

# Biologics for Severe Asthma: Treatment-Specific Effects Are Important in Choosing a Specific Agent



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**List of Design Committee Members:** James G. Krings, MD, Mary Clare McGregor, MD, Leonard B. Bacharier, MD, and Mario Castro, MD, MPH (authors); Michael Schatz, MD, MS (editor)

### Learning objectives:

1. To appreciate that an increasing number of biological therapies are being approved that directly alter the immunopathogenesis that leads to asthma and can have benefits that previous therapies did not.

2. To understand the mechanism of action, specific indications, and anticipated effects of each of the Food and Drug Administration (FDA)—approved biological therapies.

3. To appreciate how various phenotypes that a clinician may see in his or her clinic, such as patients with frequent exacerbations, fixed airway obstructions, or corticosteroid resistance, could influence his or her decision in choosing among the only increasing number of biological therapies.

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**Abbreviations used**

EMA- European Medicines Agency  
 FDA- Food and Drug Administration  
 FENO- Fractional exhaled nitric oxide  
 ICS- Inhaled corticosteroid  
 IU- International unit  
 IV- Intravenous/intravenously  
 OCS- Oral corticosteroid  
 SC- Subcutaneous/subcutaneously  
 T2- Type 2 cell endotype  
 TSLP- Thymic stromal lymphopoietin

**Patients with uncontrolled severe persistent asthma have greater morbidity, greater use of health care resources, and more impairment in health-related quality of life when compared with their peers with well-controlled disease. Fortunately, since the introduction of biological therapeutics, patients with severe eosinophilic asthma now have beneficial treatment options that they did not have just a few years ago. In addition to anti-IgE therapy for allergic asthma, 3 new biological therapeutics targeting IL-5 and 1 targeting IL-4 and IL-13 signaling have recently been approved by the Food and Drug Administration for the treatment of severe eosinophilic asthma, and approval of more biological therapeutics is on the horizon. These medications decrease the frequency of asthma exacerbations, improve lung function, reduce corticosteroid usage, and improve health-related quality of life. This article reviews the mechanisms of action, specific indications, benefits, and side effects of each of the approved biological therapies for asthma. Furthermore, this article reviews how a clinician could use specific patient characteristics to decide which biologic treatment may be optimal for a given patient. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1379-92)**

**Key words:** Asthma; Severe asthma; Eosinophilic asthma; Asthma treatments; Biologics; Monoclonal antibodies

## INTRODUCTION

Asthma is a heterogeneous disorder that is characterized by chronic airway inflammation, airway hyperresponsiveness, and variable obstruction. Asthma affects more than 300 million people worldwide and is expected to only increase in prevalence.<sup>1,2</sup> Approximately 5% to 10% of patients with asthma have severe disease, which is defined as asthma that requires high-dose inhaled corticosteroids (ICSs) plus a second controller to prevent it from becoming “uncontrolled” or which remains “uncontrolled” despite this therapy.<sup>3,4</sup> Patients with severe disease have worse quality of life, and disproportionately high morbidity, mortality, and use of health care resources when compared with their peers with well-controlled disease.<sup>5-7</sup> Furthermore, roughly 40% of patients with severe disease are reliant on maintenance or frequent use of oral corticosteroids (OCSs) in an attempt to maintain adequate control of their disease.<sup>8-10</sup> The side effects from this significant corticosteroid exposure are unacceptable and new management strategies are needed.

Fortunately, the management of severe asthma has significantly progressed as recently updated in the Global Initiative for Asthma.<sup>11</sup> Today, patients with severe persistent asthma are treated with Global Initiative for Asthma step 4 or 5 medications including medium-to-high-dose ICSs, typically in combination with a long-acting beta-agonist. When control is not achieved with these medications and when adherence and inhaler technique have been assured, then long-acting muscarinic antagonists and/or biologics should be considered. In addition to these therapies, asthma specialists can consider use of add-on azithromycin, chronic low-dose OCSs ( $\leq 7.5$  mg prednisone equivalent/d), or nonpharmacologic treatments such as bronchial thermoplasty in selected patients.<sup>12,13</sup>

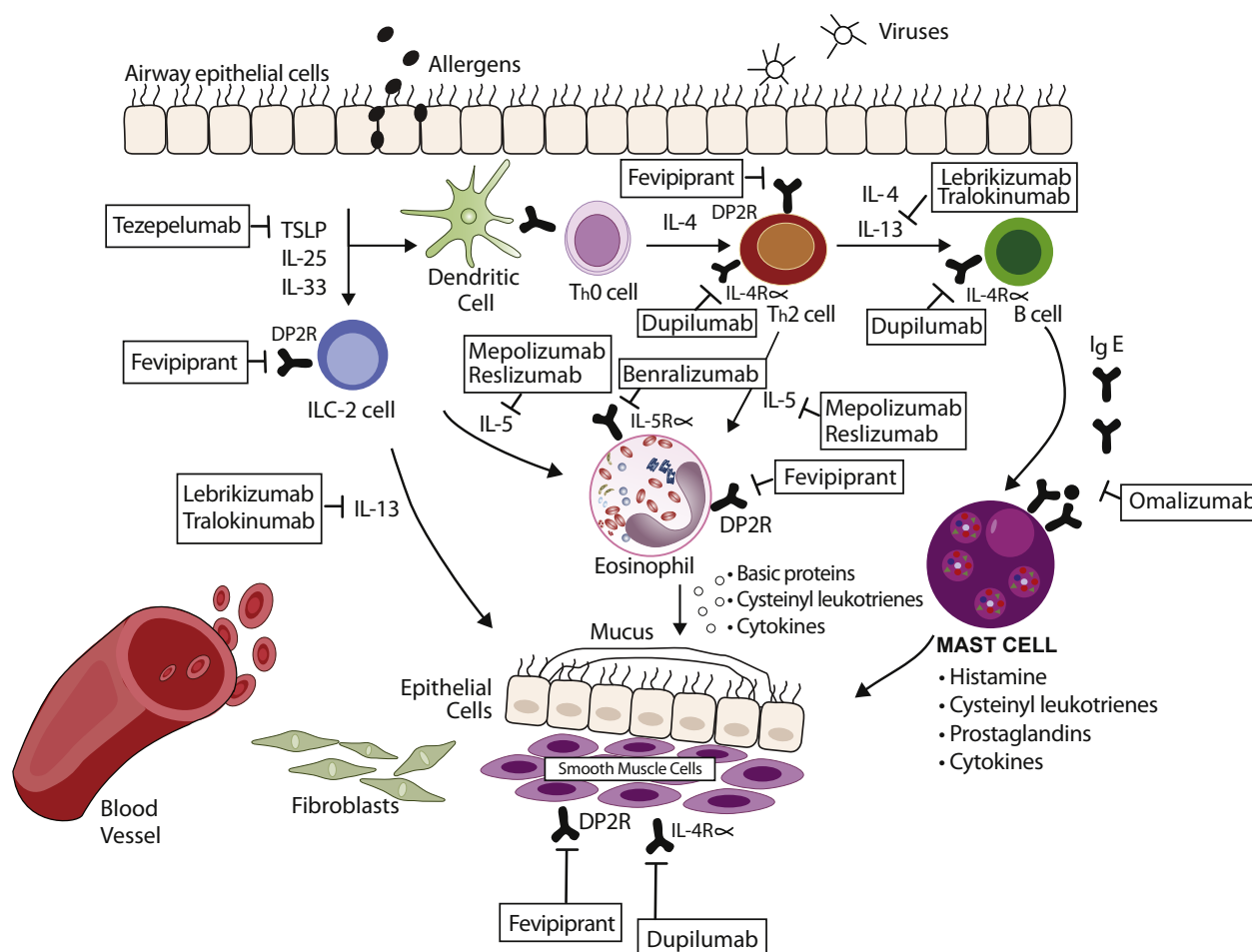
The biological therapies act directly to alter the immunopathogenesis leading to asthma rather than simply treating the downstream airway inflammation and bronchospasm. The processes that lead to asthma are complex and not the same for each individual patient.<sup>14</sup> However, 2 major endotypes—or subtypes of asthma based on their specific pathophysiologic mechanisms—have been identified. These endotypes are type 2 cell (T2)-high asthma and T2-low asthma. These are defined on the basis of level of expression of the T2 cytokines, IL-4, IL-5, and IL-13 produced by T<sub>H</sub>2 lymphocytes, and innate lymphoid cell-2 activity within a given patient.<sup>15,16</sup> Discerning whether T2 inflammation is a main driver of a patient's disease is important because current biologics are most effective in the T2-high endotype.<sup>17</sup> In the past few years, 3 new biologics targeting IL-5—mepolizumab, reslizumab, and benralizumab—have been approved for the treatment of severe eosinophilic asthma.<sup>18-26</sup> In addition, a mAb directed against the IL-4 receptor alpha-chain, dupilumab, which blocks IL-4 and IL-13 signaling, was recently approved by the Food and Drug Administration (FDA).<sup>27,28</sup> These anti-IL-5 and anti-IL-4 therapies add to the previous anti-IgE biologic therapy, omalizumab.<sup>29-31</sup>

This article will review the mechanism of action, specific indications, and anticipated effects of each of the aforementioned biological therapies. In addition, this article aims to review how various phenotypes that a clinician may see in practice—characterized by frequent exacerbations, fixed airway obstruction, or corticosteroid resistance—could influence one's decision in choosing between the biological therapies.

## PHENOTYPES AND ENDOTYPES OF ASTHMA

As more and more treatments for asthma emerge, more precise understanding and characterization of the various asthma phenotypes is needed to help guide therapeutic decisions that are most likely to help each individual patient.<sup>32,33</sup> A wide variety of approaches have been proposed to define the phenotypes of asthma including classifying asthma on the basis of factors such as clinical characteristics, physiologic and imaging characteristics, environmental triggers, and pathobiology.<sup>34,35</sup> Ongoing research using data from the Severe Asthma Research Program has identified 5 clusters of asthma that are distinguished primarily on lung function and age of onset.<sup>36</sup> Other cohorts, such as U-BIOPRED (Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes), have confirmed this approach to cluster analyses to suggest various phenotypes of asthma.<sup>37-40</sup>

In addition to classifying asthma phenotypes, there is an ongoing effort to elucidate endotypes (a specific biologic pathway



**FIGURE 1.** Schematic of the mechanism of type 2 inflammation in asthma with the site of action of the biologic therapeutics. *DP2*, Prostaglandin D2 receptor (also known as CRTh2 receptor); *ILC-2*, innate lymphoid cell-2. Figure adapted from separate figures by Pelaia et al<sup>43</sup> and Fajt and Wenzel.<sup>44</sup>

that explains the observable properties of a phenotype), or subtypes on the basis of specific pathophysiology and functional mechanisms rather than on clinical characteristics alone.<sup>41,42</sup> Today, most experts agree that both a T2-high endotype and a T2-low endotype exist. The T2-high endotype is mediated by the type 2 inflammatory pathways, which are characterized by the effects of the cytokines IL-4, IL-5, and IL-13, with elevated biomarkers including fractional exhaled nitric oxide (FENO), serum IgE, and blood and sputum eosinophil levels.<sup>15</sup> Conversely, the T2-low subtype is characterized by neutrophilic or pauci-granulocytic airway inflammation with normal levels of eosinophils both in the sputum and in the airway.<sup>16</sup>

## **PATHOBIOLOGY OF T2-HIGH ASTHMA**

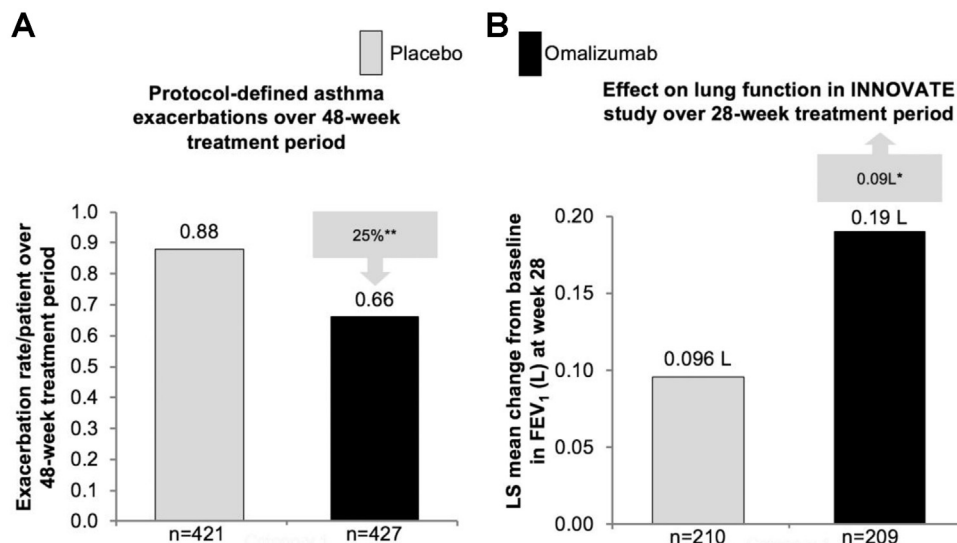
In asthma, genetic susceptibility and exposure to environmental factors—such as allergens, viruses, pollutants, and specific irritants—interact to create airway inflammation (Figure 1). In T2-high asthma, the interaction of allergens, pollutants, or microbes with the airway epithelium results in release of mediators such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 and subsequent increased production of the type 2 cytokines

including IL-4, IL-5, and IL-13.<sup>45–47</sup> Then, a proinflammatory cascade of events ensues that can result in chemoattraction of mast cells, eosinophils, and basophils, secretion of IgE by B cells, smooth muscle bronchoconstriction, and cellular remodeling of the airways. ICSs and OCSs can suppress the T2-high phenotype in most, but not all, patients. Biological agents act in a more targeted way on these pathways, offering many of the same benefits of OCSs, but without the plethora of OCS-induced side effects.

## **IgE-TARGETED THERAPIES**

### **Omalizumab**

**Mechanism of action and indications.** Omalizumab was the first biologic therapy for asthma approved in the United States and European Union, and now has been clinically used for more than a decade. Many patients with severe asthma have an allergic phenotype and IgE is central to the pathogenesis of this subtype.<sup>48–50</sup> Omalizumab is a recombinant humanized mAb that binds directly to free IgE, forming complexes that block IgE from binding to cell membrane IgE receptors.<sup>51</sup> This mechanism prevents the release of further inflammatory mediators and the



**FIGURE 2.** Findings from the EXTRA<sup>54</sup> and INNOVATE<sup>55</sup> trials demonstrated that omalizumab (A) reduced the rate of future asthma exacerbations and (B) improved lung function. At 48 weeks, omalizumab reduced the rate of asthma exacerbations by 25% (95% CI, 8%-39%). In the INNOVATE study, as measured by least squares (LS) mean change in FEV<sub>1</sub>, omalizumab improved lung function by 94 mL more than placebo ( $P = 0.043$ ). \* $P < .05$ . \*\* $P < .01$ .

downstream inflammatory cascade propagated by IgE.<sup>52</sup> Furthermore, omalizumab ultimately leads to downregulation of IgE receptors on mast cells and basophils, further blunting a patient's allergic response.<sup>53</sup>

In the United States, omalizumab is approved for use in adults and children older than 6 years with moderate-to-severe persistent allergic asthma with positive IgE specific test results or positive skin test results to a perennial aeroallergen, incomplete control with an ICS, and a total serum IgE level of 30 to 700 international unit (IU)/mL in patients 12 years and older, and 30 to 1300 IU/mL for patients aged 6 to 11 years (of note, omalizumab is approved for an IgE level of up to 1500 IU/mL in the European Union in all age groups). As of today, omalizumab is the only biologic for asthma in the United States that is approved for use in children younger than 12 years.

**Efficacy.** Omalizumab reduces the rate of asthma exacerbations by 25% to 50%, improves health-related quality of life, improves lung function, and decreases the use of ICSs as found in numerous randomized controlled trials in adults and children (Figure 2).<sup>29,54-62</sup> In addition, several "real-world" studies of omalizumab have now been completed, demonstrating its efficacy.<sup>63-66</sup> A Cochrane review from 2014 evaluated 25 randomized controlled trials demonstrating that a patient's absolute risk of having an acute asthma exacerbation over a time period of 16 to 60 weeks was 16% with omalizumab as compared with 26% with placebo.<sup>29</sup> In addition, patients used their rescue beta-agonist less often and were more likely to be able to reduce their daily ICS dosage when using omalizumab as compared with placebo.<sup>29,30</sup> In regard to the patient on chronic OCS, some studies found that omalizumab decreases the total dosage of OCS a patient requires.<sup>67,68</sup> However, in a large systematic review, omalizumab did not improve a patient's likelihood of completely discontinuing chronic OCS.<sup>29,31</sup> Finally, some studies have shown that omalizumab leads to a modest improvement in lung

function, but in general a significant effect on lung function has not been seen with omalizumab.<sup>29,30,55,59-61,64</sup>

Omalizumab has been specifically approved for use in patients as young as 6 years with an elevated IgE level and evidence of allergic sensitization to a perennial aeroallergen. However, the absolute level of IgE elevation does not accurately determine degree of treatment response to omalizumab.<sup>69</sup> As such, several recent studies have been undertaken in an attempt to discern which patients are likely to benefit the most from treatment. In retrospective analyses, patients who received omalizumab, as compared with placebo, had greater decrements in their risk of having an exacerbation if they had higher levels of T2 inflammation (FENO and blood eosinophil levels above the median cutoff point).<sup>54,70,71</sup> However, a recent uncontrolled real-world study showed that regardless of eosinophil level, use of omalizumab resulted in some improvement in asthma control in the approved patient population.<sup>64</sup>

### Administration, duration of therapy, and precautions.

Before the administration of omalizumab, the total IgE level must be checked. The dose of omalizumab for the treatment of asthma is a total of 0.016 mg/kg per IU of IgE in a 4-week period (Table I). Generally, 150 to 375 mg of omalizumab is given every 2 to 4 weeks subcutaneously (SC) on the basis of the above dosing calculation, with upper limits for patients with high IgE levels and increased weight. Laboratory monitoring is not required while on omalizumab, and IgE levels should not be followed because total serum IgE levels often rise while the patient is on treatment. Typically, 3 to 6 months of treatment with omalizumab is given before assessing response. If no improvement is observed in this time frame, further treatments are unlikely to yield benefit. The recommended duration of treatment is not clear, but many patients are continued long-term. A few studies looking at patients who discontinued omalizumab after years of treatment

**TABLE 1.** Characteristics of the biologics that are FDA-approved for the treatment of moderate-to-severe persistent asthma with a T2-high phenotype

Medication	Mechanism of action	FDA-approved indication	Dosing and administration	Warnings and precautions
Omalizumab	Binds free IgE; decreases expression of high-affinity IgE receptors on mast cells	≥6-y-old with moderate-to-severe persistent asthma, an IgE level of 30-700 IU/mL (US ≥12 y), 30-1300 IU/mL (US 6-11 y), or 30-1500 IU/mL (EU), positive IgE specific test results or positive skin test results to a perennial aeroallergen, and incomplete control with an ICS	150-375 mg SC q2-4 wk based on dosing calculation of 0.016 mg/kg per IU of IgE in a 4-wk period*	Contains black box warning as 0.1%-0.2% of patients experienced anaphylaxis in clinical trials
Mepolizumab	Binds to IL-5 ligand; blocks signaling of IL-5	≥12-y-old (US) or ≥6-y-old (EU) with severe eosinophilic asthma unresponsive to appropriate GINA step 4 or 5 therapy. No strict eosinophil cutoff exists but generally ≥150-300 cells/μL is used	100 mg SC q4 wk	Can cause hypersensitivity reactions (eg, anaphylaxis, angioedema, and bronchospasm)
Reslizumab	Binds to IL-5 ligand; blocks signaling of IL-5	≥18-y-old with severe eosinophilic asthma unresponsive to appropriate GINA step 4 or 5 therapy. No strict eosinophil cutoff exists but generally ≥400 cells/μL in the past year is used	3 mg/kg IV q4 wk	Contains black box warning as ~0.3% of patients experienced anaphylaxis in clinical trials
Benralizumab	Binds to IL-5 receptor alpha; results in death of eosinophils and basophils	≥12-y-old with severe eosinophilic asthma unresponsive to appropriate GINA step 4 or 5 therapy. No strict eosinophil cutoff exists but generally ≥300 cells/μL is used	30 mg SC q4 wk for first 3 doses followed by 30 mg q8 wk	Can cause hypersensitivity reactions (eg, anaphylaxis, angioedema, and bronchospasm)
Dupilumab	Binds to IL-4 receptor alpha; blocks signaling of IL-4 and IL-13	≥12-y-old with severe eosinophilic asthma unresponsive to appropriate GINA step 4 or 5 therapy	400-600 mg SC loading dose followed by 200-300 mg SC q2 wk†	Can cause hypersensitivity reactions (eg, anaphylaxis, angioedema, and bronchospasm)

EU, European Union; GINA, Global Initiative for Asthma.

\*Upper limits for patients with high IgE levels and increased weight exist.

†The higher dose of dupilumab (600 mg load, 300 mg q2 wk) is indicated for those with OCS dependence or comorbid moderate-to-severe atopic dermatitis. Dupilumab is the only biologic now approved for self-injection at home.

showed continued good asthma control and no “rebound effect” after discontinuing treatment.<sup>72-74</sup>

Omalizumab is typically very well tolerated. Approximately 0.1% to 0.2% of patients experience anaphylaxis, which is most likely to occur after 1 of the first 3 doses.<sup>75,76</sup> Because of this risk, the FDA placed a black box warning on the medication and certain precautions are recommended such as providing patients with an epinephrine autoinjector and administering the medication in a health care setting.<sup>75</sup>

## IL-5—Targeted THERAPIES

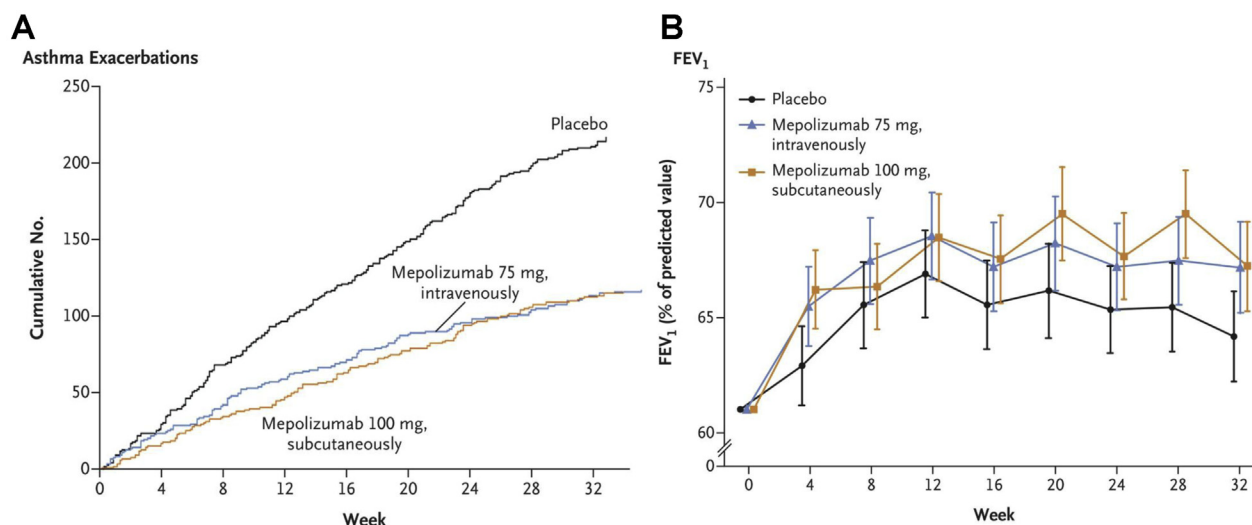
IL-5 causes the differentiation, migration, activation, and recruitment of eosinophils.<sup>77</sup> Healthy patients without asthma normally do not have a significant number of eosinophils in their airways. When present in the airways, eosinophils can result in the

release of proinflammatory cytokines and other mediators that ultimately result in increased airway smooth muscle contraction, angiogenesis, mucus production, and airway remodeling.<sup>78-80</sup> As such, studies have demonstrated that directing treatment toward the normalization of lung eosinophilia is beneficial and that increases in sputum eosinophil count can predict loss of asthma control.<sup>81,82</sup> Three mAbs that interfere with the effects of IL-5 have been approved by the regulatory agencies to date: mepolizumab, reslizumab, and benralizumab.

## Mepolizumab

**Mechanism of action and indications.** Mepolizumab is a mAb that binds directly to IL-5 and thus prevents the binding of IL-5 to the alpha chain of the IL-5 receptor on eosinophils and basophils (Figure 1).<sup>83</sup> Additional consequences of this blockade include decreased recruitment, maturation, differentiation, and





**FIGURE 3.** Findings from the MENSA trial demonstrated that mepolizumab (A) reduced the cumulative number of asthma exacerbations and (B) improved lung function.<sup>19</sup> In the MENSA trial, at 32 weeks mepolizumab reduced the rate of asthma exacerbations by 47% (95% CI, 28%-60%) in the intravenous arm and 53% (95% CI, 36%-65%) in the subcutaneous arm. As measured by FEV<sub>1</sub>, mepolizumab improved lung function by 100 mL (95% CI, 13-187 mL) more than placebo in the intravenous arm and 98 mL (95% CI, 11-184 mL) more than placebo in the subcutaneous arm. I demonstrate 95% CIs.

activation of eosinophils in the airway and decreased expression of the IL-5 receptor on the eosinophil and basophil.<sup>84</sup> Therefore, blockade of IL-5 by mepolizumab results in a reduced number of peripheral blood and tissue eosinophils.

Mepolizumab 100 mg SC once monthly was approved as an add-on therapy by the FDA and the European Medicines Agency (EMA) in 2015 for the management of patients who have severe eosinophilic asthma. The FDA has approved mepolizumab for patients 12 years or older, whereas the EMA has approved mepolizumab in adults and children 6 years or older. The FDA did not set a specific eosinophil threshold required for usage, but a cutoff of 300 cells/ $\mu$ L is often used. However, when stratified by eosinophil count in clinical trials, clinically important improvements in exacerbation frequency did occur in patients with severe asthma with a blood eosinophil count of 150 to 300 cells/ $\mu$ L.<sup>85</sup> If a patient is on chronic OCSs, the recommended eosinophil threshold is greater than or equal to 150 cells/ $\mu$ L.

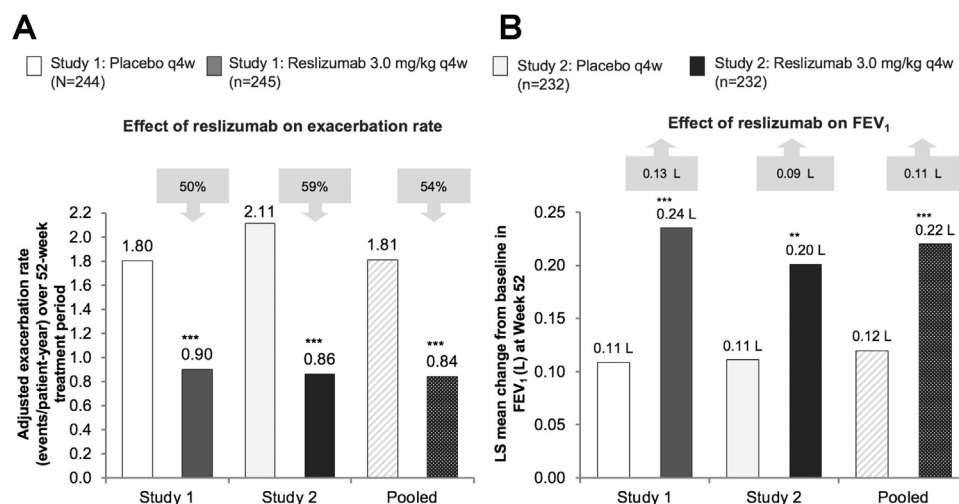
**Efficacy.** Mepolizumab has been shown to be efficacious at reducing the rate of asthma exacerbations, improving asthma control and health-related quality of life, and improving lung function in patients with uncontrolled severe persistent eosinophilic asthma (Figure 3).<sup>19,20,85-92</sup> A Cochrane review from 2017 found that patients treated with mepolizumab had approximately half as many exacerbations requiring OCSs over the observed time frame when compared with those who received placebo.<sup>93</sup> In regard to patients requiring chronic OCSs, the SIRIUS (Steroid Reduction with Mepolizumab Study) trial specifically evaluated patients with chronic blood eosinophilia despite the daily use of systemic corticosteroids. This study showed that patients who received mepolizumab were able to reduce their OCS dosage by 50%, and 14% of patients who received mepolizumab were able to completely discontinue their OCSs.<sup>20</sup>

Mepolizumab's effect on lung function is less clear. Although some studies have shown an improvement in lung function, one of

the large clinical trials (DREAM [Dose Ranging Efficacy and Safety with Mepolizumab Study] trial) and a recent Cochrane review did not show any clear improvement in lung function with mepolizumab.<sup>91-93</sup> This inconsistent effect on lung function may be related to the dosage of mepolizumab used in asthma and its effect on tissue eosinophilia. A subgroup analysis of the DREAM trial demonstrated that only the highest intravenous (IV) dose of mepolizumab (750 mg) was effective at reducing sputum eosinophils by 88%. The lowest IV dose (75 mg), which is similar to the approved 100 mg SC dose, did not significantly reduce sputum eosinophils, and similar lack of effect on sputum eosinophils by standard-dose mepolizumab was recently confirmed in an independent study by Mukherjee et al.<sup>94</sup> Furthermore, a recent study showed that although mepolizumab decreases eosinophil numbers, the remaining eosinophils may retain their functionality when treated with an IL-5–blocking agent.<sup>95</sup> Of note, mepolizumab has been approved for the treatment of eosinophilic granulomatosis with polyangiitis at a higher dose (300 mg SC every 4 weeks).

In a post hoc analysis of the DREAM and MENSA (Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma) studies, patients had a greater decrease in their exacerbation rate if they had higher blood eosinophil levels.<sup>85</sup> One recent study showed that prior unresponsiveness to omalizumab did not predict unresponsiveness to mepolizumab.<sup>90</sup> In addition, a recent uncontrolled trial (OSMO [Efficacy and Safety of Mepolizumab in Uncontrolled Patients with Severe Eosinophilic Asthma Following a Switch From Omalizumab] study) of patients not optimally controlled on omalizumab showed that when patients were switched to mepolizumab, they demonstrated a 64% reduction in exacerbations and 120 mL improvement in FEV<sub>1</sub>.<sup>96</sup>

**Administration, duration of therapy, and precautions.** Mepolizumab is administered at a dose of 100 mg SC every 4 weeks (Table I). After drug initiation, routine blood testing is not required. Similar to omalizumab, a clinical



**FIGURE 4.** Findings from 2 of the randomized trials as part of the BREATH program demonstrated that reslizumab (A) reduced the rate of future asthma exacerbations and (B) improved lung function.<sup>22</sup> In 2 separate randomized controlled trials, treatment with reslizumab was found to reduce the rate of asthma exacerbations by 54% (95% CI, 42%–63%) at 52 weeks. As measured by least squares (LS) mean change in FEV<sub>1</sub>, reslizumab improved lung function by 110 mL (95% CI, 67–150 mL) more than placebo. \*\**P* < .01. \*\*\**P* < .001.

assessment of treatment response is recommended after 3 to 6 months to determine whether treatment should be continued. If a patient demonstrates clinical response to mepolizumab, they should be continued on this treatment indefinitely because blood eosinophil levels start to rise 12 weeks after discontinuation.

The clinical trials did not show an increased risk of adverse reactions in those who received mepolizumab as compared with placebo; however, acute and delayed systemic reactions including hypersensitivity reactions (eg, anaphylaxis, urticaria, angioedema, rash, bronchospasm, and hypotension) have occurred following administration of mepolizumab.<sup>6,19,20,93</sup> In addition, cases of activation of herpes zoster have been reported with mepolizumab. Generally, assurance of zoster vaccination is recommended for adults 50 years or older (which is now FDA's lower age of indication for zoster vaccination in the general population) 4 weeks before initiation of mepolizumab unless the patient is at heightened risk of disseminated infection with vaccination (eg, on prednisone ≥20 mg daily for >2 weeks).<sup>97,98</sup> In the 52-week COSMOS (Long-term Efficacy and Safety of Mepolizumab in Patients with Severe Eosinophilic Asthma Study) trial, mepolizumab was found to have durable effects and a good long-term safety profile.<sup>89</sup>

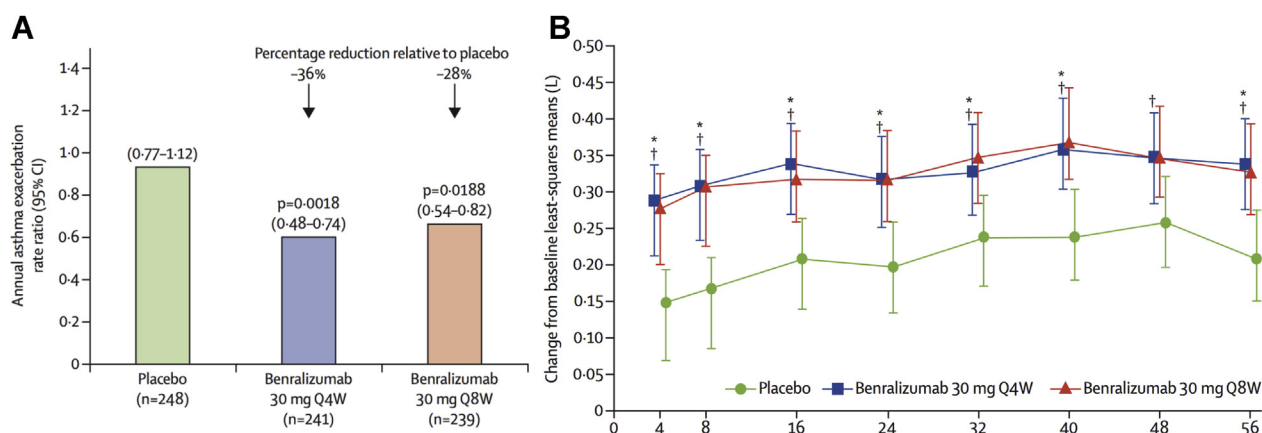
## Reslizumab

**Mechanism of action and indications.** Reslizumab was the second anti-IL-5 biologic that was approved by the FDA and the EMA for the treatment of severe eosinophilic asthma. Similar to mepolizumab, reslizumab is a mAb aimed at the IL-5 ligand that disrupts binding to the IL-5 receptor on eosinophils and basophils (Figure 1). While reslizumab is a mAb with recognition sites that were incorporated from a rat antibody, mepolizumab has a murine origin.<sup>99,100</sup> Otherwise, these 2 therapies are mechanistically very similar. In early 2016, the FDA and the EMA approved reslizumab as an add-on therapy for patients 18 years or older who have severe eosinophilic asthma. The FDA did not set a specific eosinophil threshold required for

usage. However, the clinical trials included patients with an induced sputum eosinophil count of greater than or equal to 3% or blood eosinophil count of greater than or equal to 400 cells/μL.<sup>21,22</sup> Today, a blood eosinophil cutoff of greater than or equal to 400 cells/μL is usually used clinically.

**Efficacy.** Reslizumab has been shown to reduce the frequency of exacerbations, improve lung function, reduce rescue beta-agonist usage, and improve health-related quality of life and asthma control in 4 randomized trials called the BREATH program (Figure 4).<sup>21–23,26</sup> Similar to mepolizumab, clinically significant asthma exacerbations were reduced by 50% to 59% in patients receiving reslizumab as compared with placebo.<sup>93</sup> The ability of reslizumab to reduce the usage of OCSs remains unclear because this has not been evaluated as an end point in any study to date. However, a recent study looked at a small number of patients chronically on OCSs who continued to have sputum eosinophilia associated with asthma exacerbations when treated with mepolizumab 100 mg SC. When switched to weight-adjusted dosing with reslizumab (3 mg/kg IV), these patients had elimination of their airway eosinophilia and improved asthma control.<sup>94</sup> Interestingly, in this study, switching to weight-based IV reslizumab not only attenuated sputum eosinophil levels and eosinophil activity (eosinophil peroxidase levels), but also sputum IL-5 levels predicted response to reslizumab. These results, as well as the findings described above that higher doses of mepolizumab (that are closer to weight-based IV reslizumab dosing) are needed to reduce sputum eosinophil count and attenuate eosinophil activity in some patients, lead to the conjecture that weight-based reslizumab may have a role in certain patients nonresponsive to standard-dose SC mepolizumab.<sup>101</sup> In regard to lung function, reslizumab demonstrated a modest improvement in lung function of approximately 90 to 180 mL in each of the major clinical trials.<sup>21–23,26</sup>

**Administration, duration of therapy, and precautions.** Reslizumab should be administered IV at a dose of 3 mg/kg over 20 to 50 minutes every 4 weeks (Table 1). Reslizumab is the only approved biological therapy for asthma that is



**FIGURE 5.** Findings from the CALIMA trial demonstrated that benralizumab (A) reduced the rate of future asthma exacerbations and (B) improved lung function.<sup>24</sup> In the CALIMA trial, at 56 weeks benralizumab reduced the rate of asthma exacerbations by 36% (95% CI, 26%-52%) in the q4-week regimen and 28% (95% CI, 18%-46%) in the q8-week regimen. As measured by FEV<sub>1</sub>, benralizumab improved lung function by 125 mL (95% CI, 37-213 mL) more than placebo in the q4-week regimen and 116 mL (95% CI, 28-204 mL) more than placebo in the q8-week regimen. I demonstrate 95% CIs. Of note, data are shown only for those with a serum eosinophil level of greater than or equal to 300 cells/ $\mu$ L; however, in this trial, benralizumab was found to reduce asthma exacerbations but not improve lung function in those with an eosinophil level of less than 300 cells/ $\mu$ L. \* $P < .05$  for q4-week regimen. † $P < .05$  for q8-week regimen.

clinically administered IV as opposed to SC. Results from the clinical trials looking at the efficacy of reslizumab 110 mg SC have not been published. However, SC reslizumab appears to have not reached its primary end point in the most recent clinical trials.<sup>102</sup> Although there may be clinical consequences of the choice of weight-based IV versus standard SC dosing, both routes have similar safety profiles with hypersensitivity reactions noted. However, practically SC dosing is often considered less invasive.<sup>103</sup> Indicators of response to reslizumab include an improvement in lung function (improvement of  $\geq 100$  mL in FEV<sub>1</sub>) and asthma control (improvement of  $\geq 0.5$  in Asthma Control Questionnaire score) at 16 weeks.<sup>104</sup> Similar to mepolizumab, treatment is recommended long-term because blood eosinophils start to rise 12 weeks after discontinuation. In the clinic trials, there was no difference in the risk of adverse events in those taking reslizumab versus placebo. However, 3 cases of anaphylaxis were seen in the BREATHE trials.<sup>22</sup> Thus, the FDA placed a black box warning on reslizumab and, as with all the biologics, providers should be prepared to handle anaphylaxis after administration. A recent open-label study found reslizumab to have a good long-term safety profile when evaluated over the course of 24 months.<sup>105</sup>

## Benralizumab

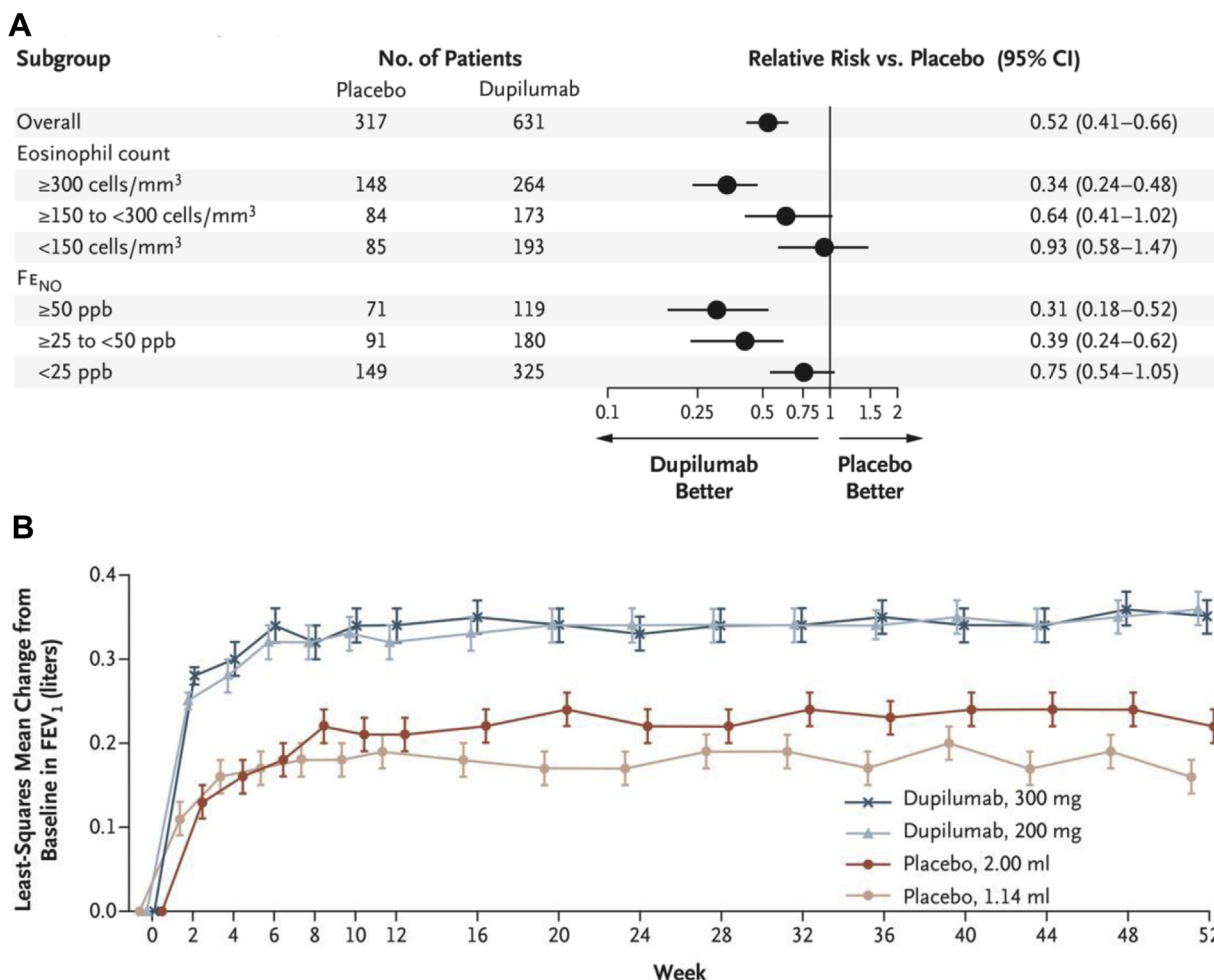
**Mechanism of action and indications.** Benralizumab is the most recently FDA-approved anti-IL-5 treatment for severe eosinophilic asthma. While the other approved anti-IL-5 treatments target the IL-5 ligand, benralizumab directly binds the IL-5 alpha receptor expressed on the surface of eosinophils and basophils (Figure 1). In addition to preventing IL-5 from binding to the alpha receptor, benralizumab results in death of eosinophils and basophils via antibody-dependent cell-mediated cytotoxicity. Benralizumab was approved by the FDA and the EMA as an add-on therapy for patients 12 years or older with severe eosinophilic asthma in late 2017 and early 2018,

respectively. As with the other anti-IL-5 treatments, the FDA did not set an eosinophil cutoff; however, the primary end point was based on patients with an absolute eosinophil count of greater than or equal to 300 cells/mL.<sup>24,25</sup>

**Efficacy.** Benralizumab has been shown to be efficacious at improving exacerbation frequency, asthma symptom scores, and lung function, as well as facilitating weaning from OCSs. Similar to the other anti-IL-5 treatments, clinically significant asthma exacerbations were reduced by 28% (CALIMA [Efficacy and Safety of Benralizumab in Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting  $\beta$ 2 Agonist Study]) and 51% (SIROCCO [Efficacy and Safety of Benralizumab Added to High-dose Inhaled Corticosteroid Plus LABA in Patients with Uncontrolled Asthma Study]) with benralizumab as compared with placebo (Figure 5).<sup>24,25,106</sup> In these trials, benralizumab was found to improve lung function by 116 to 159 mL over placebo. The ZONDA (Efficacy and Safety of Benralizumab to Reduce OCS Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid Plus LABA and Chronic OCS Therapy Study) trial specifically evaluated the OCS-sparing effect of benralizumab in patients with severe persistent asthma with an eosinophil count of greater than or equal to 150 cells/ $\mu$ L despite chronic OCS use. This study showed that patients receiving benralizumab were able to reduce their OCS dose by 75%, and 52% of patients who received benralizumab were able to completely discontinue OCSs.<sup>106</sup> In this trial, despite the reduction in OCS use, there was a 70% reduction in asthma exacerbations in those who received benralizumab every 8 weeks.

Predictors of response to benralizumab include OCS use, history of nasal polyposis, reduced lung function (forced vital capacity  $< 65\%$  predicted), 3 or more exacerbations in the previous year, age 18 years or more, and a higher eosinophil count.<sup>107</sup> Given the unique mechanism of action of benralizumab, it may be reasonable to assume that weight-based dosing is less important with this mAb. This is supported by a substudy





**FIGURE 6.** Findings from the QUEST trial demonstrated that dupilumab (**A**) reduced the rate of future asthma exacerbations and (**B**) improved lung function.<sup>27</sup> In the QUEST trial, at 52 weeks, dupilumab reduced the rate of asthma exacerbations (data shown only for 200-mg dosing) by 48% (95% CI, 34%–59%), with Forest Plots shown by eosinophil count and F<sub>ENO</sub>. As measured by FEV<sub>1</sub>, dupilumab improved lung function by 200 mL (95% CI, 140–250 mL) more than placebo in the lower dose regimen and 130 mL (95% CI, 80–190 mL) more than placebo in the higher dose regimen. I demonstrate 95% CIs.

from ZONDA, which demonstrated a reduction in sputum eosinophils when treated with benralizumab at standard dosing.<sup>108</sup>

**Administration, duration of therapy, and precautions.** Benralizumab is administered SC at a dose of 30 mg every 4 weeks for the first 3 doses, which is followed by 30 mg every 8 weeks subsequently (Table I). Benralizumab is the only biologic for asthma that has been approved with every 8-week dosing. As with the other anti-IL-5 treatments, 3 to 6 months should be allotted to assess treatment response. The expected treatment duration is long-term, and benralizumab is normally well tolerated. However, patients may experience hypersensitivity reactions such as anaphylaxis, angioedema, rashes, or urticaria.

## IL-4— AND IL-13—Targeted THERAPIES Dupilumab

**Mechanism of action and indications.** Dupilumab is a mAb directed against the IL-4 receptor alpha subunit that

inhibits signaling of both IL-4 and IL-13. The IL-4 and IL-13 cytokines promote the recruitment of eosinophils, goblet cell hyperplasia, and the differentiation of T cells into T<sub>H</sub>2 cells (Figure 1).<sup>17</sup> Dupilumab was approved by the FDA for the treatment of severe asthma in patients 12 years or older with an eosinophilic phenotype or with corticosteroid-dependent asthma. Approval by the EMA is expected shortly.

**Efficacy.** Two recent phase 3 randomized controlled trials showed a reduction in asthma exacerbations and improvement in lung function in patients who received dupilumab at a dosing of either 200 or 300 mg SC every 2 weeks (Figure 5).<sup>27,28</sup> In the QUEST (Evaluation of Dupilumab in Patients with Persistent Asthma Study) trial, which recruited patients irrespective of baseline biomarkers of T2 inflammation, a patient's risk of having an asthma exacerbation was approximately cut in half when taking dupilumab as compared with placebo. However, an even greater effect was seen in those with an absolute eosinophil count of greater than or equal to 300 cells/μL (a 67% reduction)

**TABLE II.** Efficacy of the biologics that are FDA-approved for the treatment of moderate-to-severe persistent asthma with a T2-high phenotype

Medication	Frequency of exacerbations	Lung function improvement	Corticosteroid weaning
Omalizumab <sup>29,54-61</sup>	Reduces the risk of asthma exacerbations 25%-50% when compared with placebo	Minimal improvement in lung function	Decreases total use of ICSs and OCSs; however, no clear evidence exists that it facilitates discontinuation of chronic OCSs
Mepolizumab <sup>20,91-93</sup>	Reduces the risk of asthma exacerbations ~50% when compared with placebo	Some, but not all, studies showed some improvement in lung function	Has been shown to facilitate a decrease in total OCS use and facilitate discontinuation of chronic OCSs
Reslizumab <sup>21-23,26,91-93</sup>	Reduces the risk of asthma exacerbations ~50%-60% when compared with placebo	All phase 3 clinical trials showed an improvement in lung function if patients had eosinophilia $\geq 400$ cells/ $\mu$ L	OCS weaning has not been evaluated as an end point with reslizumab
Benralizumab <sup>24,25,93,106</sup>	Reduces the risk of asthma exacerbations ~40%-50% when compared with placebo	All phase 3 clinical trials showed an improvement in lung function	Has been shown to facilitate a decrease in total OCS use and facilitate discontinuation of chronic OCS
Dupilumab <sup>27,28</sup>	Reduces the risk of asthma exacerbations ~50%-70% when compared with placebo	All phase 3 clinical trials showed an improvement in lung function	Has been shown to facilitate a decrease in total OCS use and facilitate discontinuation of chronic OCS

and with an elevated FENO level of 25 ppb or greater (a 61%-65% reduction) (Figure 6).<sup>27</sup> Importantly, these findings suggest that this biologic therapy may have a beneficial effect in the subset of patients without significant blood eosinophilia ( $\leq 300$ ) but with an elevated FENO. Furthermore, these findings suggest that the disease process in patients without eosinophilia, but with elevated FENO, is driven by IL-13.

The VENTURE (Evaluation of Dupilumab in Patients with Severe Steroid Dependent Asthma Study) trial specifically looked at patients chronically on OCSs and demonstrated that dupilumab decreased the OCS dose by 70% and more than half the patients were able to completely discontinue OCS use. Furthermore, in this study, use of dupilumab decreased a patient's risk of having an exacerbation by 59% as compared with placebo.<sup>28</sup> Interestingly, the reduction in exacerbations and improvement in lung function seen in this study occurred despite the fact that a prespecified eosinophil count was not required for study enrollment. In this trial, participants on chronic OCSs at baseline who received dupilumab as compared with placebo had less exacerbations (60% reduction) even if their eosinophil count was less than 150 cells/ $\mu$ L.

**Administration, duration of therapy, and precautions.** Dupilumab is administered SC at a dose of 400 or 600 mg followed by 200 or 300 mg every 2 weeks. The higher dose of dupilumab is indicated for those with oral corticosteroid dependence or comorbid moderate-to-severe atopic dermatitis. Dupilumab is the first biologic therapeutic that can be self-administered by patients at home after proper training. Overall safety data with dupilumab were similar to those of anti-IL-5 mAbs; however, use of dupilumab did result in a higher incidence of injection-site reactions (in up to 18% of patients) and hypereosinophilia (in 4%-14% of patients). The hypereosinophilia observed with dupilumab is transient and returned to baseline in the clinical trials when withdrawing therapy. The

clinical significance of this eosinophilia remains unclear and was rarely reported as a serious adverse event in the clinical trials. Mechanistically, the hypereosinophilia associated with dupilumab is likely related to the drug blocking survival, activation, and recruitment of eosinophils to the tissue, but not progression or egress of eosinophils from the bone marrow, which is influenced by IL-5.<sup>28,109</sup> In addition, IL-4 and IL-13 increase eotaxin release and increase adhesiveness of eosinophils to the endothelium via vascular cell adhesion molecule 1 (VCAM-1)/integrin  $\alpha 4$  interactions, thus likely explaining why eosinophils are "trapped" in the vascular space transiently with dupilumab treatment.<sup>110,111</sup> The recent FDA approval of dupilumab offers a new biologic medication with a different mechanistic target that may benefit those who experienced suboptimal responses to, or did not qualify for, the previously approved biologic therapeutics (such as those without allergic asthma or eosinophilia but with high FENO levels).

## BIOLOGICAL THERAPIES IN CLINICAL DEVELOPMENT

Continued advancements in the understanding of the pathogenesis of asthma has led to the development of numerous new biological therapeutics that are in various stages of clinical development. Some of the biological targets that are important in recent clinical trials include those that target IL-4, IL-13, and TSLP.<sup>112</sup> Lebrikizumab and tralokinumab are mAbs that specifically target IL-13. Unfortunately, recent studies of these medications have not shown the consistent clinical improvements seen with the other biologics.<sup>113,114</sup> While the FDA-approved biologics target the downstream cytokines found in T2-high inflammation, ongoing work is being done investigating medications that target upstream mediators such as IL-25, IL-33, and TSLP (Figure 1). Targeting upstream mediators affects all the subsequent T2-mediated pathways, and early results of these

biologics' efficacy are encouraging. For example, in a recent phase 2 randomized controlled trial, tezepelumab, an mAb that binds TSLP, significantly decreased a patient's risk of asthma exacerbation even in patients with an eosinophil count of less than 250 cells/ $\mu$ L.<sup>115</sup> Finally, a recent study looked at the possibility of using a nebulizer to deliver mAb fragments directly into the terminal bronchioles. This delivery mode was well tolerated and decreased airway eosinophilia in those receiving treatment.<sup>116,117</sup> One could imagine how one day new delivery techniques could offer increased convenience, avoid bothersome injections, and deliver the biologic medications directly to the bronchioles, limiting the risk of adverse systemic side effects.

## USING CLINICAL PHENOTYPES TO SELECT BIOLOGICAL THERAPIES

### Fixed airway obstruction

Although asthma has been characterized by having reversible airway obstruction, a subset of patients with severe asthma develop fixed or irreversible airway obstruction.<sup>118</sup> This group of patients with severe asthma can be more difficult to treat, have more impairment, and are at greater risk of having future exacerbations.<sup>119</sup> Many, but not all, of the studies of biological therapies have shown significant improvement in lung function in a patient population that has reversible airflow obstruction (Table II). Use of reslizumab, benralizumab, and dupilumab has resulted in improvements in FEV<sub>1</sub> of approximately 100 to 110 mL over placebo with treatment.<sup>21-26,93,106</sup> However, omalizumab and mepolizumab have not shown consistent improvements in lung function in all studies, with some studies showing no improvement in FEV<sub>1</sub> with treatment.<sup>91,120</sup> However, it should be noted that a Cochrane review from 2015 did not find a difference in the improvement in lung function between the anti-IL-5 therapies.<sup>93</sup> Furthermore, all the therapeutics to date showed only modest improvements in lung function over placebo and none has specifically evaluated patients with fixed airway obstruction.<sup>121,122</sup> We continue to await clinical trials of the biologic agents in those with fixed airway obstruction or in "real-world" pragmatic trials. Furthermore, we await trials evaluating the effect of biologics on remodeling end points such as airway wall thickness on quantitative computed tomography.

### OCS resistance

A subgroup of patients exists who have persistent airway symptoms, tissue inflammation, and sputum/blood eosinophilia despite the prolonged use of OCSs. These patients are often termed "steroid-resistant" or "steroid-refractory" asthmatic patients.<sup>123</sup> Fortunately, many of the recent studies of biological therapies have shown significant benefit in weaning patients off chronic OCSs (Table II). The data on omalizumab's ability to facilitate OCS discontinuation are equivocal, and reslizumab has not been specifically studied for this indication.<sup>29,31</sup> However, mepolizumab, benralizumab, and dupilumab have been studied specifically in the OCS-dependent patient, and have been found to have consistent and substantial success in decreasing the burden of OCS usage.<sup>20,28,106</sup> When choosing a biologic for the patient who the clinician is attempting to wean down or off chronic OCSs and who has evidence of eosinophilia ( $\geq 150$ -300 cells/ $\mu$ L), mepolizumab, benralizumab, or dupilumab would be appropriate. If the patient has no evidence of eosinophilia, but a high FENO, dupilumab may be appropriate.

## Exacerbation-prone

Finally, clinicians and researchers have noted that a subset of patients with severe asthma accounts for a disproportionately high proportion of the total asthma exacerbation burden. These patients are referred to as "frequent exacerbators" and are being increasingly recognized as an important group to focus on due to their increased risk of adverse events and compromised quality of life.<sup>124-126</sup> A recent study found that many of the factors associated with disease severity itself were not associated with exacerbation frequency; however, an increased eosinophil count in the blood or sputum or an elevated FENO was strongly associated with exacerbation risk.<sup>124</sup> Not surprisingly, the patients who had the most exacerbations before enrollment in the trials of the biologic therapies often had the greatest decrements in their risk of future exacerbations if they received treatment as compared with placebo.<sup>22,24,91</sup> Put simply, it is the patients who are "frequent exacerbators" who have the most room for improvement with a biologic. Clearly, the patient who is having frequent exacerbations should be carefully considered for a biological therapy.

Recently, several indirect comparisons between the anti-IL-5 agents have been published. One meta-analysis that attempted to correct for baseline eosinophil count suggested that mepolizumab may be associated with a greater improvement in asthma exacerbations when compared with the other anti-IL-5 agents.<sup>127</sup> Another indirect comparison using a network meta-analysis concluded that reslizumab may be more efficacious than benralizumab at reducing asthma exacerbations in patients who had at least 2 asthma exacerbations in the previous year.<sup>128</sup> Although indirect comparisons can be provocative, no true direct head-to-head comparisons exist between the biologic therapies for asthma at this time. Concluding one biologic to be superior to an alternative, simply on the basis of indirect treatment comparisons, often is misleading and can be invalid. Therefore, we believe that indirect comparisons to date are insufficient to make treatment decisions, and true direct head-to-head comparisons of the biologics are needed. In summary, at this time, no good data exist to conclude that one biologic therapy is superior to the others in improving exacerbation frequency or other asthma outcomes.

## CONCLUSIONS

Patients with uncontrolled severe asthma have higher morbidity, mortality, and use of health care resources when compared with their peers with well-controlled disease. Over the past few years, multiple new biologics have been approved for these patients with encouraging results. Asthma clinicians need to become comfortable with the use of biomarkers to aid in the appropriate selection of biologic agents for patients with severe asthma given the high efficacy of these treatments with relatively low risk. Consideration of the mode and frequency of administration (as outlined in Table I), underlying comorbidities, weight, lung function, and shared decision making (eg, capacity for self-administration) with the patient should all be considered in the selection of a biologic. Generally, for the uncontrolled allergic asthmatic patient with or without eosinophilia, omalizumab should be considered once Global Initiative for Asthma step 4 therapy fails to achieve control (however, consideration for an anti-IL-4 receptor antibody in patients with elevated FENO should be given). For the nonallergic patient with eosinophilia,

the anti-IL-5 or anti-IL-4 receptor antibodies are first-line therapy.<sup>64,70</sup>

Although the clinical benefits of the biologics have been well established, their use requires frequent clinic visits for those requiring administration by a health care provider and the economic cost of their use remains high. Recent cost-effectiveness analyses have varied in their conclusions. For example, a recent independent analysis demonstrated that the current cost of these agents does not meet prespecified thresholds for cost-effectiveness for quality-adjusted life-years gained.<sup>129-135</sup> These results argue that continuing work is needed to better predict responders to a particular biologic and how to identify nonresponders early so that treatment can be discontinued.

Ongoing work is being done to develop new targeted therapies and delivery modes that will hopefully one day help address the various phenotypes in noneosinophilic/T2-low patients. In addition, more work is needed to understand whether the use of these biologics could be disease modifying and perhaps used earlier in the disease process of asthma. Eventually, head-to-head comparisons of the various biologic treatments would be ideal to help clinicians make the most informed treatment decisions when deciding between the biological agents. Finally, trials of most of these biologics have included relatively small numbers of patients younger than 18 years, highlighting the importance of additional trials focused on pediatric patients to better understand the roles of these therapies in this age group. Despite these modest limitations, even today the clinician can use a detailed understanding of the data to help make the most evidence-based choice of the appropriate biological treatment for a given patient.

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