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Interleukin-5 Antagonists Usher in a New Generation of Asthma Therapy

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Abstract Asthma is the most common chronic respiratory disease in the USA. A subset of patients with asthma have refractory symptoms, persistent eosinophilic inflammation, and recurrent exacerbations despite maximal medical therapy. The monoclonal antibodies targeting the IL-5 pathway are a new class of medications designed to target severe eosinophilic asthma. There are two medications clinically available: mepolizumab and reslizumab, both of which target IL-5. A third medication, benralizumab, is currently under development and targets the IL-5 receptor. Clinical data suggest these medications can reduce asthma exacerbations and improve lung function in patients with peripheral eosinophilia and poorly controlled asthma despite maximal medical therapy. The anti-IL-5 medications are among the first targeted molecular therapies for asthma and will usher in an exciting new era in the treatment of severe asthma.

Keywords Eosinophil · Severe asthma · Interleukin-5 · Mepolizumab · Benralizumab · Reslizumab · Anti-IL-5

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Introduction

Asthma is the most common chronic respiratory disease and is characterized by reversible airway inflammation and bronchial hyperresponsiveness. An estimated 8.4 % of the United States population has asthma [1]. Worldwide, more than 300 million people are estimated to suffer from asthma [2]. The majority of patients with asthma are well controlled with standard therapies. However, 5–10 % of patients have severe asthma and persistent symptoms despite maximal medical therapy. This population accounts for up to 50 % of asthma-related health care costs [3, 4]. There is a lack of treatment options and a clear need for novel therapies in order to improve outcomes in patients with severe asthma.

Over the past 20 years, asthma has been redefined as a heterogeneous collection of multiple pathophysiologic mechanisms rather than a single disease entity [5]. Study of the clinical and laboratory characteristics of asthma has led to the recognition of phenotypes and endotypes: distinct disease entities described by clinical or molecular mechanisms, respectively [6, 7]. One well-described phenotype is characterized by sputum and peripheral blood eosinophilia, and airway eosinophilic inflammation [8]. The eosinophilic asthma phenotype includes up to half of patients with mild–moderate asthma and approximately, a third of patients seen in secondary care for severe asthma [9, 10]. Since interleukin-5 (IL-5) is a central cytokine in the differentiation, proliferation, activation, and survival of eosinophils [11], the development of anti-IL-5 monoclonal antibodies is an exciting new therapeutic option for the treatment of severe eosinophilic asthma. These medications are one of the first available targeted molecular therapies in a new era of asthma therapy.

Eosinophils and IL-5 in Asthma

The Eosinophil in Asthma and Eosinophilic Asthma Phenotypes

The eosinophil was first described by Paul Ehrlich 1879 after he developed eosin, a stain which colored basic proteins bright red [12]. Twenty years after definitive identification of the eosinophil, it was linked to asthma by Dr. Fraenkel, who noted occlusion of the small airways and "numerous eosinophil cells" in an autopsy of a 48-year-old male patient who died of status asthmaticus [13]. Throughout the early 1900s, much was learned about asthma via autopsy and the presence of eosinophils in the blood, sputum, and bronchial tissue after fatal asthma attacks became well established [14].

Although the mechanistic role of the eosinophil in asthma is not completely understood, there are several proposed links between eosinophils and asthma pathophysiology. Eosinophil peroxidase activity can induce degranulation of mast cells [15]. Release of mast cell mediators such as histamine and cysteinyl leukotrienes are well known to cause bronchoconstriction [16]. Another eosinophil product, major basic protein, is elevated in asthma and can independently mediate airway constriction both ex vivo and in vivo [17–19]. In addition, major basic protein has been shown to cause release of histamine from basophils [15], which can potentiate bronchoconstriction.

Translational studies of asthmatic patients with eosinophilia reveal an association between eosinophil count and disease activity [20, 21]. Louis et al. showed that patients with severe asthma had increased sputum eosinophilia and levels of eosinophil cationic protein [22]. Eosinophils and IL-5 in bronchoalveolar lavage (BAL) fluid increase during an exacerbation [23]. Sputum eosinophil levels are associated with asthma exacerbations and play a role in driving uncontrolled asthma [24]. Finally, changes in sputum eosinophilia can be used to guide asthma therapy [24, 25].

More recently, asthma phenotyping has used clinical data to define subpopulations of asthma [9, 26]. Cluster analyses have shown two distinct populations of patients with eosinophilia [9, 26–28]. The first population consists of young, atopic individuals with moderate asthma. The second group is comprised of older individuals with adult-onset severe asthma [9, 26]. Although the severity of asthma differs between the groups, both phenotypes are characterized by sputum eosinophilia and frequent health care utilization. Asthma phenotyping has also described severe asthma phenotypes that are characterized in part by the absence of eosinophilia [9, 26]. Although eosinophils are not always present, approximately half of patients with asthma have sputum eosinophilia, and the eosinophil remains a frequent feature of severe asthma [10].

Despite the advances in our understanding of asthma, there remains a population of patients with poor asthma control while on maximal medical therapy. Many of these patients have persistent sputum and peripheral blood eosinophilia despite high-dose inhaled corticosteroids and often systemic steroids. Management of these patients is challenging as there is no targeted therapy available for these patients. This realization, in combination with the advances in understanding the relationship between IL-5, eosinophils, and asthma, led to the idea of IL-5 inhibition as a therapy.

Role of IL-5 in Asthma

IL-5 is a homodimeric cytokine (115 amino acids per chain) that belongs to the hematopoietic growth factor cytokine family, which also includes IL-3 and GM-CSF [29]. IL-5 protein is secreted primarily by activated Th2 cells, ILC2s, and mast cells [11, 30]. NK, NKT, and eosinophils also produce IL-5 [31, 32]. Interleukin-5 has pleiotropic effects on the immune system although it is best known for its actions on eosinophils, which include differentiation, proliferation, migration, activation, and survival [11, 33]. Signal transduction occurs exclusively through the IL-5 receptor, which is a heterodimer composed of the common β-chain (shared with GM-CSF and IL-3) and the specific IL-5Rα-chain [34]. Engagement of the IL-5 receptor by IL-5 triggers an intracellular signaling cascade involving JAK2 and STAT5 [35].

Overproduction of IL-5 was first linked to asthma in the early 1990s. The association began with the observation that transgenic mice overexpressing IL-5 developed profound peripheral eosinophilia with eosinophilic infiltrate of the lung and lymphoid tissue [36]. Concurrently, Azzawi et al. reported that activated T cells—a presumed source of IL-5—were found in human asthmatic airways [37]. This was then supported by the finding of activated (CD4 + CD45RO+) T cells in the airways of asthmatic patients, and increased levels of IL-5 transcript in the active T cells [38, 39].

In the next several years, multiple studies reported a central role for the IL-5 in the initiation and propagation of pulmonary inflammation. Foster et al. showed that IL-5-deficient mice do not have airways hyperresponsiveness to methacholine or inhaled allergen in an OVA sensitization model [40]. Corrigan et al. demonstrated that serum IL-5 levels normalize after systemic glucocorticoid therapy and that IL-5 levels track with FEV_1 [41]. Finally, anti-IL-5 treatment led to a reduction in pulmonary eosinophilia and airway hyperreactivity to histamine in a primate model of asthma [42]. These data led to the understanding of IL-5 as a crucial cytokine that influences circulating eosinophils, airways hyperreactivity, and pulmonary inflammation, and that targeting IL-5 is a potential therapeutic strategy for asthma.

Clinical Trials Involving Anti-IL-5

The first clinical trial with anti-IL-5 therapy was published in 2000. In the subsequent 15 years, multiple clinical trials involving three monoclonal antibodies targeting the IL-5 pathway have been published (Table 1). The following section will review the hallmark trials for each agent.

Mepolizumab

Mepolizumab is a fully humanized IgG1 monoclonal antibody, which binds IL-5 and prevents binding to the α-chain of the IL-5 receptor [51]. It was the first anti-IL-5 therapy to be tested in a clinical trial in 2000.

Mepolizumab was first studied in patients with mild asthma on β-agonist monotherapy. This study showed a marked reduction in blood and sputum eosinophils but failed to modify bronchial hyperresponsiveness to histamine and the late asthmatic response [43•]. The second mepolizumab trial enrolled patients with moderate–severe asthma on inhaled corticosteroids regardless of peripheral eosinophil levels [52]. Mepolizumab again reduced sputum and peripheral eosinophilia but did not affect morning peak expiratory flow (PEF) or quality of life. There was a non-significant trend toward decreased asthma exacerbations [52]. At this point, there were

Table 1 Selected clinical trials involving anti-IL-5 therapies in asthma

First author Journal; year (reference number)	Medication Dose	Number of patients (age (years))	Notable inclusion criteria	Duration	Primary endpoint (1) Secondary endpoint (2)	Relevant findings
Leckie Lancet; 2000 [43•]	Mepolizumab 2.5 mg/kg IV 10.0 mg/kg IV	24 (18–45)	• Only on β-agonist • Atopy (one positive skin test)	29 days	Blood eosinophils (1) Late asthmatic response (2) Histamine AHR (2)	• Decrease in blood eosinophils • No change in late asthmatic response • No change in AHR to histamine
Bel NEJM; 2014 [44•]	Mepolizumab 100 mg subQ	135 (16–74)	• 5-35 mg prednisone daily • Blood eosinophils ≥300/μL	32 weeks	% Reduction in OCS (1) Asthma exacerbations (2)	• Median 50 % reduction in OCS • 32 % reduction in exacerbations
Ortega NEJM; 2014 [45••]	Mepolizumab 100 mg subQ 75 mg IV	576 (18–82)	• Two exacerbations in past year • Blood eosinophils ≥150 at screen OR ≥300 in past year	40 weeks	Annualized exacerbations (1) FEV_1 (2)	• 47 % reduction in exacerbations for IV • 53 % reduction in exacerbations for subQ • 100-mL increase in FEV_1 for IV • 98-mL increase in FEV_1 for subQ
Castro Lan. Res. Med; 2015 [46]	Reslizumab 3.0 mg/kg IV	953 (12–75)	• Blood eosinophils ≥400/μL • Inadequate control (ACQ-7 > 1.5)	52 weeks	Number of exacerbations (1) Change in FEV_1 (2)	• Decreased exacerbations (1.81 vs. 0.84 per patient per year) • FEV_1 increase of 110 mL
Bjermer Chest; 2016 [47••]	Reslizumab 0.3 mg/kg IV 3.0 mg/kg IV	315 (12–75)	• Blood eosinophils ≥400/μL • Inadequate control (ACQ-7 > 1.5)	20 weeks	Change in FEV_1 (1) AQLQ (2)	• FEV_1 increase 160 mL in 3.0 mg/kg • FEV_1 increase 115 mL in 0.3 mg/kg
Corren Chest; 2016 [48•]	Reslizumab 3.0 mg/kg IV	496 (18–65)	• Inadequate control (ACQ-7 > 1.5) • No eosinophilia requirement	16 weeks	Change in FEV_1 (1) ACQ-7 (2)	• No change in FEV1 • In subgroup with eosinophils >400/μL, FEV_1 did improve
Bleecker Lancet; 2016 [49••]	Benralizumab 30 mg subQ q4 weeks 30 mg subQ q8 weeks	1205 (12–75)	• High-dose ICS + LABA • Two exacerbations in past year • Blood eosinophils ≥300/μL (primary analysis)	48 weeks	Annual exacerbation rate (1) Change in FEV_1 (2) Asthma symptom score (2)	• For q4 week dosing 45 % reduction in exacerbations/year 106-mL increase in FEV_1 • For q8 week dosing 51 % reduction in exacerbations/year 159-mL increase in FEV_1
FitzGerald Lancet; 2016 [50••]	Benralizumab 30 mg subQ q4 weeks 30 mg subQ q8 weeks	1306 (12–75)	• MedHigh dose ICS + LABA • Two exacerbations in past year • Blood eosinophils ≥300/μL (primary analysis)	56 weeks	Annual exacerbation rate (1) Change in FEV_1 (2) Asthma symptom score (2)	• For q4 week dosing 36 % reduction in exacerbations/year 125-mL increase in FEV_1 • For q8 week dosing 28 % reduction in exacerbations/year 116-mL increase in FEV_1

serious concerns about the efficacy of anti-IL-5 therapy in asthma. To further those concerns, Flood-Page et al. reported that mepolizumab treatment only decreased airway eosinophils by 55 % (peripheral eosinophils decreased 100 %) and there was no change in major basic protein staining in the bronchial mucosa. This provided a potential explanation for the lack of clinical efficacy.

Although the mepolizumab data only showed a trend toward decreased exacerbations, the trials were conducted with an unselected population of patients with asthma. The efficacy of mepolizumab to decrease exacerbations on a more selective population was tested in a pair of exploratory randomized controlled trials. The first trial examined 20 patients with persistent sputum eosinophilia despite maintenance therapy with systemic oral corticosteroids (OCS) [53]. In addition to a decrease in sputum and peripheral eosinophils, there was an 84 % reduction in systemic steroid use (absolute reduction of 8 mg/day) and a reduction in the time to the first exacerbation (20 vs. 12 weeks). Notably, 75 % of the exacerbations in the placebo group were associated with sputum eosinophilia but 0 % of the exacerbations in the mepolizumab group were associated with sputum eosinophilia. The second trial included 61 patients with severe asthma, greater than 3 % sputum eosinophils and a history of two asthma exacerbations in the past year [54]. Mepolizumab reduced exacerbations from 3.4 to 2.0 per person per year and improved quality of life. There was no change in FEV_1 or bronchial hyperresponsiveness. These studies suggested that patients with poorly controlled asthma and peripheral eosinophilia despite high-dose glucocorticoids may experience a decrease in asthma exacerbation frequency with anti-IL-5 therapy.

Given the success of the previous small trials, the "DREAM" trial was initiated. Six hundred twenty-one patients were carefully selected for sputum (>3 %) or peripheral eosinophilia (>300/μL) and randomized to mepolizumab or placebo. Exacerbations were reduced from 2.4 to 1.15 exacerbations per patient per year. In addition, the decrease in peripheral eosinophils and sputum eosinophils was confirmed [55•]. This trial identified mepolizumab as an effective medication to prevent exacerbations in eosinophilic asthma and led to two additional phase III studies to examine endpoints such as reduction in systemic corticosteroids and change in FEV_1. The first study by Bel et al. included 135 patients on maintenance therapy with OCS [44•]. On average, there was a 50 % reduction in OCS use. There was also a reduction in the exacerbation rate from 2.12 to 1.44 exacerbations/year. The companion study, published by Ortega et al., studied 576 patients with 2+ exacerbations in the past year [45••]. The study showed a 53 % reduction in clinically significant exacerbations, a 98-mL increase in FEV_1, and an improvement in ACQ-5. This was the first major anti-IL-5 study that showed an increase in FEV_1 in any patient population.

The above studies provided evidence that mepolizumab is effective for a highly selected group of patients. The FDA approved mepolizumab for use in severe asthma with eosinophilia in November 2015.

Reslizumab

Reslizumab is a humanized IgG4 monoclonal antibody, which binds IL-5 and prevents interaction with the IL-5 receptor [56]. It is the second anti-IL-5 agent and has a mechanism of action similar to mepolizumab.

The first reslizumab clinical trial was a pilot study involving 26 patients with severe asthma (eosinophilia was not an entry requirement). The data show a reduction in peripheral and sputum eosinophils, a trend toward increased FEV_1, and few adverse events [56]. Reslizumab was then studied in a larger trial involving 106 patients with poorly controlled asthma and sputum eosinophilia. There was an improvement in FEV_1 and a trend toward improved asthma symptom scores [57]. Given the favorable early data, reslizumab was advanced to a phase III study. Enrolled patients had inadequately controlled asthma, peripheral eosinophilia, and at least one exacerbation in the past 12 months despite therapy with medium-dose inhaled corticosteroid (ICS) [46]. Reslizumab reduced annualized exacerbations (from 1.81 to 0.84) and reduced sputum eosinophilia. The study also reported an improvement in FEV_1 (by 120 mL).

This positive result triggered two additional phase III studies to examine FEV_1 as a primary endpoint. The first study, by Bjermer et al., examined 315 patients with inadequately controlled asthma on medium-dose ICS and peripheral eosinophilia >400 cells/μL [47••]. This study was unique because there was no requirement for asthma exacerbations or baseline FEV_1 and the primary outcome was change in FEV_1. Reslizumab improved FEV_1 by an average of 130 mL and also improved asthma control (AQLQ). The second study by Corren et al. examined the efficacy of reslizumab in 492 patients on medium-dose ICS [48•]. There were no entry criteria for eosinophilia, FEV_1, or asthma exacerbations. The primary outcome was change in FEV_1 from baseline to week 16. Overall, the study did not show an improvement in FEV_1 in an unselected patient population. However, a subgroup analysis showed a 270-mL improvement in FEV_1 in patients with eosinophils >400/μL and no change in FEV_1 in patients with eosinophils <400/uL.

With the completion of these successful phase III clinical trials, reslizumab was approved by the FDA for use in severe asthma with eosinophilia.

Benralizumab

The third anti-IL-5 medication, benralizumab, is currently under investigation. Benralizumab was designed to address the

concern that targeting IL-5 does not adequately deplete tissue eosinophils (it reduces eosinopoesis and peripheral eosinophilia) [58, 59]. It is a humanized, afucosylated monoclonal IgG1 antibody directed at the α-chain of the IL-5 receptor [60]. The afucosylated Fc oligosaccharide region increases binding to FcRγIIIa and enhances antibody-dependent cell-mediated cytotoxicity (ADCC) 1000-fold [61, 62]. As a result, benralizumab is expected to mediate cytotoxity against all cells that express the IL-5 receptor such as eosinophils and basophils.

The first clinical trial with benralizumab was a phase I study that demonstrated a reduction in eosinophils in peripheral blood, sputum, airway mucosa, and bone marrow [63]. A subsequent phase 2b study by Castro et al. recruited 609 patients between 18 and 75 years of age and showed that 100 mg benralizumab reduced exacerbation rates [64]. In patients with peripheral eosinophils >300/uL, the reduction in asthma exacerbations was significant for the two benralizumab doses tested, both 20 and 100 mg benralizumab.

The positive data from the above earlier phase trials led to the development of a pair of phase III studies that were published in late 2016. The first study, "SIROCCO," included 1205 patients on high-dose ICS and long-acting β_2-agonists (LABA) with two or more exacerbations in the past year; a subgroup of participants had low peripheral blood eosinophils (<300/uL) [49••]. Participants were randomized to receive either benralizumab 30 mg every 4 week, 30 mg every 8 weeks, or placebo. The primary analysis only included the subgroup with elevated peripheral blood eosinophils. Benralizumab decreased the annualized exacerbation rate by 45 % when administered every 4 weeks and by 51 % when administered every 8 weeks. In addition, FEV_1 improved in both the groups (by 106 and 159 mL in the every 4- and every 8-week dosing group, respectively). The sister trial, "CALIMA," used a similar protocol but included patients on both high and medium doses of ICS [50••]. Benralizumab reduced the annualized exacerbation rate by 36 % when administered every 4 weeks and by 28 % when administered every 8 weeks. FEV_1 improved in both the treatment groups. Unexpectedly, both the trials reported reduced exacerbations in patients with non-eosinophilic severe asthma.

Safety of Anti-IL-5 Therapy

Safety data from mepolizumab and reslizumab suggest that both the medications are well tolerated. The most common side effects are headache and nasopharyngitis, which occur approximately at the same frequency in treatment and placebo groups.

Mepolizumab injection is associated with hypersensitivity reactions (injection-site reaction, urticaria, and angioedema) [65]. The risk of anaphylaxis is not increased over placebo. Of note, there were two cases of severe herpes zoster infection in mepolizumab patients. Reslizumab is administered via IV infusion and does not have an increase in local-site reactions [66]. However, anaphylaxis occurred in 0.3 % of patients. The FDA did not mandate a prescription for intramuscular epinephrine, but providers should be aware of the elevated risk of anaphylaxis and monitor patients accordingly.

Gaps in the Literature

Clinical trials have demonstrated the benefit of anti-IL-5 medications in patients with severe asthma and persistent eosinophilia. Anti-IL-5 therapy can reduce exacerbations, decrease the maintenance dose of systemic corticosteroids, and increase FEV_1. However, there are still many unanswered questions regarding IL-5 therapy.

The most pressing need to is to better define the ideal patient population. For example, the Bel study (2014) reported a 50 % median reduction in OCS use in the mepolizumab group [44•]. However, a deeper look into the data reveals significant heterogeneity: 23 % of patients had a 90–100 % decrease in steroid dose while 36 % of patients had no change in steroid dose or withdrew from the trial. What accounts for the patient-to-patient discrepancy? Are there biomarkers beyond peripheral eosinophilia that can better predict response to therapy? Data show that sputum eosinophils can persist despite anti-IL-5 therapy [58]. Because only several of the primary clinical trials collected sputum eosinophils, there are limited data to determine whether the monitoring of sputum eosinophils can distinguish nonresponders from responders. Unfortunately, sputum analysis is not readily available at all clinical centers so this may not be a practical method to stratify patients.

An important unanswered question is the optimal duration of anti-IL-5 therapy. There are limited data to guide the discontinuation of therapy. A single observational follow-up study monitored 56 patients (27 mepolizumab and 29 placebo) for 12 months after cessation of mepolizumab treatment [67••]. Within 3 months of therapy cessation, both sputum and blood eosinophils increased. This was associated with a return to baseline exacerbation frequency 6 months after discontinuation of therapy. To date, there are no other published trials that monitored patients after discontinuation of therapy.

Another question involves criteria for initiation of anti-IL-5 therapy. There is a subset of patients whose symptoms are suboptimally controlled on OCS but do not have eosinophilia, making them ineligible for anti-IL-5 therapy. However, these patients may not have eosinophilia because of the eosinophilopenic activity of OCS. If OCS were weaned, then eosinophilia may arise, making these patients eligible for anti-

IL-5 therapy, but at the undue risk of uncontrolled asthma. There is no existing data or biomarkers to determine whether these patients would benefit from anti-IL-5 therapy without weaning OCS.

A final remaining question is the cost vs. expected benefit of anti-IL-5 therapy. The current standard of care is oral corticosteroids, a medication with significant side effects but low cost. One published cost analysis suggests that at a price of $32,000/year, the cost of anti-IL-5 therapy would outweight the potential benefits [68]. Regardless, more data is needed to address cost vs. benefit concern.

Conclusions

Asthma is the most common chronic respiratory disease in the USA. Although the majority of patients with asthma are well controlled on standard therapies, there is a subset of patients with severe asthma and frequent exacerbations despite maximal medical therapy. Recognition of the severe asthma with eosinophilia phenotype has fostered understanding that eosinophils and IL-5 play a critical role in severe asthma. In turn, this led to anti-IL-5 agents as a novel therapeutic option for severe asthma.

There are three medications that target the IL-5 pathway in asthma. Two drugs bind IL-5 and prevent interaction with the IL-5 receptor (mepolizumab and reslizumab), and one targets the IL-5 receptor and mediates cytotoxicity to the target cell (benralizumab). Data from existing clinical trials suggest that all the three medications are effective in reducing exacerbations and increasing FEV_1 in a well-selected patient population. Patients who are most likely to benefit from anti-IL-5 therapy have frequent exacerbations despite systemic corticosteroids or high-dose inhaled corticosteroids. Most importantly, they have persistent peripheral eosinophils >300/μL or sputum eosinophils >3 % despite maximal medical therapy.

Ongoing research has advanced our understanding of the heterogeneity within asthma. Asthma phenotyping is a powerful tool to group patients with similar subtypes of asthma. This understanding, combined with the development of precise biologic therapeutics, has paved the way for a targeted molecular approach to the treatment of asthma. The anti-IL-5 medications are one of the first available therapies in the exciting new age of targeted asthma treatment.

Compliance with Ethical Standards

Conflict of Interest Drs. Giannetti and Cardet declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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