Published in final edited form as:

Immunol Allergy Clin North Am. 2015 August ; 35(3): 577–598. doi:10.1016/j.iac.2015.05.007.

Novel Therapies for Eosinophilic Disorders

Bruce S. Bochner, MD

Department of Medicine, Division of Allergy-Immunology, Northwestern University, Feinberg School of Medicine, Chicago, IL 60611

Synopsis

Current therapies for eosinophilic disorders are limited. Most treatment approaches remain empirical, are not supported by data from controlled clinical trials, involve the off-label use of agents developed for treatment of other diseases, and tend to rely heavily on the use of glucocorticoids and other agents with significant toxicity. Also lacking are validated outcome metrics and clinically relevant biomarkers to help guide treatment choices, efficacy and assessment of disease activity. Over the last decade, great progress has been made in the discovery, preclinical development and clinical testing of a variety of biologics and small molecules that have the potential to directly or indirectly influence eosinophils, eosinophilic inflammation and the consequences of eosinophil activation. Particularly advanced are studies with biologics that target eosinophil-selective cytokines and their receptors. In addition, other therapies that have received FDA approval in recent years for non-eosinophil-related indications can be considered for testing in eosinophilic disorders. Overall, the landscape of therapeutic options for those suffering from eosinophilic disorders has never been brighter, with many new choices on the horizon.

Keywords

eosinophil; therapies; antibodies; targets; pharmacology; biomarkers

Introduction

Eosinophilic disorders, also referred to as eosinophil-associated diseases, consist of a range of infrequent conditions affecting virtually any body compartment and organ.¹ Most commonly affected areas include the bone marrow, blood, mucosal surfaces and skin, often

Correspondence to: Bruce S. Bochner, MD, Samuel M. Feinberg Professor of Medicine, Division of Allergy-Immunology, 240 E. Huron St., Room M-306, Chicago, IL 60611, Phone (312) 503-0068, FAX (312) 503-0078, bruce.bochner@northwestern.edu.

Disclosure statement: Dr. Bochner has current or recent consulting or scientific advisory board arrangements with, or has received honoraria from, Sanofi-Aventis, Pfizer, Svelte Medical Systems, Biogen Idec, TEVA, and Allakos; and owns stock in Allakos and Glycomimetics, Inc. He receives publication-related royalty payments from Elsevier and UpToDate, and is a co-inventor on existing and pending Siglec-8-related patents and thus may be entitled to a share of future royalties received by Johns Hopkins University on the potential sales of such products. Dr. Bochner is also a co-founder of Allakos, which makes him subject to certain restrictions under University policy. The terms of this arrangement are being managed by the Johns Hopkins University and Northwestern University in accordance with their conflict of interest policies.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

with immense disease- and treatment-related morbidity, while involvement of other organs, such as the cardiovascular system, have a particularly prominent impact on disease mortality. At the present time, treatment efficacy based on results from controlled clinical trials is almost nonexistent. Instead, empirically derived “standard-of-care” disease management typically involves the off-label prescription of drugs whose use is more commonly associated with autoimmune diseases, leukemia and lymphoma. A mainstay of initial treatment involves the use of glucocorticosteroids, which are usually, but not always, effective in controlling eosinophilia and end-organ damage, but are fraught with undesirable side effects when used for long-term disease management. Even though “steroid-sparing activity” may not be a sufficient reason for drug approval², both physicians and those afflicted with eosinophilic disorders yearn for the day when other more eosinophil-directed, disease-specific, and perhaps disease-modifying agents will be available.

Other articles in this issue of *Immunology and Allergy Clinics of North America* focus on the spectrum of eosinophil-associated diseases from diagnosis to treatment, so the purpose of this section is to provide a perspective on where the field stands when it comes to innovative new therapies for eosinophilic disorders, focusing mainly those that are eosinophil-specific or at least eosinophil selective. As will become clear, many such promising and exciting agents, including small molecules and biologics, are in various stages of clinical development, with some on the verge of FDA approval in 2015 or soon thereafter.

As part of the discussion of eosinophil-selective therapies, the surface phenotype of the eosinophil will be reviewed, in part to explain the current rationale behind drugs that directly target the eosinophil, but also to hopefully serve as a spring board for future ideas and efforts. Given that eosinophil activation and eosinophilic inflammation are often part of a spectrum involving a range of cells and mediators, novel therapies that indirectly target eosinophils by neutralizing eosinophil-related pathways will also be covered. Finally, a discussion of future therapeutic considerations and unmet needs is included. For completeness, the reader is referred on to other recent excellent, relevant reviews on similar or overlapping topics.^{3, 4}

The eosinophil surface as a target

The eosinophil arises from precursors in the bone marrow, just like all other leukocytes.^{5, 6} Not surprisingly, this cell has its own unique set of intracellular signaling pathways that are necessary for specific differentiation into the eosinophil lineage.⁷ Also not surprisingly, the mature eosinophil has its own specific characteristics such as mediator release profiles, granule contents, tinctorial properties, and surface phenotype.^{8–11} The latter is particularly relevant when it comes to consideration of developing eosinophil-targeting drugs (see Figure 1).^{8, 9, 12–14} Until very recently, it was felt that there were no 100% purely eosinophil-specific cell surface proteins. With the discovery of epidermal growth factor-like module containing mucin-like hormone receptor 1 (EMR1, the human counterpart of F4/80 in the mouse), a member of the G protein-coupled EGF-7-transmembrane family, this changed when it was reported that EMR1 is truly eosinophil specific (see Figure 2).¹⁵ Expression was conserved in monkeys, and targeting with an afucosylated IgG1 antibody that is particularly effective at engaging NK cell antibody-dependent cellular cytotoxicity (ADCC)

resulted in selective eosinophil depletion in vitro and in vivo.¹⁶ Thus, EMR1 antibody has potential as a possible future option for highly selective and specific targeting and depletion of eosinophils.

There are many cell surface proteins that are selectively, albeit not exclusively, expressed by eosinophils. Probably due to similarities in their hematopoietic pathways, there is a subset of surface markers whose expression is shared among basophils and/or mast cells (Figure 2). Such examples include the heterodimeric receptor for IL-5 (CD125/CD131)¹⁷, the chemokine receptor CCR3 (CD193)¹⁸, and the sialic acid-binding immunoglobulin-like inhibitory receptor Siglec-8.^{19–21} Among these three potential targets, biologics targeting IL-5 or its receptor, and small molecules targeting CCR3, are in various stages of clinical trials, as discussed below. Another cell surface receptor expressed by eosinophils and a relatively small subset of other leukocytes includes CRTh2 (also called DP2 or CD294, a receptor for prostaglandin D2 found on eosinophils, basophils, mast cells and Th2 lymphocytes), for which small molecule antagonists are advancing in the clinic (also see below). Some receptors, such as Siglec-8²², Fas (CD95)²³ and others on eosinophils, can upon engagement, directly activate cell death.²⁴ Finally, the surface of the eosinophil is equipped with a broad range of other proteins, glycans and lipids involved in cell signaling, migration, activation and other biological processes (Figure 1) that are too numerous to review here in their entirety, yet each of which could potentially be targeted with varying degrees of eosinophil selectivity. Just like the trend in the cancer field of using tumor surface markers to facilitate delivery of toxic payloads via antibody-drug conjugates or liposomes, and nanoparticles, such strategies might someday become available for eosinophil targeting by leveraging the eosinophil phenotype.

The eosinophil interior as a target

Eosinophils possess a number of intracellular structures that provide opportunities for therapeutic targeting.⁹ A prime example among these is the glucocorticoid receptor (GR), which can exist in different splice variants and isoforms.^{25, 26} In human eosinophils, the GR- α splice variant is present in particularly high copy number.²⁷ Furthermore, the pro-apoptotic GR-A isoform was five-fold higher in eosinophils than in neutrophils, whereas the non-apoptotic GR-D isoform was five-fold higher in neutrophils compared to eosinophils, making eosinophils particularly susceptible (and the neutrophil much less or non-susceptible) to clinically beneficial effects of glucocorticoids such as apoptosis.²⁸ It is clear that some patients with hypereosinophilic syndrome (HES) fail to respond to glucocorticoid therapy²⁹, perhaps due to reduced GR expression³⁰, or perhaps because these cells are deficient in the steroid-sensitive GR isoform. Whether conditions exist to enhance the function or expression of the GR-D isoform in eosinophils, rendering them more sensitive to lower concentrations of steroids, is not yet known.

Eosinophils also possess a number of unique cytoplasmic granule proteins such as eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), and the highly specific eosinophil cationic protein (EPX) that, once released, can have putative toxic effects on bystander cells. Previous studies using these granule proteins, or antagonists thereof, in animal models of eosinophilic inflammation showed promise,^{31–33} raising the possibility

that future therapies focusing on reducing or neutralizing eosinophil-derived substances, rather than eosinophils per se, might be of clinical benefit. A similar example of this would include therapies targeting sulfidopeptide leukotrienes, some of which are made and released in the form of LTC₄ by activated eosinophils. It also underscores our lack of understanding of exactly how targeting eosinophils favorably impacts disease, a perfect example being why it is that the use of eosinophil-selective therapies reduce asthma exacerbations (^{34, 35} and see below).

One other aspect worth mentioning in this section relates to genetic abnormalities associated with certain forms of eosinophilia. As a result of truly paradigm-changing findings, it is now known that at least some forms of HES are the result of chromosomal defects leading to clonal forms of disease including eosinophilic leukemia. For example, the discovery that the tyrosine kinase inhibitor imatinib mesylate can reverse virtually all aspects of disease in patients with the FIP1L1-PDGFR deletion mutation on chromosome 4, as well as some other HES patients without this detectable mutation, suggests that molecular gain-of-function mutations are causal in a subset of eosinophilic disorders.^{36–38}

Approved therapies that also target eosinophils or eosinophil-related pathways

Current standard of care for treatment of eosinophil-associated disorders including HES, EoE and others are the subject of their own chapters in this volume of *Immunology and Allergy Clinics of North America*, so they will only be mentioned in passing for completeness and for comparison to future therapies. As mentioned above, the current mainstay of initial treatment for nearly all forms of eosinophilic disorders begins with glucocorticoids. For HES, where imatinib mesylate therapy is not indicated or effective, the most common agent to be added next to maintain disease control and facilitate oral steroid tapering or elimination is hydroxyurea. Although there are no controlled trials of this agent in HES, there are strong indications from the literature that it can be quite effective, presumably as a result of diminished hematopoiesis of many leukocyte types including eosinophils.²⁹ If still ineffective, hydroxyurea is most often replaced by parenteral administration of IFN- α .^{39, 40} Other immunosuppressive agents are sometimes tried, with only modest benefit at best.²⁹ For eosinophilic esophagitis (EoE), mainstays of treatment include food elimination diets, swallowed topical steroids and mechanical dilation for severe strictures.⁴¹

When considering other potential therapies for eosinophilic disorders, opportunities may exist to try other agents approved for other clinical indications. For instance, therapies targeting surface structures (Table 1) whose expression is shared by differing subsets of cell types that include eosinophils, such as CD25 (daclizumab), CD33 (gemtuzumab), $\alpha 4\beta 1$ integrin (CD49d/CD29, VLA-4, natalizumab), $\alpha 4\beta 7$ integrin (vedolizumab) and CD52 (alemtuzumab) would also bind to eosinophils, offering opportunities for their potential use in eosinophil-associated diseases provided the cost and risk-benefit ratio favors such use. So far, it is known that natalizumab use increases blood eosinophil counts^{42, 43}, presumably by blocking leukocyte emigration from the circulation, while vedolizumab appears to lack this property.^{44, 45} The effects of VCAM-1 or MAdCAM-1 blockade, the ligands for $\alpha 4\beta 1$

integrin and $\alpha 4\beta 7$ integrin, in eosinophil-associated diseases including EGID have not been studied in humans. The use of alemtuzumab in advanced stages of HES or chronic eosinophilic leukemia has been reported in small numbers of patients with some patients undergoing disease remission but not without drug-related toxicities.⁴⁶ Whether the potential beneficial effects of alemtuzumab were due to direct targeting of eosinophils versus targeting of other cells cannot be determined.

Novel eosinophil-selective therapies being tested in clinical trials

Currently, the eosinophil-selective therapies being tested in humans that are looking very promising include antibodies to IL-5 (mepolizumab [IgG1, GlaxoSmithKline] and reslizumab [IgG4, TEVA]) and the IL-5 receptor (benralizumab [afucosylated IgG1, Medimmune, formerly called MEDI-563]) (Table 1). Each of these antibodies neutralizes IL-5 biology, but given the enhanced ADCC activity of the benralizumab formulation, it actively depletes IL-5 receptor-bearing cells, which includes eosinophils and basophils (Figure 2).^{47, 48}

Among these three biological agents, the most published information exists for mepolizumab. It has shown efficacy in controlled trials of eosinophilic asthma (e.g., reduced exacerbations, improved lung function),^{49–54} nasal polyposis (e.g., reduced polyp size),⁵⁵ and in idiopathic and lymphocytic HES syndrome (e.g., steroid-sparing effects).^{56–58} These studies showed fairly consistent, prompt reductions (~ 80% declines within days) in circulating eosinophil counts and partial (≈ 50 – 60%) reductions in extravascular eosinophils in affected organs when studied.^{59, 60} It is also interesting to note that given the enrollment criteria of persistent eosinophilia in the mepolizumab asthma studies cited above, cohorts ended up being enriched to 10% to 35% with subjects that had concomitant nasal polyposis. One additional study with mepolizumab failed to find any changes in normal levels of cells, including mucosal eosinophils, in duodenal biopsies in subjects with EoE, despite finding a decrease in esophageal eosinophilia.⁶¹ In open label studies, efficacy was also seen in eosinophilic granulomatosis with polyangiitis^{62–64} with a double-blind, placebo-controlled clinical trial underway. In an open label study of EoE, reduced tissue eosinophils was seen with mepolizumab.⁶⁵ In controlled mepolizumab trials in EoE, reduced tissue eosinophils were also seen but unfortunately there were no clear clinical benefits.⁶⁶

There are fewer published clinical data available for reslizumab and benralizumab. Both have shown reductions in exacerbations in controlled trials of eosinophilic asthma,^{67, 68} but not with benralizumab in COPD,⁶⁹ and while not published as of January 2015, an online press release on September 2, 2014 from TEVA (<http://www.tevapharm.com/Media/News/Pages/2014/1962753.aspx>) stated that reslizumab “demonstrated clear levels of efficacy in achieving the primary endpoint of reduction in the frequency of clinical asthma exacerbations (CAE) compared to placebo in two pivotal Phase III studies in patients with inadequately controlled moderate to severe asthma with elevated levels of blood eosinophils.” Unique to benralizumab was a study showing that a single dose given in the emergency room for an acute exacerbation of asthma reduced exacerbation and hospitalization rates over the subsequent 3 month period by 50–60%.⁷⁰ Like with mepolizumab treatment of EoE, reslizumab reduced tissue eosinophils but without a

concomitant improvement, compared to placebo, in symptoms.⁷¹ All studies with either benralizumab or reslizumab showed prompt reductions (~80% declines within days and even more pronounced and prolonged with benralizumab) in circulating eosinophil counts and reductions in airway eosinophils and in esophageal biopsies.^{71, 72}

Other eosinophil-related receptors have been targeted in recent or ongoing clinical trials. Given the selective expression of CCR3, a G protein-coupled seven-spanner receptor, on eosinophils and its important role in eosinophil migration and accumulation suggested in preclinical models, it seemed likely that this receptor would be an obvious small molecule therapeutic target for eosinophil-associated disease.^{18, 73–76} So far, one such antagonist (GW766994) was tested in human asthma and was well tolerated, but despite effectively blocking CCR3 activity, it failed to have an effect on levels of eosinophils in blood or sputum, nor did it significantly impact lung function.⁷⁷ As of January 2015, no other studies with GW766994 were listed in clinicaltrials.gov, making it questionable as to whether additional indications or studies will be pursued. Another G protein-coupled seven-spanner receptor with a similar pattern of expression to CCR3 is CRTh2, also called DP2, a receptor for prostaglandin D2. So far, one oral small molecule antagonist (OC000459) showed modest efficacy in asthma^{78, 79} and in EoE.⁸⁰ As of January 2015, the only studies of this class of agents listed as active on clinicaltrials.gov involved a study with OC000459 in moderate to severe atopic dermatitis, while another with AZD1981, a different small molecule CRTh2 antagonist being tested in chronic idiopathic urticaria.

Etrolizumab is a humanized monoclonal antibody that distinguishes itself from natalizumab and vedolizumab in that it uniquely recognizes $\alpha 4\beta 7$ integrin and $\alpha E\beta 7$ integrin, the latter not expressed on eosinophils but recognizing E-cadherin. A recent phase 2 study in moderate-to-severe ulcerative colitis was positive, but there was no mention of effects on circulating numbers of eosinophils.⁸¹ Additional studies in ulcerative colitis are ongoing. An antibody against CD131, the common β chain shared by the IL-3, IL-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor, is in early clinical trials for asthma (see NCT01759849 on the clinicaltrials.gov website). Finally, dexpropionexole (KNS-760704) is an oral drug originally developed for the treatment of amyotrophic lateral sclerosis, but it failed in phase 3 studies.⁸² During its development, subjects receiving this drug were coincidentally noted to have a gradual decline in blood eosinophil counts. As a result, it is now being tested in HES (see NCT02101138 on the clinicaltrials.gov website) and chronic sinusitis with nasal polyps (see NCT02217332 on the clinicaltrials.gov website). The exact mechanism of action of this agent, including its anti-eosinophil properties, is unknown but it is believed to enhance mitochondrial function.

Novel therapies that may indirectly affect eosinophils that are being tested in clinical trials

Agents moving forward

The cytokines IL-4 and IL-13 have a number of important biological properties relevant to eosinophilic inflammatory responses, including their ability to induce pro-eosinophil recruitment responses via induction of the adhesion molecule VCAM-1 and of CCR3-active

chemokines.^{83, 84} The receptors for IL-4 and IL-13 are heterodimeric, sharing a common IL-4 receptor α chain (IL-4R α 1) while also using the common γ c chain or IL-13 receptor α 1 chains, respectively. Although eosinophils express the IL-13 receptor,⁸⁵ the clinically beneficial effects of antagonizing IL-13 in vivo are more likely to be due to its effects on other cells, thereby secondarily improving eosinophilic inflammation. Several monoclonal antibodies that specifically block IL-13 biology are in clinical trials for either asthma, ulcerative colitis or EoE and include lebrikizumab,^{86–88} anrukinzumab,⁸⁹ tralokinumab,^{90–92} GSK679586^{93, 94} and RPC4046 (<https://clinicaltrials.gov/ct2/show/NCT02098473>). However, by targeting IL-4R α 1 instead, blockade of both IL-4 and IL-13 biology can be achieved, as was explored with monoclonal antibody AMG 317 in asthma⁹⁵ and so far, more successfully in atopic dermatitis and asthma with dupilumab.^{96, 97} Also to be mentioned in this section is an antibody to thymic stromal lymphopoietin (TSLP), a highly pro-inflammatory and pro-allergic cytokine produced by tissue resident cells. In one proof-of-concept phase 2 study, the anti-TSLP antibody AMG 157 attenuated both the acute and late phase airway allergic response, as well as reducing blood and airway eosinophilia.⁹⁸ Finally, given the fact that eosinophils are highly susceptible to the pro-apoptotic effects of glucocorticoids, it was of interest that in a very similar phase 2 proof-of-concept study, AZD5423, an inhaled non-steroidal agonist of the GR that, in theory, should have reduced side effects compared to glucocorticoids, significantly blocked the late phase airway allergic response, as well as reducing sputum eosinophilia.⁹⁹ While showing extremely promising clinical benefits in early phase clinical trials, along with reductions in eosinophilic inflammation, none of these agents have been tested in HES, and none show anywhere near the same magnitude and specificity of reductions in eosinophils as has been seen with IL-5 or IL-5 receptor targeting drugs.

Agents whose development is not currently moving forward

Several other anti-cytokine and anti-chemokine therapies that either directly or indirectly target eosinophils have been tested, mainly in asthma, but have not fared as well, so they will only be reviewed briefly. One set consists of agents targeting Th2 cytokines other than IL-5, namely IL-4 and IL-9, with specific biologics. Agents whose development has been discontinued due to lack of efficacy include pascolizumab (anti-IL-4 antibody), soluble IL-4 receptor (altrakinept), pitrakinra, a mutein of IL-4, and an anti-IL-9 antibody MEDI-528.^{100, 101} For MEDI-528 where it was reported, there was no effect on blood eosinophil counts. For antagonism of eotaxin-1, the antibody bertilimumab was developed and tested in allergic disorders about a decade ago, but apparently without success because further testing was not pursued. It is currently about to begin testing in ulcerative colitis and bullous pemphigoid.¹⁰² As of this writing, there are no known antibodies against eotaxin-2 or eotaxin-3 in clinical trials. If true, this would be unfortunate, especially given compelling data suggesting a prominent role for eotaxin-3 in the pathophysiology of EoE and eosinophilic gastritis.^{103, 104} KB003, an antibody to GM-CSF, a cytokine with overlapping biology to that of IL-5, was tested in a phase 2, double-blind, placebo controlled trial in asthmatics inadequately controlled with corticosteroids, and according to the website of KaloBios, the company developing this antibody, it failed to meet its endpoint of improved pulmonary function (<http://ir.kalobios.com/releasedetail.cfm?ReleaseID=821931>). No data were released regarding any specific aspects of eosinophil biology, such as effects on blood

levels or airway eosinophilia, but it is known that infusion with GM-CSF causes eosinophilia,¹⁰⁵ and some patients with hypereosinophilic syndrome and exacerbations of chronic rhinosinusitis with nasal polyposis have elevated levels of GM-CSF in their blood.^{106, 107} Finally, development of TPI ASM8, a formulation of inhaled antisense oligonucleotides designed to reduce allergic inflammation by down-regulating both CCR3 and the common β chain (CD125) of the IL-3, IL-5, and GM-CSF receptor, appears to have been discontinued, but had shown some favorable impact on allergen-induced sputum eosinophilia in initial trials.^{108–110}

Future considerations

Although many novel small molecule and biologics are advancing in clinical trials, there still are no FDA approved drugs that would meet the criteria often referred to as “personalized” or “precision” medicine for eosinophil-associated diseases with one exception: imatinib mesylate for FIP1L1-PDGFR-associated proliferative disorders. Yet excitement is building with the reasonable anticipation that within the next few years, agents that selectively or specifically target eosinophils (e.g., those targeting IL-5 or its receptor) may actually become approved for clinical use. Since all of these agents are new, the excitement among physicians and patients who will finally gain access to these potential paradigm-changing treatments must be mitigated by what will still be unknown about these drugs. Questions that remain include their cost, safety and side effect profiles, longevity of responses, safety of discontinuation of therapy and potential for the development of human-anti-human antibodies (HAHAs) against biologics. Overall, mepolizumab has a good safety profile, with rare infusion or injection reactions, insignificant rates of human anti-human antibody formation, and prolonged efficacy, even with reduced dosing intervals for maintenance therapy, but stoppage of treatment leads to disease recurrence, suggesting that this is not a disease-remitting agent.^{62, 64, 111, 112} Dosing intervals can be expanded without loss of efficacy, and there has been no evidence of neutralizing HAHAs, but more information is needed for this and other agents. One report identified rebound blood eosinophilia following discontinuation of reslizumab.¹¹³ In early studies of benralizumab, some cases of transient neutropenia were reported.⁴⁸ So far, it appears that one can maintain normal immune function with very low numbers of eosinophils or without eosinophils entirely.¹¹⁴ We know virtually nothing about the combined use of multiple anti-eosinophil biologics in the same patient at the same time, nor if any of these treatments are disease modifying, meaning that they can be used for a defined period of time then stopped, with prolonged disease remission. So far this does not seem to be the case for mepolizumab in asthma,¹¹² or for imatinib mesylate and HES,¹¹⁵ with disease recurrence seen following discontinuation of either treatment.¹¹⁵ Sorely needed are ways of detecting organ-specific disease activity, such as the “string test” in EoE¹¹⁶ and nuclear medicine-based scans of eosinophil trafficking and accumulation.^{117–119} Reliable biomarkers of disease activity, remission and drug responsiveness other than blood eosinophil counts would improve disease management, including confidence and safety during tapering of treatment.^{120, 121} Examples of such biomarkers might include the presence of an activated eosinophil surface phenotype as detected by flow cytometry,^{122, 123} and a variety of measurements in biological fluids such as serum periostin in IL-13-driven asthma;^{124, 125} serum CCL17 in HES and atopic dermatitis;^{29, 126} serum levels of soluble receptors such as for IL-5, EMR1

and Siglec-8 in various forms of HES;^{16, 121, 127} and detection of EPX in biological fluids.¹²⁸ Some studies suggest that elevated levels of IL-5 might be a feature of certain subsets of eosinophilic disorders^{129, 130} as well as responsiveness to anti-IL-5 treatment.¹³¹ These and other approaches will require rigorous validation in controlled clinical trials before garnering confidence as clinically-useful parameters in eosinophil-associated disease assessment and management.

Conclusions

There is still much to be learned about eosinophil-associated diseases, in part because they tend to be uncommon disorders, and in part because the best way to test mechanistic hypotheses in human diseases that lack a clear genetic origin is with pharmacology. Such types of unique and novel eosinophil-targeted treatments, including monoclonal antibodies, are finally in development, with many showing safety and efficacy. While none are yet FDA-approved, each offers promise as we strive to provide the best possible treatment for patients suffering from eosinophilic disorders, including the ability to replace drugs with unacceptable side effects, especially when used chronically, with others of equal if not superior efficacy and reduced toxicity. Together with an improved panel of biomarkers to help guide diagnosis, treatment, and assessment of disease activity, we may soon see a remarkable new era of management of these difficult conditions.

Abbreviations

ADCC	antibody-dependent cellular cytotoxicity
ECP	eosinophil cationic protein
EDN	eosinophil-derived neurotoxin
EPX	eosinophil cationic protein
EMR1	epidermal growth factor-like module containing mucin-like hormone receptor 1
EoE	eosinophilic esophagitis
GM-CSF	granulocyte-macrophage colony-stimulating factor
GR	glucocorticosteroid receptor
HES	hypereosinophilic syndrome
TSLP	thymic stromal lymphopoietin

References

1. Bochner BS, Book W, Busse WW, et al. Workshop report from the National Institutes of Health Taskforce on the Research Needs of Eosinophil-Associated Diseases (TREAD). *J Allergy Clin Immunol.* 2012; 130:587–96. [PubMed: 22935587]
2. Boucher RM, Gilbert-McClain L, Chowdhury B. Hypereosinophilic syndrome and mepolizumab. *N Engl J Med.* 2008; 358:2838–9. author reply 9–40. [PubMed: 18579821]
3. Radonjic-Hoesli S, Valent P, Klion AD, et al. Novel targeted therapies for eosinophil-associated diseases and allergy. *Annu Rev Pharmacol Toxicol.* 2015; 55:633–56. [PubMed: 25340931]

4. Fulkerson PC, Rothenberg ME. Targeting eosinophils in allergy, inflammation and beyond. *Nat Rev Drug Discov.* 2013; 12:117–29. [PubMed: 23334207]
5. Iwasaki H, Mizuno S, Mayfield R, et al. Identification of eosinophil lineage-committed progenitors in the murine bone marrow. *J Exp Med.* 2005; 201:1891–7. [PubMed: 15955840]
6. Gauvreau GM, Ellis AK, Denburg JA. Haemopoietic processes in allergic disease: eosinophil/basophil development. *Clin Exp Allergy.* 2009; 39:1297–306. [PubMed: 19622087]
7. Ackerman SJ, Bochner BS. Mechanisms of eosinophilia in the pathogenesis of hypereosinophilic disorders. *Immunol Allergy Clin North Am.* 2007; 27:357–75. [PubMed: 17868854]
8. Rothenberg ME, Hogan SP. The eosinophil. *Annu Rev Immunol.* 2006; 24:147–74. [PubMed: 16551246]
9. Kita, H.; Bochner, BS. Biology of eosinophils. In: Adkinson, NF., Jr; Bochner, BS.; Busse, WW., et al., editors. *Middleton's Allergy Principles and Practice.* 8. Philadelphia: Elsevier Sanders; 2014. p. 265–79.
10. Lee, JJ.; Rosenberg, HF., editors. *Eosinophils in Health and Disease.* Amsterdam: Elsevier; 2012.
11. Rosenberg HF, Dyer KD, Foster PS. Eosinophils: changing perspectives in health and disease. *Nat Rev Immunol.* 2013; 13:9–22. [PubMed: 23154224]
12. von Gunten, S.; Ghanim, V.; Valent, P., et al. Appendix A. CD molecules. In: Adkinson, NF., Jr; Bochner, BS.; Busse, WW., et al., editors. *Middleton's Allergy Principles and Practice.* 8. Philadelphia: Elsevier Sanders; 2014. p. 1663–87.
13. Tachimoto H, Bochner BS. The surface phenotype of human eosinophils. *Chem Immunol.* 2000; 76:45–62. [PubMed: 10761304]
14. Bochner BS. Verdict in the case of therapies versus eosinophils: the jury is still out. *J Allergy Clin Immunol.* 2004; 113:3–9. [PubMed: 14713900]
15. Hamann J, Koning N, Pouwels W, et al. EMR1, the human homolog of F4/80, is an eosinophil-specific receptor. *Eur J Immunol.* 2007; 37:2797–802. [PubMed: 17823986]
16. Legrand F, Tomasevic N, Simakova O, et al. The eosinophil surface receptor epidermal growth factor-like module containing mucin-like hormone receptor 1 (EMR1): a novel therapeutic target for eosinophilic disorders. *J Allergy Clin Immunol.* 2014; 133:1439–47. [PubMed: 24530099]
17. Migita M, Yamaguchi N, Mita S, et al. Characterization of the human IL-5 receptors on eosinophils. *Cell Immunol.* 1991; 133:484–97. [PubMed: 2015632]
18. Heath H, Qin SX, Rao P, et al. Chemokine receptor usage by human eosinophils - The importance of CCR3 demonstrated using an antagonistic monoclonal antibody. *J Clin Invest.* 1997; 99:178–84. [PubMed: 9005985]
19. Kikly KK, Bochner BS, Freeman S, et al. Identification of SAF-2, a novel siglec expressed on eosinophils, mast cells and basophils. *J Allergy Clin Immunol.* 2000; 105:1093–100. [PubMed: 10856141]
20. Bochner BS. Siglec-8 on human eosinophils and mast cells, and Siglec-F on murine eosinophils, are functionally related inhibitory receptors. *Clin Exp Allergy.* 2009; 39:317–24. [PubMed: 19178537]
21. Kiwamoto T, Kawasaki N, Paulson JC, et al. Siglec-8 as a drugable target to treat eosinophil and mast cell-associated conditions. *Pharmacol Ther.* 2012; 135:327–36. [PubMed: 22749793]
22. Nutku E, Aizawa H, Hudson SA, et al. Ligation of Siglec-8: a selective mechanism for induction of human eosinophil apoptosis. *Blood.* 2003; 101:5014–20. [PubMed: 12609831]
23. Matsumoto K, Schleimer RP, Saito H, et al. Induction of apoptosis in human eosinophils by anti-fas antibody treatment in vitro. *Blood.* 1995; 86:1437–43. [PubMed: 7543306]
24. Shen Z, Malter JS. Determinants of eosinophil survival and apoptotic cell death. *Apoptosis.* 2015; 20:1007/s10495-014-1072-2
25. Bender IK, Cao Y, Lu NZ. Determinants of the heightened activity of glucocorticoid receptor translational isoforms. *Mol Endocrinol.* 2013; 27:1577–87. [PubMed: 23820903]
26. Oakley RH, Cidlowski JA. The biology of the glucocorticoid receptor: new signaling mechanisms in health and disease. *J Allergy Clin Immunol.* 2013; 132:1033–44. [PubMed: 24084075]

27. Pujols L, Mullol J, Roca-Ferrer J, et al. Expression of glucocorticoid receptor alpha- and beta-isoforms in human cells and tissues. *Am J Physiol Cell Physiol*. 2002; 283:C1324–31. [PubMed: 12225995]
28. Hsu J, Cao Y, Bender IK, et al. Glucocorticoid receptor translational isoforms contribute to distinct glucocorticoid responses of neutrophils and eosinophils. *J Allergy Clin Immunol*. 2012; 129:AB62 (abstr.).
29. Ogbogu PU, Bochner BS, Butterfield JH, et al. Hypereosinophilic syndrome: A multicenter, retrospective analysis of clinical characteristics and response to therapy. *J Allergy Clin Immunol*. 2009; 124:1319–25. [PubMed: 19910029]
30. Prin L, Lefebvre P, Gruart V, et al. Heterogeneity of human eosinophil glucocorticoid receptor expression in hypereosinophilic patients: absence of detectable receptor correlates with resistance to corticotherapy. *Clin Exp Immunol*. 1989; 78:383–9. [PubMed: 2612051]
31. Gundel RH, Letts LG, Gleich GJ. Human eosinophil major basic protein induces airway constriction and airway hyperresponsiveness in primates. *J Clin Invest*. 1991; 87:1470–3. [PubMed: 2010556]
32. Uchida DA, Ackerman SJ, Coyle AJ, et al. The effect of human eosinophil granule major basic protein on airway responsiveness in the rat in vivo. *Am Rev Respir Dis*. 1993; 147:982–8. [PubMed: 8466137]
33. Lefort J, Nahori MA, Ruffie C, et al. In vivo neutralization of eosinophil-derived major basic protein inhibits antigen-induced bronchial hyperreactivity in sensitized guinea pigs. *J Clin Invest*. 1996; 97:1117–21. [PubMed: 8613536]
34. Wenzel SE. Eosinophils in asthma--closing the loop or opening the door? *N Engl J Med*. 2009; 360:1026–8. [PubMed: 19264692]
35. Bochner BS, Gleich GJ. What targeting eosinophils has taught us about their role in diseases. *J Allergy Clin Immunol*. 2010; 126:16–25. [PubMed: 20434203]
36. Cools J, DeAngelo DJ, Gotlib J, et al. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med*. 2003; 348:1201–14. [PubMed: 12660384]
37. Klion AD, Noel P, Akin C, et al. Elevated serum tryptase levels identify a subset of patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome associated with tissue fibrosis, poor prognosis, and imatinib responsiveness. *Blood*. 2003; 101:4660–6. [PubMed: 12676775]
38. Jain N, Cortes J, Quintas-Cardama A, et al. Imatinib has limited therapeutic activity for hypereosinophilic syndrome patients with unknown or negative PDGFRalpha mutation status. *Leuk Res*. 2009; 33:837–9. [PubMed: 19013640]
39. Butterfield JH, Gleich GJ. Response of six patients with idiopathic hypereosinophilic syndrome to interferon- α . *J Allergy Clin Immunol*. 1994; 94:1318–26. [PubMed: 7798572]
40. Butterfield JH. Treatment of hypereosinophilic syndromes with prednisone, hydroxyurea, and interferon. *Immunol Allergy Clin North Am*. 2007; 27:493–518. [PubMed: 17868861]
41. Kern E, Hirano I. Emerging drugs for eosinophilic esophagitis. *Expert Opin Emerg Drugs*. 2013; 18:353–64. [PubMed: 23937314]
42. Ghosh S, Goldin E, Gordon FH, et al. Natalizumab for active Crohn's disease. *N Engl J Med*. 2003; 348:24–32. [PubMed: 12510039]
43. Miller DH, Khan OA, Sheremata WA, et al. A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2003; 348:15–23. [PubMed: 12510038]
44. Fedyk ER, Wyant T, Yang LL, et al. Exclusive antagonism of the $\alpha 4\beta 7$ integrin by vedolizumab confirms the gut-selectivity of this pathway in primates. *Inflamm Bowel Dis*. 2012; 18:2107–19. [PubMed: 22419649]
45. Soler D, Chapman T, Yang LL, et al. The binding specificity and selective antagonism of vedolizumab, an anti- $\alpha 4\beta 7$ integrin therapeutic antibody in development for inflammatory bowel diseases. *J Pharmacol Exp Ther*. 2009; 330:864–75. [PubMed: 19509315]
46. Verstovsek S, Tefferi A, Kantarjian H, et al. Alemtuzumab therapy for hypereosinophilic syndrome and chronic eosinophilic leukemia. *Clin Cancer Res*. 2009; 15:368–73. [PubMed: 19118067]

47. Kolbeck R, Kozhich A, Koike M, et al. MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. *J Allergy Clin Immunol.* 2010; 125:1344–53. e2. [PubMed: 20513525]
48. Busse WW, Katial R, Gossage D, et al. Safety profile, pharmacokinetics, and biologic activity of MEDI-563, an anti-IL-5 receptor alpha antibody, in a phase I study of subjects with mild asthma. *J Allergy Clin Immunol.* 2010; 125:1237–44. [PubMed: 20513521]
49. Nair P, Pizzichini MM, Kjarsgaard M, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med.* 2009; 360:985–93. [PubMed: 19264687]
50. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet.* 2012; 380:651–9. [PubMed: 22901886]
51. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med.* 2014; 371:1198–207. [PubMed: 25199059]
52. Liu Y, Zhang S, Li DW, et al. Efficacy of anti-interleukin-5 therapy with mepolizumab in patients with asthma: a meta-analysis of randomized placebo-controlled trials. *PLoS One.* 2013; 8:e59872. [PubMed: 23544105]
53. Haldar P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med.* 2009; 360:973–84. [PubMed: 19264686]
54. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med.* 2014; 371:1189–97. [PubMed: 25199060]
55. Gevaert P, Van Bruaene N, Cattaert T, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. *J Allergy Clin Immunol.* 2011; 128:989–95. [PubMed: 21958585]
56. Garrett JK, Jameson SC, Thomson B, et al. Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. *J Allergy Clin Immunol.* 2004; 113:115–9. [PubMed: 14699394]
57. Rothenberg ME, Klion AD, Roufosse FE, et al. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med.* 2008; 358:1215–28. [PubMed: 18344568]
58. Roufosse F, de Lavarelle A, Schandene L, et al. Mepolizumab as a corticosteroid-sparing agent in lymphocytic variant hypereosinophilic syndrome. *J Allergy Clin Immunol.* 2010; 126:828–35. [PubMed: 20810155]
59. Plotz SG, Simon HU, Darsow U, et al. Use of an anti-interleukin-5 antibody in the hypereosinophilic syndrome with eosinophilic dermatitis. *N Engl J Med.* 2003; 349:2334–9. [PubMed: 14668459]
60. Flood-Page P, Menzies-Gow A, Phipps S, et al. Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. *J Clin Invest.* 2003; 112:1029–36. [PubMed: 14523040]
61. Conus S, Straumann A, Bettler E, et al. Mepolizumab does not alter levels of eosinophils, T cells, and mast cells in the duodenal mucosa in eosinophilic esophagitis. *J Allergy Clin Immunol.* 2010; 126:175–7. [PubMed: 20542323]
62. Kim S, Marigowda G, Oren E, et al. Mepolizumab as a steroid-sparing treatment option in patients with Churg-Strauss syndrome. *J Allergy Clin Immunol.* 2010; 125:1336–43. [PubMed: 20513524]
63. Kahn JE, Grandpeix-Guyodo C, Marroun I, et al. Sustained response to mepolizumab in refractory Churg-Strauss syndrome. *J Allergy Clin Immunol.* 2010; 125:267–70. [PubMed: 20109753]
64. Herrmann K, Gross WL, Moosig F. Extended follow-up after stopping mepolizumab in relapsing/refractory Churg-Strauss syndrome. *Clin Exp Rheumatol.* 2012; 30:S62–5. [PubMed: 22512988]
65. Stein ML, Collins MH, Villanueva JM, et al. Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. *J Allergy Clin Immunol.* 2006; 118:1312–9. [PubMed: 17157662]
66. Straumann A, Conus S, Grzonka P, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. *Gut.* 2010; 59:21–30. [PubMed: 19828470]
67. Castro M, Mathur S, Hargreave F, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med.* 2011; 184:1125–32. [PubMed: 21852542]

68. Castro M, Wenzel SE, Bleecker ER, et al. Benralizumab, an anti-interleukin 5 receptor alpha monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med.* 2014; 2:879–90. [PubMed: 25306557]
69. Brightling CE, Bleecker ER, Panettieri RA Jr, et al. Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study. *Lancet Respir Med.* 2014; 2:891–901. [PubMed: 25208464]
70. Nowak RM, Parker JM, Silverman RA, et al. A randomized trial of benralizumab, an antiinterleukin 5 receptor alpha monoclonal antibody, after acute asthma. *Am J Emerg Med.* 2015; 33:14–20. [PubMed: 25445859]
71. Spergel JM, Rothenberg ME, Collins MH, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol.* 2012; 129:456–63. 63 e1–3. [PubMed: 22206777]
72. Laviolette M, Gossage DL, Gauvreau G, et al. Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. *J Allergy Clin Immunol.* 2013; 132:1086–96. e5. [PubMed: 23866823]
73. Fulkerson PC, Fischetti CA, McBride ML, et al. A central regulatory role for eosinophils and the eotaxin/CCR3 axis in chronic experimental allergic airway inflammation. *Proc Natl Acad Sci U S A.* 2006; 103:16418–23. [PubMed: 17060636]
74. Humbles AA, Lu B, Friend DS, et al. The murine CCR3 receptor regulates both the role of eosinophils and mast cells in allergen-induced airway inflammation and hyperresponsiveness. *Proc Natl Acad Sci U S A.* 2002; 99:1479–84. [PubMed: 11830666]
75. Ma W, Bryce PJ, Humbles AA, et al. CCR3 is essential for skin eosinophilia and airway hyperresponsiveness in a murine model of allergic skin inflammation. *J Clin Invest.* 2002; 109:621–8. [PubMed: 11877470]
76. Wise EL, Duchesnes C, da Fonseca PC, et al. Small molecule receptor agonists and antagonists of CCR3 provide insight into mechanisms of chemokine receptor activation. *J Biol Chem.* 2007; 282:27935–43. [PubMed: 17635911]
77. Neighbour H, Boulet LP, Lemiere C, et al. Safety and efficacy of an oral CCR3 antagonist in patients with asthma and eosinophilic bronchitis: a randomized, placebo-controlled clinical trial. *Clin Exp Allergy.* 2014; 44:508–16. [PubMed: 24286456]
78. Barnes N, Pavord I, Chuchalin A, et al. A randomized, double-blind, placebo-controlled study of the CRTH2 antagonist OC000459 in moderate persistent asthma. *Clin Exp Allergy.* 2012; 42:38–48. [PubMed: 21762224]
79. Singh D, Cadden P, Hunter M, et al. Inhibition of the asthmatic allergen challenge response by the CRTH2 antagonist OC000459. *Eur Respir J.* 2013; 41:46–52. [PubMed: 22496329]
80. Straumann A, Hoesli S, Bussmann C, et al. Anti-eosinophil activity and clinical efficacy of the CRTH2 antagonist OC000459 in eosinophilic esophagitis. *Allergy.* 2013; 68:375–85. [PubMed: 23379537]
81. Vermeire S, O'Byrne S, Keir M, et al. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. *Lancet.* 2014; 384:309–18. [PubMed: 24814090]
82. Cudkowicz ME, van den Berg LH, Shefner JM, et al. Dexamipexole versus placebo for patients with amyotrophic lateral sclerosis (EMPOWER): a randomised, double-blind, phase 3 trial. *Lancet Neurol.* 2013; 12:1059–67. [PubMed: 24067398]
83. Zimmermann N, Hershey GK, Foster PS, et al. Chemokines in asthma: cooperative interaction between chemokines and IL-13. *J Allergy Clin Immunol.* 2003; 111:227–42. [PubMed: 12589338]
84. Steinke, JW.; Rosenwasser, LJ.; Borish, L. Cytokines in allergic inflammation. In: Adkinson, NF., Jr; Bochner, BS.; Busse, WW., et al., editors. *Middleton's Allergy Principles and Practice.* 8. Philadelphia: Elsevier Sanders; 2014. p. 65-82.
85. Luttmann W, Knoechel B, Foerster M, et al. Activation of human eosinophils by IL-13. Induction of CD69 surface antigen, its relationship to messenger RNA expression, and promotion of cellular viability. *J Immunol.* 1996; 157:1678–83. [PubMed: 8759755]
86. Corren J, Lemanske RF, Hanania NA, et al. Lebrikizumab treatment in adults with asthma. *N Engl J Med.* 2011; 365:1088–98. [PubMed: 21812663]

87. Noonan M, Korenblat P, Mosesova S, et al. Dose-ranging study of lebrikizumab in asthmatic patients not receiving inhaled steroids. *J Allergy Clin Immunol.* 2013; 132:567–74. [PubMed: 23726041]
88. Scheerens H, Arron JR, Zheng Y, et al. The effects of lebrikizumab in patients with mild asthma following whole lung allergen challenge. *Clin Exp Allergy.* 2014; 44:38–46. [PubMed: 24131304]
89. Reinisch W, Panes J, Khurana S, et al. Anrukinzumab, an anti-interleukin 13 monoclonal antibody, in active UC: efficacy and safety from a phase IIa randomised multicentre study. *Gut.* 2015
90. Danese S, Rudzinski J, Brandt W, et al. Tralokinumab for moderate-to-severe UC: a randomised, double-blind, placebo-controlled, phase IIa study. *Gut.* 2014
91. Murray LA, Zhang H, Oak SR, et al. Targeting interleukin-13 with tralokinumab attenuates lung fibrosis and epithelial damage in a humanized SCID idiopathic pulmonary fibrosis model. *Am J Respir Cell Mol Biol.* 2014; 50:985–94. [PubMed: 24325475]
92. Piper E, Brightling C, Niven R, et al. A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma. *Eur Respir J.* 2013; 41:330–8. [PubMed: 22743678]
93. Hodsman P, Ashman C, Cahn A, et al. A phase I, randomized, placebo-controlled, dose-escalation study of an anti-IL-13 monoclonal antibody in healthy subjects and mild asthmatics. *Br J Clin Pharmacol.* 2013; 75:118–28. [PubMed: 22616628]
94. De Boever EH, Ashman C, Cahn AP, et al. Efficacy and safety of an anti-IL-13 mAb in patients with severe asthma: a randomized trial. *J Allergy Clin Immunol.* 2014; 133:989–96. [PubMed: 24582316]
95. Corren J, Busse W, Meltzer EO, et al. A randomized, controlled, phase 2 study of AMG 317, an IL-4R α antagonist, in patients with asthma. *Am J Respir Crit Care Med.* 2010; 181:788–96. [PubMed: 20056900]
96. Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med.* 2013; 368:2455–66. [PubMed: 23688323]
97. Beck LA, Thaci D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med.* 2014; 371:130–9. [PubMed: 25006719]
98. Gauvreau GM, O'Byrne PM, Boulet LP, et al. Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. *N Engl J Med.* 2014; 370:2102–10. [PubMed: 24846652]
99. Gauvreau GM, Boulet LP, Leigh R, et al. A non-steroidal glucocorticoid receptor agonist inhibits allergen-induced late asthmatic responses. *Am J Respir Crit Care Med.* 2014; 1164:rccm.201404-0623OC
100. Akdis CA. Therapies for allergic inflammation: refining strategies to induce tolerance. *Nat Med.* 2012; 18:736–49. [PubMed: 22561837]
101. Oh CK, Leigh R, McLaurin KK, et al. A randomized, controlled trial to evaluate the effect of an anti-interleukin-9 monoclonal antibody in adults with uncontrolled asthma. *Respir Res.* 2013; 14:93. [PubMed: 24050312]
102. Ding C, Li J, Zhang X. Bertilimumab Cambridge Antibody Technology Group. *Curr Opin Investig Drugs.* 2004; 5:1213–8.
103. Blanchard C, Wang N, Stringer KF, et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J Clin Invest.* 2006; 116:536–47. [PubMed: 16453027]
104. Caldwell JM, Collins MH, Stucke EM, et al. Histologic eosinophilic gastritis is a systemic disorder associated with blood and extragastric eosinophilia, TH2 immunity, and a unique gastric transcriptome. *J Allergy Clin Immunol.* 2014; 134:1114–24. [PubMed: 25234644]
105. Groopman JE, Mitsuyasu RT, DeLeo MJ, et al. Effect of recombinant human granulocyte-macrophage colony-stimulating factor on myelopoiesis in the acquired immunodeficiency syndrome. *N Engl J Med.* 1987; 317:593–8. [PubMed: 3497344]
106. Bochner BS, Friedman B, Krishnaswami G, et al. Episodic eosinophilia-myalgia-like syndrome in a patient without L-tryptophan use: association with eosinophil activation and increased serum levels of granulocyte-macrophage colony-stimulating factor. *J Allergy Clin Immunol.* 1991; 88:629–36. [PubMed: 1918729]
107. Divekar RD, Samant S, Rank MA, et al. Immunological profiling in chronic rhinosinusitis with nasal polyps reveals distinct VEGF and GM-CSF signatures during symptomatic exacerbations. *Clin Exp Allergy.* 2014

108. Gauvreau GM, Boulet LP, Cockcroft DW, et al. Antisense therapy against CCR3 and the common β chain attenuates allergen-induced eosinophilic responses. *Am J Respir Crit Care Med*. 2008; 177:952–8. [PubMed: 18244953]
109. Gauvreau GM, Pageau R, Seguin R, et al. Dose-response effects of TPI ASM8 in asthmatics after allergen. *Allergy*. 2011; 66:1242–8. [PubMed: 21605124]
110. Imaoka H, Campbell H, Babirad I, et al. TPI ASM8 reduces eosinophil progenitors in sputum after allergen challenge. *Clin Exp Allergy*. 2011; 41:1740–6. [PubMed: 21762225]
111. Roufosse FE, Kahn JE, Gleich GJ, et al. Long-term safety of mepolizumab for the treatment of hypereosinophilic syndromes. *J Allergy Clin Immunol*. 2013; 131:461–7. [PubMed: 23040887]
112. Haldar P, Brightling CE, Singapuri A, et al. Outcomes after cessation of mepolizumab therapy in severe eosinophilic asthma: a 12-month follow-up analysis. *J Allergy Clin Immunol*. 2014; 133:921–3. [PubMed: 24418480]
113. Kim YJ, Prussin C, Martin B, et al. Rebound eosinophilia after treatment of hypereosinophilic syndrome and eosinophilic gastroenteritis with monoclonal anti-IL-5 antibody SCH55700. *J Allergy Clin Immunol*. 2004; 114:1449–55. [PubMed: 15577851]
114. Gleich GJ, Klion AD, Lee JJ, et al. The consequences of not having eosinophils. *Allergy*. 2013; 68:829–35. [PubMed: 23742015]
115. Klion AD, Robyn J, Maric I, et al. Relapse following discontinuation of imatinib mesylate therapy for FIP1L1/PDGFR α -positive chronic eosinophilic leukemia: implications for optimal dosing. *Blood*. 2007; 110:3552–6. [PubMed: 17709602]
116. Furuta GT, Kagalwalla AF, Lee JJ, et al. The oesophageal string test: a novel, minimally invasive method measures mucosal inflammation in eosinophilic oesophagitis. *Gut*. 2013; 62:1395–405. [PubMed: 22895393]
117. Lukawska JJ, Livieratos L, Sawyer BM, et al. Real-time differential tracking of human neutrophil and eosinophil migration in vivo. *J Allergy Clin Immunol*. 2014; 133:233–9. e1. [PubMed: 23953710]
118. Farahi N, Loutsios C, Peters AM, et al. Use of technetium-99m-labeled eosinophils to detect active eosinophilic inflammation in humans. *Am J Respir Crit Care Med*. 2013; 188:880–2. [PubMed: 24083867]
119. Wen T, Besse JA, Mingler MK, et al. Eosinophil adoptive transfer system to directly evaluate pulmonary eosinophil trafficking in vivo. *Proc Natl Acad Sci U S A*. 2013; 110:6067–72. [PubMed: 23536294]
120. Loutsios C, Farahi N, Porter L, et al. Biomarkers of eosinophilic inflammation in asthma. *Expert Rev Respir Med*. 2014; 8:143–50. [PubMed: 24460178]
121. Na HJ, Hamilton RG, Klion AD, et al. Biomarkers of eosinophil involvement in allergic and eosinophilic diseases: review of phenotypic and serum markers including a novel assay to quantify levels of soluble Siglec-8. *J Immunol Methods*. 2012; 383:39–46. [PubMed: 22683541]
122. Mawhorter SD, Stephany DA, Ottesen EA, et al. Identification of surface molecules associated with physiologic activation of eosinophils - application of whole-blood flow cytometry to eosinophils. *J Immunol*. 1996; 156:4851–8. [PubMed: 8648134]
123. Bochner BS. Systemic activation of basophils and eosinophils: markers and consequences. *J Allergy Clin Immunol*. 2000; 106:S292–S302. [PubMed: 11080745]
124. Jia G, Erickson RW, Choy DF, et al. Periostin is a systemic biomarker of eosinophilic airway inflammation in asthmatic patients. *J Allergy Clin Immunol*. 2012; 130:647–54. [PubMed: 22857879]
125. Nair P, Kraft M. Serum periostin as a marker of T(H)2-dependent eosinophilic airway inflammation. *J Allergy Clin Immunol*. 2012; 130:655–6. [PubMed: 22935590]
126. Hijnen D, De Bruin-Weller M, Oosting B, et al. Serum thymus and activation-regulated chemokine (TARC) and cutaneous T cell-attracting chemokine (CTACK) levels in allergic diseases: TARC and CTACK are disease-specific markers for atopic dermatitis. *J Allergy Clin Immunol*. 2004; 113:334–40. [PubMed: 14767451]
127. Wilson TM, Maric I, Shukla J, et al. IL-5 receptor α levels in patients with marked eosinophilia or mastocytosis. *J Allergy Clin Immunol*. 2011; 128:1086–92. [PubMed: 21762978]

128. Nair P, Ochkur SI, Protheroe C, et al. Eosinophil peroxidase in sputum represents a unique biomarker of airway eosinophilia. *Allergy*. 2013; 68:1177–84. [PubMed: 23931643]
129. Butterfield JH, Leiferman KM, Abrams J, et al. Elevated serum levels of interleukin-5 in patients with the syndrome of episodic angioedema and eosinophilia. *Blood*. 1992; 79:688–92. [PubMed: 1732010]
130. Simon HU, Plotz SG, Dummer R, et al. Abnormal clones of T cells producing interleukin-5 in idiopathic eosinophilia. *N Engl J Med*. 1999; 341:1112–20. [PubMed: 10511609]
131. Gevaert P, Lang-Loidolt D, Lackner A, et al. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. *J Allergy Clin Immunol*. 2006; 118:1133–41. [PubMed: 17088140]

Key Points

- A sizable unmet need exists for new, safe, selective and effective treatments for eosinophil-associated diseases such as hypereosinophilic syndrome, eosinophilic gastrointestinal disorders, nasal polyposis and severe asthma.
- An improved panel of biomarkers to help guide diagnosis, treatment, and assessment of disease activity is also needed.
- An impressive array of novel therapeutic agents, including small molecules and biologics, that directly or indirectly target eosinophils and eosinophilic inflammation are undergoing controlled clinical trials, with many already showing promising results.
- A large list of additional eosinophil-related potential therapeutic targets remains to be pursued, including cell surface structures, soluble proteins that influence eosinophil biology, and eosinophil-derived mediators that have the potential to contribute adversely to disease pathophysiology.

Chemokine, complement and other chemotactic factor receptors

CD35	CCR1
CD88	CCR2
C3aR	CCR3
PAFR	CCR6
LTB ₄ R	CCR8
CysLT1	CXCR1
CysLT2	CXCR2
fMLPR	CXCR3
Histamine (H4 receptor)	CXCR4
	CRTh2

Adhesion molecules

CD11a	CD44
CD11b	CD49d
CD11c	CD49f
CD15	CD62L
CD15s	CD147
CD18	CD162
CD29	CD174
αd integrin	CD321
β7 integrin

Apoptosis, signaling and others

CD9	CD134	EMR1
CD12	CD137	Glucocorticoid receptor
CD17	CD139	Siglec-8
CD24	CD148	Siglec-10
CD28	CD151	LIR1
CD30	CD153	LIR2
CD37	CD154	LIR3
CD39	CD161	LIR7
CD40	CD165	TLR2
CD43	CD172a	TLR3
CD52	CD178	TLR4
CD53	CD226	TLR8
CD58	CD244	TLR9
CD60a	CD253	TLR10
CD63	CD261	
CD65	CD262	
CD66	CD263	
CD69*	CD264	
CD71	CD265	
CD80	CD295	
CD81	CD298	
CD82	CD300a	
CD86*	CD300f	
CD92	CD302	
CD93	CD352	
CD95	PIRA	
CD97	PIRB	
CD98	PZX	
CD99	PZY	

Immunoglobulin receptors and related immunoglobulin family members

CD4	CD58
CD16*	CD66
CD31	CD84
CD32	CD85
CD33	CD89
CD47	CD100
CD48	CD101
CD50	CD112
CD54*	HLA class I
	HLA-DR*

Cytokine receptors

GM-CSF	IL-6
IFN-α	IL-9
IFN-γ	IL-13
Leukemia inhibitory factor	IL-33
IL-3	Stem cell factor
IL-4	TNFα
IL-5	TNFβ

Enzymes

CD10
CD13
CD45
CD45RB
CD45RC
CD45RO
CD46
CD55
CD59
CD87
CD156a
PAR-2

Figure 1.

Surface molecules expressed by human eosinophils. There is some overlap among categories for some of these proteins. Common names for chemokine receptors, toll-like receptors (TLRs) and others were sometimes used instead of the CD names due to greater use and familiarity among most readers of the former. The asterisk indicates activated eosinophils. Artwork by Jacqueline Schaffer.

Figure 2.

Examples of surface receptors that are selectively expressed on human eosinophils and therefore of potential therapeutic relevance. Note that almost all of these are also expressed on basophils and mast cells. Artwork by Jacqueline Schaffer.

Table 1
Examples of molecules being targeted with drugs (including biologics) to directly or indirectly affect human eosinophils

Strategy	Target	Drug	Cells targeted besides eosinophils	Anti-eosinophil effects in vitro	Anti-eosinophil effects in vivo	Status
Cell surface protein	$\alpha 4\beta 1, \alpha 4\beta 7$ integrins	Natalizumab	T cells, B cells, NK cells, monocytes, basophils	Inhibits leukocyte adhesion to VCAM-1, MAdCAM-1 and fibronectin	Increases number of circulating eosinophils; inhibits their accumulation at sites of inflammation	Approved for relapsing, remitting multiple sclerosis (Tysabri®, Biogen Idec)
	$\alpha 4\beta 7$ integrin	Vedolizumab	T cells, B cells, NK cells, monocytes, basophils	Inhibits leukocyte adhesion to MAdCAM-1	No effect on numbers of circulating eosinophils	Approved for inflammatory bowel disease (Entyvio®, Takeda)
	$\beta 7$ integrins ($\alpha 4\beta 7$ and $\alpha E\beta 7$)	Etrulizumab	T cells, B cells, NK cells, monocytes, basophils	Inhibits leukocyte adhesion to MAdCAM-1 and E-cadherin	Unknown	Phase 3 for inflammatory bowel disease (Genentech)
	CCR3	GW766944 (small molecule)	Basophils and mast cells	Blocks chemokine-mediated migration	No significant effect on sputum or blood eosinophils	Phase 2 for asthma (GlaxoSmithKline)
	CD52	Alentuzumab	Most leukocytes	Unknown	Depletes eosinophils	Approved for cancer (Campath®, Bayer)
	CD131 (common β -chain)	CSL311 monoclonal antibody	Cells expressing the common β chain for the IL-3, IL-5 and GM-CSF receptor	Unknown	Unknown	Phase 2 in asthmatics (CSL Limited)
	CRTh2	OC000459 (small molecule)	Basophils, mast cells, Th2 cells	Blocks PGD2 effects	Reduces numbers of tissue eosinophils	Various phases for asthma, eosinophilic esophagitis, atopic dermatitis (Oxigen, Atopix Therapeutics)
	EMRI	afucosylated anti-EMRI monoclonal antibody	None	Targets cells for ADCC	Depletes primate eosinophils	Preclinical (KaloBios)
	IL-4 receptor α chain	Dupilumab and AMG 317 monoclonal antibody	All IL-4 receptor α chain-bearing cells	Inhibits IL-4 and IL-13 biology	Dupilumab reduces numbers of airway eosinophils but AMG317 did not	Phase 2–3 for atopic dermatitis and asthma (Regeneron, Amgen)
	IL-5 receptor	benralizumab	Basophils and mast cells	Targets cells for ADCC	Eosinophil and basophil depleting	Phase 2 for eosinophilic asthma (AstraZeneca/Medimmune)
Soluble mediator antagonist	Siglec-8	Siglec-8 monoclonal antibody	Basophils and mast cells	Engagement causes eosinophil death and inhibits mast cell degranulation	Unknown	Preclinical
	Eotaxin-1	Bertilimumab	Basophils and mast cells	Inhibits eotaxin-1-mediated eosinophil activation	Unknown	Various phases for ulcerative colitis and bullous pemphigoid (Immune Pharmaceuticals)
	GM-CSF	KB003 monoclonal antibody	All GM-CSF receptor-bearing cells	Inhibits GM-CSF biology	Unknown	Development discontinued
	IgE	Omalizumab	Basophils and mast cells	No direct effects	Reduces numbers of eosinophils at sites of allergic inflammation	Approved for asthma and urticaria (Xolair®, Genentech/Novartis)
	IL-4	pitakinra, altrakincept and pascolizumab	Leukocytes and tissue-resident cells	No direct effects	Reduces numbers of eosinophils at sites of allergic inflammation	Development discontinued

Strategy	Target	Drug	Cells targeted besides eosinophils	Anti-eosinophil effects in vitro	Anti-eosinophil effects in vivo	Status
	IL-5	Mepolizumab, Reslizumab	None	Inhibits IL-5 biology	Reduces bone marrow, circulating and tissue eosinophils	Phase 3 for eosinophilic asthma; some data in HES, eosinophilic granulomatosis and polyangitis, EoE, atopic dermatitis and chronic rhinosinusitis/nasal polyposis (GlaxoSmithKline, TEVA)
	IL-9	MEDI-528 monoclonal antibody	All IL-9 receptor-bearing cells	Inhibits IL-9 biology	No effect on blood eosinophil counts or asthma	Development discontinued
	IL-13	Tralokinumab Lebrikizumab Anrukinzumab RPC4046 QAX576 monoclonal antibodies	All IL-13 receptor-bearing cells	Inhibits IL-13 biology	Reduces numbers of eosinophils in blood and at sites of allergic inflammation	Various phases for asthma and eosinophilic esophagitis (AstraZeneca/Medimmune, Genentech/Roche, Receptos, Novartis)
	Sulfidopeptide leukotrienes	montelukast, zileuton (small molecules)	Leukocytes and tissue-resident cells	Inhibits effects of LTC4, LTD4 and LTE4 on eosinophil activation and migration	Reduces numbers of eosinophils in blood and at sites of allergic inflammation	Approved for asthma (Singulair®, Merck; Zflo CR®, Cornerstone Therapeutics) and allergic rhinitis (Singulair®)
	Thymic stromal lymphopoietin (TSLP)	AMG 157 monoclonal antibody	Many leukocyte types	Inhibits TSLP biology	Reduces numbers of eosinophils in blood and at sites of allergic inflammation	Phase 2 for asthma (Amgen)
	CCR3 and CD131 (common β chain)	TPI ASM8, antisense oligonucleotides, inhaled	Basophils, mast cells and others	Downregulates expression of CCR3 and CD131 common β chain transcripts	Reduces numbers of eosinophils in blood and at sites of allergic airways inflammation	Development discontinued
	FIPL1-PDGFR deletion mutation	Imatinib and next generation tyrosine kinase inhibitors	Any cell possessing this deletion mutation; also cells possessing the BCR-ABL mutation	Inhibits gain-of-function activity	Normalizes numbers of bone marrow, circulating and tissue eosinophils	Approved for chronic myelogenous leukemia and hypereosinophilic syndrome (Gleevec®, Novartis)
	Food elimination diets	Specific food avoidance	Unknown but likely mucosal and immunological cells	No direct effects	Reduces numbers of eosinophils in blood and at sites of esophageal inflammation	Often prescribed for EoE and gastritis
	Glucocorticosteroid receptor	Glucocorticoids	Virtually all cells	Causes eosinophil death and reduces production of eosinophil-recruitment factors	Reduces bone marrow, circulating and tissue eosinophils	Many approved for oral, topical and inhaled use; new formulations under development for use in EoE
	Mitochondrial function	Dexpramipexole	Unknown	Unknown	Found incidentally in clinical trials of amyotrophic lateral sclerosis to gradually reduce blood eosinophil counts; mechanism unknown	Phase 2 for HES and chronic rhinosinusitis/nasal polyposis (Knopp Biosciences)
	Interferon-α	Intron A®, Pegasys®, PegIntron®	All Interferon-α receptor-bearing cells	No direct effects	Reduces bone marrow, circulating and tissue eosinophils	Used to treat HES, mainly as a steroid-replacing agent
	Ribonucleotide reductase	Hydroxyurea	Virtually all hemato-poietic cells and some cancers	No direct effects	Reduces bone marrow, circulating and tissue eosinophils	Used off-label for HES, mainly as a steroid-sparing or steroid-replacing agent