Novel Therapies for Eosinophilic Disorders

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KEYWORDS

• Eosinophil • Therapies • Antibodies • Targets • Pharmacology • Biomarkers

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.

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] The most commonly affected areas include the bone marrow, blood, mucosal surfaces, and skin, often with immense disease- and treatment-related morbidity,

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whereas involvement of other organs, such as the cardiovascular system, have a particularly prominent impact on disease mortality. 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 approval,[2] 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 on 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 approval by the Food and Drug Administration (FDA) in 2015 or soon thereafter.

As part of the discussion of eosinophil-selective therapies, the surface phenotype of the eosinophil is reviewed, in part to explain the current rationale behind drugs that directly target the eosinophil but also, it is hoped, to serve as a springboard 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 is also 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] Surface phenotype is particularly relevant when it comes to consideration of developing eosinophil-targeting drugs (**Fig. 1**).[8,9,12–14] Until very recently, it was thought that there were no 100% purely eosinophil-specific cell surface proteins. With the discovery of epidermal growth factor–like module containing mucin-like hormone-like receptor 1 (EMR1, the human counterpart of F4/80 in the mouse), a member of the G protein–coupled epidermal growth factor-7-transmembrane family, this changed when it was reported that EMR1 is truly eosinophil specific (**Fig. 2**).[15] Expression was conserved in monkeys, and targeting with an afucosylated immunoglobulin G1 (IgG1) antibody that is particularly effective at engaging natural killer (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 because of similarities in their hematopoietic

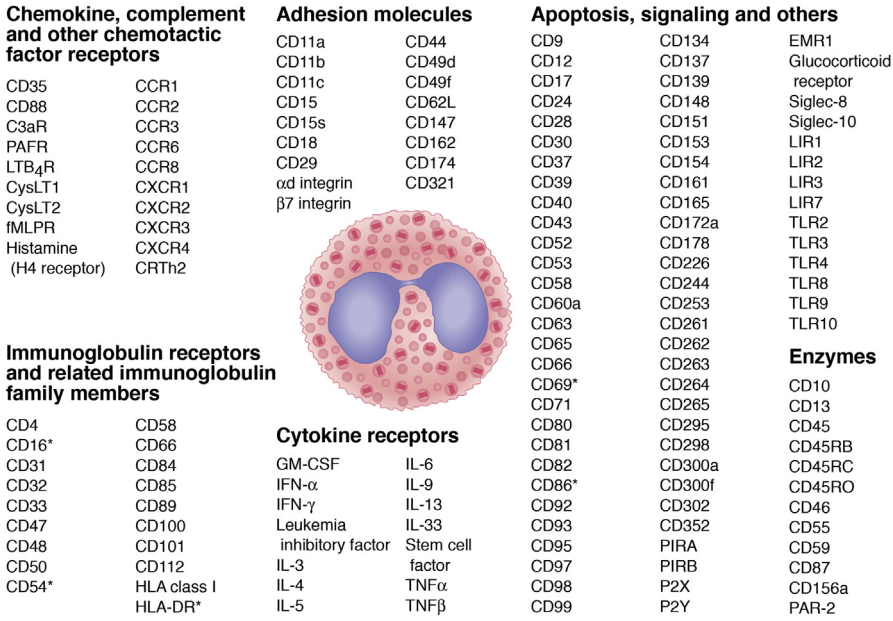

Fig. 1. Surface molecules expressed by human eosinophils. There is some overlap among categories for some of these proteins. Common names for chemokine (CC and CXC) receptors, toll-like receptors (TLRs), and others were sometimes used instead of the CD names because of the greater use and familiarity among most readers of the former. The asterisk indicates activated eosinophils. C3aR, C3a receptor; CysLT, cysteinyl leukotriene receptor type; EMR1, epidermal growth factor–like module containing mucin-like hormone receptor-like 1; fMLPR, formyl-methionyl-leucyl-phenylalanine receptor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; LIR, leukocyte immunoglobulin-like receptor; LTB4R, leukotriene B4 receptor; P2X and P2Y, two types of purinergic receptors; PAFR, platelet activating factor receptor; PIR, paired immunoglobulin-like receptor; TNF, tumor necrosis factor. (*Courtesy of* Jacqueline Schaffer, MAMS, Chicago, IL.)

pathways, there is a subset of surface markers whose expression is shared among basophils and/or mast cells (see **Fig. 2**). Such examples include the heterodimeric receptor for interleukin 5 (IL-5) (CD125/CD131),[17] the type 3 CC chemokine receptor (CCR3, CD193),[18] and the sialic acid-binding immunoglobulin-like lectin inhibitory receptor Siglec-8.[19–21] Among these, biologics targeting IL-5 or its receptor and small molecules targeting CCR3 are in various stages of clinical trials, as discussed later. Another cell surface receptor expressed by eosinophils and a relatively small subset of other leukocytes includes the chemoattractant receptor expressed on type 2 helper T cells (CRTh2, also called DP2, the type 2 prostaglandin D2 receptor or CD294 found on eosinophils, basophils, mast cells, and Th2 lymphocytes), for which small molecule antagonists are advancing in the clinic (also see later discussion). Some receptors, such as Siglec-8,[22] Fas (CD95),[23] and others on eosinophils, can on 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 (see **Fig. 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

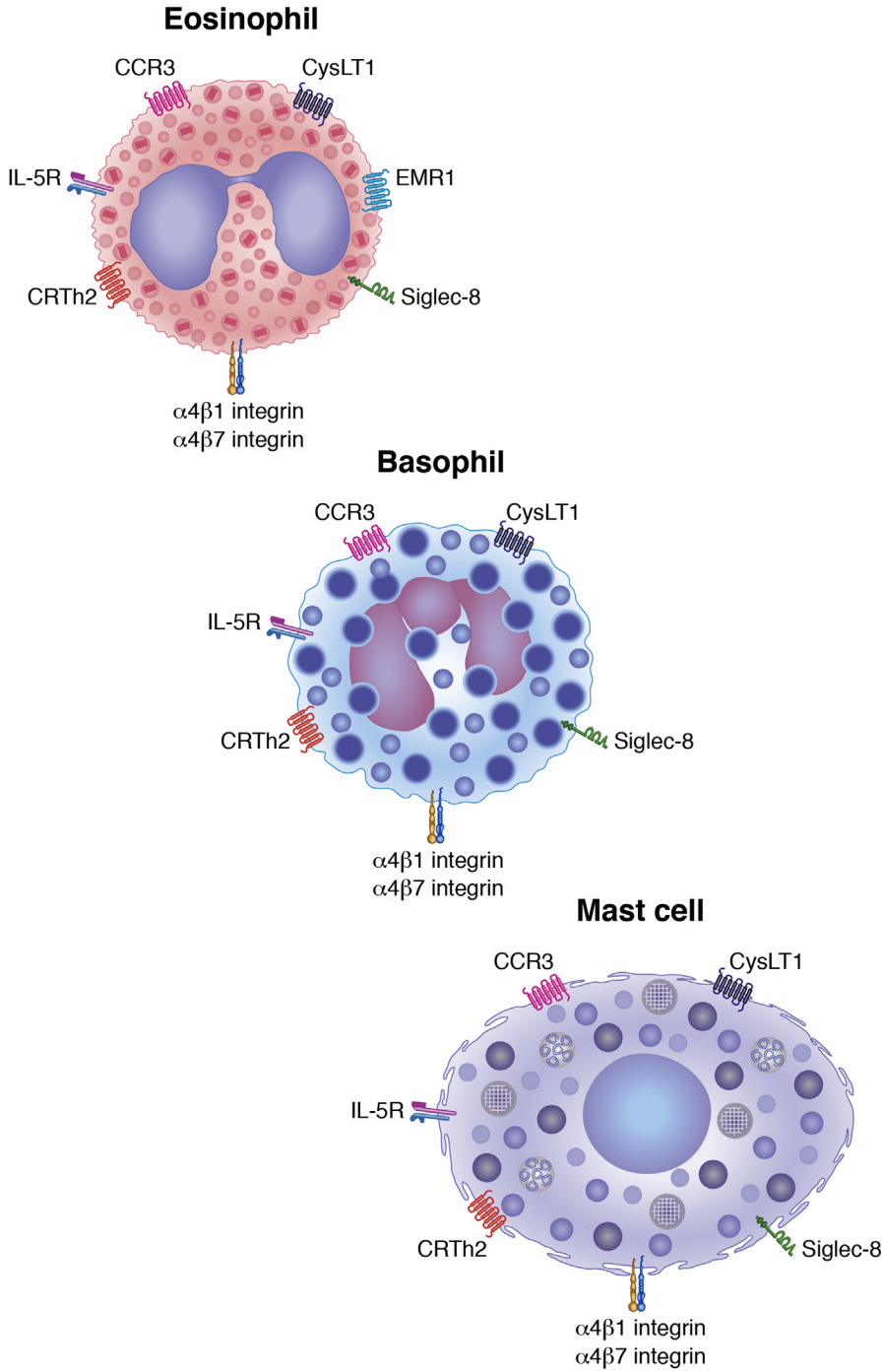

Fig. 2. Examples of surface receptors that are selectively expressed on human eosinophils and, therefore, of potential therapeutic relevance. Note that almost all of these are also expressed on basophils and mast cells. EMR1, epidermal growth factor–like module containing mucin-like hormone receptor-like 1; IL, interleukin. (*Courtesy of* Jacqueline Schaffer, MAMS, Chicago, IL.)

via antibody-drug conjugates, liposomes, or nanoparticles, such strategies might someday become available for eosinophil targeting by leveraging the eosinophil phenotype.

THE EOSINOPHIL INTERIOR AS A TARGET

Eosinophils possess several 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 proapoptotic GR-A isoform was 5-fold higher in eosinophils than in neutrophils, whereas the nonapoptotic GR-D isoform was 5-fold higher in neutrophils compared with eosinophils, making eosinophils particularly susceptible (and the neutrophil much less or nonsusceptible) 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 therapy,[29] perhaps because of reduced GR expression[30] 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-A isoform in eosinophils, rendering them more sensitive to lower concentrations of steroids, is not yet known.

Eosinophils also possess several unique cytoplasmic granule proteins, such as eosinophil cationic protein (ECP), eosinophil-derived neurotoxin, and eosinophil peroxidase (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 leukotriene C4 (LTC_4) 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 later discussion).

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 Fip1-like 1 gene fused with the platelet-derived growth factor receptor α (FIP1L1-PDGFR) deletion mutation on chromosome 4, as well as some other patients with HES 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

The current standards of care for the treatment of eosinophil-associated disorders, including HES, eosinophilic esophagitis (EoE), and others, are the subject of their own articles in this volume of *Immunology and Allergy Clinics of North America*, so they will only be mentioned in passing for completeness and for comparison with future therapies. As mentioned earlier, the current mainstay of the initial treatment of nearly all forms of eosinophilic disorders begins with glucocorticoids. For HES, when 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 interferon-α.[39,40] Other immunosuppressive agents are sometimes tried, with only modest benefit at best.[29] For EoE, the 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), α4β1 integrin (CD49d/CD29, natalizumab), α4β7 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, whereas vedolizumab seems to lack this property.[44,45] The effects of blockade of vascular cell adhesion molecule 1 (VCAM-1, CD106) or mucosal addressin cell adhesion molecule 1 (MAdCAM-1), the ligands for α4β1 integrin and α4β7 integrin, in eosinophil-associated diseases, including eosinophilic gastrointestinal disorders 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 caused by 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] and reslizumab [IgG4]) and the IL-5 receptor (benralizumab [afucosylated IgG1, formerly called MEDI-563]) (see **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 (see **Fig. 2**).[47,48]

Among these 3 biological agents, the most published information exists for mepolizumab. It has shown efficacy in controlled trials of eosinophilic asthma (eg, reduced exacerbations, improved lung function),[49–54] nasal polyposis (eg, reduced polyp size),[55] and in idiopathic and lymphocytic HES syndrome (eg, 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 earlier, 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

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	Antieosinophil Effects In Vitro	Antieosinophil Effects In Vivo	Status
Cell surface protein	$\alpha4\beta1$, $\alpha4\beta7$ 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 (natalizumab [Tysabri])
	$\alpha4\beta7$ 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 (vedolizumab [Entyvio])
	$\beta7$ integrins ($\alpha4\beta7$ and $\alpha E\beta7$)	Etrolizumab	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	Alemtuzumab	Most leukocytes	Unknown	Depletes eosinophils	Approved for cancer (alemtuzumab [Campath])

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Table 1 (*continued*)

Strategy	Target	Drug	Cells Targeted Besides Eosinophils	Antieosinophil Effects In Vitro	Antieosinophil Effects In Vivo	Status
	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 asthmatic patients (CSL Limited)
	CRTh2	OC000459 (small molecule)	Basophils, mast cells, Th2 cells	Blocks PGD2 effects	Reduces numbers of tissue eosinophils	Various phases for asthma, EoE, atopic dermatitis (Oxagen, Atopix Therapeutics)
	EMR1	Afucosylated anti-EMR1 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 3 for eosinophilic asthma (AstraZeneca/ Medimmune)
	Siglec-8	Siglec-8 monoclonal antibody	Basophils and mast cells	Engagement causes eosinophil death and inhibits mast cell degranulation	Unknown	Preclinical

Soluble mediator antagonist	Eotaxin-1	Bertilimumab	Basophils and mast cells	Inhibits eotaxin-1–mediated eosinophil activation	Unknown	Various phases of development 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 (omalizumab [Xolair])
	IL-4	Pitrakinra, altrakincept, and pascolizumab	Leukocytes and tissue-resident cells	No direct effects	Reduces numbers of eosinophils at sites of allergic inflammation	Development discontinued
	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 polyangiitis, EoE, atopic dermatitis, and chronic rhinosinusitis/nasal polyposis (GlaxoSmithKline, TEVA)

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Table 1 (*continued*)

Strategy	Target	Drug	Cells Targeted Besides Eosinophils	Antieosinophil Effects In Vitro	Antieosinophil Effects In Vivo	Status
	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 EoE (AstraZeneca/ Medimmune, Genentech/ Roche, Receptos)
	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 (montelukast [Singulair]; zileuton [Zyflo CR]) and allergic rhinitis (montelukast [Singulair])
	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)
Others	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
	FIP1L1-PDGFR deletion mutation	Imatinib and next-generation tyrosine kinase inhibitors	Any cell possessing this deletion mutation; also cells possessing the chromosomal translocation t(9;22)(q34;q11)	Inhibits gain-of-function activity	Normalizes numbers of bone marrow, circulating and tissue eosinophils	Approved for chronic myelogenous leukemia and HES (imatinib mesylate [Gleevec])

Food-elimination diets	Specific food avoidance	Unknown but likely mucosal and immunologic cells	No direct effects	Reduces numbers of eosinophils in blood and at sites of esophageal inflammation	Often prescribed for EoE and eosinophilic gastritis
Glucocorticoid steroid 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 specific 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	Interferon alfa-2b (Intron A), peginterferon alfa-2a (Pegasys), peginterferon alfa-2b (Peg-Intron)	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 hematopoietic 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

Abbreviations: PGD2, prostaglandin 2; TSLP, thymic stromal lymphopoietin.

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[67–69] but not with benralizumab in chronic obstructive pulmonary disease (COPD).[70] Unique to benralizumab was a study showing that a single dose given in the emergency department for an acute exacerbation of asthma reduced exacerbation and hospitalization rates over the subsequent 3-month period by 50% to 60%.[71] Like with mepolizumab treatment of EoE, reslizumab reduced tissue eosinophils but without a concomitant improvement, compared with placebo, in symptoms.[72] All studies with either benralizumab or reslizumab showed prompt reductions ($\geq$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.[72,73]

Other eosinophil-related receptors have been targeted in recent or ongoing clinical trials. Given the selective expression of CCR3, a G protein–coupled 7-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.[18,74–77] 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.[78] 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 7-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[79,80] and in EoE.[81] 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 and 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.[82] 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 Web site). Finally, dexpramipexole (KNS-760704) is an oral drug originally developed for the treatment of amyotrophic lateral sclerosis, but it failed in phase 3 studies.[83] 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 Web site) and chronic sinusitis with nasal polyposis (see NCT02217332 on the clinicaltrials.gov Web site). The exact mechanism of action of this agent, including its antieosinophil properties, is unknown; but it is thought to alter 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 several important biological properties relevant to eosinophilic inflammatory responses, including their ability to enhance eosinophil recruitment responses via induction of the adhesion molecule VCAM-1 and of CCR3-active chemokines.[84,85] The receptors for IL-4 and IL-13 are heterodimeric, sharing a common IL-4 receptor α chain (IL-4Rα1) while also using the common γc chain or IL-13 receptor α1 chains, respectively. Although eosinophils express the IL-13 receptor,[86] the clinically beneficial effects of antagonizing IL-13 in vivo are more likely to be caused by 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,[87–89] anrukinzumab,[90] tralokinumab,[91–93] GSK679586,[94,95] and RPC4046 (https://clinicaltrials.gov/ct2/show/NCT02098473). However, by targeting IL-4Rα1 instead, blockade of both IL-4 and IL-13 biology can be achieved, as was explored with monoclonal antibody AMG 317 in asthma[96] and, so far, more successfully in atopic dermatitis and asthma with dupilumab.[97,98] Also to be mentioned in this section is an antibody to thymic stromal lymphopoietin (TSLP), a highly proinflammatory and proallergic 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 reduced blood and airway eosinophilia.[99] Finally, given the fact that eosinophils are highly susceptible to the proapoptotic effects of glucocorticoids, it was of interest that in a very similar phase 2 proof-of-concept study, AZD5423, an inhaled nonsteroidal agonist of the GR that, in theory, should have reduced side effects compared with glucocorticoids, significantly blocked the late-phase airway allergic response as well as reduced sputum eosinophilia.[100] Although 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; 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 anticytokine and antichemokine therapies that either directly or indirectly target eosinophils have been tested, mainly in asthma, but have not fared as well, so they are only 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 because of a lack of efficacy include pascolizumab (anti-IL-4 antibody), soluble IL-4 receptor (altrakincept), pitrakinra, a mutein of IL-4, and an anti-IL-9 antibody MEDI-528.[101,102] 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 for this indication was not pursued. It is currently about to begin testing in ulcerative colitis and bullous pemphigoid.[103] 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.[104,105] 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 asthmatic patients inadequately controlled with corticosteroids; according to a

press release dated January 29, 2014 from KaloBios, the company developing this antibody, it failed to meet its end point of improved pulmonary function.[106] No data were released regarding any specific aspects of eosinophil biology, such as the effects on blood levels or airway eosinophilia; but it is known that infusion with GM-CSF causes eosinophilia,[107] and some patients with HES and exacerbations of chronic rhinosinusitis with nasal polyposis have elevated levels of GM-CSF in their blood.[108,109] Finally, development of TPI ASM8, a formulation of inhaled antisense oligonucleotides designed to reduce allergic inflammation by downregulating both CCR3 and the common β chain (CD125) of the IL-3, IL-5, and GM-CSF receptor, seems to have been discontinued but had shown some favorable impact on allergen-induced sputum eosinophilia in initial trials.[110–112]

FUTURE CONSIDERATIONS

Although many novel small molecule and biologic agents 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 (eg, those targeting IL-5 or its receptor) may actually become approved for clinical use. Because 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-antihuman antibodies (HAHAs) against biologics. Overall, mepolizumab has a good safety profile, with rare infusion or injection reactions, insignificant rates of HAHA 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.[62,64,113,114] Dosing intervals can be expanded without loss of efficacy; 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.[115] In early studies of benralizumab, some cases of transient neutropenia were reported.[48] So far, it seems that one can maintain normal immune function with very low numbers of eosinophils or without eosinophils entirely.[116] We know virtually nothing about the combined use of multiple antieosinophil biologics in the same patient at the same time or 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. Unfortunately, this does not seem to be the case for mepolizumab in asthma[114] or for imatinib mesylate and HES,[117] with disease recurrence seen following discontinuation of either treatment.[117] Sorely needed are ways of detecting organ-specific disease activity, such as the esophageal string test in EoE[118] and nuclear medicine–based scans of eosinophil trafficking and accumulation.[119–121] 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.[122,123] Examples of such biomarkers might include the presence of an activated eosinophil surface phenotype as detected by flow cytometry[124,125] and a variety of measurements in biological fluids, such as serum periostin in IL-13–driven asthma[126,127]; serum CCL17 in HES and atopic dermatitits[29,128]; serum levels of soluble receptors, such as for IL-5, EMR1, and

Siglec-8 in various forms of HES[16,123,129]; and detection of EPX in biological fluids.[130] Some studies suggest that elevated levels of IL-5 might be a feature of certain subsets of eosinophilic disorders[131,132] as well as responsiveness to anti–IL-5 treatment.[133] These approaches and others will require rigorous validation in controlled clinical trials before garnering confidence as clinically useful parameters in eosinophil-associated disease assessment and management.

SUMMARY

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. Although none are yet FDA approved, each offers promise as we strive to provide the best possible treatment of patients with 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.

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