



The role of eosinophils in immunotherapy

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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 were not the primary outcome of interest in many studies, some patterns did emerge. Cytolytic mAbs 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

aeroallergen immunotherapy, atopic disease, biologic therapy, biomarkers, eosinophilia, food immunotherapy

INTRODUCTION

Allergist is frequently consulted to manage patients with peripheral eosinophilia. However, the differential diagnosis for eosinophilia is broad and the cause 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 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 (Table 1).

Disease states that alters the homeostatic balance regulating eosinophil production, recruitment or activation can result in elevated peripheral or tissue eosinophilia. Hypereosinophilia is formally defined as AEC more than 1500 cells/ μ l for 6 months' time in the presence of end-organ damage [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 *PDGFR α* , *PDGFR β* , *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

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KEY POINTS

- Eosinophils are both a biomarker and target for therapy in allergic disorders.
- Lower eosinophil counts are seen in patients with milder disease for asthma.
- Biologics that target eosinophils or their receptors or growth factors have been shown to be effective in the treatment of asthma, and atopic dermatitis.

secondary eosinophilia, such as B-cell 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 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 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 atopic dermatitis lesions. Significantly, Rossberg *et al.* [8] demonstrate that AEC may have value as an early biomarker for predicting atopic dermatitis and other atopic disorders. Their data indicates that elevated AEC in 4-week-old infants were significantly associated with the occurrence of atopic dermatitis through 3 years of life ($P = 0.006$).

Table 1. Classification schema for peripheral eosinophilia

Classification	Peripheral blood AEC (cells/ μ l)
Mild	500–1500
Moderate	1500–5000
Severe	>5000

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

Table 2. Causes of peripheral eosinophilia

Primary	Clonal neoplasm Myeloid and lymphoid neoplasms (rearrangement of <i>PDGFRA</i> , <i>PDGFRB</i> , <i>FGFR1</i> , <i>PCM1-JAK2</i> , <i>ETV6-JAK2</i> or <i>BCR-JAK2</i>) Chronic eosinophilic leukemia Systemic mastocytosis with clonally driven eosinophil proliferation Other myeloproliferative process in which clonal eosinophil proliferation plays a role (i.e., 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 vs. 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: <i>ZAP70</i> deficiency, <i>ALPS</i> , <i>LRBA</i> deficiency, <i>PGM2</i> deficiency Respiratory Acute or chronic eosinophilic pneumonia Idiopathic No detectable cause despite investigation of secondary and primary causes

AML, acute myeloid leukemia; CML, Chronic myeloid leukemia; GI, gastrointestinal.

Allergic rhinitis may present with a mild peripheral eosinophilia [20]. Peripheral eosinophilia might predict mucosal sinus disease as Poznanovic and Kingdom [9] found that an AEC over 550 cells/ μ l had a strong correlation with mucosal disease. 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 at least 300 cells/ μ l was significantly elevated in adults with severe asthma [38.5% with median 228 cells/ μ l interquartile (IQ) range (134–399)] when compared with those with nonsevere asthma [28.2% with median 189 cells/ μ l IQ range (111–320)] [13]. In contrast, approximately 55–60% of pediatric patients had AEC over 300 cells/ μ l 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]. Significantly, 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 gastrointestinal 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 3 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. Similar to results seen in environmental allergen immunotherapy, OIT for food allergy has been shown to decrease AECs. In 2016, Salmivesi *et al.* [29] completed a double-blind placebo-controlled design to monitor changes in biomarkers during a 6-month OIT intervention for cow's milk allergy among 28 school aged children. The post-OIT AEC was significantly decreased [median 600 cells/ μ l (range 200–1250) pre-OIT vs. 410 cells/ μ l (140–1200) 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 gastrointestinal side effects. The authors suggest that pre-OIT baseline AEC of 1140 cells/ μ l 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 EoE.

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 mAb to Siglec-8, an inhibitory receptor expressed on mast cells and eosinophils, and has been shown to deplete circulating eosinophils within 1 h of administration [34²²]. In a phase 2 trial with AK002, patients with eosinophilic gastritis and eosinophilic gastroenteritis (≥ 30 eosinophils/High power field (HPF), moderately to severely symptomatic) had statistically significant reductions in tissue eosinophil count (95% reduction compared with 10% in placebo group), and symptoms (53% AK002 vs. 24% placebo). In addition, in the 14 patients with comorbid EoE, 13 (93%) had a reduction in esophageal eosinophils to less than 5/HPF, with significant reduction of dysphagia.

Anti-IL5R α : Benralizumab is a mAb 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 mAb lacks key glycosylation residues which prevent NK-natural killer 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.* [37²] performed a randomized, controlled, double-blind study of 324 asthma patients categorized as eosinophilic or

noneosinophilic based on the fraction of exhaled nitric oxide. 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 HES due to *FIP1L1-PDGFR*A 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-PDGFR*A associated chronic eosinophilic leukemia [38]. Pardanani *et al.*, retrospectively identified 22 patients with to *FIP1L1-PDGFR*A mutation with a median AEC of 530 cells/ μ l (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. Qu *et al.* [39] validated these findings in a study of 33 patients with *FIP1L1-PDGFR*A mutation positive HES. The average initial AEC was 1700 cells/ μ l (range 1600–7880), and 97% of patients receiving imatinib achieved remission, which was defined as a decrease in the AEC 0–50 cells/ μ l, within 1.5–12 months.

Indirect eosinophil inhibition

IL-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 mAb 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].

Bachert *et al.* [43] completed a randomized, double blind, placebo-controlled trial of 750 mg mepolizumab for 24 weeks in 105 patients with severe nasal polyposis. At week 25, there was a significant improvement in self-reported symptoms

Table 3. Biologics targeting eosinophils		
	Molecular target	Medication
Direct	Siglec-8	AK002
	Anti-IL5R α	Benralizumab
	Tyrosine kinase inhibitor	Imatinib
Indirect	IL-5	Mepolizumab Reslizumab
	IL-13	Lebrikizumab Tralokinumab Dectrekumab
	Anti-IL4R α	Dupilumab
	IgE	Omalizumab
	TSLP	Tezepelumab

TSLP, thymic stromal lymphopoietin.

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 25 (mepolizumab 500–50 cells/ μ l vs. placebo 470–380 cells/ μ l).

Mepolizumab is United States Food and Drug Administration (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 more than 150 cells/ μ l at baseline had significant greater likelihood of disease remission [mepolizumab: 33% vs. placebo: 0% at ≥ 24 weeks; odds ratio, 26.10; 95% confidence interval (CI), 7.02–97.02] [44]. Patients with FIP1L1-PDGFR α mutation-negative HES were studied by Rothenberg *et al.* [45] in a randomized, placebo-controlled double blind trial of 750 mg mepolizumab every 4 weeks for 36 weeks. In the mepolizumab arm, more patients achieved an AEC of less than 600 cells/ μ l when compared with 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 eosinophils/HPF) [46]. Similarly, in a 2005 randomized, placebo-controlled trial by Oldhoff *et al.* [47], 43 patients with moderate-to-severe atopic dermatitis treated with mepolizumab had a significant decrease in AEC when compared with placebo (521 cells/ μ l $\pm$ 79–203 $\pm$ 54 vs. 647 cells/ μ l $\pm$ 81–679 $\pm$ 80, $P<0.05$) yet there was no significant improvement in the atopic dermatitis based on the SCORAD scoring system.

Reslizumab is a mAb 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 forced expiratory volume at 1 second (FEV1) in those receiving reslizumab compared with placebo [difference vs. placebo (reslizumab 0.3 and 3.0 mg/kg): 115 ml (95% CI 16–215; $P=0.0237$) and 160 ml (95% CI 60–259; $P=0.0018$)] [48[¶]]. Reslizumab also reduced the AEC in both doses [0.3 mg/kg dose: 323 cells/ μ l ($P=0.0000$) and 3.0 mg/kg dose: 494 cells/ μ l ($P=0.0000$)]. In a companion phase 3 trial, Corren *et al.* [48[¶]] revealed that in patients with an AEC at least 400 cells/ μ l, FEV1 improved 270 ml more in

those treated with reslizumab when compared with placebo ($P=0.04$).

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 with placebo) [49]. Similar to the mepolizumab trial, few patients reached normal levels of tissue eosinophilia as all groups including placebo had response to therapy for symptoms.

IL-13: Lebrikizumab and Tralokinumab, IgG4 antibodies which neutralize IL-13, are currently undergoing evaluation for use in asthma and atopic dermatitis. In a phase 2 study in those with moderate-to-severe atopic dermatitis, patients who received lebrikizumab were significantly more likely to report a 50% reduction in physician reported eczema area and severity scores compared with placebo (82.4 vs. 62.3%; $P=0.026$) [50]. Of note, five 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 3 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 [51]. Analysis revealed a significantly increased FEV1 from baseline in the group given tralokinumab 300 mg every 2 weeks compared with placebo [mean change 0.13 l (0.07–0.20), $P=0.002$]. Of note, week 52 AECs were raised in patients receiving tralokinumab compared with placebo.

Dectrekumab is an IgG1 mAb directed to IL-13. During a phase 2 trial, patients with proton pump inhibitor-resistant esophageal eosinophilia, who received dectrekumab, had significantly decreased tissue eosinophils compared with placebo (60 vs. 23%, respectively) [52]. There was no relationship with AEC.

Anti-IL4 α : Dupilumab is a fully human mAb approved for use in patients with atopic dermatitis, 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. IL4 α 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 2 trials of asthmatic

adults [53[¶]]. Patients with a higher initial AEC (≥ 300 cells/ μ l) were specifically noted to experience this treatment-related effect. Importantly, one patient with a history of high eosinophil counts discontinued dupilumab therapy due to HES 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 14.7–56% [54–56,57[¶]].

Anti-IgE: Elevated levels of IgE are typically seen in conjunction with eosinophilia in atopic disease. Omalizumab is a mAb 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 with placebo (321 cells/ μ l to 262 vs. 332 cells/ μ l to 320, $P < 0.0001$) [58]. Decreased AEC were associated with improved clinical outcomes during the trials; significantly, 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/ μ l were shown to have greater response to omalizumab treatment, resulting in a 59% reduction in asthma exacerbations vs. placebo ($P = 0.0125$) [59]. Omalizumab was trialed for treatment of EoE however failed to reduce symptoms or tissue eosinophil counts compared with placebo [60].

Thymic stromal lymphopoietin (TSLP): Tezepelumab is a fully human mAb which binds and neutralizes circulating TSLP. In a phase 2 trials, tezepelumab had significantly lower rates of asthma exacerbations compared with placebo (70 mg every 4 weeks dose 61%, 210 mg every 4 weeks dose 71%, and 280 mg every 2 weeks dose 66% of the exacerbations seen in the placebo group) [61]. 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 *et al.* [62], in which tezepelumab-treated patients had significantly improved performance during allergen challenge, with decreased reduction in FEV1 compared with placebo group (45.9%, $P = 0.02$). AEC at day 29 were significantly decreased in the tezepelumab group compared with placebo (posttreatment 121.9 cells/ μ l $\pm$ 14.7 vs. 224.1 cells/ μ l $\pm$ 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 suboptimally controlled atopic dermatitis, 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 mAbs 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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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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