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The Role of Eosinophils in Immunotherapy

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Abstract

Purpose of Review—The purpose of this review is to provide a brief discussion on the differential diagnosis for peripheral eosinophilia. We will then focus on targeted immunotherapies for atopic disease, their effects on absolute peripheral eosinophil counts, and use of peripheral eosinophils as a predictor of treatment response.

Recent Findings—In atopic disease, lower absolute peripheral eosinophil counts are typically associated with improved outcomes. Much of the current evidence on eosinophils as a biomarker comes from post-hoc analyses in therapeutic immunotherapy. While changes in eosinophilia was not the primary outcome of interest in many studies, some patterns did emerge. Cytolytic monoclonal antibodies AK002 and benralizumab completely reduce peripheral and tissue eosinophil numbers. Dupilumab may have paradoxical transient eosinophilia despite observed clinical efficacy.

Summary—Atopic inflammation is complex largely due to the various cytokines which affect eosinophils activation, proliferation, differentiation, and survival. This demonstrates the challenges of using peripheral eosinophilia alone as a biomarker for atopic disease activity. More attention should spotlight how different immunotherapy modalities affect eosinophil-driven responses.

Keywords

Eosinophilia; Atopic Disease; Aeroallergen Immunotherapy; Food Immunotherapy; Biomarkers; Biologic Therapy

INTRODUCTION

Allergist are frequently consulted to manage patients with peripheral eosinophilia. However, the differential diagnosis for eosinophilia is broad and the etiology can range from physiologic to pathologic. In this review, we briefly discuss known common causes of peripheral eosinophilia. We will discuss the use of eosinophils as a biomarker in atopic

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3. Conflicts of interest:
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disorders. Our primary focus will be on targeted immunotherapies for atopic disease, their effects on absolute peripheral eosinophil counts (AEC), and use of peripheral eosinophils as a predictor of treatment response.

Disease states that alter the homeostatic balance regulating eosinophil production, recruitment or activation can result in elevated peripheral or tissue eosinophilia. Hypereosinophilia is formally defined as AEC >1500 cells/μL for six-months' time in the presence of end-organ damage (Table 1) [1]. Primary eosinophilia arises from a clonal expansion of eosinophils, and due to hyperproliferative states, the peripheral eosinophil count can be severely elevated resulting in end-organ damage. Hypereosinophilic syndrome (HES) has been associated with molecular defects in *PDGFRα, PDGFRβ, FGFR1, or PCM1-JAK2,* though the molecular cause of primary HES is still unknown in many cases [2]. These mutations result in uninhibited tyrosine kinase activity which results in overproduction and inappropriate activation of eosinophils. Clonal eosinophil populations can be seen in other hematologic malignancies, including chronic myelogenous leukemia, acute myeloid leukemia, and in some cases of systemic mastocytosis.

Secondary eosinophilia is typically caused by a dysregulation in cytokine production that favors eosinophil production or survival. There are several clinical causes which result in secondary eosinophilia (Table 2). Physiologic eosinophilia can occur with infection, and typically resolves once the infection has been cleared. Some malignancies can cause secondary eosinophilia, such as B- or T- cell leukemia, Hodgkin's' lymphoma, T-cell lymphoma, and certain solid tumors [3–6].

Allergic Disorders

Although the differential for eosinophilia is broad (Table 2), eosinophilia secondary to atopy is common due to the frequency of atopy in the population at large. Tissue eosinophils are thought to contribute to end-organ fibrosis and damage in uncontrolled atopic inflammation in diseases like asthma and eosinophilic gastrointestinal (GI) disorders. Mild to moderate peripheral eosinophilia is a common finding seen in atopic diseases, however eosinophils in atopic disorders typically do not infiltrate additional tissues beyond those primarily affected by the atopic disorder. There is growing evidence that the peripheral eosinophil count can potentially be used as a biomarker, which may correlate with disease activity in some atopic disorders.

Atopic dermatitis (AD) disease activity has been correlated with both peripheral eosinophilia as well as peripheral eosinophil-derived protein levels [7]. Localized tissue eosinophilia is also a frequent finding in AD lesions. Interestingly, Rossberg et al demonstrate that AEC may have value as an early biomarker for predicting AD and other atopic disorders [8]. Their data indicates that elevated AEC in 4-week-old infants were significantly associated with the occurrence of AD through 3 years of life ($p = 0.006$).

Allergic rhinitis may present with a mild peripheral eosinophilia [20]. Peripheral eosinophilia might predict mucosal sinus disease as Poznanovic and Kingdom found that an AEC over 550 cells/μL had a strong correlation with mucosal disease [9]. Peripheral

eosinophilia outperformed total IgE levels in predicting mucosal disease in this cohort, with a positive predictive value of 89% and negative predictive value of 99%.

Both sputum eosinophilia and peripheral eosinophilia have been correlated with increased asthma severity and poor lung function [10–12]. Recent analysis of the phenotypes and endotypes of asthma patient subpopulations has identified a group of patients with peripheral eosinophilia. In the NIH Severe Asthma Program III cohort, AEC ≥300 cells/μL was significantly elevated in adults with severe asthma (38.5% with median 228 cells/ μL IQ range (134–399)) when compared to those with non-severe asthma (28.2% with median 189 cells/ μL IQ range (111–320)) [13]. In contrast, approximately 55–60% of pediatric patients had AEC over 300 cells/ μL regardless of asthma severity. These can be used to define a Th2-high subset of patients with asthma [14].

Eosinophilic Gastrointestinal disorders

Eosinophilic esophagitis (EoE) is a chronic immune-mediated and allergen-specific disease characterized by eosinophilic inflammation of the esophageal mucosa associated with esophageal dysfunction [15, 16, 30]. Interestingly, EoE does not always present with peripheral eosinophilia [17], whereas peripheral eosinophilia can be seen in up to 90% of patients with eosinophilic gastrointestinal disease affecting lower GI sites [18]. The AEC correlates with the tissue eosinophil count in patients with eosinophilic gastritis [19].

IMMUNOTHERAPY AND EOSINOPHILIA

Immunotherapy can be broadly defined as the prevention or treatment of disease with a substance intended to modify the immune system response. Subcutaneous aeroallergen immunotherapy for allergic rhinitis has existed for over a century [20]. However, the last several decades have seen an exponential increase in the use of many types of immunotherapy across medical disciplines for a broad range of diagnoses. Within the field of allergy, there is growing use of food allergen immunotherapies as well as biologics targeting eosinophils for the treatment of atopic disorders.

ALLERGEN IMMUNOTHERAPY

Allergen Immunotherapy is the controlled process of allergen introduction over a period of time with the end goal of inducing desensitization or tolerance to food or environmental allergens [21–23]. Subcutaneous allergen immunotherapy (SCIT) has been in clinical use for over a century. Allergic rhinitis patients treated with ragweed SCIT had significantly lower levels of eosinophils in the nasal mucosa after three years than untreated patients [24]. The significance of these findings is somewhat unclear; however, one hypothesis is that the eosinophil count decreases as systemic Th2-skewing decreases. Therapeutic response to SCIT has been associated with dampening of the transient increases of AEC and basophils during the pollen season [25]. Sublingual aeroallergen immunotherapy (SLIT) has been approved for grass, and ragweed in the United States, with additional products approved for use internationally. AECs have been shown to have modest decreases of approximately 70–75% following SLIT [26, 27]. Clinical response was correlated with lower initial AEC,

and significant reduction in the AEC for both SLIT and SCIT (65% reduced in SCIT, 69% reduced in SLIT) [28].

FOOD ALLERGY IMMUNOTHERAPY

Various modalities have been investigated for food allergy immunotherapy, including oral immunotherapy (OIT), SLIT, and epicutaneous immunotherapy (EPIT). Similar to results seen in environmental allergen immunotherapy, OIT for food allergy has been shown to decrease AECs. In 2016, Salmivesi et al completed a double-blind placebo-controlled design to monitor changes in biomarkers during a six-month OIT intervention for cow's milk allergy among 28 school aged children [29]. The post-OIT AEC was significantly decreased (median 600 cells/μL (range 200–1,250) pre-OIT vs 410 cells/μL (140–1,200) post-OIT, p= 0.003). In contrast, milk-specific IgG and IgG4, serum IL-4 and IL-6, and serum leptin and resistin increased significantly in patients' serum following OIT.

An interesting potential application of peripheral eosinophil count may be as a biomarker to predict the risk of OIT-associated side effects. A constellation of side effects in IgE-mediated food allergy patients on OIT has been described which is comprised of abdominal symptoms (abdominal pain, nausea, vomiting) and peripheral eosinophilia [30, 31]. In a recent review of 794 OIT patients, Goldberg et al found that patients with a higher baseline AEC were more likely to reach a high peak AEC during immunotherapy, and were significantly more likely to develop GI side effects. The authors suggest that pre-OIT baseline AEC of 1140 cells/μL represents a cutoff for predicting risk of future recurrent OIT-associated gastrointestinal side effects with a sensitivity of 85% and a specificity of 73% [32]. Prospective studies in other OIT cohorts will be needed to determine the accuracy of peripheral eosinophilia as a biomarker in OIT, additional research is needed to determine if the peripheral eosinophilia seen in OIT is correlated with the development of eosinophilic esophagitis.

BIOLOGIC THERAPIES TARGETING EOSINOPHILS

Direct Eosinophil Inhibition—Glucocorticoids are a well-known medication with direct effects on eosinophil survival. One mechanism of glucocorticoid action is to induce eosinophil apoptosis [33]. There are several other medications which also act directly on eosinophils, inducing apoptosis or inhibiting proliferation (Table 3).

Siglec-8: AK002 is a monoclonal antibody to Siglec-8, an inhibitory receptor expressed on mast cells and eosinophils, and has been shown to deplete circulating eosinophils within 1 hour of administration [34]. In a phase 2 trial with AK002, patients with eosinophilic gastritis and eosinophilic gastroenteritis (≥30 eosinophils/HPF, moderately to severely symptomatic) had statistically significant reductions in tissue eosinophil count (95% reduction compared to 10% in placebo group), and symptoms (53% AK002 vs 24% placebo). Additionally, in the 14 patients with comorbid EoE, 13 (93%) had a reduction in esophageal eosinophils to < 5/HPF, with significant reduction of dysphagia.

Anti-IL5Rα: Benralizumab is a monoclonal antibody which targets the IL-5 receptor alpha-chain on eosinophils, blocking IL-5 induced maturation and proliferation of eosinophils.

However, it has also been shown that this monoclonal antibody lacks key glycosylation residues which prevent NK-mediated antibody-dependent mediated cellular cytotoxicity [35]. Therefore, benralizumab targets eosinophil survival both by direct cytotoxicity as well as preventing IL-5 mediated survival signals [36].

The AEC also has value as a biomarker in benralizumab therapy. Castro et al. performed a randomized, controlled, double-blind study of 324 asthma patients categorized as eosinophilic or non-eosinophilic based on the fraction of exhaled nitric oxide (FeNO) [37]. In eosinophilic patients, exacerbation rates in the benralizumab 20 mg group and 100 mg group were significantly lower than placebo (reduction 57% and 80%; respectfully). Post-hoc analysis demonstrated that in patient subgroups with a higher AECs, benralizumab had greater efficacy in reducing asthma exacerbations however these values were not reported.

Kinase Inhibitors: In hyper-eosinophilic syndrome (HES) due to *FIP1L1-PDGFRA* mutation (seen in 10% of patients), imatinib has been effective in reducing eosinophilia. The mechanism of imatinib is not well understood but thought to result from inhibition of the various kinases required for eosinophil survival. Imatinib therapy has been highly effective in treating those with a known mutation, and there are some reports of imatinib-induced remission in patients with *FIP1L1-PDGFRA* associated chronic eosinophilic leukemia [38]. Pardanani et al., retrospectively identified 22 patients with to *FIP1L1-PDGFRA* mutation with a median AEC of 530 cells/μL (range 100–1100). Many suffered from organ involvement, with the most common symptoms being 68% bone pain, 45% weight loss, and 32% cardiac involvement. Eighteen patients received treatment with imatinib and 17 (94%) patients achieved complete hematological remission. Que et al. validated these findings in a study of 33 patients with *FIP1L1-PDGFRA* mutation positive HES [39]. The average initial AEC was 1700 cells/μL (range 1600–7880), and 97% of patients receiving imatinib achieved remission, which was defined as a decrease in the AEC 0–50 cells/μL, within 1.5–12 months.

Indirect Eosinophil Inhibition

Interleukin-5: Targeting IL-5 directly can help to reduce eosinophil commitment, proliferation, and activation while also minimizing effects on other cell lines [40]. Mepolizumab, a humanized monoclonal antibody that neutralizes IL-5, is approved for treatment of severe asthma as it has been shown to reduce the number of exacerbations and improve asthma control. In a randomized, double-blind, double-dummy study of 576 patients with severe asthma, eosinophils were reduced over 80% by week 12 in patients receiving 75 or 100 mg mepolizumab [41]. In an open label extension, patients continued to receive 100 mg of subcutaneous mepolizumab every 4 weeks and sustained reduction of AEC by 78% during the duration of treatment [42].

Bechert et al., completed a randomized, double blind, placebo-controlled trial of 750 mg mepolizumab for 24 weeks in 105 patients with severe nasal polyposis [43]. At week 25, there was a significant improvement in self-reported symptoms in patients who received mepolizumab, and a significant number of patients in the mepolizumab group no longer

required surgery (30% vs 10%, p=0.006). There was also a reduction in mean AEC from week 1 to week 25 (mepolizumab 500 to 50 cells/μL vs placebo 470 to 380 cells/μL).

Mepolizumab is FDA-approved for the treatment of eosinophilic granulomatosis with polyangiitis (EGPA). In a randomized, double blind study of mepolizumab in 136 patients with relapsing or refractory EGPA on a stable dose of steroid, results revealed that patients with an AEC > 150 cells/μL at baseline had significant greater likelihood of disease remission (mepolizumab: 33% vs placebo: 0% at ≥24 weeks; odds ratio, 26.10; 95% CI, 7.02 to 97.02) [44]. Patients with FIP1L1-PDGFRA mutation-negative HES were studied by Rothenberg et al. in a randomized, placebo-controlled double bind trial of 750 mg mepolizumab every 4 weeks for 36 weeks [45]. In the mepolizumab arm, more patients achieved an AEC of <600 cells/μL when compared to placebo (95% vs 45%, p<0.001).

However, reduction in peripheral eosinophilia is not universally associated with treatment success with anti-IL5 antibody therapy. Mepolizumab has also been trialed for use in EoE, where despite a reduction in peripheral and tissue eosinophilia, clinical symptoms were unchanged as few patients reached normal levels of tissue eosinophilia (<15 eos/hpf) [46]. Similarly, in a 2005 randomized, placebo-controlled trial by Oldhoff et al., 43 patients with moderate to severe AD treated with mepolizumab had a significant decrease in AEC when compared to placebo (521 cells/μL+/−79 to 203 +/− 54 vs 647 cells/μL +/−81 to 679+/−80, p<0.05) yet there was no significant improvement in the AD based on the SCORAD scoring system [47].

Reslizumab is a monoclonal antibody to IL-5 which is FDA approved for patients 18 years and older with an eosinophilic phenotype of severe persistent asthma. In a phase 3 trial, asthmatics with inadequately controlled disease on medium-dose inhaled corticosteroid, noted significantly improved FEV1 in those receiving reslizumab compared to placebo (difference vs placebo [reslizumab 0.3 and 3.0mg/kg]:115mL[95% CI 16–215; P= .0237] and 160mL[95% CI 60–259; P= .0018]) [48]. Reslizumab also reduced the AEC in both doses [0.3 mg/kg dose: 323 cells u/L [p= .0000] and 3.0 mg/kg dose: 494 cells u/L [p= .0000]). In a companion phase 3 trial, Corren et al. revealed that in patients with an AEC ≥400 cells/μL, FEV1 improved 270mL more in those treated with reslizumab when compared to placebo ($p = 0.04$) [49].

In EoE, there was a significant reduction in median eosinophil counts on esophageal biopsy from baseline to the end of therapy (59%, 67%, and 64% in the 1, 2, and 3 mg/kg reslizumab as compared to placebo) [50]. Similar to the mepolizumab trial, few patients reached normal levels of tissue eosinophilia as all groups including placebo had response to therapy for symptoms.

Interleukin-13: Lebrikizumab and Tralokinumab, IgG4 antibodies which neutralize IL-13, are currently undergoing evaluation for use in asthma and AD. In a phase 2 study in those with moderate-to-severe AD, patients who received lebrikizumab were significantly more likely to report a 50% reduction in physician reported eczema area and severity scores compared to placebo (82.4% vs 62.3%; $p = 0.026$) [51]. Of note, 5 patients who received lebrikizumab reported an adverse event due to rise in AEC. While exact eosinophil values

were not reported, it was noted that events were not serious or associated with clinical symptoms. Phase III trials which treated moderate-to-severe asthmatics with lebrikizumab have reported variable results.

Tralokinumab was studied in a phase 2b trial for treatment of severe asthmatics with two to six exacerbations in a year [52]. Analysis revealed a significantly increased FEV1 from baseline in the group given tralokinumab 300mg every 2 weeks compared to placebo (mean change 0.13L (0.07 to 0.20), p=0.002). Of note, week 52 AECs were raised in patients receiving tralokinumab compared to placebo.

Dectrekumab is an IgG1 monoclonal antibody directed to IL-13. During a Phase II trial, patients with proton pump inhibitor-resistant esophageal eosinophilia, who received dectrekumab, had significantly decreased tissue eosinophils compared to placebo (60% vs 23%, respectively) [53]. There was no relationship with AEC.

Anti-IL4Rα: Dupilumab is a fully human monoclonal antibody approved for use in patients with AD, asthma, and chronic sinusitis with polyposis. It targets the alpha subunit of the IL-4 receptor, which is shared between the IL-4 receptor and IL-13 receptor. IL4Rα is broadly expressed on eosinophils, basophils, mast cells, and lymphocytes and therefore dupilumab modulates signaling in multiple cell types and not eosinophils alone. Although dupilumab has shown efficacy in treating eosinophil-related atopic disorders, there has not been a clear link established between the depletion of AEC and efficacy using this agent. In fact, transient elevation of AEC was noted in phase II trials of asthmatic adults [54]. Patients with a higher initial AEC (≥ 300 cells/μL) were specifically noted to experience this treatment-related effect. Importantly, one patient with a history of high eosinophil counts discontinued dupilumab therapy due to hypereosinophilic syndrome that was successfully managed with glucocorticoids. Although some trials suggest the prevalence of eosinophilia following dupilumab is approximately 2.5%, others have suggested rates as high as 14.7 to 56% [55–58].

Anti-Immunoglobulin E (IgE): Elevated levels of IgE is typically seen in conjunction with eosinophilia in atopic disease. Omalizumab is a monoclonal antibody that binds free IgE and has been approved for the treatment of asthma and chronic urticaria. In a combined analysis of data from five clinical trials of omalizumab for allergic asthma, AEC were significantly reduced from baseline in patients receiving omalizumab as compared to placebo (321 cells/μL to 262 vs 332 cells/μL to 320, p<0.0001) [59]. Decreased AEC were associated with improved clinical outcomes during the trials; interestingly, this was observed for both omalizumab and placebo treatment. As a potential biomarker, patients with an AEC of greater than or equal to 300 cells/μL were shown to have greater response to omalizumab treatment, resulting in a 59% reduction in asthma exacerbations versus placebo (p=0.0125) [60]. Omalizumab was trialed for treatment of EoE however failed to reduce symptoms or tissue eosinophil counts compared to placebo [61].

Thymic Stromal Lymphopoietin (TSLP): Tezepelumab is a fully human monoclonal antibody which binds and neutralizes circulating TSLP. In a phase 2 trials, tezepelumab had significantly lower rates of asthma exacerbations compared to placebo (70 mg every 4

week dose 61%, 210 mg every 4 week dose 71%, and 280 mg every 2 week dose 66% of the exacerbations seen in the placebo group) [62]. Of note, decreased AEC were seen in all dosage groups after week 4 of therapy however exact quantification was not reported. These results are in agreement with an earlier study completed in 2014 by Gauvreau, in which tezepelumab treated patients had significantly improved performance during allergen challenge, with decreased reduction in FEV1 compared to placebo group (45.9%, p=0.02) [63]. AEC at day 29 were significantly decreased in the tezepelumab group compared to placebo (post-treatment 121.9 cells/μL+/−14.7 vs. 224.1 cells/μL +/−36.5, p=0.004).

CONCLUSION

The differential diagnosis of peripheral eosinophilia is broad and requires thorough knowledge of the patient's history, medications, and duration of eosinophilia. In atopic disease, lower AEC are typically associated with improved outcomes, however, there are some unaddressed questions when considering the use of eosinophils as a biomarker in this context. The majority of studies examining eosinophils as a biomarker are small, and are either not designed or adequately powered to address how multiple comorbid atopic disorders in the same patient may influence AEC. For example, if an individual has sub-optimally controlled AD, allergic rhinitis and asthma, what is the significance of changes in the AEC? Does one atopic disorder drive the AEC more than others or is it an aggregate measure? Further targeted studies would help to guide understanding of the immune response in atopic disease and during immunotherapy, and aid in the development of new therapies for people with eosinophil-driven diseases.

Additional attention should be given to how different immunotherapy modalities affect eosinophil-driven responses. The majority of the current evidence comes from post-hoc analyses in therapeutic immunotherapy trials, in which examination of eosinophils as a biomarker was not the primary outcome of interest. Nonetheless, some patterns emerge regarding how these medications affect eosinophil numbers. Some biologics like the cytolytic monoclonal antibodies AK002 and benralizumab completely reduce peripheral and tissue eosinophil numbers. However, dupilumab have paradoxical transient eosinophilia despite observed clinical efficacy which illustrates the complexity of atopic inflammation and challenges the use of peripheral eosinophilia alone as a biomarker in atopic disorders. As we continue to understand more about eosinophil involvement and trafficking, we can continue to improve therapies for disorders involving this relatively poorly understood cell type.

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Abbreviations:

AEC	absolute eosinophil count

IL	interleukin
GM-CSF	granulocyte-macrophage colony-stimulating factor
TSLP	thymic stromal lymphopoietin
HES	hypereosinophilic syndrome
GI	gastrointestinal
AD	atopic dermatitis
EoE	eosinophilic esophagitis
SCIT	subcutaneous allergen immunotherapy
SLIT	sublingual aeroallergen immunotherapy
OIT	oral immunotherapy
EPIT	epicutaneous immunotherapy
EGPA	eosinophilic granulomatosis with polyangiitis
IgE	Immunoglobulin E

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Table 1:

Classification schema for peripheral eosinophilia

Classification	Peripheral blood absolute eosinophil count (AEC)
Mild	500–1500 cells/μL
Moderate	1500–5000 cells/μL
Severe	>5000 cells/μL

This classification schema has been recommended by WHO [11] as well as the Task Forces of the British Committee for Standards in Haematology [10].

Table 2:

Causes of peripheral eosinophilia

Primary	Clonal neoplasm ○ Myeloid and lymphoid neoplasms (rearrangement of *PDGFRA, PDGFRB, FGFR1, PCM1-JAK2, ETV6-JAK2* or *BCR-JAK2*) ○ Chronic eosinophilic leukemia ○ Systemic Mastocytosis with clonally driven eosinophil proliferation ○ Other myeloproliferative process in which clonal eosinophil proliferation plays a role (ie: CML, AML, etc.)
Secondary	Allergic ○ Allergic Bronchopulmonary Aspergillosis ○ Allergic Rhinitis ○ Asthma ○ Atopic Dermatitis ○ Drug allergy
	Gastrointestinal ○ Eosinophilic GI disorders ○ Inflammatory Bowel Disease ○ Celiac
	Hematologic / Oncologic ○ Graft versus Host Disease ○ Cytokine-driven eosinophil proliferation in Systemic Mastocytosis ○ Lymphocytic-variant Hypereosinophilic syndrome
	Infectious ○ Parasitic ○ Fungal ○ HIV
	Inflammatory ○ Eosinophilic granulomatosis with polyangiitis ○ Wells syndrome ○ Polyarteritis nodosum ○ Less commonly: sarcoidosis, rheumatoid arthritis, IgG4 disease
	Immunologic ○ Gleich Syndrome ○ Hyper-IgE syndromes ○ Wiskott Aldrich Syndrome ○ Omenn's Syndrome ○ Less commonly: *ZAP70 deficiency, ALPS, LRBA deficiency, PGM2 deficiency*
	Respiratory ○ Acute or chronic eosinophilic pneumonia
Idiopathic	No detectable cause despite investigation of secondary and primary causes

Table 3:

Biologics Targeting Eosinophils

	Molecular Target	Medication
Direct	Siglec-8	○ AK002
	Anti-IL5Rα	○ Benralizumab
	Tyrosine kinase inhibitor	○ Imatinib
Indirect	IL-5	○ Mepolizumab ○ Reslizumab
	IL-13	○ Lebrikizumab ○ Tralokinumab ○ Dectrekumab
	Anti-IL4Rα	○ Dupilumab
	IgE	○ Omalizumab
	TSLP	○ Tezepelumab