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