



Role of biologics targeting type 2 airway inflammation in asthma: what have we learned so far?

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Purpose of review

Severe asthma is a heterogeneous syndrome that can be classified into distinct phenotypes and endotypes. In the type 2 (T2)-high endotype, multiple cytokines are produced that lead to eosinophilic inflammation. These cytokines and their receptors are targets for biologic therapies in patients with severe asthma who do not respond well to standard therapy with inhaled corticosteroids.

Recent findings

In the last decade, an increasing number of biologic therapies have been developed targeting T2 inflammation. Clinical trials of therapies targeting immunoglobulin E as well as the T2 cytokines interleukin (IL)-4, IL-5, and IL-13 have demonstrated that these treatments improve asthma-related clinical outcomes and/or have steroid-sparing properties. The use of biomarkers of T2 inflammation can help to identify the subset of patients in whom these therapies may be most efficacious. Multiple biologic agents that are directed at other targets are currently in development, including thymic stromal lymphopoietin (TSLP), prostaglandin (PG)D2 receptor, IL-25, and IL-33.

Summary

Biologics are emerging as a key component of severe asthma management. In patients with T2-high severe asthma, the addition of treatments targeting immunoglobulin E and IL-5 to standard therapy may lead to improvement in clinical outcomes. Other biologic therapies have shown promising preliminary results and need to be studied in further clinical trials. These biologic therapies in conjunction with biomarkers will lead to tailored therapy for asthma.

Keywords

biologics, immunoglobulin E, interleukin 13, interleukin 4, interleukin 5, severe asthma

INTRODUCTION

Although severe asthma accounts for less than 10% of all asthma, patients with severe disease have significant morbidity and disproportionate healthcare utilization [1]. The American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines define severe asthma as asthma requiring treatment with high-dose inhaled corticosteroids (ICSs) and a second controller in order to maintain control or which remains uncontrolled despite these therapies [2]. Severe asthma is a heterogeneous disease with clinical, physiological, and biological variability among patients. Classification of asthma into distinct clinical phenotypes and molecular endotypes has led to the development of targeted treatment modalities.

ASTHMA ENDOTYPES

Asthma has most recently been characterized into type 2 (T2)-high asthma and non-T2/T2-low asthma

based on the type of underlying airway inflammation [3]. In T2-high asthma, inhaled allergens activate antigen-presenting cells in the airway, leading to the release of interleukin (IL)-4 and OX40 ligand. These, in turn, promote differentiation of T lymphocytes into T-helper 2 (T_H2) cells, which then produce cytokines such as IL-4, IL-5, and IL-13 (see Fig. 1) [4–7].

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KEY POINTS

- Severe asthma is a heterogeneous syndrome that can be classified into distinct phenotypes and endotypes; T2-high is currently the only well-defined asthma endotype.
- Biologics provide the opportunity to target certain molecular pathways of asthma, facilitating a more precise approach to this disease.
- The majority of biologics currently available for clinical use and in development target T2-high asthma.
- Biologics targeting IgE and IL-5 are currently approved for clinical use in many countries.
- Emerging data regarding biologics currently in development are forthcoming.
- T2-low/non-T2 asthma still represents an unmet need.

T_H2 cells also stimulate immunoglobulin E (IgE) isotype switching in B cells [4]. IgE bound to mast cells and basophils subsequently binds antigen and leads to the release of histamines, leukotrienes, and cytokines [8]. Recent studies have also highlighted the role of type 2 innate lymphoid cells (ILC2) in T2-high asthma. These ILC2 cells stimulate the release of IL-5 and IL-13 in conjunction with T_H2 cells, but do so in direct response to activation stimuli and cytokines such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) [9,10]. In contrast, the molecular pathways of non-T2/T2-low asthma, which accounts for 40–50% of severe asthma, have not been well established but may be propagated by cells such as T-helper 17 (T_H17) cells and neutrophils [3]. The majority of biologic agents currently in development target T2-high asthma. This review will focus on biologics targeting T2-high asthma.

THERAPEUTIC TARGETS

IgE

Omalizumab is a recombinant humanized monoclonal antibody that binds free IgE, forming omalizumab–IgE complexes that block the interaction between IgE and high-affinity receptors on mast cells, basophils, and dendritic cells (see Table 1) [11–24,25²²,26²²,27,28²²,29²²,30–32,33²²,34,35²²,36,37²²]. Omalizumab also downregulates the expression of high-affinity IgE receptors on these cells [38]. Omalizumab also downregulates the expression of high-affinity IgE receptors on these cells [38]. Omalizumab has been approved as

add-on therapy to patients with moderate-to-severe allergic asthma whose symptoms are inadequately controlled with ICS. It is administered by subcutaneous injection, and dosing is based on pretreatment serum total IgE level and body weight.

Omalizumab has been studied in randomized controlled trials in adolescents and adults (>12 years) [11–18] and children (≤12 years) [39,40] with moderate-to-severe asthma. A recent *Cochrane* meta-analysis found that in patients with moderate or severe persistent asthma receiving background ICS, omalizumab treatment significantly decreased exacerbations and hospitalizations compared with placebo [41]. In studies that also included a steroid reduction phase, patients receiving omalizumab had a significantly greater reduction in ICS dose and greater likelihood of withdrawing ICS completely [12,15,39]. However, there was no difference in the likelihood of being able to withdraw completely from oral steroid therapy between patients treated with omalizumab versus placebo [13]. In some studies, omalizumab improved asthma symptoms [12–15] and health-related quality of life [13,14]. Findings from several ‘real world’ studies, which followed patients in clinical practice receiving omalizumab, support the results of the efficacy studies, demonstrating that omalizumab was associated with decrease in exacerbations [42,43], hospitalizations or emergency visits [44], and ICS use [43], and improved quality of life [42] compared with baseline. A study of children and adolescents aged 6–17 years with one or more recent exacerbations compared the effect of omalizumab versus placebo and omalizumab versus increased ICS on fall exacerbation rates [45]. When compared with placebo, omalizumab treatment decreased exacerbation (defined as worsening of asthma control requiring systemic corticosteroids or hospitalization) rates, but when compared with increased ICS, omalizumab treatment only decreased exacerbation rates in the subgroup of patients with an exacerbation during the run-in phase.

As shown from combined data from more than 7000 asthma patients, omalizumab has a favorable safety and tolerability profile [46]. Hypersensitivity reactions occurred rarely with omalizumab treatment in clinical trials. Anaphylaxis occurred in 0.14% of omalizumab-treated patients and in 0.07% of controls. Analysis of postmarketing safety data determined that 124 cases of anaphylaxis were reported among an estimated 57 300 patients exposed to omalizumab [47]. Pooled data from phase I, II, and III studies demonstrated a difference in the incidence of malignancy between patients receiving omalizumab (0.5%) and those receiving placebo (0.18%) [46]. However, in a prospective

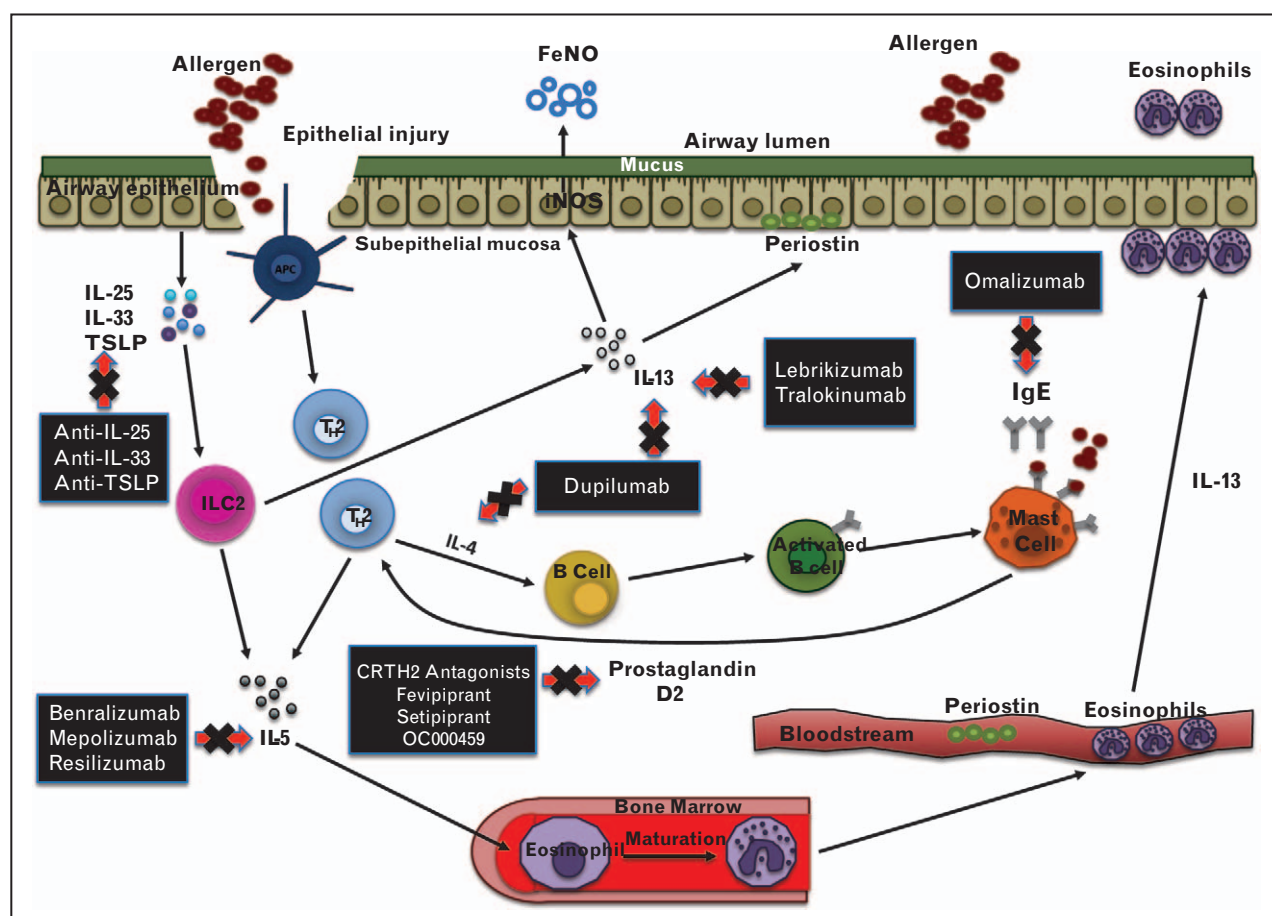


FIGURE 1. Targets of type 2 inflammation and biologic therapies: after differentiation of naive T lymphocytes into T-helper type 2 cells (T_H2-cells) in response to antigen stimulation, T_H2 cells secrete IL-4, IL-5, and IL-13 [4,5]. The epithelial-derived cytokines IL-25, IL-33, and TSLP can stimulate IL-4, IL-5, and IL-13 secretion from ILC2 cells in the absence of T effector cells [6]. AMG-157 is a monoclonal antibody that binds TSLP and prevents interaction with its receptor. IL-4 stimulates isotype class switching of B cells, leading to the production of IgE. Omalizumab is an antibody against IgE. IL-5 promotes the maturation of eosinophils and their release from the bone marrow. Mepolizumab and reslizumab are monoclonal antibodies against IL-5, and benralizumab binds IL-5 receptor α leading to cell-mediated cytotoxicity. IL-13 secretion leads to mucus hypersecretion and production of inducible nitric oxide and periostin in airway epithelial cells. Lebrizumab and tralokinumab are monoclonal antibodies targeting IL-13. Dupilumab is a monoclonal antibody to the α subunit of the IL-4 receptor that inhibits both IL-4 and IL-13 signaling. Prostaglandin D₂ is released mainly from mast cells in response to allergen. The prostaglandin D₂ receptor, also known as CRTH2, is expressed on T_H2 lymphocytes and mediates T_H2 cell migration and production of effector cytokines [7]. Fevipirant, setipirant, and OC000459 are antagonists of CRTH2. APC, antigen-presenting cell; CRTH2, chemoattractant receptor-homologous molecule expressed on T_H2 cells; FeNO, fractional excretion of nitric oxide; IgE, immunoglobulin E; IL, interleukin; ILC2, type-2 innate lymphoid cells; iNOS, inducible nitric oxide synthase; T_H2, T-helper type 2; TSLP, thymic stromal lymphopoietin.

study of patients with a median of 5-year follow-up, malignancy rates were similar for patients who received omalizumab and those who never received omalizumab [48].

Not all patients with inadequately controlled asthma respond to omalizumab treatment. Although there is a decrease in serum free IgE following treatment with omalizumab, omalizumab forms a complex with previously unbound IgE, leading to an increase in total IgE. Therefore,

response to treatment cannot be assessed by measurement of total IgE [49]. In a pooled analysis of two randomized controlled trials, Bousquet *et al.* [50] demonstrated that difficult-to-treat asthma patients, defined as those receiving higher ICS doses, patients with poor lung function, and patients with a history of emergency asthma treatment, had the greatest benefit from omalizumab. In another study of seven pooled randomized controlled trials, the physician's overall assessment of

Table 1. Targets and efficacy of biologic therapies for asthma

Target	Drugs	Route	Target patient population	Clinical outcomes	Biomarkers identifying responders
IgE	Omalizumab [11–18]	SC	Allergic asthma	↓ Exacerbations ↓ Hospitalizations ↓ ICS use	FeNO Blood eosinophils Periostin
IL-5	Mepolizumab [19–23]	SC, IV	Eosinophilic asthma	↓ Exacerbations ↓ Glucocorticoid use	Blood eosinophils
	Reslizumab [24,25 [■] ,26 [■]]	IV	Eosinophilic asthma	↓ Exacerbations ↑ FEV ₁	
IL5Rα	Benralizumab [27,28 [■] ,29 [■]]	SC	Eosinophilic asthma	↓ Exacerbations ↑ FEV ₁	
IL-13	Lebrikizumab [30–32,33 [■]]	SC	T2-high asthma	↑ FEV ₁ ↓ Exacerbations	Periostin FeNO Blood eosinophils
	Tralokinumab [34,35 [■]]	SC	T2-high asthma	↑ FEV ₁	DPP-4
IL-4Rα (IL-4 and IL-13)	Dupilumab [36,37 [■]]	SC	Eosinophilic asthma	↓ Exacerbations	Blood eosinophils

DPP-4, dipeptidyl peptidase-4; FeNO, fractional exhaled nitric oxide; FEV₁, forced exhaled volume in 1 s; Ig, immunoglobulin; IL, interleukin; IL-4Rα, α subunit of the IL-4 receptor; IL5Rα, IL-5 receptor α; IV, intravenous; SC, subcutaneous; T2, type 2.

asthma control (graded as a five-level evaluation where responders were defined as having marked improvement in control or complete control) was the most meaningful measure of treatment response, which included a marked decrease in exacerbation rates [51]. Biomarkers of T2-high inflammation may also identify patients who respond to omalizumab. Patients with high baseline concentrations of fractional exhaled nitric oxide (FeNO), blood eosinophils, and serum periostin have greater benefit from omalizumab treatment [52].

The optimal duration of treatment with omalizumab is unclear. In one study, only 38% of patients responded to therapy (defined as reduced symptoms, reduced usage of rescue medication, improved lung function, or improved quality of life) after 4 weeks, but responders increased to 64% at week 16 [50]. On the basis of these data, a minimum of 12 weeks of treatment was suggested. In a small study of 18 patients who received omalizumab for 6 years, patients had clinically stable asthma in the 3 years following withdrawal with no significant change in lung function [53]. In another study, patients who had received long-term omalizumab therapy (≥5 years) were randomized to continuation of omalizumab or switch to placebo for 1 year. Although significantly more patients in the omalizumab continuation group had persistency of prevention of exacerbation, a substantial number of patients in the placebo group (47.7%) continued to be exacerbation free as well [54].

The severe asthma (ATS/ERS) guidelines suggest a therapeutic trial of omalizumab both in adults and children with severe allergic asthma. The guidelines also suggest that if patients do not respond within 4 months of initiation of therapy, further administration of omalizumab is unlikely to be beneficial [2].

Interleukin-5

IL-5 plays a key role in production, maturation, recruitment, survival, and activation of eosinophils [6,55]. In mice, administration of anti-IL-5 antibody blocks the development of eosinophilia, and transgenic mice expressing IL-5 show long-lasting eosinophilia [56]. Thus, IL-5 is an important therapeutic target in asthma and blocking IL-5 could decrease tissue eosinophilia and subsequently improve asthma control. Three drugs targeting IL-5 have been studied in asthma. Mepolizumab and reslizumab are humanized monoclonal antibodies against IL-5 that have recently been approved for use in several countries worldwide. Benralizumab is a humanized monoclonal antibody that targets the interleukin 5 receptor α (IL5Rα) on eosinophils and basophils, leading to eosinophil and basophil depletion through antibody-dependent cell-mediated cytotoxicity.

Initial studies of intravenous mepolizumab in unselected patients with allergic asthma demonstrated a reduction in blood and sputum eosinophils without effect on allergen-induced airway late phase

response and associated airway hyperresponsiveness [57,58]. However, in a small study of patients with sputum eosinophilia, patients treated with mepolizumab subcutaneously had a greater reduction in oral steroid dose compared with placebo [19]. This finding was confirmed in a larger study of patients with eosinophilic asthma, in which intravenous mepolizumab treatment had a significant glucocorticoid-sparing effect compared with placebo as well as a reduction in exacerbation rate [20]. Other large, randomized controlled studies of over 500 patients each (DREAM and MENSA) have similarly shown improvement in exacerbation rates in patients with severe eosinophilic asthma receiving mepolizumab either intravenously or subcutaneously [21,22]. However, treatment with mepolizumab has no consistent effects on asthma symptoms, quality of life, forced exhaled volume in 1 s (FEV₁), or airway hyperreactivity [19–23]. These findings suggest that in these patients, asthma exacerbations but not day-to-day symptoms may be driven by eosinophilic inflammation, although in patients with asthma in general, not all exacerbations are eosinophilic [59]. Furthermore, mepolizumab administered both intravenously and subcutaneously appears to reduce exacerbations specifically in the subgroup of patients with persistent eosinophilia despite oral corticosteroid usage.

In the DREAM study, Pavord *et al.* [21] used exploratory modeling of baseline characteristics and determined that response to intravenous mepolizumab varied based on blood eosinophil count of at least 150 cells/ μ l and number of prior exacerbations. Sputum eosinophilia ($\geq 3\%$) did not correlate with clinical response. Despite fluctuations in eosinophil counts, subsequent analysis of patients randomized to placebo demonstrated that a single measurement of 150 cells/ μ l or greater was predictive of average subsequent eosinophil measurements in 85% of patients [60]. However, the optimal cutoff of blood eosinophil count that predicts clinical response to mepolizumab has yet to be determined. Using supervised cluster analysis on data from the DREAM study, Ortega *et al.* [61] found four primary clusters with differing clinical responses to intravenous mepolizumab. Patients with a relatively low level of blood eosinophils had the least response to mepolizumab, whereas patients with higher airway reversibility, obesity, and more comorbid conditions showed the greatest response.

Reslizumab neutralizes circulating IL-5 and prevents the binding of IL-5 to eosinophils. This biologic is administered intravenously every 4 weeks. In a study of patients with asthma and sputum eosinophils, patients treated with

reslizumab had a greater reduction in sputum eosinophils and improvement in FEV₁ compared with placebo [24]. Improvement in asthma symptoms was seen in patients with nasal polyposis. In a phase III study of patients with inadequately controlled asthma and elevated blood eosinophils of at least 400 cells/ μ l, treatment with reslizumab led to improvement in FEV₁, asthma control and symptoms, and quality of life [26^{***}]. A larger randomized controlled trial of patients with asthma inadequately controlled with medium-to-high doses of ICS and elevated blood eosinophils of at least 400 cells/ μ l demonstrated a significant reduction in exacerbations as well as improvement in FEV₁ with reslizumab treatment [25^{***}]. A subcutaneous formulation of this biologic is currently in development.

Treatment with benralizumab also leads to the depletion of sputum and blood eosinophils [62]. In a phase IIb study, benralizumab reduced exacerbations at both 20 and 100 mg subcutaneous doses in patients with a blood eosinophil count of at least 300 cells/ μ l [27]. Recently, two large randomized controlled phase III trials of benralizumab in patients with severe asthma and elevated blood eosinophils were published [28^{***},29^{***}], each with over 1000 patients enrolled. Both studies demonstrated that benralizumab decreased the annual rate of exacerbation as well as lung function compared with placebo when administered either every 4 weeks or every 8 weeks in patients with severe eosinophilic asthma inadequately controlled with high-dose ICS and long-acting β agonist (LABA). Compared with placebo, benralizumab improved asthma symptom scores when given every 8 weeks.

Interleukin-4/interleukin-13

IL-4 and IL-13 are T2 cytokines implicated in the pathogenesis of asthma. They share structural similarities as well as a shared functional receptor complex (IL-4R α /IL-13R α 1) [63]. IL-4 is a key to the differentiation of CD4⁺ lymphocytes and the production of IgE. IL-13 is involved in airway hyperresponsiveness, mucus production, and subepithelial fibrosis [64]. Treatments to reduce IL-4 activity include anti-IL-4 antibody, soluble IL-4 receptor, IL-4 transcription inhibitors, and combined IL-4/IL-13 receptor antagonists.

Lebrikizumab is a humanized monoclonal antibody targeting IL-13 that inhibits its function [65]. In a randomized, phase II trial of adults with inadequately controlled asthma despite ICS use, treatment with lebrikizumab produced a significant increase in FEV₁ compared with placebo treatment [30]. Periostin is an extracellular protein that is

secreted by airway epithelial cells in response to stimulation by IL-4 and IL-13 and is a biomarker of T2 inflammation [66]. Patients with high serum periostin receiving lebrikizumab had a greater improvement in FEV₁ than patients with low serum periostin. Similarly, a subsequent study found that lebrikizumab improved FEV₁ and decreased the rate of exacerbations in patients with uncontrolled asthma and high baseline serum periostin levels [32]. Elevated FeNO levels and blood eosinophil count were also predictive of response to lebrikizumab. Two recently published replicate phase III trials (LAVOLTA I and LAVOLTA II) of lebrikizumab failed to show a consistent reduction in the exacerbation rate in biomarker high patients [33[¶]]. The strongest treatment-by-biomarker interaction was found for blood eosinophils, but treatment-by-biomarker interaction testing failed to show statistical significance. The reason for the different outcomes of lebrikizumab in phase III versus phase II studies is unclear. Nevertheless, other ongoing clinical studies of lebrikizumab in asthma have been terminated and reports of the available findings are pending.

Tralokinumab is another injectable humanized monoclonal IgG₄ monoclonal antibody against IL-13. In a study of 194 adults with moderate-to-severe uncontrolled asthma, treatment with tralokinumab improved FEV₁ compared with placebo [34]. However, in a phase IIb study, patients with severe uncontrolled asthma and 2–6 exacerbations in the prior year treated with tralokinumab did not have an improvement in annual asthma exacerbation rate, and only patients receiving tralokinumab every 2 weeks had an improvement in FEV₁ [35[¶]]. The findings from ongoing phase III studies are awaited.

Dupilumab is a fully human monoclonal antibody to the α subunit of the IL-4 receptor that inhibits both IL-4 and IL-13 signaling. In a phase IIa trial, patients with moderate-to-severe asthma with evidence of blood or sputum eosinophilia were randomized to receive either dupilumab 300 mg subcutaneously every week for 12 weeks or placebo [36]. Patients then discontinued maintenance medications during the study. Dupilumab treatment was associated with an 87% reduction in asthma exacerbations. Treatment with dupilumab also resulted in significant improvement in FEV₁ and reduction in FeNO, but no change in blood eosinophil counts. Despite these results suggesting that blockade of both IL-4 and IL-13 may be more beneficial than blocking either cytokine alone, inducing exacerbation by withdrawal of LABA and ICS is not representative of 'real world' treatment of asthma [67]. In a recent phase IIb randomized controlled study, dupilumab improved lung function when compared with placebo in patients with uncontrolled

persistent asthma on medium-to-high dose ICS and LABA [37[¶]]. This improvement was found independent of the baseline blood eosinophil count. Combining these promising data with evidence from other studies [68,69], dupilumab shows potential as (add-on) controller therapy for a wider range of patients with severe uncontrolled asthma as it may also treat their comorbidities, including chronic rhinosinusitis with nasal polyps and atopic dermatitis.

OTHER TARGETS

The prostaglandin D₂-prostaglandin D₂ receptor (DP₂) pathway plays an important role in mediating eosinophilic airway inflammation in asthma. DP₂ [also known as chemoattractant receptor-homologous molecule expressed on T_H2 cells (CRTH2)] is expressed on T_H2 lymphocytes and eosinophils and mediates T_H2 cell migration and production of IL-4, IL-5, and IL-3 as well as eosinophil chemotaxis and degranulation. DP₂ is also present on ILC2 and epithelial cells. Like with mepolizumab [57], the first proof-of-concept studies with early CRTH2 antagonists, such as OC000459 and setipiprant [70,71], yielded only modest protection against the allergen-induced airway inflammation (late phase response and sputum eosinophils) in unselected patients with mild-moderate allergic asthma. Later studies showed more promising data following DP₂-antagonism in patients with eosinophilic esophagitis [72] and in eosinophilic (≥ 250 cells/ μ l) asthma [73]. Fevipiprant is a novel, orally administered, potent antagonist of DP₂. In a proof-of-concept trial, patients who were being treated with ICS and had a sputum eosinophil count of at least 2% were given fevipiprant for 12 weeks and had a greater decrease in sputum eosinophilia and a reduction in eosinophilic inflammation in bronchial mucosa compared with patients given placebo [74[¶]]. However, there was no change in peripheral eosinophil counts. Further studies are needed to determine the clinical benefits of this class of drugs in patients with severe asthma.

IL-25, IL-33, and TSLP are epithelial-cell-derived cytokines that can stimulate IL-4, IL-5, and IL-13 secretion from ILC2 cells and eosinophils without the presence of T effector cells [6]. Patients with asthma have increased expression of TSLP in their airways [75]. AMG 157 is a human monoclonal antibody that binds TSLP and prevents interaction with its receptor. In a randomized, controlled trial of patients with mild allergic asthma, AMG 157 attenuated early and late phase allergen-induced asthmatic response [76]. Treatment with AMG 157 also led to decreased sputum eosinophil levels and FeNO.

Studies targeting IL-25 and IL-33 are in early stages of development.

FUTURE NEEDS

Asthma is a heterogeneous disease with a large healthcare burden, especially the more severe disease. Despite international guidelines and optimal standard therapy, many patients continue to have poorly controlled disease. Significant strides have been made in identifying and defining asthma phenotypes and endotypes and validating biomarkers to predict and monitor response to targeted treatment. These advances have paved the way for the development of biologics that target specific disease pathways. For the existing targeted biologics that are effective in T2-high asthma, more longitudinal data are needed on optimal duration of therapy, long-term safety profile, the impact of withdrawal of drug after achieving disease control, and cost-benefit analyses. Lastly, more attention is required to define and target distinct phenotypes and endotypes for the approximately 50% of asthma that is not driven by the classic T2 pathway. Such targets may include cytokines such as IL-17, IL-24, IL-25, IL-27, and IL-33.

CONCLUSION

Biologics are emerging as a substantial part of severe asthma management. There are currently three biologics that are approved for the treatment of severe asthma in the United States and Europe: omalizumab, mepolizumab, and reslizumab. Aside from these drugs that target IgE and IL-5, respectively, additional biologics targeting T2 inflammation (i.e., IL-4 and/or IL-13) and CRTH2 antagonists are also in advanced phases of clinical development. These biologics provide a unique advantage of targeting molecular pathways of asthma, instead of using a one size fits all approach to clinical asthma features. As more data emerge, these biologics in conjunction with biomarkers may allow for a more personalized management of asthma in the near future.

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A.D.P. has received compensation for scientific consulting from AstraZeneca. Z.D. is affiliated with a contract research organization performing early phase clinical drug development studies for pharmaceutical and biotech

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