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Biologic Therapies Targeting Eosinophils: Current Status and Future Prospects

Fanny Legrand, PhD, PharmD and **Amy Klion, MD**

Human Eosinophil Section Laboratory of Parasitic Diseases NIAID, NIH Bethesda, MD

Abstract

The recent explosion in the number of biologic therapies in clinical development for the treatment of eosinophilic disorders is unprecedented. As these agents become available for clinical use, the selection of the most appropriate agent for a given patient will become increasingly complicated. The aims of this review are twofold: 1) to present the lessons learned from clinical trials using the first generation of eosinophil-targeted biologics (anti-IL-5 antibodies), and 2) to discuss the advantages and potential limitations of currently available and novel targeted therapies to treat eosinophilic disorders.

Keywords

hypereosinophilic syndrome; eosinophilic gastrointestinal disorders; asthma; monoclonal antibody; mepolizumab; reslizumab; benralizumab

Introduction

The term “eosinophil-associated diseases” (EAD) refers to a spectrum of disorders in which eosinophils are believed to play a central role in the pathophysiology.[1] Some disorders, including hypereosinophilic syndrome (HES) and eosinophilic gastrointestinal disorders (EGID) are EAD by definition; other (more common) diagnoses have clinical subtypes that are considered EAD. Among these, the best example is eosinophilic asthma, a subtype of asthma characterized by sputum eosinophilia ≥2% and peripheral eosinophilia.[2] Whereas topical and/or systemic corticosteroids remain the cornerstone of therapy for EAD and are initially effective in controlling eosinophilia and symptoms in many patients, resistance and toxicity become increasingly common over time and second-line agents are often needed.[3, 4]

Biologic therapies provide the advantage of targeting specific cells or pathways, theoretically increasing efficacy and limiting complications related to non-specific effects of more traditional therapies. In this regard, eosinophils provide an ideal target. Not only do they express lineage-restricted surface receptors,[5] but evidence from eosinophil-deficient

Corresponding Author: Amy Klion, MD Bldg 4, Rm B1-28 National Institutes of Health Bethesda, MD 20892 Tel: 301-435-8903 FAX: 301-451-2029 aklion@nih.gov.

mouse models and case reports in humans suggests that eosinophil depletion has little, if any, effect on immunity to infection and other essential host functions.[6] Although early efforts focused primarily on blocking the action of IL-5, the number of biologic agents in clinical development for the treatment of EAD has expanded dramatically in the last 5 years (Table 1, Figure 1).[7, 8] As these agents become commercially available, careful assessment of the potential advantages and limitations of an increasing number of treatment options will be required to select the most appropriate agent for a given patient.

The first part of this review will summarize the clinical development and current status of anti-IL-5 therapy for EAD with special emphasis on the lessons learned from early trials. This will be followed by a discussion of currently available and new biologic therapies in development.

1) Targeting IL-5 for the treatment of EAD

IL-5 is an ideal target for the treatment of EAD for several reasons. Central to the differentiation, activation and survival of eosinophils, IL-5 has little, if any, effect on other lineages.[9] Pre-clinical studies in mice and a monkey model of allergic asthma demonstrated a sustained decrease in eosinophils in bronchoalveolar lavage following treatment with anti-IL-5 antibody.[10, 11] These data led to the clinical development of two different humanized monoclonal antibodies that specifically bind IL-5 with high affinity: mepolizumab (GlaxoSmithKline) and reslizumab (SCH55700; Teva Pharmaceuticals).

Asthma

Early asthma trials using single dose intravenous reslizumab and mepolizumab failed to demonstrate clinical efficacy (improvement in baseline FEV_1, late asthmatic response to allergen challenge, and clinical symptoms) despite reduction in blood eosinophilia.[12-14] At the time, the lack of effect was attributed primarily to a failure of anti-IL-5 therapy to adequately deplete tissue eosinophils and/or an overestimation of the role of eosinophils in allergic asthma. As the concept of asthma phenotypes gained acceptance, new clinical trials were designed targeting subjects with objective evidence of eosinophilic asthma. Two landmark studies published in 2009 demonstrated that monthly mepolizumab therapy reduced asthma exacerbations and improved asthma symptoms compared to placebo in patients with treatment-refractory eosinophilic asthma.[15, 16] A significant reduction in maintenance corticosteroid therapy was also achieved in patients on oral corticosteroid therapy for asthma control.[16] No safety concerns were identified, although severe asthma exacerbations were transiently increased in the 3-6 months following cessation of mepolizumab therapy in one study[17]. Monthly reslizumab was also effective in the treatment of poorly controlled eosinophilic asthma despite inhaled corticosteroids.[18] These studies convincingly demonstrated that eosinophils play an important role in the pathogenesis of eosinophilic asthma and paved the way for further studies.

The DREAM study assessed three different monthly dosing regimens of intravenous mepolizumab in 621 patients with recurrent exacerbations of eosinophilic asthma. Asthma exacerbations were decreased by 39–52% in patients receiving mepolizumab[19]. Cluster analysis identified three predictors of response to mepolizumab: absolute eosinophil count,

airway reversibility and BMI[20]. In contrast, oral corticosteroid use was not associated with exacerbation rate. [21]

In a second multicenter study, 576 patients with recurrent asthma exacerbations and eosinophilic inflammation despite corticosteroid therapy received monthly mepolizumab (100 mg subcutaneously or 75 mg intravenously) or placebo. [22] Both formulations were equally effective in reducing asthma exacerbations, FEV_1 and clinical symptoms. The clinical efficacy of subcutaneous monthly dosing was confirmed in a second placebo-controlled study, with significantly fewer exacerbations in the mepolizumab group despite reduction in median corticosteroid dose by 50%.[23] Based on the data described above, GlaxoSmithKline filed regulatory applications with the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) for mepolizumab as maintenance treatment for severe eosinophilic asthma in November of this year (http://www.gsk.com/en-gb/media/press-releases/2014/gsk-announces-regulatory-submissions-for-mepolizumab-in-severe-eosinophilic-asthma/).

Four phase 3 trials of reslizumab for the treatment of eosinophilic asthma have been completed Data from two of these were presented at the European Respiratory Society Conference in September 2014. In one study, intravenous reslizumab (0.3 or 3 mg/kg) or placebo was administered monthly to 311 patients with uncontrolled asthma and peripheral eosinophilia ≥400/μL despite moderate dose ICS. After 16 weeks of therapy, FEV_1 and clinical symptoms were significantly improved in patients receiving reslizumab therapy. [24] A second trial explored the relationship between blood eosinophil count and response to reslizumab therapy. Intravenous reslizumab (3 mg/kg) or placebo was administered monthly to 492 patients with uncontrolled asthma despite ICS. Pulmonary function and clinical symptoms were significantly improved at 16 weeks in subjects who received reslizumab. Patients with an absolute eosinophil count ≥400/μL experienced significantly greater improvement than those with lower counts.[25] No safety issues were reported in either trial.

HES

Hypereosinophilic syndrome (HES) is a heterogeneous group of disorders defined by peripheral eosinophilia ≥1500/μL and eosinophil-related end organ manifestations.[1, 26] After several small open-label trials of anti-IL-5 antibody for treatment-refractory HES,[27-29] a placebo-controlled, multicenter trial of mepolizumab treatment as a steroid-sparing agent was initiated in 85 *FIP1L1/PDGFRA*-negative patients with stable HES on 20-50 mg prednisone daily. Not only did 84% of subjects who received mepolizumab meet the primary endpoint (a prednisone dose ≤10 mg daily for ≥8 consecutive weeks) as compared to 43% in the placebo group ($p<0.001$), but 47% were prednisone-free at the end of the 9 month trial as compared to 5% (2 subjects) in the placebo group.[30, 31]

Eosinophil counts were dramatically reduced by mepolizumab, and no safety concerns were identified. Serum IL-5 levels did not predict response. In a long-term, open-label extension study, 62% of the 78 subjects were on mepolizumab monotherapy after a mean of 251 weeks on trial (range 4-302 weeks).[32] Despite these results, mepolizumab was not approved by the FDA for the treatment of HES[33] and is available only for compassionate use in patients with life-threatening, treatment-refractory disease.

Eosinophilic granulomatosis with polyangiitis (EGPA)

EGPA is a multisystem disorder characterized by asthma, peripheral eosinophilia, and small to medium vessel eosinophilic vasculitis. Following a case report of successful mepolizumab treatment of a patient with treatment-refractory EGPA,[34] two small open-label pilot studies of monthly mepolizumab infusions were conducted in patients with corticosteroid-dependent EGPA.[35, 36] In both studies, eosinophilia and symptoms were suppressed during mepolizumab therapy, despite tapering of maintenance corticosteroid therapy, but recurred once mepolizumab was discontinued, consistent with an important role for eosinophils in disease pathogenesis.[35, 37] A multicenter placebo-controlled trial of mepolizumab for relapsing or refractory EGPA is ongoing.

Eosinophilic esophagitis

Eosinophilic esophagitis (EoE) is a chronic disorder defined by the presence of esophageal eosinophilia. Despite the results of an early safety trial of monthly mepolizumab demonstrating symptomatic improvement and a dramatic decrease in peripheral and esophageal eosinophilia in 4 patients with EoE,[38] subsequent placebo-controlled and/or double-blind studies have failed to demonstrate clinical efficacy of mepolizumab or reslizumab in adult or pediatric patients with EoE, despite reduction in blood and esophageal eosinophilia.[39-41] Whether the failure of clinical response reflects incomplete depletion of tissue eosinophils, irreversible structural changes, or involvement of other cell lineages or factors unaffected by anti-IL-5 therapy is unclear. A randomized, double-blind, placebo-controlled, trial of mepolizumab for pediatric EoE is in progress in Great Britain.

Other

Eosinophils are typically prominent in skin biopsies from patients with atopic dermatitis and have been implicated in disease pathogenesis. Although intravenous administration of mepolizumab reduced eosinophilic infiltration in skin biopsies following allergen challenge, the size of the reaction was unaffected.[42] Two weekly doses of mepolizumab were also ineffective in abrogating clinical symptoms or reducing the size of the reaction to allergy patch testing in 18 patients with severe atopic dermatitis despite marked reduction of peripheral eosinophil counts.[43, 44]

Mepolizumab and reslizumab have also been studied in patients with nasal polyposis. In the first study, 24 patients received a single dose of intravenous reslizumab. The nasal polyp score improved in 50% of subjects and correlated with IL-5 levels in nasal secretions at baseline.[45] A subsequent placebo-controlled study in 30 patients with treatment-refractory severe nasal polyposis demonstrated a statistically significant reduction in polyp size in patients who received two intravenous doses of mepolizumab. A European multicenter, placebo-controlled study of mepolizumab for nasal polyposis is underway.

Lessons learned

The successes and failures of anti-IL-5 therapy have contributed significantly to our understanding of the heterogeneity of EAD and the role of eosinophils in disease pathophysiology. Furthermore, long-term safety data in patients with HES has been reassuring with respect to concerns that sustained depletion of eosinophils would lead to

impaired tumor surveillance or dysregulated immune responses.[32] Nevertheless, a number of issues remain. The most important of these is the inconsistent correlation between depletion of peripheral eosinophilia, reduction of tissue eosinophilia and improvement in clinical manifestations. Although the reasons for this are clearly multifactorial, data from clinical trials of additional biologic agents targeting eosinophils and molecules that modulate eosinophilia in diverse populations of patients with EAD will be crucial in addressing this issue.

2) New therapeutic strategies for eosinophil associated disorders

Targeting eosinophil surface receptors

Among the plethora of eosinophil surface receptors described to date, four are relatively specific for the eosinophil lineage: IL5Rα, CCR3, Siglec-8 and EMR1, making them logical targets for the treatment of EAD.[5]

IL-5Rα—The IL-5 receptor (IL-5R) is a high-affinity receptor expressed on eosinophils, basophils, mast cells, and their precursors in the bone marrow.[46, 47] IL-5Rα occurs as a heterodimer with the β subunit common to IL-5, IL-3, and GM-CSF receptors, and decreased surface expression of IL-5Rα, accompanied by a reciprocal increase in sIL-5Rα in culture supernatants, has been reported after *in vitro* incubation of eosinophils with IL-5, IL-3, GM-CSF, or IL-9.[48] A similar IL-5Rα regulatory pathway has been demonstrated in human eosinophils *in vivo*.[48, 49]

Benralizumab is an afucosylated humanized monoclonal antibody to IL5Rα that both inhibits IL-5–mediated cell proliferation by reducing IL-5 binding to its receptor and depletes IL-5Rα-bearing cells through enhanced antibody-dependent cell-mediated cytotoxicity (ADCC).[50] In an early phase 1 trial, benralizumab induced peripheral blood eosinopenia for 12 weeks following a single intravenous dose in patients with mild asthma.[51] These results were confirmed and extended in a multicenter, double-blind, placebo-controlled phase 1 study, in which 3 monthly subcutaneous doses of benralizumab reduced airway eosinophil counts by 95.8%, sputum eosinophil counts by 89.9%, and blood eosinophilia by 100% in patients with eosinophilic asthma.[52] Eosinophil precursors were also reduced in 5 subjects who consented to bone marrow examination. No safety concerns were identified in either trial.

Although benralizumab administered every 4-8 weeks for 48 weeks failed to show efficacy in patients with chronic obstructive pulmonary disease (COPD) and sputum eosinophilia,[53] a similar study in asthmatics demonstrated reduction in asthma exacerbations in patients with blood eosinophilia >300/μL[54]. In addition, a single dose of intravenous benralizumab for treatment of acute asthma reduced the rate and severity of subsequent exacerbations for 12 weeks.[55] Phase 3 trials of benralizumab in asthma and COPD, as well as a phase 2 trial in treatment-refractory HES, are currently underway.

Potential advantages of benralizumab therapy for EAD are several. First, the efficacy of benralizumab should not be substantially affected by elevated serum IL-5 levels, as can be seen in some patients with HES. Although sIL-5Rα has been documented in the serum of

eosinophilic patients, reported levels are unlikely to be sufficient to reduce drug efficacy.[49] Second, preliminary data suggest that benralizumab depletes both mature eosinophils and their precursors in the bone marrow. This has important implications for primary EAD and may explain the prolonged eosinopenia observed after a single intravenous dose. Potential disadvantages of benralizumab include the possibility of adverse events related to cell lysis in patients with marked peripheral eosinophilia, as well as the theoretical consequences of prolonged and profound eosinopenia on eosinophil homeostatic functions, including tumor surveillance and plasma cell maintenance.

CCR3 and eotaxin—The chemokine receptor, CCR3, is expressed primarily on eosinophils and basophils and has multiple ligands, including CCL-11, -24, and -26 (eotaxins). CCR3 undergoes ligand-induced internalization from the eosinophil plasma membrane and is also found intracellularly on eosinophil granule membranes.[56] In contrast to IL-5Rα, expression of CCR3 on eosinophils is relatively unaffected by Th2 cytokines and is positively correlated with disease severity in patients with asthma.[57] Despite reduction of airway eosinophilia with anti-CCR3 antibody treatment in a murine model, [58] human trials have not been initiated.

Bertilimumab is a humanized anti-CCL11 IgG4 antibody (CAT-213; Immune Pharmaceuticals) in clinical trials for ulcerative colitis and bullous pemphigoid, disorders characterized by elevated eotaxin-1 levels. Studies in severe asthma are planned (www.immunepharmaceutical.com). Theoretical advantages of agents targeting the CCR3-CCL11 axis are a preferential effect on eosinophil recruitment to affected organs. Whether targeting eotaxin will prove more effective than CCR3 blockade remains to be seen, although the redundancy of the chemokine network and potential for interaction of other eosinophil chemoattractants with CCR3 may limit the therapeutic potential of this approach.

Siglec-8 and other inhibitory receptors—Sialic acid-binding immunoglobulin-like lectin (Siglec)-8 is an inhibitory receptor that is highly expressed on mature eosinophils, mast cells and basophils.[59] Antibody to Siglec-F, the murine orthologue of Siglec-8, reduces blood and tissue eosinophilia in mice.[60] Anti-Siglec-8 antibody induces apoptosis of human eosinophils *in vitro*.[61] Paradoxically, costimulation of eosinophils with cytokines that promote eosinophil survival, such as IL-5, IL-33 and GM-CSF, enhance Siglec-8-mediated apoptosis *in vitro*.[61] Eosinophils isolated from the bronchoalveolar fluid of allergen-challenged patients also display enhanced susceptibility to apoptosis induced by anti–Siglec-8 antibodies.[59] Soluble Siglec-8 can be detected in the serum of eosinophilic patients, albeit at low levels (<150 ng/mL).[62]

Still in preclinical development, anti-Siglec-8 antibodies have some unique advantages as therapeutic agents for EAD due to their mechanism of action. First, adverse effects due to release of eosinophil granule proteins and other mediators are unlikely to occur with apoptotic cell death, even in patients with marked eosinophilia. Second, efficacy may be increased in patients with activated eosinophils. Finally, Siglec-8 inhibits degranulation of mast cells. This may be particularly useful in disorders, such as EoE, where tissue mast cells may play a role in disease pathogenesis. Although other inhibitory receptors, including CD300a, Siglec-7 and paired immunoglobulin receptor A (PIR-A), have been described on

eosinophils, they are also expressed on other cells and, consequently, may induce unwanted side effects. Bispecific antibodies to CCR3 and CD300a have been shown to circumvent this problem in a murine model of asthma.[63]

EMR1—Human epidermal growth factor (EGF)–like module containing mucin-like hormone receptor 1 (EMR1) is a surface receptor of unknown function that belongs to the EGF-7-transmembrane family of G protein–coupled receptors. Human EMR1 expression is restricted to mature blood and tissue eosinophils.[64, 65] Afucosylated monoclonal anti-EMR1 antibody (Kalobios) dramatically enhanced natural killer cell–mediated killing of eosinophils from healthy and eosinophilic donors *in vitro* and induced a rapid and sustained depletion of eosinophils in monkeys.[65]

Eosinophil- modulating therapies

Although not specific for eosinophils, a wide variety of soluble mediators, including IgE, IL-4, IL-13, thymic stromal lymphopoietin (TSLP), IL-25 and IL-33, are associated with eosinophilic inflammation *in vivo*. Biologic therapies targeting several of these mediators are currently available or being developed for clinical use. Small molecule antagonists are also in development against a number of additional receptors and mediators that are likely to be involved in the pathogenesis of EAD, but are beyond the scope of this review.

IgE—Elevated serum IgE levels accompany eosinophilia in a wide range of EAD, including allergic asthma, EGID and lymphocytic variant HES, and have been implicated in disease pathogenesis in some settings. The anti-IgE antibody, omalizumab (Xolair; Genentech/ Novartis), which is FDA-approved for the treatment of allergic asthma, has been shown to significantly decrease peripheral blood eosinophilia in patients with asthma.[66] Furthermore, high baseline eosinophil count is a predictor of clinical response.[67] Nevertheless, despite a moderate reduction in peripheral eosinophilia and clinical improvement in 9 subjects with eosinophilic gastritis or duodenitis treated in an open-label study of omalizumab, tissue eosinophilia was not significantly decreased.[68] A subsequent placebo-controlled study of omalizumab in 30 patients with eosinophilic esophagitis also failed to demonstrate an effect of drug on clinical symptoms or tissue eosinophilia.[69]

IL-4 and IL-13—IL-4 and IL-13 are pleiotropic cytokines produced by a variety of cell types, including CD4+ Th2 lymphocytes, type 2 innate lymphoid cells (ILC2), mast cells, basophils and eosinophils. The receptors for IL-4 and IL-13 share a common α chain (IL-4Rα) and are expressed on many different cells, including eosinophils. Both IL-4 and IL-13 play a major role in promoting class switching to IgE antibodies, but have also been implicated in eotaxin-mediated recruitment of eosinophils to areas of allergic inflammation and promotion of eosinophil survival. IL-4 is also required for Th2 polarization of CD4+ cells, production of IL-5[70] and eosinophil differentiation in the bone marrow in the presence of IL-5.[71] Monoclonal antibodies to IL-4, IL-13, and their receptors have shown promise in reducing blood and airway eosinophilia in murine models of allergic inflammation, prompting the initiation of clinical trials targeting the IL4/IL-13 axis in asthma, atopic dermatitis and EoE.

Despite promising preclinical and phase 1/2 data in asthma,[72, 73] subsequent clinical trials of monoclonal antibodies targeting IL-4 (pascolizumab; SB 240683; GlaxoSmithKline) or its receptor (Nuvance; altrakincept; Immunex) have been disappointing.[4] Clinical trials of anti-IL-13 antibody have provided conflicting results depending on the asthma subgroup studied. In a phase 2 trial in patients with poorly-controlled asthma despite inhaled corticosteroid (ICS) therapy, monthly lebrikizumab (MILR1444A; Hoffmann-La Roche) improved lung function at 12 weeks, but only in a subset of patients with a Th2 phenotype and elevated periostin levels.[74] Although a similar trial with tralokinumab (CAT-354; MedImmune) failed to meet its primary endpoint, clinical improvement was observed, especially in patients with increased levels of sputum IL-13. [75] In contrast, a clinical trial of lebrikizumab in asthmatic patients who were not receiving ICS failed to demonstrate an effect irrespective of serum periostin levels.[76]

Although the reasons for the discrepancy between murine and human studies of monotherapy targeting IL-4 or IL-13 are not entirely clear, redundancy between the biologic activities of two cytokines has been proposed as a plausible explanation. Dupilumab (REGN668; Regeneron Pharmaceuticals and Sanofi) and AMG 317 (Amgen) are antibodies to IL-4Rα that inhibit signaling of both IL-4 and IL-13. Weekly dupilumab treatment decreased asthma exacerbations and improved lung function following the withdrawal of ICS and long-acting beta-agonist therapies in a placebo-controlled trial in patients with eosinophilic asthma[77] and led to improvement in clinical symptoms in a placebo-controlled trial in patients with atopic dermatitis.[78] Although a phase 2 trial of AMG 317 in patients with moderate to severe asthma failed to demonstrate clinical efficacy overall, subjects with more severe disease were more likely to respond and a dose effect was observed.[79]

A consistent finding in studies targeting IL-4 and/or IL-13 has been the lack of effect on peripheral blood eosinophilia.[74, 75, 77, 78, 80]. Whereas reduction of exhaled nitric oxide (FE_{NO}), a surrogate marker of sputum eosinophilia, has correlated with treatment response in some studies,[74, 77] suggesting a relatively greater effect of IL-4/IL-13 blockade on airway eosinophils, this has not been confirmed in all studies and could be confounded by the direct effect of IL-13 on nitric oxide synthase. A recent placebo-controlled study of the anti-IL-13 antibody, QAX576 (Novartis), demonstrating a reduction in esophageal eosinophilia by 60% in patients with eosinophilic esophagitis (as compared to 23% in patients receiving placebo; p=004) provides interesting new data in this regard.[80]

TSLP, IL-25, and IL-33—TSLP, IL-33 and IL-25 (known as IL-17E) are released primarily from epithelial cells in response to irritating stimuli and play a crucial role in driving Th2-mediated immune-inflammatory responses, including eosinophilia, through induction of Th2-type cytokine production (including IL-5) by activated Th2 lymphocytes and ILC2.[81,82]

Substantial data from murine models and human samples provide the rationale for targeting these mediators in EAD. Moreover, single nucleotide polymorphisms in TSLP are associated with increased and decreased susceptibility to asthma, atopic disease and EoE, [83] providing additional justification for targeting this molecule. In a multicenter proof-of-concept trial in 31 patients with asthma, treatment with AMG 157 (anti-TSLP antibody; MEDI9929;

MedImmune) significantly reduced peripheral and sputum eosinophilia, allergen-induced bronchoconstriction and airway inflammation.[84]

Additional studies of AMG 157 in asthma are underway. Brodalumab (Amgen), a human monoclonal antibody against interleukin-17 receptor A (IL17RA) that also blocks the effects of IL-25, did not reduce clinical symptoms, airway reactivity or eosinophilia in patients with severe asthma.[85]

Conclusions

A wide variety of biologics are currently in clinical trials for EAD. Despite theoretical concerns regarding the potential toxicity of rapidly lowering eosinophil counts and the long-term consequences of eosinophil depletion on immune function and tumor surveillance, no safety concerns have been raised in clinical trials to date. Efficacy has been mixed, depending on the specific agent and disorder under study. Furthermore, post hoc analyses of clinical trials in asthma have highlighted the importance of clinical phenotype and biomarkers in the evaluation of therapeutic response. As the number of biologic therapies continues to grow, selection of the best initial therapy for an individual patient with EAD will require an understanding of the advantages and disadvantages of available agents in relation to the pathogenesis of the underlying disorder.

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Abbreviations

COPD	chronic obstructive pulmonary disease
EAD	eosinophil-associated diseases
EGID	eosinophilic gastrointestinal disorders
EGPA	eosinophilic granulomatosis with polyangiitis
EMA	European Medicines Agency
EMR1	Human epidermal growth factor (EGF)–like module containing mucin-like hormone receptor 1
EoE	eosinophilic esophagitis
FDA	Food and Drug Administration
HES	hypereosinophilic syndrome
ILC	innate lymphoid cell
PIR A	paired immunoglobulin receptor A
TSLP	thymic stromal lymphopoietin

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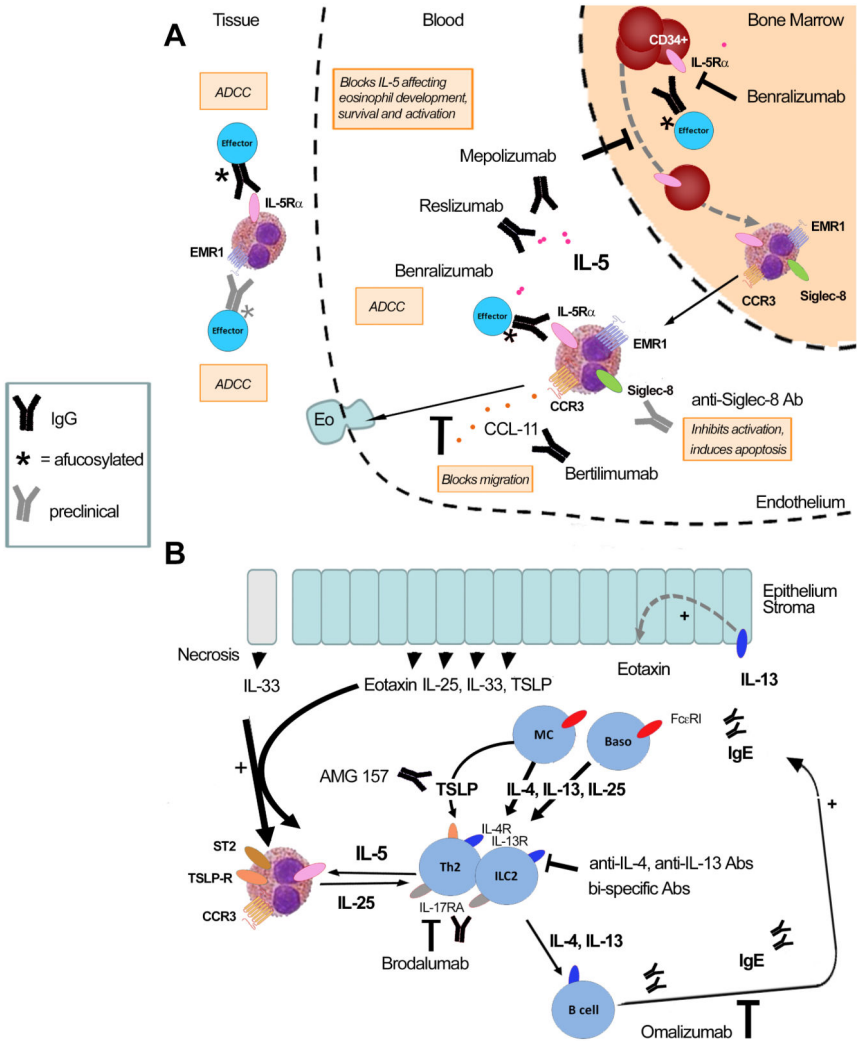

FIGURE 1.

Mechanism of action of biologic therapies for treatment of EAD. Agents targeting eosinophil surface receptors are shown in panel A and mediators associated with eosinophilic inflammation in vivo in panel B. MC = mast cell, baso = basophil.

Table 1

Summary of biologics in development for the treatment of eosinophil associated disorders

Target	Drug	Mechanism of Action	Status*
IL-5	**Mepolizumab** SB-240563	• Block IL-5	• Submitted to FDA and EMA for asthma in November 2014 • Ongoing trials in asthma, COPD, HES, EoE, EGPA, nasal polyposis and eosinophilic cystitis
	Reslizumab SCH55700		• Phase 3 trials in asthma and EoE completed and open-label extension ongoing
IL-5Rα	**Benralizumab** MEDI-563	• Inhibits IL-5 binding to receptor • Depletes eosinophils through enhanced ADCC	• Ongoing trials in asthma, COPD and HES
CCL-11	**Bertilimumab**	• Blocks CCL-11	• Not yet recruiting in ulcerative colitis and bullous pemphigoid; planned in asthma
Siglec-8		• Induces eosinophil apoptosis	• In pre-clinical development
EMR1		• Depletes eosinophils through enhanced ADCC	• In pre-clinical development
IgE	**Omalizumab** *Xolair*®	• Blocks IgE	• Approved by FDA and EMA for asthma in June 2013 and for chronic idiopathic urticaria in March 2014 • Ongoing trials in mastocytosis, chronic urticaria, asthma, AERD, nasal polyposis, EoE, eosinophil gastroenteritis, and hyper IgE syndrome
IL-4Rα/IL-13Rα1	**Dupilumab** REGN668 **AMG 317**	• Inhibit binding of IL4 and/or IL13 to IL4Rα	• Ongoing trials in asthma, nasal polyposis, atopic dermatitis and ulcerative colitis • Ongoing trials in asthma
IL-13	**Lebrikizumab** MILR1444A	• Block IL-13	• Ongoing trials in asthma and idiopathic pulmonary fibrosis
	Tralokinumab CAT-354		• Ongoing trials in asthma, ulcerative colitis and idiopathic pulmonary fibrosis
	GSK679586		• Ongoing trials in asthma
	Anrukinzumab IMA638		• Ongoing trials in ulcerative colitis
	AMG 317 **QAX576**		• Ongoing trials in asthma • Ongoing trial in asthma, idiopathic pulmonary fibrosis, EoE, Crohn's Disease and allergic rhinitis
IL-4/IL-13	**QBX258** VAK694 +QAX576	• Block both IL-4 and IL-13	• Ongoing trials in asthma
	SAR156597 Bispecific antibody		• Ongoing trial in idiopathic pulmonary fibrosis
TSLP	**AMG 157** MEDI9929	• Blocks TSLP	• Ongoing trials in asthma and atopic dermatitis
IL-17Rα	**Brodalumab**	• Inhibits IL-17A, IL-17F and IL-25 binding to receptor	• Ongoing trials in asthma and psoriasis

ADCC, Antibody-dependent cell-mediated cytotoxicity; AERD, aspirin-exacerbated respiratory disease; COPD, chronic obstructive pulmonary disease; EMA, European Medicines Agency; FDA, Food and Drug Administration.

*Based on data from clinicaltrials.gov and clinicaltrialsregister.eu as of January 13, 2015.