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Biological therapies for eosinophilic asthma

Shiven S. Patel, Thomas B. Casale, and Juan Carlos Cardet

Division of Allergy and Immunology, Department of Internal Medicine, University of South Florida
Morsani College of Medicine and James A. Haley Veterans' Affairs Hospital, Tampa, FL, USA

Abstract

Introduction: Severe uncontrolled asthma is by definition refractory to traditional therapies or can be controlled only with therapies that have intolerable side effects. Monoclonal antibodies that target interleukin (IL)-5/IL-5R α , IgE, and IL-4R α have shown favorable results in clinical trials, including reductions in asthma exacerbations and other important clinical outcomes. These biological agents offer treatment alternatives to patients with uncontrolled severe eosinophilic asthma.

Areas covered: This article reviews how the shifting emphasis toward identifying distinct asthma phenotypes has led to the approval of biological therapies that preferentially benefit patients with severe eosinophilic asthma. The clinical trials that led to the approval of these biologic treatments are discussed in detail.

Expert opinion: Biologic therapies targeting the IL-5, IgE, IL-4/IL-13 signaling pathways have been successful in clinical trials in subjects with severe eosinophilic asthma. Some of these agents have also been successful regardless of peripheral blood eosinophil counts. These treatments have shown a relatively favorable safety profile in clinical trials, although long-term safety data for some of these agents are limited. Due to the high costs associated with these medications, they should be reserved for select patients where they yield a therapeutic and pharmacoeconomic advantage.

Keywords

Asthma; eosinophil; monoclonal antibody; mepolizumab; reslizumab; omalizumab; dupilumab; benralizumab; IL-5; IgE; IL-4; IL-13

1. Introduction

Asthma is a chronic inflammatory airway disease characterized by respiratory symptoms, hyperresponsiveness to bronchoconstrictors, and usually reversible obstruction [1]. It affects ~300 million people globally and accounts for ~1 in 250 deaths worldwide [2]. Around 8% of the population has asthma in the United States [3]. Approximately 5–10% of asthmatics

CONTACT Juan Carlos Cardet juan.carlos.cardet16@gmail.com 13000 Bruce B Downs Blvd (111D), Tampa, FL 33612, USA.

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have severe asthma despite maximal treatment; this population accounts for approximately 50% of asthma-related health-care costs [4,5]. Individualized therapy based on asthma phenotype is being pursued as a more efficacious alternative for patients with symptoms refractory to guideline-based therapies with inhaled and/or oral corticosteroids (OCS) and bronchodilators.

Emphasis has been placed over the past two decades on recognizing asthma phenotypes and endotypes (defining subtypes by pathobiologic molecular mechanisms) with the hope of identifying novel therapeutic targets for individuals with severe asthma [6–9]. The eosinophilic asthma phenotype is characterized by sputum or peripheral blood eosinophilia and airway eosinophilic infiltration [10]. As discussed below, multiple cytokines or molecules are either implicated in producing or associated with eosinophilic inflammation. Several monoclonal antibodies that target either these molecules or their receptors have shown favorable results in clinical trials and are now or soon will be commercially available (Table 1). This review details the clinical trials involving monoclonal antibodies for eosinophilic asthma that target interleukin (IL)-5/IL-5R α , IgE, and IL-4R α (Figure 1).

2. Targeting IL-5

IL-5 is a cytokine central to eosinophilopoiesis, and to the maturation, activation and survival of eosinophils in peripheral tissues [11]. The association between eosinophils and asthma was first uncovered approximately one century ago. More recently, Louis *et al.* showed that severe asthmatics have increased levels of eosinophils and eosinophil cationic protein in sputum relative to non-severe subjects [12]. The overproduction of IL-5 was first linked to asthma in the 1990s. Transgenic mice overexpressing IL-5 were found to have profound eosinophilia and eosinophilic infiltrates of the lung and lymphoid tissue. Foster *et al.* showed that IL-5-deficient mice do not have airway hyperresponsiveness to methacholine or inhaled allergen [13]. These results evidenced a central role for IL-5 and eosinophilic airway disease and spurred the development of monoclonal antibodies against IL-5 as a potential therapy for asthma.

Mepolizumab and reslizumab are humanized monoclonal antibodies that bind IL-5. Benralizumab is a humanized, afucosylated, monoclonal antibody that binds to the IL-5 receptor alpha subunit (IL-5R α) [14]. Mepolizumab and reslizumab are approved for clinical use and commercially available in the United States and Europe. In November 2017, benralizumab was approved by the US Food and Drug Administration (FDA) and was also given a favorable opinion by the EU Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency. Mepolizumab and reslizumab are currently recommended by the Global Initiative for Asthma 2016 guidelines as an add-on option for patients aged ≥ 12 years with severe uncontrolled eosinophilic asthma [15].

Mepolizumab, a murine humanized IgG1 monoclonal antibody, is the most studied anti-IL-5 in the treatment of severe asthma [16,17]. It was also the first agent in its class to be tested in a clinical trial in 2000 [18]. Early studies documented mepolizumab to be ineffective in improving clinical symptoms. The first study was conducted over 16 weeks and included subjects with mild asthma treated with β -agonist therapy alone [16,19]. The second trial was

conducted over 12 weeks and enrolled subjects with moderate persistent asthma on inhaled corticosteroids (ICS). Neither one of these studies recruited subjects based on IL-5 pathway biomarkers such as peripheral blood eosinophil counts [20]. Neither study improved clinical symptoms, thereby raising concern over the efficacy of anti-IL-5 as a therapeutic option in asthma [18,21]. However, both of these trials did show reductions in blood and sputum eosinophils and one showed a trend in reduction in asthma exacerbations. Nonetheless, concerns were raised due to a lack of significant reduction in bronchial eosinophils even in patients with substantial reductions in blood eosinophils subsequent to mepolizumab therapy [22]. Subsequent studies were thus designed with a focus on subjects with persistent peripheral blood (> 300 cells/ μ L) or sputum eosinophils ($> 3\%$), and on those with frequent exacerbations, which led to the first positive trials showing a decrease in exacerbation frequencies and a reduction in systemic corticosteroid use [21,23,24].

After documenting clinical success in carefully selected subjects in these small trials, the phase II DREAM trial was initiated. This trial assessed 3 different monthly intravenous doses (75/250/750 mg) of mepolizumab in 621 subjects with peripheral blood (> 300 cells/ μ L) or sputum ($> 3\%$) eosinophilia. Mean annual exacerbation reduction rates were as follows, delineated by dose: 75 mg, 48% (95% confidence interval [CI], 31–61% [$p < 0.01$]); 250 mg, 39% (95% CI, 19–54% [$p < 0.01$]); and 750 mg, 52% (95% CI, 36–64% [$p < 0.01$]). The dose–response relationship between mepolizumab and sputum and blood eosinophils suggests that the lowest dose (75 mg) administered intravenously is near the top of the dose–response curve [25].

Subsequent studies on eosinophilic asthma assessed other end points such as reduction in systemic corticosteroids and improvement in FEV₁. The SIRIUS study by Bel *et al.* included 135 subjects on maintenance therapy with OCS assigned to 100 mg of mepolizumab administered subcutaneously versus placebo. There was a 50% median reduction in OCS use compared to placebo ($p < 0.01$) [26]. The MENSA study by Ortega *et al.* randomized 576 subjects to 75 mg intravenous dose, 100 mg subcutaneous dose or placebo. With subcutaneous administration, there was a 98-mL increase in FEV₁ ($p = 0.03$), a 0.44-point improvement in Asthma Control Questionnaire (ACQ) (minimum clinically importance difference [MCID] = 0.5) ($p < 0.01$), and a 47% reduction in clinically significant exacerbations ($p < 0.01$). With intravenous administration, there was a 100-mL increase in FEV₁ ($p = 0.02$), a 0.42-point improvement in ACQ ($p < 0.01$), and a 53% reduction in clinically significant exacerbations ($p < 0.01$) [27]. In this trial, intravenous and subcutaneous administrations were thus similarly effective. These studies provided evidence that mepolizumab is a clinically effective therapy in carefully selected subjects.

A *post-hoc* analysis of the DREAM and MENSA studies showed that the exacerbation rate reduction with mepolizumab versus placebo increased progressively from 52% (RR 0.48, 95% CI, 0.39–0.58) in patients with a baseline blood eosinophil count of at least 150 cells/ μ L to 70% (RR 0.30, 95% CI, 0.23–0.40) in patients with a baseline count of at least 500 cells/ μ L [28]. At a baseline count less than 150 cells/ μ L predicted efficacy of mepolizumab was reduced. The FDA approved mepolizumab, administered subcutaneously, for severe eosinophilic asthma in November 2015.

There are no established guidelines on when to discontinue mepolizumab. As a follow-up study of subjects who completed 12 months of mepolizumab versus placebo, Haldar *et al.* monitored 56 subjects every 3 months after cessation of therapy for a year. Significant increases were seen in the peripheral blood eosinophil count between visits at 0–3 months (from approximately 45 to 125 cells/ μ L [$p < 0.01$]) and at 3–6 months (from approximately 125 to 295 cells/ μ L [$p < 0.01$]) relative to the time of mepolizumab discontinuation. No such changes were observed in the group assigned to placebo. The frequency of severe exacerbations was significantly increased after discontinuing mepolizumab, from 0.56/subject during months 0–3 to 1.2/subject during months 3–6 of follow-up ($p < 0.01$) [29]. This study recognized that a sustained therapeutic benefit of anti-IL-5 therapy likely requires continued dosing.

Reslizumab, a murine humanized IgG4 monoclonal antibody, has a similar mechanism of action to mepolizumab in terms of binding IL-5. The first pilot study of 32 subjects with severe uncontrolled asthma (eosinophilia was not an inclusion criterion) failed to show improvement in asthma control with reslizumab. The data did show a reduction in peripheral blood eosinophil count and a trend toward improvement in FEV₁ [30,31]. Reslizumab was then studied in subjects with poorly controlled eosinophilic asthma (sputum eosinophils 3%) on high-dose ICS in a 15-week phase II study. This study by Castro *et al.* examined 106 subjects receiving 3.0 mg/kg infusion of reslizumab versus placebo. This study showed a trend toward improvement in asthma control (mean difference -0.38 , 95% CI, -0.76 – 0.01 [$p = 0.054$]) and a 240-mL improvement in FEV₁ (95% CI, 88–392 [$p < 0.01$]) [31]. The improvement in ACQ score achieved statistical and clinically meaningful significance (mean difference -0.94 , 95% CI, -1.22 to -0.22 [$p = 0.01$]) in subjects with nasal polyposis, suggesting that this subset may benefit more from reslizumab [16]. A subsequent phase III study enrolled 953 subjects with severe uncontrolled asthma with peripheral blood eosinophilia and at least 1 exacerbation in the past 12 months despite therapy with medium-dose ICS. The study reported a reduction in annualized exacerbations from 1.81 to 0.84 (54% reduction in annualized exacerbation rate [AER], 95% CI, 42–63% reduction [$p < 0.01$]). Subjects in the treatment group also experienced improvements in FEV₁ and ACQ scores, and a reduction in sputum eosinophils [32].

Two additional phase III studies examining FEV₁ as a primary outcome were conducted [18]. Bjermer *et al.* examined 315 subjects with poorly controlled asthma on medium-dose ICS and peripheral eosinophilia (> 400 cells/ μ L). Both reslizumab doses (0.3 and 3.0 mg/kg) improved FEV₁, by 115 mL (95% CI, 16–215 [$p = 0.02$]) and 160 mL (95% CI, 60–259 [$p < 0.01$]), respectively. Reslizumab also improved scores on ACQ (-0.35) and Asthma Quality of Life Questionnaire (AQLQ) (0.36; MCID = 0.5) in the 3.0 mg/kg treatment group ($p < 0.05$). The proportion of subjects with an MCID of ≥ 0.5 improvement from baseline to end point in AQLQ score was higher with reslizumab 3.0 mg/kg versus placebo (64% vs. 48%, respectively; $p = 0.0189$). A similar proportion of subjects in the treatment groups and placebo group achieved a 0.5-point reduction from their baseline score to end point in ACQ score [33]. Corren *et al.* examined 492 subjects on medium-dose ICS with no criterion for eosinophilia. This study in an unselected population did not show an improvement in FEV₁. However, a subgroup analysis showed a 270-mL improvement in FEV₁ in subjects with eosinophils > 400 cells/ μ L ($p = 0.04$). There was no significant change in FEV₁ in subjects

with eosinophils <400 cells/ μ L [34]. With these favorable studies, the FDA approved reslizumab, administered intravenously, for severe eosinophilic asthma in March 2016.

Benralizumab represents a different strategy aimed at depleting eosinophils and basophils by targeting IL-5 receptor alpha subunit. This murine humanized monoclonal antibody was developed due to the concern that targeting IL-5 may not adequately deplete tissue-dwelling eosinophils, which may derive survival signals from cytokines other than IL-5, such as IL-33 and granulocyte-macrophage colony-stimulating factor (GM-CSF) [18,35]. Drugs that target IL-5 itself have been shown to reduce eosinophilopoiesis and peripheral blood eosinophilia but cause an incomplete reduction of tissue-dwelling eosinophils [18,22,35,36].

Benralizumab induces apoptosis in cells expressing this receptor (including eosinophils, basophils, and bone marrow eosinophil progenitors) via antibody-dependent cell-mediated cytotoxicity and may thus deplete more tissue-dwelling eosinophils than mepolizumab and reslizumab [14].

A phase I study with benralizumab showed a reduction in eosinophils in peripheral blood, sputum, airway mucosa, and bone marrow [37]. Castro *et al.* examined 609 subjects between 18 and 75 years of age in a phase IIB study that showed 100 mg of benralizumab-administered subcutaneously reduced exacerbation rates. In subjects with eosinophils >300 cells/ μ L, the reduction in exacerbation rates was significant for both 20 mg (43% reduction, 80% CI, 18–60% $p = 0.05$) and 100 mg (57% reduction, 80% CI, 33–72% $p = 0.02$) subcutaneously administered doses [38]. These trials led to the development of phase III studies, SIROCCO and CALIMA, which were published in May 2016. SIROCCO studied 1204 subjects on high-dose ICS and long-acting beta-agonists (LABA) with two or more exacerbations in the past year. A subgroup of individuals had low peripheral blood eosinophilia (<300 cells/ μ L, $n = 395$). Subjects were randomized to receive either benralizumab 30 mg every 4 weeks, 30 mg every 8 weeks after the first three doses at every 4 weeks, or placebo. In subjects with peripheral blood eosinophils $\geq 300/\mu$ L ($n = 809$), benralizumab decreased the AER when administered every 4 weeks by 45% (95% CI, 29–58% [$p < 0.01$]) and every 8 weeks by 51% (95% CI, 36–63% [$p < 0.01$]). Benralizumab also improved Asthma Control Questionnaire, six-question version (ACQ-6) (-0.29 ; $p < 0.01$) and Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(S) + 12) scores (0.30 ; $p < 0.01$) when administered every 8 weeks. These asthma control measures were not statistically significant in the treatment group receiving benralizumab every 4 weeks. Additionally, FEV₁ increased by 106 mL (95% CI, 16–196 mL) and 159 mL (95% CI, 68–249 mL) in the 4- and 8-week dosing groups, respectively [39]. A similar trial, CALIMA, studied a comparable population of 1306 subjects except it included subjects on both high and medium doses of ICS. In subjects with peripheral blood eosinophils $\geq 300/\mu$ L ($n = 728$), benralizumab decreased the AER when administered every 4 weeks by 36% (95% CI, 15–51% [$p < 0.01$]) and every 8 weeks by 28% (95% CI, 5–46% [$p < 0.02$]). FEV₁ also improved in both groups. Benralizumab improved ACQ-6 (-0.25 ; $p < 0.01$) and AQLQ(S) + 12 scores (0.24 ; $p = 0.02$) when administered every 8 weeks [40]. Surprisingly, both of these trials also showed reduction in exacerbation rates in subjects with peripheral blood eosinophil counts $<300/\mu$ L (156/ μ L and 177/ μ L in SIROCCO and CALIMA, respectively). In this low eosinophil group in SIROCCO, benralizumab reduced AER by 30% (95% CI, 0–50% [$p = 0.05$]) and 17% (95% CI, –16–41% [$p = 0.27$]) in the 4-

week and 8-week dosing groups, respectively. In the low eosinophil group in CALIMA, benralizumab reduced AER by 36% (95% CI, 8–55% [$p = 0.02$]) and 40% (95% CI, 14–58% [$p < 0.01$]) in the 4- and 8-week dosing groups, respectively.

The phase III ZONDA trial, published in May 2017, studied 220 subjects with severe asthma requiring OCS to manage their disease (median OCS dose was 10 mg/day at the end of the run-in period for all treatment arms). These participants received benralizumab 30 mg every 4 or 8 weeks (with the first three doses administered every 4 weeks) versus placebo. Both dosing regimens led to a 75% reduction in median OCS dose versus 25% for placebo ($p < 0.01$ for both groups). Subjects on benralizumab were more than four times likely to reduce their OCS dose from baseline. Secondary outcomes in ZONDA showed a decrease in AER by 55% in the 4-week group compared with placebo (0.83 vs. 1.83; $p < 0.01$) and a 70% reduction in AER in the 8-week group compared with placebo (0.54 vs. 1.83; $p < 0.01$). In this study, there was no difference in FEV₁ in the treatment groups as compared with placebo [41]. These studies were not designed or powered to discern differences between the two dosing regimens; administration with every 8 weeks worked as well as administration with every 4 weeks. Benralizumab (30 mg every 4 weeks for the first three doses, and then once every 8 weeks) was approved by the FDA in November 2017.

Medications targeting the IL-5 pathway have been well tolerated. The most common side effects have been nasopharyngitis and headache, but these have been reported at the same frequency in both treatment and placebo groups [18]. Mepolizumab has been associated with hypersensitivity reactions, such as injection-site reactions, urticaria, and angioedema [42]. However, the risk of anaphylaxis does not appear to be increased over placebo. In contrast, anaphylaxis did occur in 0.3% of subjects on reslizumab (3 subjects out of 1131 vs. 0 subjects out of 730 on placebo [0%]) [43]. The FDA did not require a prescription for intramuscular epinephrine, but physicians should be aware of the elevated risk of anaphylaxis with reslizumab [16]. Two subjects on mepolizumab experienced severe cases of herpes zoster infections [42]. Despite concerns of suppressing antihelminthic immunity by blocking the IL-5 pathway, thus far these drugs have not shown any evidence of increased risk of parasitic infections, but clinical trials in endogenous helminthic geographic regions are needed. A study by Murphy *et al.* examined data from 1051 subjects receiving reslizumab 3.0 mg/kg every 4 weeks for 24 months. Reslizumab displayed a favorable long-term safety profile. The most common adverse events were worsening of asthma and nasopharyngitis. Serious adverse events, such as cardiac disorders, neoplasms, and infections, affected 7% of subjects. This led to discontinuation of the study drug in 2% of subjects. It is important however to recognize that this was an open label, uncontrolled observational study [44,45].

A recent Cochrane systematic review evaluated 13 studies involving 6000 participants; 4 used mepolizumab, 4 used reslizumab, and 5 used benralizumab. Most subjects had severe eosinophilic asthma, and severity was similarly but variably defined. All three IL-5-targeting treatments led to reductions in asthma exacerbations rates by approximately 50%. The authors did not comment on superiority of one drug among the others. The authors concluded that further research is needed on biomarkers for assessing treatment response, optimal duration and long-term effects of treatment, risk of relapse on withdrawal, non-

eosinophilic subjects, children (particularly under 12 years), and comparing anti-IL-5 treatments to each other and, in people eligible for both, to anti-IgE therapy [46].

A small study by Mukherjee *et al.* recently examined 10 subjects with prednisone-dependent eosinophilic asthma who were previously on mepolizumab 100 mg subcutaneously for 1+ years. After a washout period of 1+ years, during which they were reestablished on their baseline treatment, these subjects received two infusions of placebo every 4 weeks followed by four infusions of 3.0 mg/kg reslizumab every 4 weeks in a single-blind, placebo-controlled sequential trial. Compared to mepolizumab, reslizumab was superior in improving Asthma Control Questionnaire, five-question version (ACQ-5) scores and sputum eosinophils. However, both agents showed comparable efficiency in reducing blood eosinophils. The authors speculate that these significant differences may stem from reslizumab being a weight-based agent, which may allow for optimized target drug concentrations relative to fixed dosing [47].

3. Targeting IgE

Omalizumab, a murine humanized IgG1k monoclonal antibody that binds to the CH3 domain of IgE, was developed to block interactions between IgE and the high-affinity receptor for the Fc region of IgE (FcεRI) expressed on mast cells, basophils, dendritic cells, and monocytes [48–50]. Omalizumab was the first biologic approved in the United States and Europe for the treatment of asthma. This is currently recommended by the US National Heart, Lung, and Blood Institute's commissioned National Asthma and Education Prevention Program guidelines for use in severe refractory asthma with documented specific IgE sensitivities (measured by skin or *in-vitro* testing) to one or more perennial aeroallergens [51,52]. Early studies showed that treatment with omalizumab decreases the rate of severe exacerbations, emergency room visits, hospitalizations, and the requirement for ICS and rescues bronchodilators in subjects with moderate-to-severe and severe allergic asthma. Subjects experienced improvements in asthma-related symptoms and quality of life, while the effects on lung function were inconsistent [53–55].

Peripheral blood eosinophil counts may predict those with a more favorable response to anti-IgE therapy. In the EXTRA study by Hanania *et al.*, omalizumab was associated with greater reductions in asthma exacerbations with higher peripheral blood eosinophil counts, fractional excretion of nitric oxide (FeNO), and serum periostin. Specifically, the two eosinophil groups were stratified by the median threshold, low (< 260 cells/μL) and high (>260 cells/μL). The subgroup with high eosinophils was associated with greater percentage reduction in exacerbation rates compared to low eosinophils (32% reduction, 95% CI, 11–48% [$p < 0.01$] vs. 9%, 95% CI, –24–34% [$p = 0.54$]). However, eosinophil levels did not show a clear effect on other secondary end points, such as lung function and asthma symptom scores [56].

Pooled data from two phase III clinical trials examined by Casale *et al.* showed that the reduction in exacerbation rates was more pronounced with omalizumab versus placebo in subjects with higher eosinophil counts (>300 cells/μL). Mean exacerbation reduction rates when stratified by baseline peripheral eosinophil counts were as follows: 200 cells/μL, 55%

(95% CI, 25–73% [$p < 0.01$]); 300 cells/ μ L, 67% (95% CI, 36–84% [$p < 0.01$]); and 400 cells/ μ L, 74% (95% CI, 40–88% [$p < 0.01$]) [57]. These studies suggest that higher blood eosinophil counts predict a greater response to omalizumab in subjects with severe asthma.

Omalizumab is approved in children 6 years and older, which is the youngest age indicated for currently approved biologics. Omalizumab is administered subcutaneously; dose and frequency are based on pretreatment total IgE levels and weight [52]. Common adverse effects include injection site reactions, arthralgia, nasopharyngitis, and headache. Post-marketing surveillance studies showed that anaphylaxis was reported in 0.09% of patients [14,58]. Clinical trials did show a small increase in the number of malignancies in patients treated with omalizumab versus placebo. However, in longitudinal studies, the incidence in malignancies in patients receiving omalizumab does not appear to be greater than that of the general population [14,59,60]. Ongoing and future research is investigating what the optimal duration of treatment with omalizumab should be for patients with asthma.

4. Targeting IL-4/IL-13

Dupilumab is a humanized monoclonal antibody that binds to the IL-4 receptor alpha subunit, through which both IL-4 and IL-13 signal. IL-4 and IL-13 are produced by type 2 T-helper cells and type 2 innate lymphoid cells. Dupilumab thus inhibits IgE production by inhibiting key cytokines for B-cell IgE class switch [61,62]. In addition, these cytokines facilitate many cellular responses implicated in typical pathologic features of asthma such as airway inflammation and remodeling [63]. Dupilumab is FDA approved for adults with atopic dermatitis, but not for asthma. Phase I and IIa trials showed significant efficacy with dupilumab in asthmatic subjects with peripheral blood eosinophil counts ≥ 300 cells/ μ L [64–66]. A phase IIb trial by Wenzel *et al.*, published in July 2016, studied participants with severe asthma not adequately controlled by medium-to-high dose ICS plus LABA. Subjects were assigned to subcutaneous dupilumab 200 or 300 mg every 2 weeks or every 4 weeks. In the subgroup with peripheral blood eosinophilia (≥ 300 cells/ μ L) with subjects receiving dupilumab every 2 weeks, asthma exacerbation rates decreased by 71% with 200 mg administration (95% CI, 24–89% [$p = 0.01$]) and 81% with 300 mg administration (95% CI, 44–93% [$p < 0.01$]) compared to placebo. In this same subgroup receiving dupilumab every 2 weeks, AQLQ improved with 200 mg administration (0.67; $p < 0.01$) and with 300 mg administration (0.78; $p < 0.01$) compared to placebo. ACQ-improved with both 200 mg (–0.42; $p = 0.02$) and 300 mg (–0.55; $p < 0.01$) treatment groups compared to placebo. FEV₁ improved compared to placebo by 160 mL with both 200 mg administration (95% CI, 20–310 [$p = 0.03$]) and 300 mg administration (95% CI, 10–300 [$p = 0.03$]). In subjects with eosinophilia < 300 cells/ μ L receiving dupilumab every 2 weeks, asthma exacerbation rates decreased by 68% with 200 mg administration (95% CI, 24–86% [$p < 0.01$]) and by 60% with 300 mg administration compared to placebo (95% CI, 16–81% [$p = 0.02$]). FEV₁ improved compared to placebo by 140 mL with both 200 mg administration (95% CI, 30–250 [$p = 0.01$]) and 300 mg administration (95% CI, 30–240 [$p = 0.01$]). Dupilumab, administered every 2 weeks, also reduced FeNO. Although dupilumab decreased exacerbation rates and increased FEV₁ in subjects with severe uncontrolled asthma irrespective of baseline eosinophil counts, the effects may be greater in those with peripheral blood eosinophilia particularly at the 300-mg dosing administered every 2 weeks [66].

The effects of dupilumab on asthma have been studied in phase III trials. The QUEST study had four study groups; 200 mg every other week with a loading dose of 400 mg, 300 mg every other week with a loading dose of 600 mg, and two separate placebo groups. A recent press release reported that at 52 weeks with the 300-mg dose group, dupilumab reduced exacerbations by 46% in the overall population, 60% in subjects with at least 150 eosinophils/ μ L, and 67% in subjects with at least 300 eosinophils/ μ L ($p < 0.01$ for all groups). More details regarding this study will be submitted for presentation at a future medical congress and publication. Another phase III trial being studied, VENTURE, is examining the ability of dupilumab to reduce OCS use in individuals with steroid-dependent asthma. These results are also expected soon [67].

Studies have thus far shown dupilumab to be well tolerated. The most common side effects were upper respiratory tract infection, injection-site erythema, and headache, but these have been reported at similar frequency in both treatment and placebo groups [66]. Treatment with dupilumab in the phase lib trial transiently increased peripheral blood eosinophil levels, particularly in the subgroup with baseline blood eosinophil counts of at least 300 eosinophils/ μ L; however, the transient increase did not seem to affect efficacy. One study participant in this trial developed hypereosinophilic syndrome. The subject was started on systemic corticosteroids which rapidly reduced the eosinophil count. As a result, the participant discontinued dupilumab.

Dupilumab is not yet FDA approved for the treatment of asthma but will likely be dosed subcutaneously every 2 weeks with home administration.

5. Conclusion

Asthma affects about 300 million people globally. Although the majority of asthmatic individuals are well controlled, a small subset has severe asthma despite maximal medical therapy. The recognition of phenotypes such as the eosinophilic asthma subtype has shifted the therapeutic approach to this disease. Novel therapeutic options have been studied over the past two decades for this eosinophilic subtype. These monoclonal antibodies target the IL-5, IgE, and IL-4/IL-13 pathways. Studies of mepolizumab, reslizumab, benralizumab, dupilumab, and omalizumab have consistently shown a reduction in exacerbations in subjects with uncontrolled eosinophilic asthma. These treatments have shown a favorable safety profile in clinical trials, although long-term safety data for some of these are limited.

6. Expert opinion

Although the vast majority of individuals with asthma respond to traditional therapies, a small subset of patients has severe refractory asthma which accounts for a disproportionate amount of asthma-related health-care costs. In subjects with severe eosinophilic asthma refractory to traditional treatment, newer agents are now available to improve their disease burden. Monoclonal antibodies that target IL-5/IL-5R α , IgE, and IL-4R α have shown reduction of exacerbation rates in randomized, placebo-controlled trials. These agents are all appear to have better effects in subjects with high eosinophil counts. However, FeNO might be as good or better as a biomarker to predict response to dupilumab. Since all these agents

show better efficacy with high eosinophil counts, we are somewhat limited in making specific recommendations of a specific drug for an individual patient with an eosinophilic phenotype. The high costs associated with these biologics dictate judicious use in well-selected patients. According to GoodRx in May 2018, uninsured cash price for mepolizumab and reslizumab is over \$5000 USD and omalizumab over \$1000 USD per administration. Many patients clearly warrant treatment with these efficacious drugs, and this decision should be based on a clinician's judgment of what is best for his/her patient. Studies are needed to determine novel predictive biomarkers of efficacy with these drugs considering that a sizeable proportion of patients *do not* benefit from these biologics, even when the majority does benefit. Further, studies are needed to help clinicians decide *which* biologic agent will benefit a particular patient who may otherwise qualify for any of these five biologics.

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Article highlights

- Approximately 5–10% of asthmatics have severe asthma that is refractory to treatment, accounting for approximately 50% of asthma-related health-care costs.
- Over the past two decades, emphasis has been placed on identifying asthma phenotypes and endotypes to create individualized therapy for subjects with severe asthma refractory to treatment.
- Clinical trials show efficacy and favorable safety profile for monoclonal antibodies targeting IL-5, IgE, IL-4/IL-13 signaling pathways for individuals with severe eosinophilic asthma.
- Long-term safety data are limited for many of these agents.
- High costs associated with these agents warrant careful selection.

This box summarizes key points contained in the article.

Figure 1.

Biologic targets and therapies for the treatment of severe eosinophilic asthma.

*Not currently FDA approved for asthma.

Table 1.

Biologic therapies for the treatment of severe eosinophilic asthma [42,43,52,66–69].

Target	Biologic	Mechanism	Approved for asthma	FDA requirements	Dosing	Additional information
IL-5	Mepolizumab	Binds to IL-5	Yes	Add-on maintenance treatment of subjects with severe eosinophilic asthma 12 years	100 mg SC every 4 weeks	Consider varicella vaccination prior to starting therapy FDA approved for eosinophilic granulomatosis with polyangiitis Anaphylaxis reported in 0.3% of subjects in controlled clinical trials Currently the only asthma biologic with weight-based dosing administered IV
	Reslizumab	Binds to IL-5	Yes	Add-on maintenance treatment of subjects with severe eosinophilic asthma 18 years	3 mg/kg IV infusion every 4 weeks over 20–50 min	Currently the only asthma biologic that is administered every 8 weeks as maintenance
	Benralizumab	Binds to IL-5 receptor α	Yes	Add-on maintenance treatment of subjects with severe eosinophilic asthma 12 years	30 mg SC every 4 weeks for the first 3 doses, followed by every 8 weeks thereafter	Anaphylaxis reported in 0.09% of subjects in controlled clinical trials
IgE	Omalizumab	Binds to IgE; decreases expression of FcεRI	Yes	Moderate-to-severe persistent asthma inadequately controlled with inhaled corticosteroids in subjects 6 years with a positive skin test or <i>in vitro</i> reactivity to a perennial aeroallergen	75–375 mg SC every 2 or 4 weeks, determined by pretreatment serum IgE and body weight	Currently the only asthma biologic approved for children FDA approved for chronic idiopathic urticaria refractory to H1 antihistamine treatment
IL-4/IL-13	Dupilumab	Binds to IL-4 receptor α ; blocks signaling of IL-4 and IL-13	No	Add-on maintenance treatment of subjects with severe eosinophilic asthma 18 years (<i>likely requirements</i>)	300 mg SC by self-administration every 2 weeks	Subjects had a transient increase in peripheral eosinophilia in controlled clinical trials Likely to be only asthma biologic dosed with home administration FDA approved for moderate-to-severe atopic dermatitis not adequately controlled with topical prescription therapies

FDA: US Food and Drug Administration; IL: interleukin; SC: subcutaneous; IV: intravenous; FcεRI: high-affinity IgE receptor.