved by the Food and Drug Administration (FDA) for the treatment of severe uncontrolled asthma [21]. The mechanism of action involves selective binding to IgE antibodies, reduction of free IgE levels, and inhibition of inflammatory mediator release via the inhibition of mast cell degranulation.

   The PERSIST study, a "real-life" study, demonstrated that 12-month treatment with omalizumab can significantly improve the lung function and quality of life and minimize the rate of exacerbation [22]. The APEX II multicenter observational study demonstrated a clinical response rate to omalizumab at week 16 to be 82.4%. [23]. When the pre- and post-treatment periods were compared, a decrease in the daily OCS dose and number of exacerbations requiring hospitalization was observed. Moreover, pulmonary function test findings and the quality of life of patients were significantly improved. In a newly published study by Vennera et al., 60% patients who received omalizumab treatment for 6 years showed that the drug maintained its positive effect for at least 4 years after treatment discontinuation [24]. On the basis of clinical evidence, the response to omalizumab treatment is routinely evaluated after 16 weeks of treatment [25]; this evaluation is accepted as the most meaningful measurement and indication of permanent treatment response in the world.

   In pre- and postmarketing studies, the risk of anaphylaxis was reported to be 0.1%–-0.2% [26]. It was found that 61% reactions occurred within 2 h after one of the first three doses, while 14% occurred within 30 min after a fourth or subsequent dose [27]. In another study, 3.4%, 2.2%, and 0% participants reported injection site reactions, hypersensitivity reactions (HSR), and anaphylaxis, respectively [28].

b. **Quilizumab** is a humanized mAb against the M1 major segment of membrane-bound IgE, and it causes memory depletion of B-cells and inhibits IgE production [29]. The primary indication is uncontrolled allergic asthma and chronic spontaneous urticaria. In a study by Harris et al., it was demonstrated that

Target	Generic Name	Brands	Release Status in EU
IgE	Omalizumab	Xolair®	12/2005, approved
	Quilizumab	-	Phase III
	Ligelizumab	-	Phase III
IL-5	Mepolizumab	Nucala®	12/2015, approved
	Reslizumab	Cinqaero®	08/2016, approved
IL-5R	Benralizumab	Fasenra®	01/2018, approved
IL-4R complex (IL-4/13)	Pitrakinra	Aerovant®	Phase IIb
	Dupilumab	Dupixent®	09/2018 approved
IL-13	Lebrikizumab	-	Stopped
	Tralokinumab	-	Stopped
IL-17A	Brodalumab	Kyntheum	Stopped
	Secukinumab	Cosentyx®	Phase II
IL-9	Enokizumab	—	Stopped
TSLP	Tezepelumab	—	Phase III
PG DP_2-receptor	Fevipiprant	QAW039	Phase III
	Timapiprant	OC-459	Phase II
	Setipipitrant	ACT-129968	Stopped

IgE,Immunglobulin E; IL, Interleukin; TSLP, thymic stromal lymphopoietin; EU, europa; FDA, Food and Drug Administration.

Table 3.
Overview of biological agents used in asthma.

quilizumab was well tolerated by patients and reduced the IgE levels (serum total and allergen-specific) by 30–40% [30]. However, there was no beneficial effect with regard to asthma exacerbations, lung function, and patient-reported symptom measures. At 36 weeks, the asthma exacerbation rate decreased by 19.6% relative to that in the placebo group, although this was not a statistically significant result. Significant clinical efficacy benefit has not been demonstrated in studies of various biomarker subgroups (serum IgE, blood eosinophils, exhaled NO, and periostin). The safety of the drug was evaluated in the same study, and injection site reactions (mostly pain) were reported in 6.9% patients [30]. Currently, phase III studies of this drug are in progress.

c. **Ligelizumab** is an investigational humanized mAb that binds to IgE with a higher affinity than does omalizumab. In a 2016 study of patients with mild allergic asthma, it was found that inhaled and skin allergen responses were 3-fold and 16-fold greater with ligelizumab than with omalizumab and placebo, respectively [31]. These findings suggest the effectiveness of this drug in asthma treatment; phase III studies are currently ongoing.

5.2 Anti-IL-5

a. **Mepolizumab** (Nucala®) is a humanized mAb that binds to IL-5, selectively inhibits eosinophilic inflammation, and reduces both sputum and the number of eosinophils in the blood [32]. After receiving approval for the treatment of eosinophilic and severe asthma in Europe in December 2015, it was approved for the treatment of eosinophilic granulomatosis with polyangiitis and Churg–Strauss syndrome in December 2017.

In one study, subcutaneous administration of mepolizumab 100 mg every 4 days significantly lowered the rate of asthma exacerbations and the daily dose of OCSs in patients dependent on OCSs for asthma control [33]. In another study, mepolizumab was found to be at least as effective as omalizumab, and no significant difference was found between the tolerability profiles of the two treatments [34]. The most commonly reported adverse events in the Dose Ranging Efficiency and Safety with Mepolizumab in Severe Asthma (DREAM) study were nonallergic reactions associated with infusion [35]. In addition, Lugogo et al. [36] observed HSRs in <1% patients, injection site reactions in 4%, and infusion/injection reactions (nonallergic) in 1%. None of the recent studies has reported the occurrence of anaphylaxis as a side effect [35, 36].

b. **Reslizumab** (Cinqaero®) is a humanized mAb that binds to IL-5 and is used as an adjunctive drug in the treatment of severe and uncontrolled eosinophilic asthma [37]. The drug inhibits the activation, differentiation, and growth of eosinophils by inhibiting the binding of IL-5 to eosinophils. Unlike other drugs, it is intravenously administered at a dose of 3 mg/kg every 4 weeks.

In a subgroup analysis by Corren et al., the efficacy of resolizumab for an improvement in respiratory function, Asthma Control Questionnaire (ACQ) scores, and recovery inhaler use were evaluated for patients with a blood eosinophil count of >400 cells/μL [38]. Therefore, the blood eosinophil count is a useful pre-treatment biomarker in predicting patients' response to therapy and for the appropriate patient selection. In addition, two phase III studies reported that reslizumab administration improves lung function and controls asthma and related symptoms in patients with severe, uncontrolled, eosinophilic (≥400 cells/μL) asthma [38, 39]. Murphy et al. [40] demonstrated the long-term clinical effects and reported HSRs (<1%), drug rash (<1%), and very rare local infusion-related adverse events (e.g., pain at the site of injection; <1%) during the follow-up period, with no documented case of anaphylaxis [40].

c. **Benralizumab** (Fasenra®) is the newest biologics in the family of humanized mAbs, and it is being developed for the treatment of eosinophilic and allergic asthma [41]. Its acts by binding to the α-subunit of the IL-5 receptor (IL5Rα) on eosinophils and basophils.

In the SIROCCO [42] and CALIMA [43] trials, both phase III trials, benralizumab significantly lowered the annual exacerbation rate in patients with uncontrolled asthma (despite high-dose ICS plus LABA treatment) and a blood eosinophil count of >300 cells/μL. The safety of the drug was also tested, and it was found to be well tolerated. Following these promising data, it was approved for use in Europe in the beginning of 2018. The most commonly reported side effect is mild to moderate nasopharyngitis [44]. FDA labels report a HSR (rash, urticaria) rate of 3% for patients receiving benralizumab and placebo therapy [41]. In these labels, the rate of injection site reactions was 2.2% for patients treated with benralizumab and 1.9% for those treated with placebo, with two cases of anaphylaxis [41]. Post-marketing recording and notification of side effects are currently ongoing.

5.3 Anti-IL-4/13

a. **Pitrakinra:** (Aerovant®) is a human recombinant protein that competitively inhibits the IL-4Ra complex, thus showing antagonism to IL-4 and IL-13 [45]. In phase II studies, FEV1 was measured 4–10 h after an allergen challenge in patients with atopic asthma (46), and patients treated with pitrakinra showed a lesser decrease in FEV1 than did those treated with placebo [46]. Moreover, improvements in pulmonary function test findings, decreased exhaled nitric oxide levels, and decreased allergic responses were reported [46]. Phase IIb studies of this drug, which can be taken via a dry-powder inhaler or subcutaneously, are ongoing [45].

b. **Dupilumab** (Dupixent®) is a fully human mAb that can be subcutaneously administered. It binds to the IL-4Ra complex (also inhibits the effects of both IL-4 and IL-13) [47]. In a recent randomized, double-blind, phase III study, subcutaneous administration of dupilumab 200–300 mg (once every two weeks) significantly decreased the asthma exacerbation rate in patients with severe uncontrolled asthma and type 2 inflammation [47]. In another study, placebo and dupilumab showed no significant differences in the rate of mild and severe adverse events, death, drug discontinuation due to side effects, and incidence of upper respiratory tract infections, influenza, and bronchitis [48]. However, dupilumab was associated with an increased risk of injection site reactions [48]. This BD has been approved for use in the treatment of atopic dermatitis, and its use for severe asthma was approved by the FDA in 2018.

5.4 Anti-IL-13

a. **Lebrikizumab** is a new humanized IgG4 mAb that can be subcutaneously administered. It specifically inhibits IL-13 activity [49]. This drug was administered to patients with uncontrolled asthma, and FENO significantly decreased in the high periostin group (4.3%) compared with that in the low periostin group (34.4%) [49]. In a phase III study of the drug, no clinically meaningful decrease in the asthma exacerbation rate could be found in patients with high biomarker levels (periostin ≥50 ng/mL or blood eosinophils ≥300 cells/μL) [50]. Moreover, in a study by Korenblat et al., 12 weeks of treatment for patients with mild-to-moderate asthma did not result in adequate improvements in the results of prebronchodilator lung function tests [51].

b. **Tralokinumab** is a mAb that acts on IL-13, which is still being studied today. The results of a previous study revealed that, despite a consistent improvement in FEV1 in the FENO-high group, there was no possibility of a significant clinical benefit in patients with severe uncontrolled asthma [52]. A promising biomarker to predict the responsiveness to anti-IL-13 treatment has been found, and further studies are underway [53]. It is necessary to investigate the effects of this drug on different asthma phenotypes.

5.5 Anti-IL-17

Secukinumab and Brodalumab are monoclonal antibodies that target IL-17A and IL-17RA signaling, respectively. A phase II trial of the efficacy and safety of secukinumab treatment for asthma has been completed (NCT01478360), and the results are expected. On the other hand, a phase II trial of brodalumab (NCT01902290) was terminated because of the lack of efficacy in a predetermined

intermediate analysis. Both drugs are approved and presently used for the treatment of moderate to severe plaque psoriasis.

5.6 Anti-IL-9

Enokizumab (Medi-528), which is a mAb against IL-9, is defined as a T-cell and mast cell growth factor [54]. It was initially tested in animal models of asthma and was shown to alleviate the disease [54]. Subsequently, a double-blind, multicenter study involving 329 human adults was conducted [55], and the results revealed that the addition of this drug to existing anti-asthma drugs does not improve FEV1 values, decrease the asthma exacerbation rate, or improve ACQ scores. This observation was surprising, considering the very promising initial results. The main reason for this discrepancy is thought to be the heterogeneity of the study patients and the lack of differentiation between asthma subtypes [55].

5.7 Anti-epithelial cell-derived cytokine

Tezepelumab is a human mAb specific for TSLP, which is an epithelial cytokine. TSLP is considered to play a critical role in the onset and progress of airway inflammation. In a study by Corren et al., 52-week treatment with this BD significantly decreased the asthma exacerbation rate, independent of the blood eosinophil count [56]. Moreover, the prebronchodilator FEV1 at 52 weeks was higher in all tezepelumab groups than in the placebo group (mean, 110–150 mL) [56]. This is a very promising drug for noneosinophilic, uncontrolled asthma, and phase III studies (NCT03927157, and NCT03347279) are currently ongoing.

5.8 Prostoglandin DP2 receptor antagonist

Fevipiprant and Timapiprant is a promising biologics has been set for new biological treatments in allergic asthma. This target is prostaglandin D2 (PGD2) which acts through the DP2 receptor, also known as chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTh2). DP2 is a G-protein-dependent receptor that mediates activation and migration of Th2 cells and eosinophils at the center of allergic and inflammatory processes.

Fevipiprant is a powerful, reversible and highly selective DP2 receptor antagonist that can be used orally, targeting PGD2 directly [57]. In phase 2 studies performed in patients with severe uncontrolled eosinophilic asthma, the rate of sputum eosinophils decreased, 160–207 ml increase in FEV1 level and Asthma Control Questionnaire scores was obtained [58]. Phase III studies (NCT02555683 and NCT02563067) was completed and the results are expected. If positive results are obtained in these studies, it can be thought that this oral treatment would be an alternative to the biological treatments and would be easier to access.

Timapiprant (OC000459), which also affected the same receptor, showed 95 ml FEV1 increase in mild to moderate allergic asthma compared to placebo, and in the post hoc analysis, 220 ml increase was reported in FEV1 compared to placebo when atopic eosinophilic uncontrolled asthma subjects were selected [59]. No serious drug-related side effects were reported in the same study.

6. Conclusion

In summary, BDs play an important role in the treatment of many lung diseases. Recent advances in our knowledge of asthma pathologies, the role of cytokines,

allergen-directed immune responses, and disease phenotyping have resulted in the identification of numerous potential and specific targets for BDs. Monoclonal antibodies targeting IgE, IL-5 and IL-4/IL-13 have demonstrated significant improvements in asthma control such as reduce asthma exacerbations and improve lung functions [60]. In addition, long-term benefits such as reduced need for oral corticosteroids and control medications, reduction in asthma symptoms, improving quality of life, and reduced loss of work capacity have been demonstrated [7–9]. For the future, there is a need for new biomarkers to identify asthma patients with Th2-low endotype and thus new BDs that affect inflammatory pathways [60].

On the other hand, anti-IL-9 and anti-IL-17 treatments showed no positive results in terms of clinical benefits [55]. Meanwhile, anti-TSLP and anti-PGD2 treatment has shown very promising results, and the results of phase III studies are awaited. However, because of the increasing number of BDs and associated studies, it has become very difficult to update treatment guidelines on a regular basis; this issue and personalized treatment options needs to be resolved in future. However, after the endotypes and phenotypes are classified, investigation of the effects of these drugs may yield different results.

Conflict of interest

The authors declare no conflict of interest.

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