Biological therapies targeting the type 2 inflammatory pathway in severe asthma (Review)

ARIADNA PETRONELA FILDAN[1], RUXANDRA-MIOARA RAJNOVEANU[2], ROXANA CIRJALIU[1], IONELA POHRIB[1], EMANUELA TUDORACHE[3], ADRIAN COSMIN ILIE[3], CRISTIAN OANCEA[3] and DOINA TOFOLEAN[1]

[1]Faculty of Medicine, Ovidius University, Constanța 900527; [2]Department of Pneumology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca 400371; [3]Department of Pneumology, Victor Babes University of Medicine and Pharmacy, Timisoara 300041, Romania

Received May 17, 2021; Accepted August 3, 2021

DOI: 10.3892/etm.2021.10698

Abstract. Asthma is a variable chronic respiratory disease characterized by airway inflammation and hyperresponsiveness, bronchoconstriction, and mucus hypersecretion. While most patients with asthma achieve good control of the disease, 5-10% experience severe symptoms and recurrent exacerbation despite the maximal offered therapy with inhaled corticosteroids and long acting bronchodilators. In previous years, novel biological therapies have become available, and various asthma phenotypes that are characterized by specific biomarkers have been identified. Currently approved biological agents target inflammatory molecules of the type 2 inflammatory pathway, and are effective at decreasing the frequency of asthma attacks, controlling symptoms and decreasing use of systemic steroids. The present study reviewed the effectiveness and safety profile of the currently approved biological drugs and provided an overview of the assessment of patients with severe asthma who are potentially suitable for biological therapy, in order to help clinicians to select the most appropriate biological agent.

Contents

Correspondence to: Professor Ruxandra-Mioara Rajnoveanu, Department of Pneumology, Iuliu Hatieganu University of Medicine and Pharmacy, 6 BP Hasdeu Street, Cluj-Napoca 400371, Romania
E-mail: ruxandra.rajnoveanu@umfcluj.ro

Key words: biological therapy, severe asthma, biomarkers, monoclonal antibodies, phenotype

1. Introduction

Asthma is a heterogeneous disorder characterized by chronic airway inflammation, airway hyperresponsiveness, bronchoconstriction and mucus hypersecretion, which manifests with respiratory symptoms and limited expiratory airflow that vary in intensity and duration (1). Asthma is the most common chronic respiratory disease, affecting ~339 million people worldwide in 2018 (2). Despite a reduction by ~half in asthma-associated disability and mortality reported in a number of higher income countries, such as the United States of America, Canada, United Kingdom, France, Germany and Japan from 2001-2005 to 2011-2015 (1), which is primarily attributed to the use of inhaled corticosteroid (ICS) therapy, an extensive worldwide disparity remains in years of life lost because of asthma (3).

While most patients with asthma achieve good control of the disease in terms of both the symptom burden (asthma symptoms, sleep disturbance and limited ability to exercise) and the risk of poor outcomes (limited lung function, frequent exacerbation, mortality and medication side-effects) (4,5), 5-10% experience severe symptoms and recurrent exacerbations despite maximum dose treatment with inhaled glucocorticoids and long-acting β2-agonists (LABA) (6). These patients are defined as having severe asthma and are under consideration for alternative therapies. In severe asthma, stepped care approaches in therapy are frequently ineffective, most likely reflecting asthma heterogeneity and indicating that a treatment strategy of 'one size fits all' is not efficient in maintaining optimum control of the disease. The characteristics of severe asthma result in decreased responsiveness to usual medication and require alternative therapies with higher specificity that target the mechanisms underlying the increased severity (7).

To achieve good control of asthma, novel treatments should preferably target the pathophysiological mechanism responsible for controlling disease severity and altering the responsiveness to usual therapies in most patients (4). Several pathways have garnered attention and led to the development of novel targeted interventions. Of interest has been the use of monoclonal antibodies targeting components of type 2 (T2) airway inflammation (6). To ensure a good selection of patients

for biological therapy trials, a careful phenotype assessment is required with consideration to differentiate the two major phenotypes: T2-high and -low airway inflammation (8,9), based on the degree of T2 inflammation. Type 2 inflammation involves Type 2 (Th2) lymphocytes ($CD4^+$) and the innate lymphoid cells group 2 (ILC2) that secrete proteins, such as IL-4, -5, -13, and IgE, resulting in the recruitment of cells, such as eosinophils, basophils and mast cells into the airways (8). Non-T2 asthma is defined as asthma without features of T2 asthma. The definition is arbitrary and is generally based on the presence of neutrophils in sputum, or the absence or normal levels of eosinophils or other T2 markers in sputum (paucigranulocytic), airway biopsies or in blood (10). Current approved biological agents target T2-high severe asthma, which clinically manifests with a combination of sputum eosinophilia, peripheral eosinophilia and/or elevated fractional exhaled nitric oxide (FeNO) (11,12). While relatively novel biological agents, such as mepolizumab, benralizumab and reslizumab, target IL-5 or IL-5 receptor (IL-5R), and dupilumab targets IL-4Rα signaling, previous biological agents, such as omalizumab, target IgE (13).

The present study aimed to review the effectiveness and safety profile of currently approved biological agents or those under investigation, and to provide an overview of the assessment of patients with severe asthma who are potentially suitable for biological therapy, to help clinicians select the most appropriate biological agent for managing T2 severe asthma phenotypes (Fig. 1).

2. Pathophysiology of severe asthma

Asthma is a heterogeneous, chronic inflammatory airway disease with complex pathophysiological mechanisms that impact clinical outcomes, including drug response (14,15). Knowledge of the various asthma phenotypes and their different pathophysiology is continuously growing. Nevertheless, the pathways and underlying mechanisms of severe asthma pathogenesis are not yet completely understood.

There are two major groups of asthma phenotypes that can be differentiated by the inflammatory pathway involved, namely T2 or T2-high (eosinophilic) and non-T2 or T2-low phenotypes (16). T2 or T2-high asthma is characterized by T2 inflammation involving T helper 2 (Th2) lymphocytes ($CD4^+$), which drives eosinophilic airway inflammation by producing abundant quantities of proteins such as IL-4, IL-5, IL-13 and IgE. In the past decade, evidence has demonstrated that the innate lymphoid cells group 2 (ILC2) plays an early key role in augmenting T2 inflammatory responses in the airway (6,8,9,17). Thus, the terminology has changed from 'Th2-high' to 'T2-high', reflecting the role of innate immunity, along with $CD4^+$ cells, in the pathophysiology of asthma. T2-high asthma encompasses several subtypes in both children and adults, such as early-onset allergic and late-onset eosinophilic asthma, and aspirin-exacerbated respiratory disease (18).

Non-T2 or T2-low asthma is less well characterized (10); Th1 and Th17 cells, neutrophils and proteins, such as IL-1β, IL-6, IL-8, IL-17A/F, TNF-α and IFN-γ, are involved in its pathobiology. In addition to inflammatory biomarkers, non-T2 asthma may also be driven by irregular neuronal activation as well as structural abnormalities involving airway smooth muscle (10). Non-T2 asthma is characterized by neutrophilic or paucigranulocytic inflammation and a lack of response to corticosteroid therapy (10,18). Severe neutrophilic asthma is associated with chronic infection with atypical bacteria, smoking, obesity and poorly understood underlying smooth muscle abnormalities (18).

This division of the patterns of inflammation is mostly arbitrary and it is likely that mixtures of both pathways exist, at least to some degree, in most patients (7). Exposure to different triggers, such as allergens, viruses or other irritants, activates airway epithelial cells, which leads to secretion of specific cytokines [thymic stromal lymphopoietin (TSLP), IL-25 and IL-33] that initiate an inflammatory cascade resulting in asthma symptoms (8,19). The distinct inflammatory pathway initiated differs depending on the particular trigger, patient genotype, and the subtype of immune cells stimulated and their specific secreted mediators (19).

In the T2 immune response, Th2 cells and ILC2 are activated, and the secretion of the cytokines IL-4, IL-5 and IL-13 is stimulated (20,21). Allergens trigger a direct, immediate bronchoconstrictor response by activating mast cell mediator release. Mast cells are also a potential source of T2 cytokines (6). IL-4 induces Th0 cells to differentiate into Th2 cells and Ig class switch, resulting in IgE production by B cells. Subsequently, IgE binds to mast cells and triggers the release of toxic granules (6,8,19). IL-5 is the primary regulator of eosinophil proliferation, migration, activation and survival. IL-13 stimulates IL-4-induced IgE production by B cells, mucus production by goblet cells and goblet cell metaplasia; it may also have a direct effect on airway smooth muscle, increasing airway hyperresponsiveness (6).

T2 innate lymphoid cells and activation by the innate immune system of structural cells, such as the airway epithelium, are involved in the T2 inflammatory pathway independent of exogenous allergens, without atopy and with normal levels of serum IgE. This asthma pattern is associated with nasal polyposis and aspirin sensitivity (6,8,22). ILC2 cells produce more IL-5 and IL-13 compared with CD4 Th2 cells independent of allergen exposure (22). Various harmful external triggers (microbes, air pollutants or glycolipids) cause respiratory epithelial damage and increase epithelial cell production of the alarmins IL-25, IL-33 and TSLP. Alarmins bind to the receptors on T2 ILC2 and activate them to produce T2 cytokines (6,22,23). Production of leukotriene E4 and prostaglandin D2 by recruited and activated eosinophils and mast cells may also stimulate ILC2 cells, leading to a continuous cycle of T2 inflammatory response (6), in which eosinophils serve a key role in two major events: Hyperresponsiveness and remodeling of the airways. Persistent eosinophilic inflammation maintained by these pathways leads to constant damage at the bronchial level. This airway damage is attributed to the degranulation of eosinophils and the release of toxic proteins, such as major basic protein, eosinophil peroxidase (EPO), eosinophil cationic protein and eosinophil-derived neurotoxin (6,8). In addition, the regeneration process of the airway can have harmful consequences, including goblet cell hyperplasia, smooth muscle hypertrophy and deposition of extracellular matrix proteins, which causes membrane thickening and fibrosis (24), resulting in airway mucus plugging

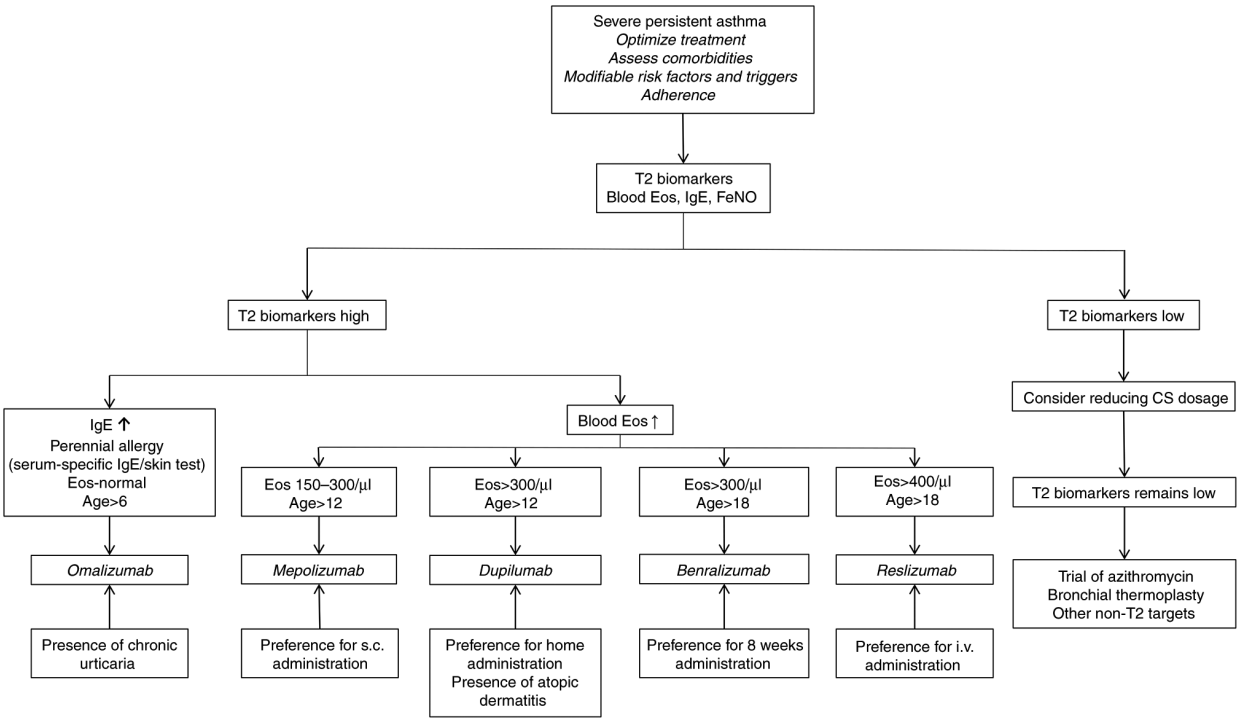

Figure 1. Primary biological drugs used to treat severe persistent asthma according to T2 biomarker profile. T2, type 2; FeNo, fractional exhaled nitric oxide; s.c., subcutaneous; Eos, eosinophils; i.v., intravenous; OCS, oral corticosteroid.

and airway wall edema. Recently, a cross-sectional analysis of CT scans of the lungs indicated that mucus plugging may be a particularly important mechanism in severe asthma, and identified EPO-associated changes in mucin structure resulting in abnormally sticky mucus as another key pathophysiological mechanism in severe asthma (6,25). Therefore inhaled corticosteroids and bronchodilators may become less effective, thus requiring novel specific therapies for patients with severe asthma.

3. Targeting T2 severe asthma phenotypes-currently approved treatments and biological drugs under investigation

Targeting IgE. Currently approved biological therapies for severe asthma are shown in Table I. Omalizumab [Xolair®] is a humanized monoclonal antibody that binds to IgE and prevents it combining with the IgE receptor on plasma cells (such as mast cells and basophils) (6,7). This blocking effect impedes mast cell activation and the subsequent production of inflammatory mediators when IgE is activated by allergens (7). Omalizumab for subcutaneous use was initially approved by the United States Food and Drug Administration (FDA) in 2003 as a biological therapy for severe allergic asthma in patients >12 years of age, and in 2016 received approval in patients >6 years of age who have moderate to severe persistent allergic asthma (26). Eligibility criteria for this biological agent are poor control using conventional asthma treatment, and allergic components revealed by a positive skin test or *in vitro* reactivity to a perennial aero-allergen, such as house dust mites, pollen and fungal mould (6,26). Furthermore, the therapeutic regime depends on levels of total IgE and patient weight [either once/month or every 2 weeks, subcutaneous (s.c.)].

Numerous clinical studies, and real-world observational studies, have demonstrated that omalizumab can decrease the frequency of exacerbations and decrease the need for additional medication, including ICS, but shows little improvement in lung function compared with high-dose combined ICS/LABA therapy (27-31). In a large study of severe asthma, Hanania *et al* (28) evaluated omalizumab in patients requiring high-dose combined ICS/LABA treatment, but still presenting with symptoms and ongoing exacerbations. The introduction of omalizumab in addition to high-dose ICS/LABA decreased asthma exacerbations (loss of asthma control requiring systemic corticosteroids) by 25%. Other trials with omalizumab have shown a significant decrease in asthma exacerbations of 35-60%, an 88% decrease in asthma-associated hospitalization in pediatric patients, as well as a decrease of ICS doses by >50% in a significant number of patients (27,29-31). In addition, it has been shown that omalizumab did not affect the frequency of exacerbations in patients with asthma receiving maintenance oral corticosteroid (OCS) treatment. Biomarkers, such as blood eosinophils and FeNO, have been reported to be representative of T2 inflammation, and high levels of these biomarkers [FeNO ≥19.5 parts per billion (ppb), peripheral blood eosinophils ≥260/μl or periostin ≥50 ng/ml] may indicate patients with the greatest potential clinical benefit from anti-IgE treatment (29). However, real-world studies suggested that eosinophil levels are not a good predictor of the potential decrease in exacerbations seen with omalizumab (31,32).

Previous studies have identified novel potential mechanisms of action of omalizumab in association with decreased viral-induced exacerbations of asthma by increasing viral clearance (33,34). The frequency of exacerbations occurring

Table I. Currently approved biological therapies for severe asthma.

Drug	Target	Administration	Patient age, years	Indications	Side effects	Peculiarities
Omalizumab	Circulating IgE	Every 2-4 weeks, s.c.	≥6	Moderate to severe persistent asthma; positive skin test or *in vitro* reactivity to perennial aeroallergen; symptoms inadequately controlled with ICS	Injection site reaction, fever, nosebleeds, joint pain, bone fractures, arm or leg pain, generalized pain, nausea, vomiting, stomach pain, headache, earache, dizziness, fatigue	IgE level and weight-based dosing
Reslizumab	IL-5 ligand	Every 4 weeks, i.v.	≥12	Severe eosinophilic asthma that remains uncontrolled despite maximal therapy with ICS plus another controller	Headache, asthma worsening, nasopharyngitis, upper respiratory tract infection, sinusitis, injection site reactions	Weight-based dosing
Mepolizumab	IL-5 ligand	Every 4 weeks, s.c.	≥12	Severe eosinophilic asthma that remains uncontrolled with ICS	Respiratory tract infection, bronchitis, worsening of asthma, headache, injection site reaction	
Benralizumab	IL-5 receptor α	Every 4 weeks, s.c.	≥12	Severe eosinophilic asthma (≥300 blood eosinophils/μl) inadequately controlled with ICS	Upper respiratory tract infection, worsening asthma, injection site reaction	Administration decreased to every 8 weeks after 3 doses
Dupilumab	IL-4 receptor α	Every 2 weeks, s.c.	≥12	Moderate to severe eosinophilic asthma or OCS-dependent asthma (FDA). Severe asthma with type 2 inflammation (increased blood eosinophils and/or raised FeNO levels) that remain inadequately controlled despite high-dose ICS plus another controller (EMA)	Allergic conjunctivitis, conjunctivitis, injection site reaction, ophthalmic inflammation, eye irritation	

s.c., subcutaneous; ICS, inhaled corticosteroid; i.v., intravenous; OCS, oral corticosteroid; FDA, Food and Drug Administration; FeNO, fractional exhaled nitric oxide; EMA, European Medicines Agency.

in spring and fall was shown to be significantly decreased by omalizumab in school-age children with moderate to severe asthma and a history of exacerbations (33). The effect of viral-induced exacerbations may be mediated by the increased production of IFN-α by plasmacytoid dendritic cells (6,33,34). Omalizumab was developed to target IgE in allergic asthma and there have been few, limited studies on omalizumab in non-allergic asthma (6,34).

The most common adverse events (AEs) of omalizumab include injection site reaction, fever, nosebleeds, joint pain, bone fractures, arm or leg pain, generalized pain, nausea, vomiting, stomach pain, headache, earache, dizziness and fatigue (26,29-37). Risk of anaphylaxis may occur up to 24 h after any dose and treatment should be discontinued if severe hypersensitivity reaction occurs (36,37). Malignant neoplasms have been reported, with a rate of 0.5% compared with a rate of 0.2% in controls in clinical trials (29-32). It is recommended to monitor patients at high risk for geohelminth infection while taking omalizumab, as well as for eosinophilia, vasculitic rash, neuropathy and/or cardiac complications, especially upon decreasing OCS dose (26,37).

Omalizumab is also indicated for the treatment of patients >12 years of age with chronic spontaneous urticaria (CSU) who remain symptomatic despite H1 antihistamine treatment (37). The association of moderate to severe persistent allergic asthma and CSU may be a strong argument for choosing the treatment with omalizumab, compared with other treatments (Fig. 1) (36).

Long-term studies of omalizumab demonstrate that it is efficient and generally well-tolerated, and is recommended as initial anti-T2 treatment of choice for patients (both adults and children >6 years old) with severe asthma and underlying allergic sensitization (35-37).

Targeting T2 cytokines.

Anti-IL-5 and IL-5Rα blockers. Anti-IL-5 and anti-IL-5R are two currently available and effective interventional strategies to regulate eosinophil involvement in airway inflammation and asthma symptoms (5,6,35,36,38). Anti-IL-5R may also have an inhibitory effect on basophils, as these cells also express IL-5R (5). IL-5 is produced by Th2 lymphocytes, ILC2 and mast cells, regulates final differentiation of eosinophils, and participates in the recruitment of eosinophils to the airway and their activation (5,6). Mepolizumab and reslizumab are monoclonal antibodies directed against IL-5 that prevent activation of IL-5R on eosinophils. Benralizumab is also a monoclonal antibody but is directed against IL-5R where antibody-dependent cell-mediated cytotoxicity (ADCC) induces cell apoptosis (5,6). Both treatment strategies efficiently and safely decrease levels of circulating and airway eosinophils (7,35,36,38).

Mepolizumab [Nucala®] is a recombinant, humanized monoclonal anti-IL-5 antibody (IgG1κ) specifically targeting the α subunit, thereby blocking the interaction between the α-subunit and IL-5R on the eosinophil cell surface. Inhibiting the binding of IL-5 to eosinophils results in inactivation of eosinophil maturation, activation and growth (35,36,39). Mepolizumab has been approved as an add-on treatment for patients ≥12 (FDA) or ≥6 years old [European Medicines Agency (EMA)] with severe refractory eosinophilic asthma that has not been well controlled with previous treatments (38,39). Mepolizumab has a standard dose of 100 mg administered every 4 weeks, s.c. In the first randomized controlled trial (RCT) in patients with mild allergic asthma, Leckie *et al* (38) demonstrated that a single dose of mepolizumab (10 mg/kg) decreased blood eosinophil count for 16 weeks and sputum eosinophil count for ≤4 weeks. Furthermore, mepolizumab prevented increased blood eosinophil levels during the late-phase response following allergen exposure. However, mepolizumab showed no effect on lung function, airway response to allergen or airway responsiveness.

In the Dose Ranging Efficacy and Safety with Mepolizumab severe asthma (DREAM) phase II RCT study of 616 patients with eosinophilic asthma, the efficacy and safety of administration of different doses of mepolizumab [75, 250 and 750 mg by intravenous (i.v.) injection] were assessed. Patients with a history of ≥2 exacerbations requiring systemic corticosteroids in the last 12 months, and those with evidence of eosinophilic airway inflammation at the study entry or documented within the previous year were used. Evidence to demonstrate eosinophilic inflammation of the airways included: i) Blood eosinophil count of 300 cells/μl; ii) sputum eosinophil count ≥3%; iii) FeNO 50 ppb or iv) prompt deterioration following ≤25% decrease in inhaled or oral corticosteroid (CS) maintenance dose (40). The trial demonstrated a decrease in asthma exacerbation by ~50% in response to all doses of mepolizumab. Only blood eosinophilia and history of recurrent asthma exacerbation were associated with a beneficial effect following treatment. A blood eosinophil count of >150 cells/μl was associated with a beneficial effect on decreasing further asthma attacks, but mepolizumab exhibited no significant effect on symptoms, FeNO, quality of life or lung function. Similar results regarding the risk of asthma exacerbation were reported in a phase III trial in patients with severe eosinophilic asthma (41). The efficacy of 100 mg mepolizumab dose given monthly via s.c. injection was demonstrated in patients with severe asthma, blood eosinophil count of >150 cells/μl (and/or >300 cells/μl within the previous year) and ≥2 exacerbations in the previous year. The study both confirmed earlier results on exacerbation and also demonstrated a beneficial effect on lung function, asthma symptoms and quality of life (41). In the Steroid Reduction with Mepolizumab Study phase III trial, which included patients with severe asthma requiring daily maintenance OCS therapy, mepolizumab decreased the required OCS dose by 50% while maintaining symptom control, and decreased the rate of asthma exacerbation by 32% compared with placebo ($P<0.05$) (42).

Through combined analysis of the aforementioned studies (38,40-42), mepolizumab has demonstrated a positive long-term safety profile. The rate of AEs has been reported to be low over the trial period or when compared with previous placebo-controlled studies (38,40-43). Respiratory tract infection (67%), bronchitis (21%), worsening of asthma (27%), headache (29%) and injection site reactions (12%) were the most common AEs reported. Hypersensitive or systemic allergic reactions were recorded in ~2% of patients and <1% experienced a non-allergic systemic reaction; there were no reports of anaphylaxis (associated with mepolizumab therapy) (16,39,43), and no malignancy risk associated with mepolizumab is known in humans (39).

Reslizumab [Cinqair(R)] is a recombinant humanized monoclonal antibody (IgG4κ) that, like mepolizumab, targets IL-5 to prevent its binding with IL-5R (36). Reslizumab has been approved by the FDA (44) and EMA (45) as an add-on treatment for patients ≥18 years with severe eosinophilic asthma that is still uncontrolled despite patients receiving maximal therapy with ICS and another controller (16). Reslizumab is used to treat patients with peripheral blood eosinophils of ≥400 cells/μl and ≥3 asthma exacerbations during the past 12 months; it is administered by i.v. injection once every 4 weeks at a dose of 3 mg/kg (16,36,44,45).

In a phase III RCT designed to establish the cut-off level of eosinophils that should be used to select patients with asthma for reslizumab treatment, Corren *et al* (46) showed that, in patients with ≥400 eosinophils/μl, treatment led to significant improvements in symptom control, lung function and the need for rescue medication. Another phase III trial demonstrated that the administration of reslizumab as an add-on therapy to ICS with or without other controllers significantly decreased the rate of asthma exacerbation compared with placebo (by 34%; P<0.0001) (47). Murphy *et al* (48), in an open-label study evaluating the efficacy and safety of reslizumab for up to 24 months, showed that both patients receiving reslizumab before the study started and reslizumab-naive patients reported improvement in asthma control and lung function through the whole study period. The most common AEs in both categories of patients were asthma worsening, upper respiratory tract infection, headache and injection site reactions. Parasitic and opportunistic infections and anaphylaxis were not reported. Reslizumab differs from mepolizumab in two ways: It is administered by i.v. injection based on weight (3 mg/kg/4 weeks) and it has a higher cut-off value for eosinophils (≥400 cells/μl).

Benralizumab [Fasenra®] is a humanized afucosylated monoclonal antibody against IL-5Rα. Unlike mepolizumab and reslizumab, it induces eosinophil apoptosis via ADCC involving natural killer cells (49,50), resulting in a more profound and potentially earlier onset of eosinophil depletion (6). However, it is difficult to estimate whether there is a clinical benefit (36). A potential advantage of the rapid decrease in circulating eosinophil number may be observed in patients who present with acute severe exacerbation associated with eosinophilia (6,36).

Benralizumab has been approved as an add-on therapy for inadequately controlled severe eosinophilic asthma in subjects >12 (FDA) or 18 years old (EMA) with ≥300 blood eosinophils/μl (51,52) and 30 mg/4 weeks (s.c.) is administered for the first 3 months and then every 8 weeks. In two pivotal phase III RCTs: i) Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO) (53) and ii) benralizumab, an anti-IL-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA) (54), benralizumab (30 mg/4 or 8 weeks) was administered as an add-on therapy to a large number of patients with severe asthma and compared with a placebo. A significant decrease in asthma exacerbation rate of 45-51% was observed in patients with peripheral blood eosinophil count ≥300 cell/μl and the forced expiratory volume in one second (FEV1) values were also significantly improved (by up to 159 ml) compared with the control (53). Another phase III RCT, the ZONDA trial (Efficacy and Safety Study of Benralizumab to Reduce OCS Use in Patients With Uncontrolled Asthma on High Dose Inhaled Corticosteroid Plus LABA and Chronic OCS Therapy) (55) investigated the effects of benralizumab therapy for 24 weeks on OCS necessity in patients with OCS-dependent asthma. The median reduction in OCS dose was 75% for patients treated with benralizumab compared with 25% following treatment with a placebo. In addition, compared with the placebo, the annual exacerbation rate was decreased by 55% but there was no improvement in lung function. In the the safety trial for benralizumab performed by Busse *et al* (56), the authors showed that the efficiency, safety and tolerability profile of benralizumab maintained for 2 years was similar to that observed over 1 year in previous RCTs (53,54). The AEs that were most frequently reported included upper respiratory tract infection (14-16%) and worsening asthma (7-10%). Parasitic infection was not reported, and the hypersensitivity reactions were similar between study groups (53,54,56).

IL-4Rα blockers. Dupilumab [Dupixent®] is a fully human monoclonal antibody directed against IL-4Rα, which is common to both IL-4 and IL-13, and therefore able to inhibit the signaling of both of these ILs (6,16). Dupilumab is approved by the FDA (57) as an add-on therapy for patients aged ≥12 years with moderate to severe eosinophilic asthma or asthma that is dependent on OCS, and by the EMA (58) as an add-on treatment for patients with severe asthma aged ≥12 years with T2 inflammation characterized by increased blood eosinophils and/or raised FeNO levels that remain inadequately controlled despite high-dose ICS plus another controller. Dupilumab (s.c.) can be administered at an initial dose of 600 mg (two 300 mg injections) followed by 300 mg/2 weeks (recommended only for patients with OCS-dependent asthma), or at an initial dose of 400 mg (two 200 mg injections) followed by 200 mg/2 weeks. Wenzel *et al* (59) in a phase II dose-ranging trial involving patients with severe uncontrolled asthma, reported that all types of administration scheme (200 or 300 mg every 2 or 4 weeks) resulted in improved asthma control and FEV1, and fewer severe exacerbations compared with placebo. Although these results were reported in all patients, those with ≥300 eosinophils/μl showed the greatest decline in annual severe exacerbation rate and improvement in lung function.

Liberty Asthma Quest phase III RCT (60) confirmed the efficacy and safety profile of add-on dupilumab (200 or 300 mg/2 weeks for 52 weeks; s.c.) in patients aged ≥12 years with moderate to severe uncontrolled asthma and a history of exacerbations. Similar to the aforementioned study, the greatest benefits, such as decreased exacerbation rate, and rapid and maintained improvement in FEV1, were observed in patients with elevated T2 biomarkers at baseline (blood eosinophils ≥150 cells/μl or FeNO ≥25 ppb), although the potential efficacy of dupilumab in T2-low disease was not confirmed. This study also demonstrated a favorable safety profile of dupilumab. The AE rates were similar across the intervention groups (81.0%). The most common serious AE was pneumonia (8.2% in the treatment group and 8.4% in the placebo group). The most

frequent AE was injection site reaction (15.2% in the low-dose dupilumab group, 18.4% in the high-dose dupilumab group vs. 5.4 and 10.3%, respectively, in the matched placebo groups). Allergic conjunctivitis, conjunctivitis, injection site reaction, ophthalmic inflammation and eye irritation may occur during therapy with dupilumab (59,60).

Liberty Asthma Venture phase III RCT (61) demonstrated the efficiency of dupilumab in decreasing the rate of asthma exacerbations (by 59.3%) and the need for OCS, while maintaining asthma control and improving lung function. The rate of AEs during the study period was similar in the two groups (62% in the treatment arm; 64% in the placebo arm). According to post hoc analysis of phase II trials, treatment with dupilumab at 200/300 mg/2 weeks was associated with a significant improvement in asthma symptom control, decreased rate of severe exacerbation and improved lung function compared with placebo, regardless of the exacerbation history of the patient (62).

Another recent post hoc analysis of the Liberty Asthma Quest study (63) demonstrated that dupilumab at 200/300 mg/2 weeks significantly decreased the rate of severe exacerbation and improved asthma control and lung function in patients with uncontrolled, moderate to severe asthma with evidence of allergic asthma, and in patients without an allergic component compared with the placebo ($P<0.01$).

Dupilumab is also indicated for the treatment of patients aged ≥6 years with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable (64). As shown in Fig. 1, a patient with moderate to severe asthma who also has moderate to severe atopic dermatitis would likely benefit most from dupilumab therapy (36).

Anti-IL-13. In a RCT involving patients with moderate to severe asthma, lebrikizumab, a monoclonal antibody targeting IL-13 (65), demonstrated only a small improvement in lung function (66). According to the result of the phase IIb study conducted by Hanania *et al* (67), the greatest benefit from lebrikizumab therapy was observed in patients with high serum periostin concentration (known biomarker of increased IL-13 activity within the airway). The treatment with lebrikizumab reduced the rate of asthma exacerbations, which was more pronounced in the periostin-high patients (all doses: 60% reduction) than in the periostin-low patients (all doses: 5% reduction); no dose-response was evident. Lung function showed a modest improvement, with greatest increase in FEV1 in periostin-high patients (all doses: 9.1% placebo adjusted improvement) compared with periostin-low patients (all doses: 2.6% placebo-adjusted improvement).

Another IL-13 monoclonal antibody, tralokinumab, has showed unimpressive effects compared with other biological agents (68,69), and this class of biological drugs has not received regulatory approval.

Targeting alarmins (TSLP, IL-25, IL-33). Alarmins are key cytokines involved in both T2 and non-T2 mechanisms of airway inflammation in asthma. Currently, several trials are evaluating different molecules targeting these cytokines (6).

Tezepelumab is a human monoclonal antibody directed against TSLP produced by epithelial cells in response to injury to dendritic cells, CD4 T cells, CD8 T cells, mast cells, B cells, eosinophils, basophils and ILC. Tezepelumab impairs the interaction of TSLP with TSLP receptor and prevents its downstream effects (6,36). TSLP is responsible for activating innate immune, dendritic, T and B cells, and induces production of cytokines by antigen-specific Th2 cells (36,70). In a phase IIb study by Corren *et al* (70), the effect of tezepelumab was evaluated in adult patients aged 18-75 years with uncontrolled asthma despite appropriate treatment with medium- to high-dose ICS plus LABA and a history of ≥2 asthma exacerbations requiring systemic glucocorticoids in the year before the start of the study. The patients were not selected based on specific markers of atopy, such as eosinophilia or high levels of total or specific IgE. The patients received either placebo or tezepelumab, administered subcutaneously, at a dose of 70 or 210 mg/4 weeks, or 280 mg/2 weeks. All dosage regimens showed a decrease in Th2 biomarkers (blood eosinophil count, FeNO and serum IgE), demonstrating an anti-inflammatory effect and suggesting inhibition of T2 cytokine production. Treatment with tezepelumab also showed a large decrease in the annualized asthma exacerbation rate and improvement in FEV1 compared with placebo. This effect on exacerbation was observed in patients with low FeNO and blood eosinophil levels, suggesting the involvement of TSLP in non-T2 airway inflammation.

Regarding drug-associated serious AEs, one patient who received low-dose tezepelumab reported pneumonia and stroke, while another patient who received medium-dose treatment reported Guillain-Barre syndrome. No anaphylactic reaction or identification of neutralizing antibodies was reported (70). The efficacy and safety of tezepelumab in severe, uncontrolled asthma patients are being investigated in a number of ongoing phase III RCTs, such as NAVIGATOR (ClinicalTrials.gov identifier, NCT03347279), SOURCE (ClinicalTrials.gov identifier, NCT03406078) and DESTINATION (ClinicalTrials.gov identifier, NCT03706079) (71-73).

IL-33 is also a potential target for biological therapy in asthma. IL-33, one of the members of the IL-1 superfamily, is an alarmin cytokine promoting inflammatory responses (74). IL-33 promotes the Th2-mediated immune response and further production of many pro-inflammatory cytokines, such as IL-4, IL-5 and IL-13. Furthermore, IL-33 promotes bronchial remodeling and lung fibrosis, causing further advancement of asthma (75). At phase 2 of the asthma clinical trial, the anti-IL-33 receptor monoclonal antibody is being investigated in subjects with moderately severe asthma and compared to the placebo fluticasone propionate/salmeterol combination and fluticasone propionate (ClinicalTrials.gov identifier, NCT03207243). Another clinical trial involving anti-IL-33 antibody in asthma patients is in a phase 1 clinical trial, and compares it to the placebo Dupilumab and fluticasone propionate (ClinicalTrials.gov identifier, NCT03112577).

Several biological agents against IL-33, such as GSK3772847 and REGN3500, are currently in different stages of development (76,77). A phase II asthma clinical trial (ClinicalTrials.gov identifier, NCT03207243) is investigating monoclonal anti-IL-33R in subjects with moderate and severe asthma compared with placebo, fluticasone propionate or fluticasone propionate/salmeterol combination (76). Another phase I clinical trial in patients with asthma is comparing

anti-IL-33 antibody with placebo, fluticasone propionate and dupilumab (ClinicalTrials.gov identifier, NCT03112577) (77).

4. Discussion

Along with other types of chronic respiratory disease, asthma, primarily the severe form, remains one of the most important health problems globally (1,78-81). The management of severe asthma has significantly changed during the past decade (1). In severe asthma, conventional treatments based on non-specific drugs, such as CS and bronchodilators, are often inefficient and should be replaced by personalized medicine based on the effective identification of different asthma phenotypes (1,6,36). The currently approved biological agents and those in development target these specific phenotypes (36). At present, there is no biological drug that is significantly more efficient than others for most patients with asthma (36). Therefore, selecting the adequate monoclonal antibody should be carefully individualized to each patient (Fig. 1).

Before starting biological therapy, it is necessary to correctly diagnose severe asthma, optimize and improve adherence to the current treatment, assess comorbidities and exclude potential confounding pathologies that mimic some of the symptoms of asthma, such as chronic obstructive pulmonary disease, laryngeal dyskinesia, bronchiectasis and hypersensitivity pneumonitis (16,82,83). The most common comorbidities associated with asthma, which require adequate treatment, are rhinosinusitis, gastroesophageal reflux disease, aspiration, cardiovascular comorbidities, obstructive sleep apnea and upper respiratory tract infection (16).

According to GINA recommendations, if available and affordable, an add-on biologic T2 agent, such as anti-IgE, anti-IL-5/5R or anti-IL-4R, should be considered in patients with severe asthma who show typical biomarkers of T2 airway inflammation (1). The T2-high phenotype is characterized by eosinophilic airway inflammation (8,16), while the T2-low phenotype is characterized by neutrophilic or paucigranulocytic airway inflammation (10,18). The most common biomarkers used for non-invasive assessment of severe asthma include peripheral blood eosinophil count, serum IgE and FeNO (1,8,16). The only evidence-based biomarker of the T2-low phenotype is sputum neutrophil count (6). To select the most effective and appropriate biological agent to treat severe asthma, not only the disease characteristics, and patient age and preference, should be considered, but also the indications and posology for biological therapies approved by international agencies and/or national guidelines, as well as biomarkers (as predictors of response) (1,36). Each biological agent has unique dosing features, which can be a key factor in determining which agent is best to use (36). For example, dosing of omalizumab is based on serum IgE levels and weight. Reslizumab and mepolizumab are administered every 4 weeks, while benralizumab, following an initial loading period, is administered every 8 weeks. Certain patients may prefer i.v. administration and therefore would rather use reslizumab. Dupilumab can be self-administered at home by the patient, but dosing is every 2 weeks; while this may be suitable for patients who are physically active and able to correctly self-administer the treatment, others who are less active or less confident in self-administration may require treatment from a health care professional (36).

At present, due to a lack of direct comparison trials, there are no recommendations for choosing among the currently approved IL-5 pathway-targeting biological agents. Therefore, in the absence of head-to-head RCTs, several network meta-analyses have been performed (84-86). A recent matching-adjusted indirect comparison meta-analysis suggested that mepolizumab and benralizumab have similar efficiency profiles (84). Another network meta-analysis indicated that reslizumab was more effective than benralizumab in patients with moderate to severe eosinophilic asthma with a history of ≥2 exacerbations in the previous year (85), whereas other indirect treatment comparisons indicated that, in comparison with reslizumab and benralizumab, mepolizumab improved disease control and decreased risk of asthma exacerbations regardless of the blood eosinophil threshold (86). A recent meta-analysis suggested that although all current biological agents were effective in improving lung function and decreasing the asthma exacerbation risk when compared with placebo, dupilumab was significantly more efficient compared with omalizumab in decreasing the risk of exacerbation, while there was no difference between reslizumab, mepolizumab, benralizumab and dupilumab. Furthermore, dupilumab was revealed to be significantly more effective than omalizumab, benralizumab and mepolizumab at improving FEV1, whereas omalizumab, benralizumab, mepolizumab and reslizumab showed similar improvements in FEV1 (87). By contrast, another arm-based network meta-analysis showed no significant difference between monoclonal antibodies regarding the effect on the rate of asthma exacerbation (88).

Regardless of the chosen biological therapy, a 4-month trial should be performed before asthma control assessment (4). In the case of a failure of biologic therapy associated with an inadequate biological effect of the treatment, a strong case could be made for switching biologic (4,6). There are several ongoing studies on biological drug switching in patients with severe asthma that is not well controlled (89-91). The results of the OSMO (Omalizumab Switch to MepOlizumab) study a multicenter, open-label, 32-week trial, demonstrated that patients with uncontrolled severe asthma receiving omalizumab showed an improvement in asthma control after switching to mepolizumab (89). A 24-week, multicenter prospective, open-label pilot study showed that patients with severe eosinophilic asthma and inadequate response to omalizumab reported a significantly improved asthma control after switching to reslizumab (90). Other preliminary findings also indicated decreased OCS maintenance dose and improved quality of life scores after switching to benralizumab in patients with sub-optimal response with mepolizumab (91).

To the best of our knowledge, only one study has investigated the effect of biological agent withdrawal in patients with severe asthma (92). The study showed the recurrence of severe eosinophilic asthma within 3-6 months of mepolizumab cessation following 12 months of continuous therapy. The first signal to return was elevated blood eosinophil levels, followed by sputum eosinophils and then asthma exacerbations.

However, how and when to switch or withdraw established biological agents and the duration of the treatment at which the patient should be characterized as either a responder or non-responder to biological agents are yet to be adequately determined. Clinical trials of biological agents targeting IL-6, IL-17 or IL-33 in patients with asthma with T2-low phenotypes are ongoing, but current data suggest that these patients should be treated with chronic macrolide, imatinib or bronchial thermoplasty (16).

5. Conclusion

The advent of biological therapy has revolutionized the management of severe asthma. The success of biological agents is primarily based on adequate selection of patients. Individual assessment of patients for allergic vs. eosinophilic asthma is possible by identifying measurable biomarkers that are predictive of treatment efficacy. The clinical effects of currently approved monoclonal antibodies are consistent, with a significant decrease in asthma exacerbation rate, and a less pronounced improvement in symptom control and lung function.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

APF, CO and DT contributed to the conception and design of the study. RC, IP, ET and ACI performed the literature review. APF wrote the first draft of the manuscript. RMR revised the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Global Initiative for Asthma. Global strategy for asthma management and prevention, 2021. Available from: https://ginasthma.org/gina-reports/. Accessed August 12, 2021.
2. The Global Asthma Report 2018. Auckland, New Zealand: Global asthma network. Available from: https://theunion.org/technical-publications/the-global-asthma-report-2018 http://globalasthmanetwork.org/. Accessed December 13, 2020.
3. D'Amato G, Vitale C, Molino A, Stanziola A, Sanduzzi A, Vatrella A, Mormile M, Lanza M, Calabrese G, Antonicelli L and D'Amato M: Asthma-related deaths. Multidiscip Respir Med 11: 37, 2016.
4. GINA Pocket Guide 2019. Difficult to treat and severe asthma in adults and adolescents. Available from: https://ginasthma.org/wp-content/uploads/2019/04/GINA-Severe-asthma-Pocket-Guide-v2.0-wms-1.pdf. Accessed September 10, 2020.
5. Munteanu LA, Fildan AP, Tudorache E, Fira-Mladinescu O, Frandes M, Timar B, Oancea C and Tofolean DE: Inhaler technique errors in Romanian patients with asthma-a multicenter study. Patient Prefer Adherence 13: 1401-1414, 2019.
6. Pavord ID, Shrimanker R and Hanania NA: Biologics targeting type 2 inflammation. In: Severe Asthma (ERS Monograph). Chung KF, Israel E and Gibson PG (eds). European Respiratory Society, Sheffield, pp285-303, 2019.
7. Busse WW: Biological treatments for severe asthma: A major advance in asthma care. Allergol Int 68: 158-166, 2019.
8. Robinson D, Humbert M, Buhl R, Cruz AA, Inoue H, Korom S, Hanania NA and Nair P: Revisiting type 2-high and type 2-low airway inflammation in asthma: Current knowledge and therapeutic implications. Clin Exp Allergy 47: 161-175, 2017.
9. Stokes JR and Casale TB: Characterization of asthma endotypes: Implications for therapy. Ann. Allergy Asthma Immunol 117: 121-125, 2016.
10. Sze E, Bhalla A and Nair P: Mechanisms and therapeutic strategies for non-T2 asthma. Allergy 75: 311-325, 2020.
11. McGregor MC, Krings JG, Nair P and Castro M: Role of biologics in asthma. Am J Respir Crit Care Med 199: 433-445, 2019.
12. Krings JG, McGregor MC, Bacharier LB and Castro M: Biologics for severe asthma: Treatment-specific effects are important in choosing a specific agent. J Allergy Clin Immunol Pract 7: 1379-1392, 2019.
13. Tan R, Liew MF, Lim HF, Leung BP and Wong WSF: Promises and challenges of biologics for severe asthma. Biochem Pharmacol 179: 114012, 2020.
14. Eger KA and Bel EH: The emergence of new biologics for severe asthma. Curr Opin Pharmacol 46: 108-115, 2019.
15. Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, Cullinan P, Custovic A, Ducharme FM, Fahy JV, *et al*: After asthma: Redefining airways diseases. Lancet 391: 350-400, 2018.
16. Rogliani P, Calzetta L, Matera MG, Laitano R, Ritondo BL, Hanania NA and Cazzola M: Severe asthma and biological therapy: When, which, and for whom. Pulm Ther 6: 47-66, 2020.
17. De Ferrari L, Chiappori A, Bagnasco D, Riccio AM, Passalacqua G and Canonica GW: Molecular phenotyping and biomarker development: Are we on our way towards targeted therapy for severe asthma? Expert Rev Respir Med 10: 29-38, 2016.
18. Kuruvilla ME, Lee FE and Lee GB: Understanding asthma phenotypes, endotypes, and mechanisms of disease. Clin Rev Allergy Immunol 56: 219-233, 2019.
19. Bernstein JA and Panettieri R Jr: Treatment of severe, uncontrolled eosinophilic asthma: Where we are heading. J Asthma 56: 459-472, 2019.
20. Voehringer D, Reese TA, Huang X, Shinkai K and Locksley RM: Type 2 immunity is controlled by IL-4/IL-13 expression in hematopoietic non-eosinophil cells of the innate immune system. J Exp Med 203: 1435-1446, 2006.
21. Chang YJ, Kim HY, Albacker LA, Baumgarth N, McKenzie AN, Smith DE, Dekruyff RH and Umetsu DT: Innate lymphoid cells mediate influenza-induced airway hyper-reactivity independently of adaptive immunity. Nat Immunol 12: 631-638, 2011.
22. King GG, James A, Harkeness L and Warki P: Pathophysiology of severe asthma: We've only just started. Respirology 23: 262-271, 2018.
23. Brusselle GG, Maes T and Bracke KR: Eosinophils in the spotlight: Eosinophilic airway inflammation in nonallergic asthma. Nat Med 19: 977-979, 2013.
24. Bakakos A, Loukides S and Bakakos P: Severe eosinophilic asthma. J Clin Med 8: 1375, 2019.
25. Dunican EM, Elicker BM, Gierada DS, Nagle SK, Schiebler ML, Newell JD, Raymond WW, Lachowicz-Scroggins ME, Di Maio S, Hoffman EA, *et al*: Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. J Clin Invest 128: 997-1009, 2018.

26. Schulman ES: Development of a monoclonal anti-immunoglobulin E antibody (omalizumab) for the treatment of allergic respiratory disorders. Am J Respir Crit Care Med 164: S6-S11, 2001.
27. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, Gruchalla RS, Kattan M, Teach SJ, Pongracic JA, *et al*: Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. N Engl J Med 364: 1005-1015, 2011.
28. Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J, Rosen KE, Eisner MD, Wong DA and Busse W: Omalizumab in severe allergic asthma inadequately controlled with standard therapy: A randomized trial. Ann Intern Med 154: 573-582, 2011.
29. Hanania NA, Wenzel S, Rosén K, Hsieh HJ, Mosesova S, Choy DF, Lal P, Arron JR, Harris JM and Busse W: Exploring the effects of omalizumab in allergic asthma: An analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med 187: 804-811, 2013.
30. Ledford D, Busse W, Trzaskoma B, Omachi TA, Rosén K, Chipps BE, Luskin AT and Solari PG: A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. J Allergy Clin Immunol 140: 162-169.e2, 2017.
31. Humbert M, Taillé C, Mala L, Le Gros V, Just J and Molimard M; STELLAIR investigators: Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: The STELLAIR study. Eur Respir J 51: 1702523, 2018.
32. Casale TB, Luskin AT, Busse W, Zeiger RS, Trzaskoma B, Yang M, Griffin NM and Chipps BE: Omalizumab effectiveness by biomarker status in patients with asthma: Evidence from PROSPERO, a prospective real-world study. J Allergy Clin Immunol Pract 7: 156-164.e1, 2019.
33. Esquivel A, Busse WW, Calatroni A, Togias AG, Grindle KG, Bochkov YA, Gruchalla RS, Kattan M, Kercsmar CM, Khurana Hershey G, *et al*: Effects of omalizumab on rhinovirus infections, illnesses, and exacerbations of asthma. Am J Respir Crit Care Med 196: 985-992, 2017.
34. Gill MA, Liu AH, Calatroni A, Krouse RZ, Shao B, Schiltz A, Gern JE, Togias A and Busse WW: Enhanced plasmacytoid dendritic cell antiviral responses after omalizumab. J Allergy Clin Immunol 141: 1735-1743.e9, 2018.
35. Busse W: Biological treatments for severe asthma: Where do we stand? Curr Opin Allergy Clin Immunol 18: 509-518, 2018.
36. Mavissakalian M and Brady S: The current state of biologic therapies for treatment of refractory asthma. Clinic Rev Allerg Immunol 59: 195-207, 2020.
37. Xolair® Full Prescribing Information. Genentech. March 21, 2014. Available from: https://www.gene.com/download/pdf/xolair_prescribing.pdf. Accessed August 12, 2021.
38. Leckie MJ, ten Brinke A, Khan J, Diamant Z, O'Connor BJ, Walls CM, Mathur AK, Cowley HC, Chung KF, Djukanovic R, *et al*: Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. Lancet 356: 2144-2148, 2000.
39. Nucala® Full Prescribing Information. GlaxoSmithKline. September 2019. Available from: https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL-IFU-COMBINED.PDF. Accessed August 12, 2021.
40. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, Ortega H and Chanez P: Mepolizumab for severe eosinophilic asthma (DREAM): A multicentre, double-blind, placebo-controlled trial. Lancet 380: 651-659, 2012.
41. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, Humbert M, Katz LE, Keene ON, Yancey SW, *et al*: Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med 371: 1198-1207, 2014.
42. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, Ortega HG and Pavord ID; SIRIUS Investigators: Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 371: 1189-1197, 2014.
43. Lugogo N, Domingo C, Chanez P, Leigh R, Gilson MJ, Price RG, Yancey SW and Ortega HG: Long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma: A multi-center, open-label, phase III study. Clin Ther 38: 2058-2070. e1, 2016.
44. US Food and Drug Administration: CINQAIR (reslizumab) Injection, for Intravenous Use. Reference ID: 3906489, 2016.
45. European Medicines Agency. EMA/450050/2016. EMEA/H/C/003912. EPAR summary for the public. CINQAERO. INN - reslizumab. https://www.ema.europa.eu/en/documents/overview/cinqaero-epar-summary-public_en.pdf, Accessed May 19, 2021
46. Corren J, Weinstein S, Janka L, Zangrilli J and Garin M: Phase 3 study of reslizumab in patients with poorly controlled asthma: Effects across a broad range of eosinophil counts. Chest 150: 799-810, 2016.
47. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, Murphy K, Maspero JF, O'Brien C and Korn S: Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: Results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 3: 355-366, 2015.
48. Murphy K, Jacobs J, Bjermer L, Fahrenholz JM, Shalit Y, Garin M, Zangrilli J and Castro M: Long-term safety and efficacy of reslizumab in patients with eosinophilic asthma. J Allergy Clin Immunol Pract 5: 1572-1581.e3, 2017.
49. Kolbeck R, Kozhich A, Koike M, Peng L, Andersson CK, Damschroder MM, Reed JL, Woods R, Dall'acqua WW, Stephens GL, *et al*: MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. J Allergy Clin Immunol 125: 1344-1353. e2, 2010.
50. Pham TH, Damera G, Newbold P and Ranade K: Reductions in eosinophil biomarkers by benralizumab in patients with asthma. Respir Med 111: 21-29, 2016.
51. US Food and Drug Administration: FASENRA (benralizumab) injection, for subcutaneous use. Reference ID: 4181236, 2019.
52. European Medicines Agency: EMEA/H/C/4433, 2019. www.ema.europa.eu/en/documents/overview/fasenra-epar-medicine-overview_en.pdf. Accessed 10 May 2021.
53. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, Sproule S, Gilmartin G, Aurivillius M, Werkström V, *et al*: Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): A randomised, multicentre, placebo-controlled phase 3 trial. Lancet 388: 2115-2127, 2016.
54. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, Ferguson GT, Busse WW, Barker P, Sproule S, *et al*: Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): A randomised, double-blind, placebo-controlled phase 3 trial. Lancet 388: 2128-2141, 2016.
55. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, Barker P, Sproule S, Ponnarambil S and Goldman M; ZONDA Trial Investigators: Oral glucocorticoid-sparing effect of benralizumab in severe asthma. N Engl J Med 376: 2448-2458, 2017.
56. Busse WW, Bleecker ER, FitzGerald JM, Ferguson GT, Barker P, Sproule S, Olsson RF, Martin UJ and Goldman M; BORA study investigators: Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. Lancet Respir Med 7: 46-59, 2019.
57. US Food and Drug Administration. DUPIXENT (dupilumab) injection, for subcutaneous use, 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761055lbl.pdf. Accessed December 11, 2020.
58. European Medicines Agency. Dupinex: EMEA/H/C/004390, 2018. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/dupixent. Accessed December 1, 2020.
59. Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, Pirozzi G, Sutherland ER, Evans RR, Joish VN, *et al*: Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: A randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet 388: 31-44, 2016.
60. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, Busse WW, Ford L, Sher L, FitzGerald JM, *et al*: Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med 378: 2486-2496, 2018.
61. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, Zhu H, Hamilton JD, Swanson BN, Khan A, *et al*: Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med 378: 2475-2485, 2018.
62. Corren J, Castro M, Ford LB, Bernstein JA, Jayawardena S, Maroni J, Rowe P, Amin N, Pirozzi G, Graham NMH, *et al*: Dupilumab improves asthma outcomes irrespective of frequency of previous asthma exacerbation history. Ann Allergy Asthma Immunol 123: 222-224.e1, 2019.
63. Corren J, Castro M, O'Riordan T, Hanania NA, Pavord ID, Quirce S, Chipps BE, Wenzel SE, Thangavelu K, Rice MS, *et al*: Dupilumab efficacy in patients with uncontrolled, moderate-to-severe allergic asthma. J Allergy Clin Immunol Pract 8: 516-526, 2020.

64. Dupixent® Full Prescribing Information. Regeneron Sanofi Genzyme. January 2021. Available from: https://www.regeneron.com/downloads/dupixent_fpi.pdf. Accessed August 12, 2021.
65. Ultsch M, Bevers J, Nakamura G, Vandlen R, Kelley RF, Wu LC and Eigenbrot C: Structural basis of signaling blockade by anti-IL-13 antibody Lebrikizumab. J Mol Biol 425: 1330-1339, 2013.
66. Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, Harris JM, Scheerens H, Wu LC, Su Z, *et al*: Lebrikizumab treatment in adults with asthma. N Engl J Med 365: 1088-1098, 2011.
67. Hanania NA, Noonan M, Corren J, Korenblat P, Zheng Y, Fischer SK, Cheu M, Putnam WS, Murray E, Scheerens H, *et al*: Lebrikizumab in moderate-to-severe asthma: Pooled data from two randomised placebo-controlled studies. Thorax 70: 748-756, 2015.
68. Piper E, Brightling C, Niven R, Oh C, Faggioni R, Poon K, She D, Kell C, May RD, Geba GP and Molfino NA: A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma. Eur Respir J 41: 330-338, 2013.
69. Brightling CE, Chanez P, Leigh R, O'Byrne PM, Korn S, She D, May RD, Streicher K, Ranade K and Piper E: Efficacy and safety of tralokinumab in patients with severe uncontrolled asthma: A randomised, double-blind, placebo-controlled, phase 2b trial. Lancet Respir Med 3: 692-701, 2015.
70. Corren J, Parnes JR, Wang L, Mo M, Roseti SL, Griffiths JM and van der Merwe R: Tezepelumab in adults with uncontrolled asthma. N Engl J Med 377: 936-946, 2017.
71. Menzies-Gow A, Colice G, Griffiths JM, Almqvist G, Ponnarambil S, Kaur P, Ruberto G, Bowen K, Hellqvist Å, Mo M and Garcia Gil E: NAVIGATOR: A phase 3 multicentre, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of tezepelumab in adults and adolescents with severe, uncontrolled asthma. Respir Res 21: 266, 2020.
72. Weschler ME, Colice G, Griffiths JM, Almqvist G, Skärby T, Piechowiak T, Kaur P, Bowen K, Hellqvist Å, Mo M and Garcia Gil E: SOURCE: A phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of tezepelumab in reducing oral corticosteroid use in adults with oral corticosteroid dependent asthma. Respir Res 21: 264, 2020.
73. Menzies-Gow A, Ponnarambil S, Downie J, Bowen K, Hellqvist Å and Colice G: DESTINATION: A phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the long-term safety and tolerability of tezepelumab in adults and adolescents with severe, uncontrolled asthma. Respir Res 21: 279, 2020.
74. Dinarello CA: Immunological and inflammatory functions of the interleukin-1 family. Annu Rev Immunol 27: 519-550, 2009.
75. Gabryelska A, Kuna P, Antczak A, Białasiewicz P and Panek M: IL-33 mediated inflammation in chronic respiratory diseases-understanding the role of the member of IL-1 superfamily. Front Immunol 10: 692, 2019.
76. Efficacy and safety study of GSK3772847 in subjects with moderately severe asthma. ClinicalTrials.gov Identifier: NCT03207243, https://clinicaltrials.gov/ct2/show/NCT03207243. Accessed August 12, 2020.
77. Study of REGN3500 and dupilumab in patients with asthma. ClinicalTrials.gov Identifier: NCT03112577, https://clinicaltrials.gov/ct2/show/NCT03112577. Accessed August 12, 2020.
78. Dantes E, Fildan AP, Toma CL, Voicu GH and Oancea C: Respiratory impact in workers exposed to air pollutants from petroleum refinery. J Environ Prot Ecol 17: 523-531, 2016.
79. Tofolean D, Popescu G, Arghir IA, Frandes M and Fildan AP: A different aproach of chronic obstructive pulmonary disease severity and plastic medical devices used for oxygenotherapy. Mater Plast 56: 295-230, 2019.
80. Barsan M, Rajnoveanu AG, Cocarla A, Bolfa P, Login CC, Socaciu AI, Decea N and Leucuta DC: A study of oxidative stress and pulmonary damage after silica instillation in rats and the effect of curcumin administration. Med Pr 72: 239-247, 2021.
81. Trenchea M, Arghir IA, Popescu GG, Rascu S, Bechir ES, Tofolean DE, Fildan AP, Ion I and Dantes E: The triad nocturia, smoking and obstructive sleep apnea. Rev Chim 70: 1839-1842, 2019.
82. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER, *et al*: International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 43: 343-373, 2014.
83. Hogea Stanca P, Tudorache E, Fildan AP, Fira-Mladinescu O, Marc M and Oancea C: Risk factors of chronic obstructive pulmonary disease exacerbations. Clin Respir J 14: 183-197, 2020.
84. Bourdin A, Husereau D, Molinari N, Golam S, Siddiqui MK, Lindner L and Xu X: Matching-adjusted indirect comparison of benralizumab versus interleukin-5 inhibitors for the treatment of severe asthma: A systematic review. Eur Respir J 52: 1801393, 2018.
85. Casale TB, Pacou M, Mesana L, Farge G, Sun SX and Castro M: Reslizumab compared with benralizumab in patients with eosinophilic asthma: A systematic literature review and network meta-analysis. J Allergy Clin Immunol Pract 7: 122-130.e1, 2019.
86. Busse W, Chupp G, Nagase H, Albers FC, Doyle S, Shen Q, Bratton DJ and Gunsoy NB: Anti-IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: Indirect treatment comparison. J Allergy Clin Immunol 143: 190-200.e20, 2019.
87. Calzetta L, Matera MG and Rogliani P: Monoclonal antibodies in severe asthma: Is it worth it? Expert Opin Drug Metab Toxicol 15: 517-520, 2019.
88. Edris A, De Feyter S, Maes T, Joos G and Lahousse L: Monoclonal antibodies in type 2 asthma: A systematic review and network meta-analysis. Respir Res 20: 179, 2019.
89. Albers F, Liu MC, Chipps BE, Chapman KR, Muñoz X, Bergna M, Devouassoux G, Azmi J, Price R and Galkin D: Therapeutic switch from omalizumab to mepolizumab in patients with uncontrolled severe eosinophilic asthma: Treatment effect by prior omalizumab treatment duration. J Allergy Clin Immunol 143 (Suppl 2): AB102, 2019.
90. Pérez de Llano LA, Cosío BG, Domingo C, Urrutia I, Bobolea I, Valero A, Entrenas Costa LM, Quirce S, Barranco P, Marina Malanda N, *et al*: Efficacy and safety of reslizumab in patients with severe asthma with inadequate response to omalizumab: A multicenter, open-label pilot study. J Allergy Clin Immunol Pract 7: 2277-2283.e2, 2019.
91. Kavanagh J, Green L, Fernandes M, Roxas C, Kent BD, Jackson DJ and d'Ancona G: Response to benralizumab after sub-optimal response to mepolizumab in oral corticosteroid dependent severe eosinophilic asthma. Am J Respir Crit Care Med 199: A2675, 2019.
92. Haldar P, Brightling CE, Singapuri A, Hargadon B, Gupta S, Monteiro W, Bradding P, Green RH, Wardlaw AJ, Ortega H and Pavord ID: Outcomes after cessation of mepolizumab therapy in severe eosinophilic asthma: A 12-month follow-up analysis. J Allergy Clin Immunol 133: 921-923, 2014.