Role of Biologics in Asthma

Mary Clare McGregor[1], James G. Krings[1], Parameswaran Nair[2], and Mario Castro[1]

[1]Division of Pulmonary and Critical Care, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri; and [2]Division of Respirology, Department of Medicine, St. Joseph's Healthcare Hamilton, McMaster University, Hamilton, Ontario, Canada

Abstract

Patients with severe uncontrolled asthma have disproportionally high morbidity and healthcare utilization as compared with their peers with well-controlled disease. Although treatment options for these patients were previously limited, with unacceptable side effects, the emergence of biologic therapies for the treatment of asthma has provided promising targeted therapy for these patients. Biologic therapies target specific inflammatory pathways involved in the pathogenesis of asthma, particularly in patients with an endotype driven by type 2 (T2) inflammation. In addition to anti-IgE therapy that has improved outcomes in allergic asthma for more than a decade, three anti–IL-5 biologics and one anti–IL-4R biologic have recently emerged as promising treatments for T2 asthma. These targeted therapies have been shown to reduce asthma exacerbations, improve lung function, reduce oral corticosteroid use, and improve quality of life in appropriately selected patients. In addition to the currently approved biologic agents, several biologics targeting upstream inflammatory mediators are in clinical trials, with possible approval on the horizon. This article reviews the mechanism of action, indications, expected benefits, and side effects of each of the currently approved biologics for severe uncontrolled asthma and discusses promising therapeutic targets for the future.

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

Asthma is a chronic inflammatory disorder of the airways characterized by bronchial hyperresponsiveness and variable airflow limitation that affects more than 300 million people worldwide (1). Although the majority of patients with asthma can achieve disease control with standard controller therapy, approximately 5% have severe asthma that remains inadequately controlled despite adherence to standard treatment with a high-dose inhaled corticosteroid (ICS) plus long-acting bronchodilator (2). Severe asthma is defined by the European Respiratory Society/American Thoracic Society as asthma that requires treatment with high-dose ICS plus a second controller with or without systemic corticosteroids to maintain control of the disease or, despite this therapy, have suboptimally controlled disease (3). Patients with severe uncontrolled asthma carry much of the morbidity, mortality, and healthcare utilization of the disease (2, 4). Specifically, patients with severe asthma have increased hospitalizations, detrimental side effects of oral corticosteroids (OCS), poor quality of life (QOL), and impaired lifestyle as compared with patients with well-controlled disease (5).

Over the past decade, an improved understanding of the complex pathophysiology of asthma has led to the development of new treatment options for asthma. Today, patients with uncontrolled severe asthma are routinely considered for candidacy of biologic therapies as well as for bronchial thermoplasty (6). Researchers and clinicians have increasingly recognized that asthma is not a uniform disease but rather a heterogeneous disease with multiple phenotypes that are caused by a variety of pathophysiologic mechanisms, or endotypes (7–10). There are two specific endotypes, type 2 (T2) high and low, that are important to distinguish when considering biologic therapy. These endotypes are defined based on their level of expression of cytokines such as IL-4, IL-5, and IL-13 that may be secreted by the classic T-helper cell type 2 (Th2)-type cells, such as the CD4 lymphocytes, or nonclassic immune cells, such as the innate lymphoid cells–type 2 (ILC-2) (hence, the change in terminology from Th2 to T2). Biologic therapies target inflammatory modulators that have been identified to play a key role in the pathogenesis of asthma predominantly in the T2-high subset of patients and have demonstrated encouraging results specifically in this group. This article reviews the mechanism of action, efficacy, and indications of the currently

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Correspondence and requests for reprints should be addressed to Mario Castro, M.D., M.P.H., Division of Pulmonary and Critical Care Medicine, Department of Medicine, Washington University School of Medicine, 660 S. Euclid Avenue, Campus Box 8052, St. Louis, MO 63110. E-mail: castrom@wustl.edu.

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approved biologics (Table 1), discusses considerations when choosing between these biologics (Table 2), and reviews potential therapeutic targets for the future (Table 3).

Type 2 High and Low Airway Inflammation

The treatment of asthma is moving toward a personalized treatment strategy that is based on patient-specific characteristics and underlying endotype rather than disease severity alone.

T2-High Asthma

T2 inflammation occurs in approximately half of patients with asthma and may be slightly more common in patients with severe asthma (11). In T2-high asthma, inhaled allergens, microbes, and pollutants interact with the airway epithelium, which subsequently leads to activation of mediators such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 (Figure 1). This process leads to activation of IL-4, IL-5, and IL-13, which can result in attraction and activation of basophils, eosinophils, and mast cells; secretion of IgE by B cells; and activation of innate cells such as the airway epithelium and smooth muscle, resulting in bronchoconstriction, airway hyperresponsiveness, mucus production, and airway remodeling (12, 13). T2-high asthma encompasses both allergic and nonallergic eosinophilic asthma. Although an allergen-specific, IgE-dependent process plays a significant role in allergic asthma, T2 cytokines play a dominant role in inflammation in nonallergic eosinophilic asthma. Sputum and blood absolute eosinophil counts (AECs), serum IgE, exhaled nitric oxide, and serum periostin are all important biomarkers of T2 inflammation that can help predict response to biologics (14).

T2-Low Asthma

T2-low asthma, which includes neutrophilic, mixed, or paucigranulocytic asthma, has a comparatively poorly understood pathophysiology and may be influenced by the concomitant use of corticosteroids suppressing underlying eosinophilia. T2-low asthma is caused by neutrophilic or paucigranulocytic inflammation that results in activation of both T1 and T17 cells, and high IL-17A mRNA levels have been found in patients with moderate to severe asthma (15). These patients are generally less responsive to corticosteroids, have fewer allergic symptoms, and are older at the time of diagnosis. Currently, there is no approved biologic for T2-low asthma, and thus therapy in this group relies on standard treatment with controller medications and possible

Table 1. Summary of the Biologics Currently Approved for the Treatment of Moderate to Severe Persistent Asthma with Type 2–High Phenotype

Therapy	Mechanism of Action	Indication	Dosing and Route	Adverse Effects
Omalizumab	Anti-IgE; prevents IgE from binding to its receptor on mast cells and basophils	⩾6 yr old with moderate to severe persistent asthma, positive allergy testing, incomplete control with an ICS, and IgE: 30–1,300 IU/ml (United States, age 6–11 yr), 30–700 IU/ml (United States, age ⩾ 12 yr), or 30–1,500 IU/ml (European Union)	0.016 mg/kg per IU of IgE (in a 4-wk period) administered every 2–4 wk s.c. (150–375 mg in United States; 150–600 mg in European Union)*	Black box warning: ~0.1–0.2% risk of anaphylaxis in clinical trials
Mepolizumab	Anti–IL-5; binds to IL-5 ligand; prevents IL-5 from binding to its receptor	⩾12 yr old with severe eosinophilic asthma unresponsive to other GINA step 4–5 therapies. Suggested AEC ⩾ 150–300 cells/μl	100 mg s.c. every 4 wk	Rarely causes hypersensitivity reactions; can cause activation of zoster
Reslizumab	Anti–IL-5; binds to IL-5 ligand; prevents IL-5 from binding to its receptor	⩾18 yr old with severe eosinophilic asthma unresponsive to other GINA step 4–5 therapies. Suggested AEC ⩾ 400 cells/μl	Weight-based dosing of 3 mg/kg i.v. every 4 wk	Black box warning: ~0.3% risk of anaphylaxis in clinical trials
Benralizumab	Anti–IL-5; binds to IL-5 receptor α; causes apoptosis of eosinophils and basophils	⩾12 yr old with severe eosinophilic asthma unresponsive to other GINA step 4–5 therapies. Suggested AEC ⩾ 300 cells/μl	30 mg s.c. every 4 wk for three doses; followed by every 8 wk subsequently	Rarely causes hypersensitivity reactions
Dupilumab	Anti–IL-4R; binds to IL-4 receptor α; blocks signaling of IL-4 and IL-13	⩾12 yr old with severe eosinophilic asthma unresponsive to other GINA step 4–5 therapies. Suggested AEC ⩾ 150 cells/μl and/or F_{ENO} level ⩾ 25 ppb	200 or 300 mg s.c. every 2 wk	Rarely causes hypersensitivity reactions; higher incidence of injection site reactions (up to 18%) and hypereosinophilia (4–14%)

Definition of abbreviations: AEC = absolute blood eosinophil count; F_{ENO} = fractional exhaled nitric oxide; GINA = Global Initiative for Asthma; ICS = inhaled corticosteroids.
*Upper limits exist for the dosing of omalizumab in patients with high IgE levels and increased weight.

Table 2. Efficacy of the Biologics That Are U.S. Food and Drug Administration Approved for the Treatment of Moderate to Severe Persistent Asthma with Type 2–High Phenotype

Therapy	Asthma Exacerbation	Lung Function	Corticosteroid Weaning	Special Considerations
Omalizumab	Reduces by 25%	Minimal or equivocal improvement	Decreases use of ICS, but no data that it helps with OCS weaning	Only s.c. biologic approved for children 6–11 yr old
Mepolizumab	Reduces by ~50%	Inconsistent effect	Decreases total use of OCS and has been shown to facilitate complete weaning from chronic OCS (14%)	Standard s.c. dosing has not been shown to decrease sputum eosinophilia; approved at higher dosing for EGPA
Reslizumab	Reduces by ~50–60%	Improved	Has not been specifically evaluated for this indication	Only weight-based dosing i.v. biologic approved for asthma
Benralizumab	Reduces by ~25–60%	Improved	Decreases total use of OCS and has been shown to facilitate complete weaning from chronic OCS (50%)	Only s.c. biologic that offers every-8-wk dosing
Dupilumab	Reduces by ~50–70%	Improved	Decreases total use of OCS and has been shown to facilitate complete weaning from chronic OCS (50%)	Only biologic that can be self-administered s.c.; showed benefit with $F_{ENO} \geq 25$ ppb regardless of eosinophil count

Definition of abbreviations: EGPA = eosinophilic granulomatosis with polyangiitis; F_{ENO} = fractional exhaled nitric oxide; ICS = inhaled corticosteroid; OCS = oral corticosteroid.

bronchial thermoplasty (14). However, one recent trial suggests macrolide therapy with azithromycin may have a role in reducing exacerbations in patients with T2-low asthma (16).

Biologics

Anti-IgE: Omalizumab

Mechanism of action. Omalizumab, a humanized anti-IgE monoclonal antibody (mAb), was the first biologic approved for the treatment of asthma in the United States and European Union. Allergic asthma accounts for approximately 70% of asthma, and IgE is essential in the inflammatory cascade of allergic asthma (17, 18). IgE is produced by B cells in response to allergen activation of the cell-mediated immune response. Omalizumab prevents IgE from binding to its high-affinity receptor (FcεRI) found on mast cells and basophils, which dampens the release of proinflammatory mediators and blunts the downstream allergic response (19, 20). Omalizumab also down-regulates the expression of the IgE receptor on mast cells, further reducing inflammation (20). Although these mechanisms are well described, clinical studies have demonstrated omalizumab can reduce exacerbations during peak viral seasons, associated with enhanced IFN-α production in response to rhinovirus, raising the possibility of alternate antiviral mechanisms of action (21).

Efficacy. Omalizumab has been used clinically for the treatment of allergic asthma for more than 15 years and has shown favorable outcomes in several randomized control trials (RCTs). In 2014, a Cochrane review evaluating 25 RCTs in patients with moderate to severe allergic asthma found omalizumab compared with placebo reduced asthma exacerbations by approximately 25%, reduced hospitalizations, and allowed reduction of ICS dose (22–26) (Figure 2). Some studies have shown a small improvement in lung function (27), although others have not. There have been no clear data that support a reduction in OCS in patients treated with omalizumab. Many of the early trials of omalizumab were in patients with moderate allergic asthma; however, subsequent trials in severe allergic asthma have demonstrated similar efficacy (28). Real-world studies have similarly demonstrated a reduction in exacerbations and hospitalizations with omalizumab (29, 30).

Efforts to better understand specific patient characteristics that would predict which patients would have the greatest benefit from omalizumab are ongoing. Retrospective analyses suggest a greater reduction in asthma exacerbations in patients who receive omalizumab with high eosinophil counts and high exhaled NO levels (31). However, this difference may be due to the higher rate of exacerbations in those with high T2 biomarkers, allowing for a greater reduction with omalizumab. Therefore, even patients with low T2 biomarker profiles who qualify for omalizumab may benefit from its use. A recent pragmatic trial of omalizumab demonstrated similar benefits in patients with T2-high and -low asthma (AEC <300 or ≥ 300 cells/μl and fractional exhaled nitric oxide [F_{ENO}] <25 or ≥ 25 ppb) (30). In addition, studies have demonstrated a similar benefit of omalizumab in patients who have IgE levels both higher and lower than the currently approved range of 30 to 700 IU/ml in the United States (30). Finally, in a proof-of-concept pilot study, omalizumab decreased expression of FcεRI on basophils in patients with nonatopic asthma, suggesting a possible role of omalizumab in a nonallergic phenotype (32).

Indications, administration, safety. In the United States, omalizumab is approved for patients aged 6 years and older who have

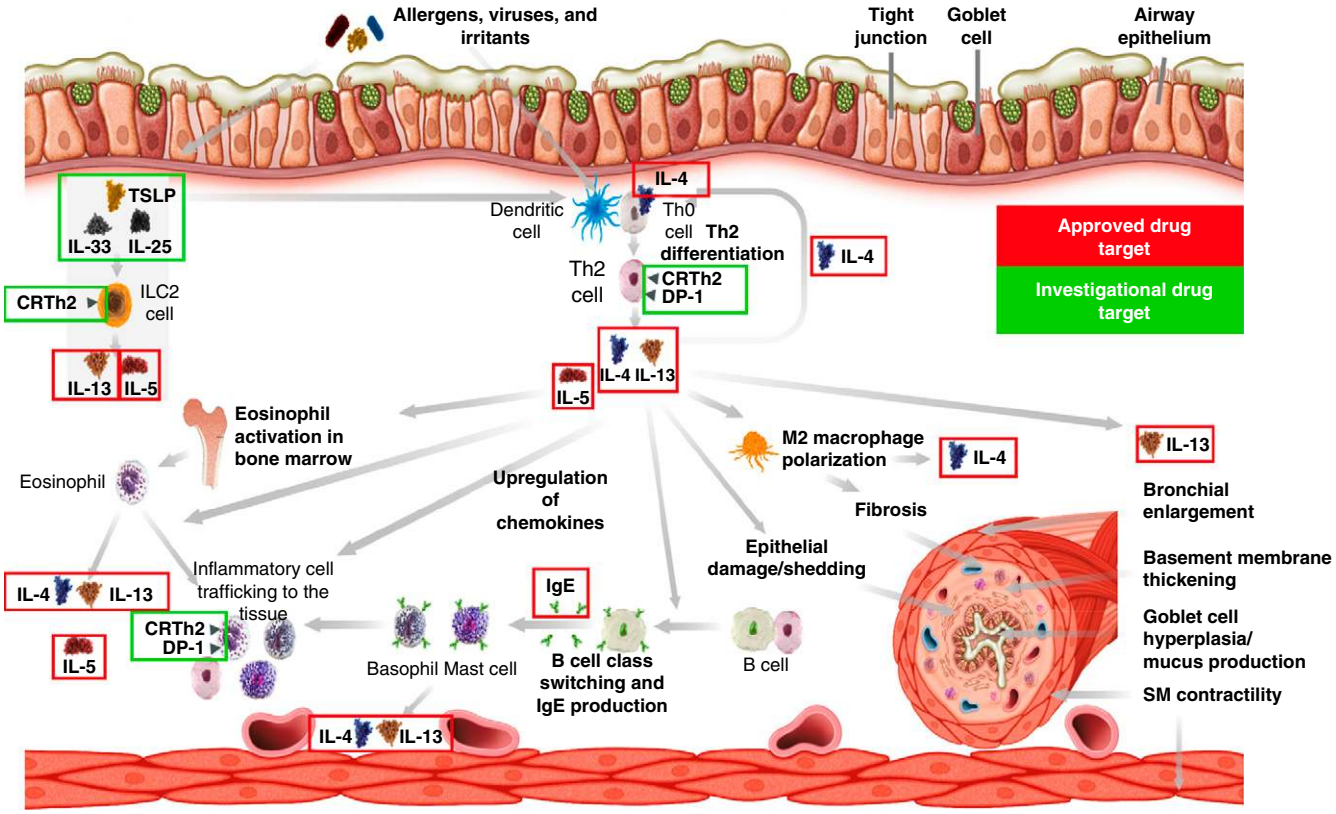

Figure 1. Schematic of the immunopathobiology of asthma with sites of the targeted treatments with approved and investigational monoclonal antibodies marked. In asthma, the interaction of genetic susceptibility and environmental exposures—such as with allergens, viruses, pollutants, and irritants—creates airway inflammation. In type 2 (T2) asthma, the interaction of environmental exposures with the airway epithelium leads to the release of the mediators IL-33, IL-25, and TSLP (thymic stromal lymphopoietin). In addition, allergens are taken up by dendritic cells and presented to naive T-helper (Th0) cells. A cascade of events as shown ensues that leads to production of the type 2 cytokines IL-4, IL-5, and IL-13; secretion of IgE by B cells; and chemoattraction of mast cells, eosinophils, and basophils. This process lends itself to numerous therapeutic targets that have already been approved by the U.S. Food and Drug Administration (outlined in red) and others that remain in investigation (outlined in green). CRTh2 = chemoattractant receptor–homologous molecule expressed on T2 cells; DP-1 = prostaglandin D2 receptor type 1; ILC2 = innate lymphoid cell type 2; M2 macrophage = alternatively activated macrophage; SM = smooth muscle. Modified by permission from Reference 98 from Sanofi.

moderate to severe persistent asthma, symptoms inadequately controlled by ICS, positive allergy testing, and a total serum IgE level between 30 and 1,300 IU/ml for patients 6 to 11 years old and between 30 and 700 IU/ml for patients 12 years and older (European Union is between 30 and 1,500 IU/ml). Omalizumab is given subcutaneously every 2 to 4 weeks, with dose and frequency based on body weight and pretreatment IgE level. Monitoring of IgE levels during treatment is not recommended. A trial of 3 to 6 months should be given to assess for clinical response, and treatment should be continued indefinitely if a patient has a favorable response as supported by the XPORT (Xolair Persistency of Response after Long-Term Therapy) trial (33). Omalizumab is generally well tolerated, with a risk of anaphylaxis of 0.1% to 0.2% (34). Despite the relatively low risk of anaphylaxis, the U.S. Food and Drug Administration (FDA) has placed a black box warning on omalizumab, and the medication should be administered in a healthcare setting that is prepared to deal with anaphylaxis. Patients should be observed for 2 hours after the first three injections and then 30 minutes with subsequent injections.

Anti–IL-5

Mechanism of action. A subset of patients with moderate to severe asthma have an eosinophilic phenotype characterized by an increase in sputum and/or blood eosinophils despite treatment with corticosteroids and are more prone to frequent exacerbations (9, 35–37). IL-5 is the primary cytokine involved in the recruitment, activation, and survival of eosinophils, and by inhibiting this pathway, anti–IL-5 biologics reduce eosinophilic airway inflammation (38). Mepolizumab and reslizumab are both mAbs that bind and inhibit IL-5, preventing IL-5 from binding to its receptor on eosinophils and reducing downstream eosinophilic inflammation. Benralizumab is a mAb that binds the α subunit of the IL-5 receptor on eosinophils and basophils, preventing IL-5 binding and the subsequent recruitment and activation of eosinophils. Furthermore, afucosylation of the benralizumab mAb enhances its ability to engage with FcγRIIIa on natural killer cells, causing aggregation around the eosinophil and resulting in

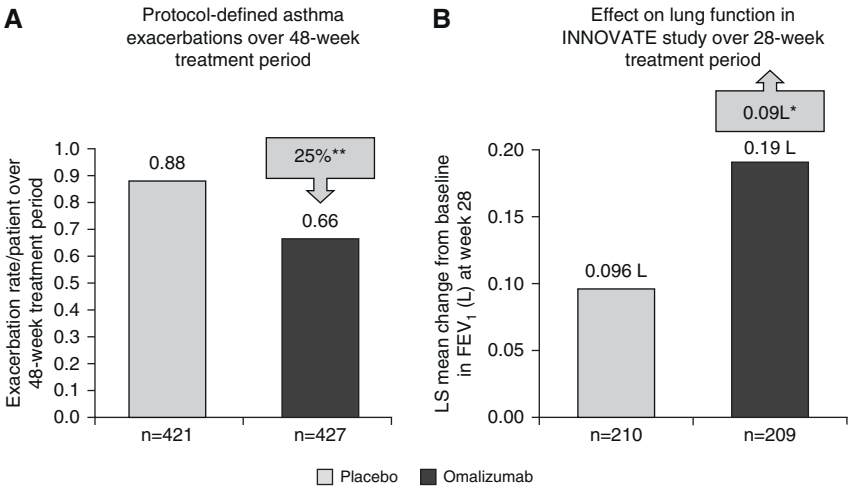

Figure 2. Effect of omalizumab on (*A*) rate of asthma exacerbations and (*B*) lung function: the EXTRA trial (28) and INNOVATE study (27). (*A*) In the EXTRA trial, when evaluated over 48 weeks, treatment with omalizumab reduced the rate of asthma exacerbations by 25% (95% confidence interval, 8–39%). (*B*) In the INNOVATE study, when evaluated over a 28-week period, treatment with omalizumab improved lung function, as measured by the least squares (LS) mean change in FEV_1, by 94 ml more than placebo ($P = 0.043$). *$P < 0.05$; **$P < 0.01$.

antibody-directed cell-mediated cytotoxicity and eosinophil apoptosis followed by phagocytosis by macrophages (39).

Mepolizumab

Efficacy. Mepolizumab has been studied in patients with uncontrolled eosinophilic asthma who have increased sputum (>3%) or AEC (≥150 or ≥300 cells/μl). Mepolizumab has been shown to reduce asthma exacerbations, improve lung function, improve asthma control, and reduce OCS use in multiple RCTs (35; 40–43). In the SIRIUS trial, treatment with mepolizumab led to a reduction in OCS dosage by 50% in patients with eosinophilic asthma on chronic OCS (Figure 3). This corticosteroid-sparing effect occurred while maintaining the effects of reduced exacerbations (32%) and improved asthma control (43). The effect of mepolizumab on lung function has been less consistent. Some trials demonstrated an improvement in FEV_1, whereas one of the largest trials, the DREAM trial, demonstrated no significant change in FEV_1 with mepolizumab (42).

A recent Cochrane review found that patients with eosinophilic asthma treated with mepolizumab had a reduction in asthma exacerbations by 50% and a small increase in FEV_1 of 110 ml over placebo. Mepolizumab resulted in a clinically and statistically significant improvement in QOL as measured by the St. George's Respiratory Questionnaire. A lack of clinical response to omalizumab does not predict a lack of response to mepolizumab (44).

Indications, administration, safety. Mepolizumab is currently approved for patients 12 years of age and older with severe asthma with an eosinophilic phenotype. Although the FDA has not set an AEC required for use, RCTs have suggested a benefit for patients with a count as low as 150 cells/μl, particularly in patients on chronic OCS (45). Mepolizumab is administered subcutaneously every 4 weeks at 100 mg per dose. A clinical response should be seen within 4 months, and treatment with mepolizumab should be continued indefinitely if a clinical response is achieved. Mepolizumab has been demonstrated to have a safety profile that is similar to placebo (46). A zoster vaccination (preferably recombinant, not live virus) should be given 4 weeks before drug initiation in those aged 50 years old or older. Mepolizumab is also approved for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) at a higher dose of 300 mg every 4 weeks.

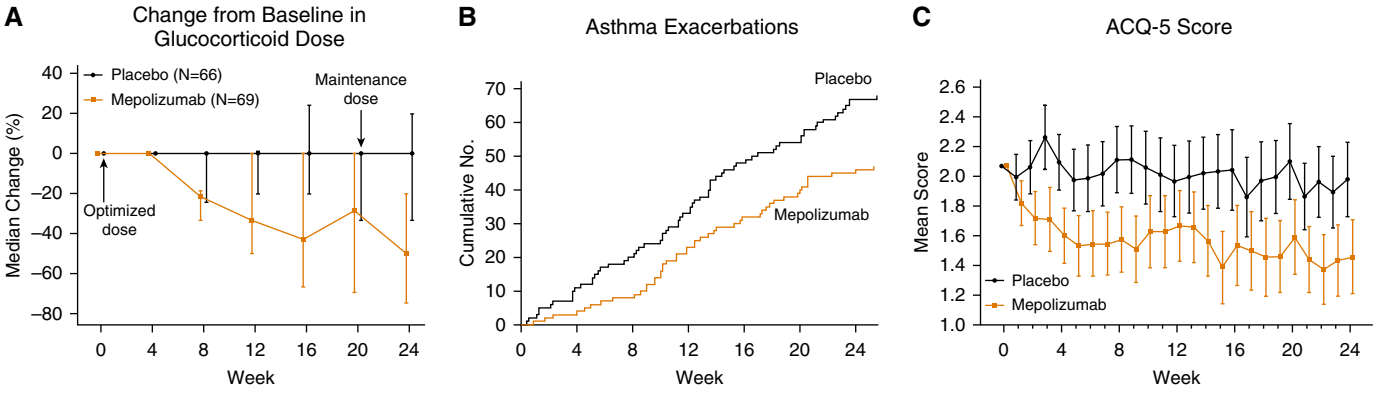

Figure 3. Effect of mepolizumab on (*A*) oral corticosteroid reduction, (*B*) asthma exacerbations, and (*C*) lung function: the SIRIUS trial. (43). (*A*) In the SIRIUS trial, the reduction in steroid dosing at 24 weeks was 50% in the group receiving mepolizumab compared with 0% in the placebo group ($P = 0.007$). (*B*) At 24 weeks, there was a relative reduction of 32% in the cumulative number of asthma exacerbations with mepolizumab ($P = 0.04$). (*C*) Based on the Asthma Control Questionnaire 5 (ACQ-5), mepolizumab resulted in improvement in asthma control at 2 weeks that was sustained through the 24-week trial ($P = 0.004$). Error bars show 95% confidence intervals around the least squares mean.

Reslizumab

Efficacy. Reslizumab has been studied in several RCTs in patients with uncontrolled eosinophilic asthma and has consistently been shown to reduce AEC, reduce asthma exacerbations, and improve lung function (47–49) (Figure 4). There are no studies to date that have evaluated the OCS-sparing effect of reslizumab. One study demonstrated no significant improvement in lung function with reslizumab in patients with AECs less than 400 cells/μl, highlighting the importance of selecting an eosinophilic phenotype (50). A recent Cochrane review found that reslizumab reduced asthma exacerbations by 50%, increased FEV_1 by 110 ml over placebo, and improved QOL (51).

Indications, administration, safety. Reslizumab is approved as add-on treatment for patients aged 18 years or older with severe eosinophilic asthma (AEC ⩾ 400 cells/μl). Reslizumab is the only biologic delivered intravenously using weight-based dosing at 3 mg/kg dose every 4 weeks. The weight-based dosing may offer a distinct advantage over fixed doses (*see* selection of IL-5 mAb below). Reslizumab is well tolerated, with adverse events similar to the placebo group. However, three cases of anaphylaxis occurred during RCTs, and thus reslizumab carries an FDA black box warning (48).

Benralizumab

Efficacy. Similar to the other anti–IL-5 biologics, benralizumab has been shown to reduce asthma exacerbation rates and improve lung function in patients with uncontrolled eosinophilic asthma (52–54). A 2017 Cochrane review demonstrated a significant reduction in asthma exacerbations in patients treated with benralizumab regardless of their AEC. However, the effect of benralizumab was greatest in patients with AEC greater than or equal to 300 cells/μl. Furthermore, improvements in lung function and QOL were only significant in the higher eosinophil group (51). In the ZONDA trial, benralizumab was shown to significantly reduce OCS use by 75% in patients on long-term OCS with AEC greater than or equal to 150 cells/μl, while reducing annualized asthma exacerbations by 70% (55) (Figure 5). Benralizumab appears to be equally effective independent of atopy (56).

Indications, administration, safety. Benralizumab is approved for patients 12 years of age or older with uncontrolled eosinophilic asthma (AEC ⩾ 300 cells/μl) (51, 54). Benralizumab is administered at 30 mg subcutaneously every 4 weeks for the first three doses as an induction phase (to reduce tissue eosinophilia), followed by every 8 weeks thereafter for maintenance. A trial of 4 months should be given to assess for response. Benralizumab is generally well tolerated but has led to hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria.

Selection of Anti–IL-5: Influence of Airway Eosinophils and Local Eosinophilopoeitic Mechanisms

Although AEC correlates fairly well with airway luminal (sputum) eosinophil numbers in patients who are on low to moderate doses of ICS (57), there is lack of concordance in those on maintenance OCS (58). Persistently raised AECs greater than 400 cells/μl are likely to be associated with sputum eosinophilia, but the converse is not true. Discordance between the systemic versus luminal anti-eosinophil effect of anti–IL-5 therapy is indicative of alternative mechanisms of *in situ* eosinophilic inflammation, which, when unsuppressed, may contribute to the ongoing clinical symptoms (59) (Figure 6). Mepolizumab 750 mg intravenous administered to patients with persistent sputum eosinophilia (41) significantly reduced both blood and sputum eosinophils and allowed significant reduction in OCS (87% of the dose) along with improved asthma control. In comparison, the OCS reduction effect of mepolizumab at the

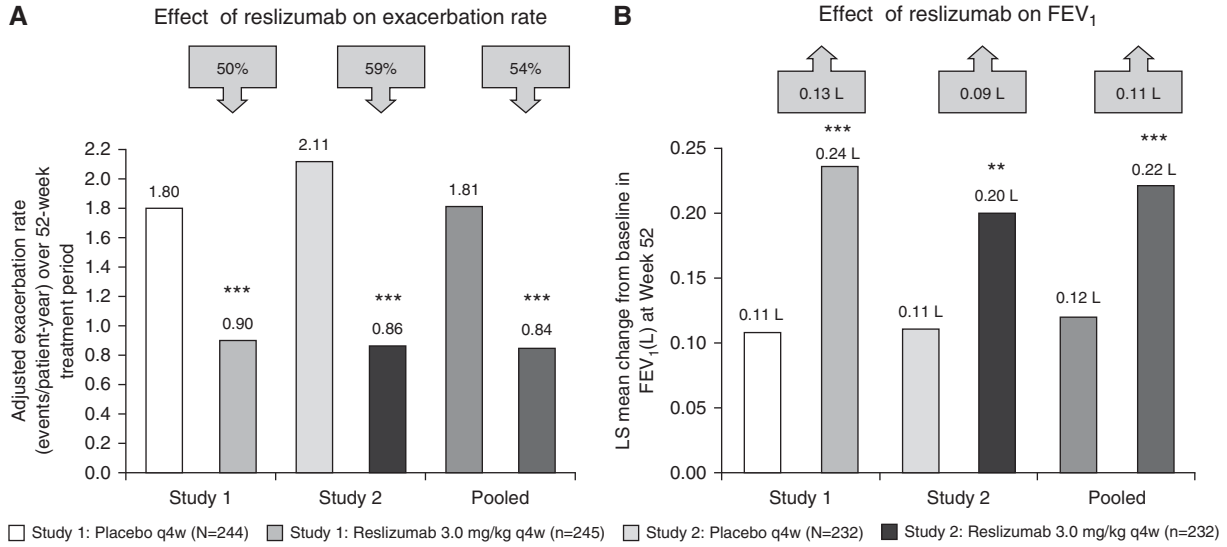

Figure 4. Effect of reslizumab on (*A*) rate of asthma exacerbations and (*B*) lung function: the BREATHE trials (48). (*A*) In two separate trials, reslizumab reduced the rate of asthma exacerbations with a pooled relative reduction in the asthma exacerbation rate of 54% (95% confidence interval, 42–63%) over 52 weeks. (*B*) Additionally, reslizumab improved lung function as measured by FEV_1 by 110 ml (95% confidence interval, 67–150 ml) more than placebo. $^{**}P < 0.01$; $^{***}P < 0.001$. LS = least squares; q4w = every 4 weeks.

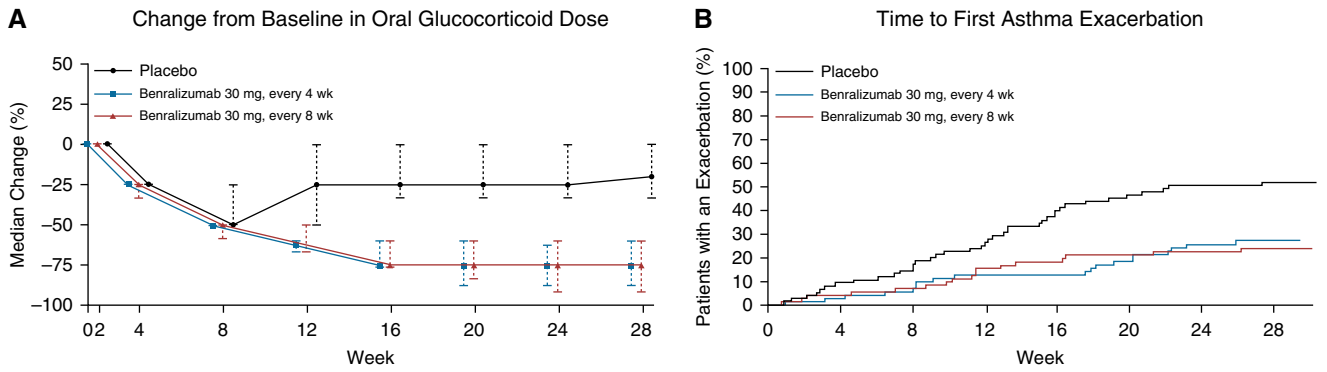

Figure 5. Effect of benralizumab on (*A*) time to first asthma exacerbation and (*B*) oral corticosteroid reduction: the ZONDA trial (55). (*A*) In the ZONDA trial, benralizumab dosed every 4 weeks or every 8 weeks led to a median percentage reduction from baseline in steroid requirement of 75% compared with a 25% reduction with placebo ($P < 0.001$). (*B*) As shown using a Kaplan-Meier cumulative incidence curve, benralizumab was associated with a longer time to first asthma exacerbation when administered every 4 weeks (hazard ratio [HR], 0.39; 95% confidence interval [CI], 0.22–0.66) or every 8 weeks (HR, 0.32; CI, 0.17–0.57). Error bars show 95% confidence intervals around the least squares mean.

100 mg subcutaneous dosing was modest in the SIRIUS study (43). A small study of 10 patients with severe uncontrolled asthma on 100 mg subcutaneous mepolizumab showed significant decline in AEC; however, an increased sputum eosinophil count correlated with asthma exacerbations (60). This lower dose of mepolizumab does not appear to suppress the local eosinophilopoietic activity, as evidenced by persistent airway eosinophil progenitor cells and ILC-2 cells that are a source of IL-5 (60, 61). Higher doses of anti–IL-5 mAbs, administered to these patients in the form of intravenous weight-adjusted reslizumab (62), attenuated both sputum eosinophils and eosinophil peroxidase and were associated with improvement in asthma control. However, these studies are limited by the lack of head-to-head comparisons of the three anti–IL-5 mAbs in patients with similar entry criteria, which are sorely needed.

The presence of Ig-bound IL-5 in the sputum of patients receiving low-dose mepolizumab, with simultaneous increases in free IL-5 and IgG autoantibodies (63), suggests the possibility of immune complex aggregation and subsequent inflammation. These immune complexes formed between cytokines and mAbs when inadequate levels of drug reach the target tissues can increase the *in vivo* potency of the bound cytokine (64). Interestingly, there was simultaneous increase in IL-5^+ ILC-2s, sputum IL-5, and Ig-bound IL-5 in those who experienced worsening with low-dose anti–IL-5 therapy (63).

Anti–IL-4/IL-13

Dupilumab. Targeting IL-4 (65) or IL-13 alone (66) has been disappointing, probably because targeting only one of these cytokines does not abrogate airway inflammation (66–68). Dupilumab is a mAb that targets the IL-4α receptor and blocks signaling of both IL-4 and IL-13, key cytokines that promote production of IgE and recruitment of inflammatory cells in addition to stimulating goblet cell hyperplasia and modulating airway hyperresponsiveness and airway remodeling (69). Dupilumab has been shown to reduce asthma exacerbations, rapidly improve lung function, and decrease OCS use while decreasing levels of T2 inflammation (Fe_{NO}, thymus and activation-regulated chemokine, eotaxin-3, and IgE) in moderate to severe asthma (70, 71). The benefits of dupilumab were greater in subjects with higher baseline AEC and Fe_{NO} levels (71). In patients previously dependent on OCS, dupilumab was found to significantly reduce OCS use by 70%, and nearly half of patients were able to discontinue OCS. These OCS reductions occurred while reducing exacerbation rates by 60% and improving lung function (72) (Figure 7). Dupilumab has improved outcomes in patients with symptomatic chronic rhinosinusitis and nasal polyposis and should be considered in patients with asthma with this comorbidity (73).

Unlike the anti–IL-5 RCTs, baseline Fe_{NO} was a predictor of clinical response to dupilumab. Because IL-4 and IL-13, through STAT-6 (signal transducer and activator of transcription 6) phosphorylation, regulate both iNOS (inducible nitric oxide synthase) and the mucin 5AC gene and mucus production, it is not surprising that Fe_{NO} was a predictor of clinical response to dupilumab. Dupilumab has a favorable safety profile, with common side effects including injection site reaction and transient blood eosinophilia. Dupilumab has been approved by the FDA for the treatment of atopic dermatitis and was recently approved for asthma.

Selection of Biologic for Severe Uncontrolled Asthma

The majority of the aforementioned RCTs on biologics in patients with uncontrolled severe asthma have demonstrated a significant response to placebo with reductions in exacerbations, improvement in lung function, and improvement in patient-reported outcomes. These findings suggest that "severe asthma" is not intrinsically severe but often poorly controlled (74, 75). Therefore, these studies suggest that although targeting the T2 cytokines with biologics may improve asthma control, many patients may not actually need them. Improving affordability, availability, and accessibility to ICS and long-acting bronchodilators, as well as emphasizing the principles of asthma management, such as shared decision making, encouraging adherence, good inhaler technique, and allergen avoidance, are sufficient to control symptoms and prevent asthma exacerbations in the vast

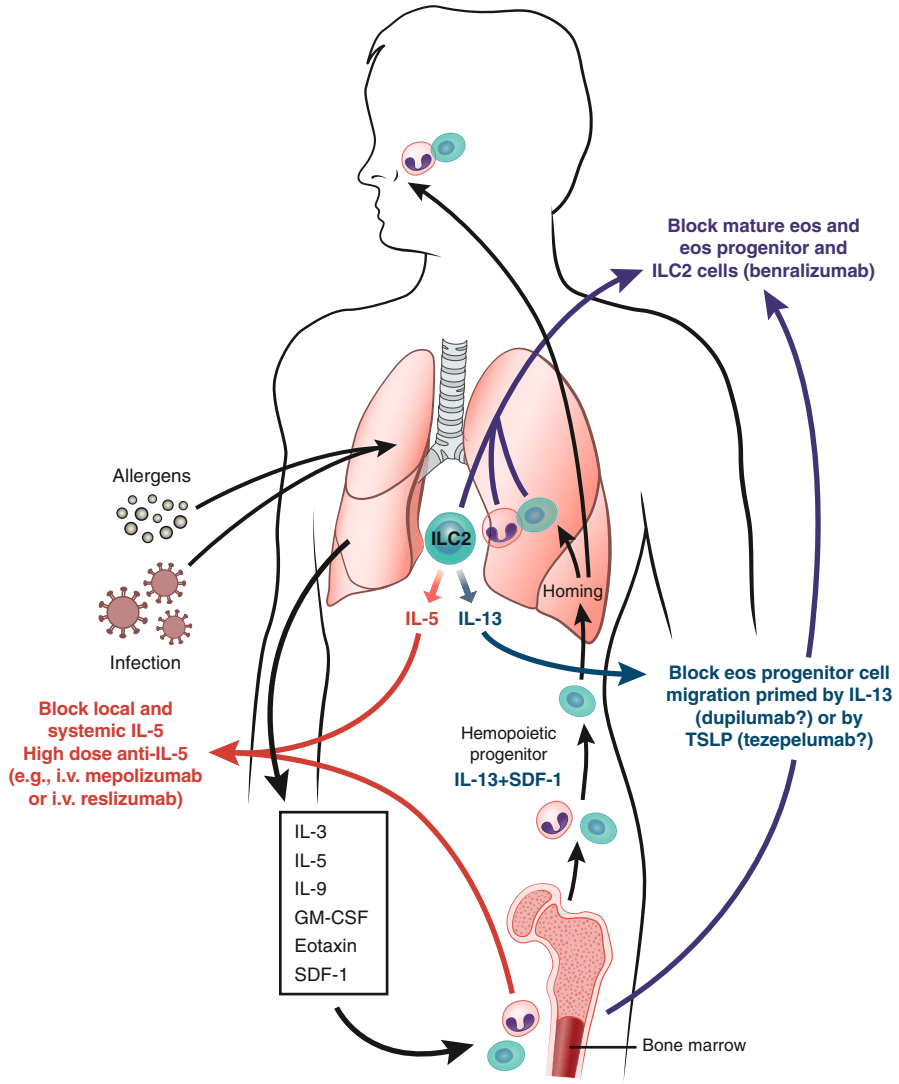

Figure 6. Schematic of airway (luminal) eosinophils and eosinophilopoeitic factors with anti–IL-5 therapy in severe eosinophilic asthma. In response to a variety of airway stimuli (such as allergens, microbes, pollutants, etc.), CD4 (classic T-helper cell type 2 [Th2] response) or non-CD4 cells (such as type 2 innate lymphoid cells [ILC2] in the airways, nonclassic T2 response), secrete eosinophilopoeitic cytokines such as IL-5 and IL-13. In patients with severe asthma who are on high doses of systemic corticosteroids, airway ILC2 cells may dominate over CD4 cells as the predominant source of IL-5 and IL-13. Although IL-13 can prime the migrational response of eosinophil progenitor cells from the bone marrow into the lung in response to SDF-1 (stromal-derived factor-1), locally derived IL-5 can promote their "*in situ* differentiation" into mature eosinophils. Pharmacokinetic data of airway levels of biologics have never been evaluated. Clinically relevant doses have been selected based on mathematical modeling of airway levels of drugs from studies in normal volunteers or subjects with mild asthma and from pharmacodynamics studies guided by absolute blood eosinophil levels. In order to suppress airway eosinophils, treatment options may include higher levels of anti–IL-5 neutralizing monoclonal antibodies such as reslizumab or mepolizumab, or inhibition of the migration of progenitor cells into the airways (e.g., anti–IL-4R or antialarmins such as anti-TSLP [thymic stromal lymphopoietin] or anti–IL-33), or depletion of both mature and immature eosinophils and possibly the ILC2 cells (those that express IL-5R) by the antibody-dependent cell–mediated cytotoxicity action of benralizumab. eos = eosinophils; GM-CSF = granulocyte–macrophage colony–stimulating factor. Illustration by Patricia Ferrer Beals.

majority of patients. In the patients with more severe disease who require three or more courses of OCS a year (despite adhering to their controller medications) or those who require chronic OCS to maintain asthma control, biologics have a more important role in disease management.

Because no head-to-head comparisons have been made between these biologics, claims of superiority of one biologic over the other as made by indirect treatment comparisons using metaregression and matching-adjusted strategies (76–78) may be invalid and misleading. Overall, all five of the currently approved biologics for severe asthma seem to reduce exacerbation rates by approximately 50%, with greater effects with higher baseline AEC. Because the predominant biological role of IL-5 is limited to eosinophil maturation, survival, and recruitment into the airway, it is logical to expect that the effects of anti–IL-5 would be predominantly seen in those patients whose airflow obstruction, symptoms, and severity are driven by luminal eosinophils. However, the roles of IL-4 and IL-13 (acting through the common IL-4R) are more pleiotropic, with effects on eosinophil recruitment, goblet cell hyperplasia and mucus secretion, smooth muscle contraction, and hyperresponsiveness. Therefore, the beneficial effects of anti–IL-4/13 treatment would be expected in a broader population of patients and not necessarily only in those with significant airway eosinophilia (79).

A more precise understanding of patient characteristics that would elucidate the greatest benefit from a specific biologic would be helpful. Use of predictive biomarkers could also help clinicians decide which biologic would lead to the most beneficial response. In addition, use of biomarkers and clinical indicators of response to biologic therapy earlier in the treatment course would allow for earlier adjustment to treatment regimens.

Unfortunately, omalizumab has no biomarker that has been useful for predicting or monitoring response. For all three anti–IL-5 mAbs, higher baseline AEC and a history of exacerbations predict enhanced response to the biologic. The presence of neutralizing antidrug antibodies has been low and not associated with loss of efficacy or predictive of side effects. In addition, baseline OCS use, history of nasal polyps, and prebronchodilator FVC less than 65% predicted were associated with enhanced response to benralizumab in reducing exacerbations, regardless of baseline AEC (80). These findings suggest that patients with these phenotypes (OCS dependent, nasal polyposis, reduced

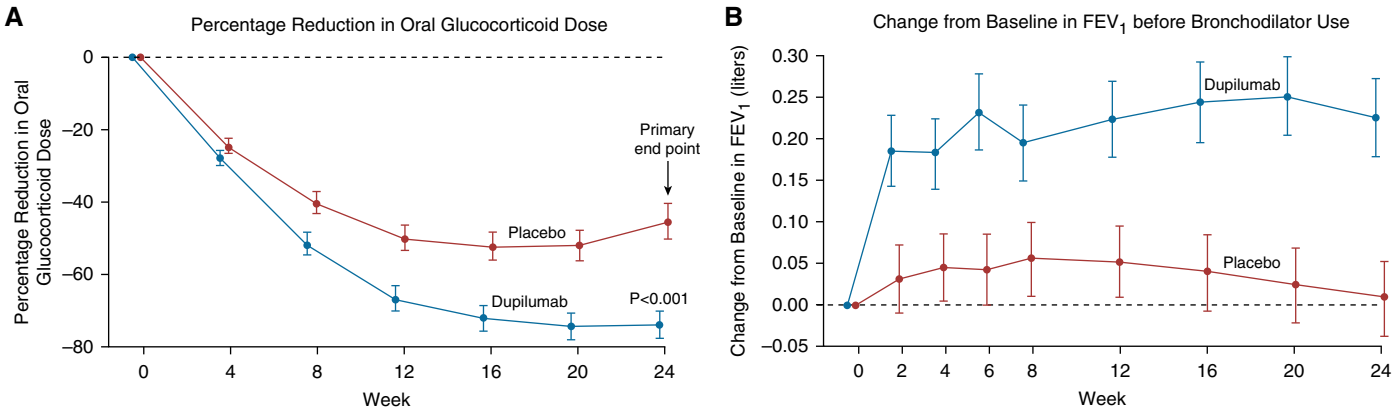

Figure 7. Effect of dupilumab on (*A*) percentage reduction in oral corticosteroid dosing and (*B*) lung function: the VENTURE trial (72). (*A*) In the VENTURE trial, the least squares mean percentage reduction in oral corticosteroid dosing in patients receiving dupilumab at 24 weeks was −70.1% (SE of ±4.9%) compared with −41.9% (SE of ±4.5%) in the group treated with placebo ($P < 0.001$). (*B*) At 24 weeks, dupilumab treatment resulted in a 220-ml (95% confidence interval, 90–340 ml) improvement in FEV_1 compared with placebo. Error bars show the SE.

lung function, and exacerbators) are most likely to respond to anti–IL-5 therapy.

Response biomarkers measured early in the course of therapy (e.g., drop in eosinophil count after anti–IL-5 administration) do not appear to predict long-term response. Use of clinical indicators (improved $FEV_1 \geqslant 100$ ml or Asthma Control Questionnaire score $\geqslant 0.5$) within the first 16 weeks of treatment with reslizumab predicted long-term response (81). These clinical indicators are easily measured by asthma specialists and can allow shared decision making with the patient early in the course of therapy to decide if the biologic should be continued or if a switch to alternate treatment is indicated.

Future Biologics

With improved understanding of the immunopathogenesis of asthma, additional inflammatory pathways have been identified as therapeutic targets, and new biologic agents are being developed. Although the currently FDA-approved biologics all target downstream pathways of T2 inflammation, researchers are studying various upstream targets of T2 inflammation, including IL-25, IL-33, and TSLP (Figure 1 and Table 3). In a recent phase 2 RCT of patients with moderate asthma, tezepelumab, a mAb against an alarmin, TSLP, reduced asthma exacerbations unrelated to baseline AEC, and decreased markers of T2 inflammation, IgE and F_{ENO} (82). Tezepelumab and other biologics that target upstream T2 inflammation may provide additional options for patients with uncontrolled noneosinophilic asthma in the future. Biologics and small-molecule antagonists targeting kinases (e.g., Janus kinase pathways) that are downstream of these T2 cytokines are also being developed (83).

Alternative modes of delivery of biologic therapies besides subcutaneous or intravenous are being evaluated. Plasma concentrations of biologics after intravenous administration are considerably higher than BAL concentrations (84). To increase drug concentration in the terminal bronchioles while decreasing systemic toxicity, researchers are studying nebulized biologic therapy. A recent animal study evaluating the use of a nebulizer to deliver fragments of anti–IL-13 mAbs to the terminal bronchioles demonstrated a reduction in allergic airway response and was well tolerated (85, 86).

Conclusions

Most patients with asthma, fortunately, do not need a biologic if they are adherent with their usual controller medications. Recognition of eosinophilic airway inflammation as a treatable trait has allowed for the emergence of biologic therapy in this specific patient population. In those patients who truly have severe asthma (and not one of the masqueraders) and whose luminal obstruction and asthma severity are predominantly mediated by eosinophils, anti–IL-5 mAbs are the therapy of choice. In patients whose luminal obstruction and severity may be driven by factors such as mucus production, eosinophils, and smooth muscle contraction and remodeling, an anti–IL-4R mAb may be the therapy of choice. Finally, patients with asthma that is clearly driven by a clinical history of allergies (rather than just an elevated IgE level) are candidates for anti-IgE therapy; however, anti–IL-5 mAbs may also be effective in some of these patients. If a patient's asthma is severe enough to require maintenance OCS, there is insufficient evidence to recommend anti-IgE therapy, as allergies may not be driving the need for OCS. There is a need to study and develop new biologics that will improve outcomes in patients with noneosinophilic or T2-low disease. Novel imaging strategies (87, 88) and immunoendotyping to develop new biomarkers (89) may lead to precise methods to identify the specific patients for the appropriate therapies. Finally, the possibility of earlier initiation of biologics to alter disease progression is exciting and needs to be explored. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Table 3. Other Biologics and Small Molecules under Development for Type 2 Inflammatory Diseases

Agent	Clinical Trial Number	Mode of Action	Mode of Administration	Current Clinical Phase	Investigated Patient Populations
Asapiprant (90)		Prostaglandin D2 antagonist	Oral	Preclinical, 3 for allergic rhinitis	Allergic asthma, allergic rhinitis
RPC4046 (91)	NCT02098473	IL-13R antagonist/anti–IL-13 mAb	s.c./i.v.	2 for EoE, 1 in asthma	EoE, moderate to severe asthma
ADC3680/ADC3608B (92)	NCT01730027	CRTh2 antagonist	Oral	2	Inadequately controlled asthma
AMG-282/RG6149	NCT01928368, NCT02170337	IL-33 antagonist/anti–IL-33 mAb	s.c./i.v.	2 for asthma, 1 for CRSwNP	Mild atopic asthma, CRSwNP
ANB020 (93)	NCT03469934, NCT02920021	IL-33 antagonist/anti–IL-33 mAb	s.c./i.v.	2	Severe asthma (eosinophilic phenotype), peanut allergy, AD
SB010 (94)	NCT01743768	Anti-GATA3 DNAzyme	Oral	2	Mild asthma
GSK3772847	NCT03207243	IL-33 antagonist/anti–IL-33 mAb	i.v.	2	Moderate to severe asthma
MK-1029 (95)	NCT02720081	CRTh2 antagonist	Oral	2	Persistent asthma uncontrolled by montelukast
SAR440340/REGN3500	NCT03387852	IL-33 antagonist/anti–IL-33 mAb	s.c.	2	Moderate to severe asthma
Timapiprant	NCT02002208	CRTh2 antagonist	Oral	2	Severe asthma of eosinophilic phenotype, moderate to severe AD
Fevipiprant	NCT03215758, NCT01785602	CRTh2 antagonist	Oral	3 for asthma, 2 in AD	Uncontrolled asthma, moderate to severe AD
Tezepelumab	NCT03347279	TSLP antagonist	s.c.	3	Inadequately controlled severe asthma
Lebrikizumab (96)	NCT02340234	IL-13R antagonist/anti–IL-13 mAb	s.c.	Discontinued in asthma, 2 in AD	Uncontrolled asthma with ICS, moderate to severe AD
Tralokinumab (97)	NCT03131648	IL-13R antagonist/anti–IL-13 mAb	s.c.	Discontinued in asthma, 3 in AD	Uncontrolled asthma, AD

Definition of abbreviations: AD = atopic dermatitis; CRSwNP = chronic rhinosinusitis without nasal polyps; CRTh2 = chemoattractant receptor–homologous molecule expressed on T-helper type 2 cells; EoE = eosinophilic esophagitis; ICS = inhaled corticosteroid; mAb = monoclonal antibody; TSLP = thymic stromal lymphopoietin.

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