Biologic Agents for the Treatment of Hypereosinophilic Syndromes

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List of Design Committee Members: Fei Li Kuang, MD, PhD, and Amy D. Klion, MD (authors); Robert S. Zeiger, MD, PhD (editor)

Learning objectives:

1. To describe the various clinical subtypes of hypereosinophilic syndrome (HES).
2. To outline a general approach to the treatment of HES.
3. To discuss the role of targeted biologic agents in the treatment of HES.

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Hypereosinophilic syndromes (HES) are a heterogeneous group of rare disorders defined by the presence of marked peripheral or tissue eosinophilia resulting in end-organ damage. Although conventional therapies, including glucocorticoids, hydroxyurea, and IFN-α, are initially effective in reducing eosinophilia and symptoms in a majority of patients with platelet-derived growth factor mutation-negative HES, the development of resistance and treatment-related toxicity are common. In contrast, targeted therapy with the tyrosine kinase inhibitor, imatinib, is well tolerated but effective only in the subset of patients with HES with a primary myeloid disorder. Eosinophil-targeted biotherapeutics offer the potential of improved efficacy with few, if any, adverse effects. The aims of this review are to provide an overview of current approaches to the use of conventional HES therapies and a discussion of existing biotherapeutics that target eosinophils and their potential use in the treatment of HES. With the continuing expansion of eosinophil-targeted biotherapeutics, the future for patients with eosinophilic disorders is promising. **Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:1502-9)**

Key words: *Hypereosinophilic syndrome; Monoclonal antibody; IL-5*

Hypereosinophilic syndromes (HES) are rare disorders defined by peripheral eosinophilia greater than 1.5×10^9/L or excessive tissue eosinophilia in the setting of clinical manifestations attributable to the eosinophilia.[1] Conventional therapies include glucocorticoids (GCs), hydroxyurea, IFN-α, imatinib, and other commercially available immunomodulatory and suppressive therapies. Although

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Abbreviations used
AEC- Absolute eosinophil count
CEL-NOS- Chronic eosinophilic leukemia-not otherwise specified
EGID- Eosinophilic gastrointestinal disorder
EGPA- Eosinophilic granulomatosis with polyangiitis
EoE- Eosinophilic esophagitis
FDA- Food and Drug Administration
GC- Glucocorticoid
HE- Hypereosinophilia
HES- Hypereosinophilic syndrome
IL-5R- IL-5 receptor
IV- Intravenously
L-HES- Lymphocytic variant HES
M-HES- Myeloid HES
PDGFR- Platelet-derived growth factor receptor
sc- Subcutaneously
Siglec- Sialic acid-binding immunoglobulin-like lectin

these agents are effective in reducing eosinophilia and controlling symptoms in many patients, resistance and drug-related toxicities lead to discontinuation of therapy in a significant proportion of cases.[2] Eosinophil-targeted biotherapeutics offer the potential of improved efficacy with few, if any, adverse effects. The past decade has seen an increase in the number of eosinophil-targeted therapies in preclinical and clinical trials for eosinophil-associated disorders, including eosinophilic asthma and HES. Although no biologic agents have been approved for use in the treatment of HES to date, 2 monoclonal antibodies—mepolizumab (Nucala; GlaxoSmithKline, London, UK) and reslizumab (Cinqair; Teva Pharmaceuticals, Petah Tikva, Israel)—that target IL-5, the cytokine critical for eosinophil maturation and activation, recently received Food and Drug Administration (FDA) approval for the treatment of eosinophilic asthma. A third monoclonal antibody, benralizumab (AstraZeneca/MedImmune, Cambridge, UK), that depletes eosinophils by binding to IL-5 receptor (IL-5R) and targeting the cell for enhanced antibody-dependent cell cytotoxicity, has completed phase 3 trials for eosinophilic asthma and is awaiting FDA approval.

As the number of potential therapies for HES continues to expand, it will become increasingly important to identify factors that may impact treatment choice for individual patients. In this clinical commentary, the overall approach to the diagnosis and treatment of HES will be reviewed with emphasis on the influence of clinical HES subtype on treatment responses. This will be followed by a discussion of the available clinical data regarding the efficacy and safety of existing biotherapeutics for which clinical data are available and the theoretical efficacy of those that are in clinical or preclinical trials. For the purposes of this commentary, the scope of biotherapeutics under discussion will be limited to monoclonal antibodies.

CLASSIFICATION OF HES

HES is a heterogeneous group of disorders unified by the presence of marked blood or tissue eosinophilia (hypereosinophilia [HE]) and clinical manifestations. A detailed description of the diagnostic evaluation of HE and HES is beyond the scope of this review, but has been recently outlined (Table I).[3] The eosinophilia in HES can be primary (due to abnormalities in the myeloid lineage) or secondary (driven by cytokines or other mediators produced by cells other than eosinophils and their precursors). Although the clinical manifestations can be similar irrespective of the cause of the eosinophilia, evidence is mounting to support the classification of patients with HES into clinical subtypes in large part because of the implications for treatment.[3] For the purposes of this review, HES will be divided into the 6 major clinical variants proposed at a series of multidisciplinary consensus conferences held between 2005 and 2012[1,4,5]: myeloid (M-HES), lymphocytic (L-HES), overlap, associated, familial, and idiopathic.

Myeloid variant HES

M-HES includes patients with definite and presumed primary myeloid disorders presenting as HES. The most common known cause of this variant is an interstitial deletion in chromosome 4q12 leading to the creation of the imatinib-sensitive fusion gene *FIP1L1-PDGFRA.* Other fusions and point mutations in *PDGFRA* have also been described. Defined mutations driving HES can also occur in other tyrosine kinases, including *PDGFRB, FGFR1, KIT,* and *JAK2*. Some patients have a clinical phenotype with myeloid features similar to what was described in *PDGFRA*-positive patients before the discovery of *FIP1L1-PDGFRA* (Table II). These patients have idiopathic M-HES. Finally, chronic eosinophilic leukemia-not otherwise specified (CEL-NOS) is also considered a form of M-HES, but will not be discussed because CEL-NOS is typically treatment refractory and most often requires bone marrow transplantation.

Lymphocytic variant HES

L-HES is defined by the presence of a clonal or phenotypically aberrant lymphocyte population (most commonly CD3−CD4+) secreting IL-5 or other eosinophil-promoting cytokines. Although intracellular flow cytometry is rarely performed to confirm cytokine secretion, a presumptive diagnosis can be made in the setting of a clonal or aberrant population and features suggestive of this clinical variant, including skin and soft tissue manifestations and an elevated serum IgE level. Occult T-cell leukemia and/or lymphoma can present as L-HES.[6,7] Conversely, some patients with L-HES progress to lymphoma after many years of stable disease.

Overlap HES

Overlap variants include eosinophilic disease restricted to a single-organ system, such as eosinophilic gastrointestinal disorder (EGID), eosinophilic fasciitis, and chronic eosinophilic pneumonia, and multisystem eosinophilic disorders with a distinct clinical phenotype, such as eosinophilic granulomatosis with polyangiitis (EGPA). Although the etiologies of these disorders are incompletely understood, they can be difficult to distinguish from idiopathic HES (especially in the setting of dramatic peripheral eosinophilia).

Associated HES

Marked peripheral eosinophilia and eosinophilic end-organ manifestations (HES) can accompany a wide variety of conditions, including helminth infections, neoplasms, and hypersensitivity disorders. Although the clinical manifestations of these associated HES can be indistinguishable from other forms of HES, treatment is focused on the underlying disorder rather than the eosinophilia itself.

Familial HE/HES

Familial HE/HES is an extremely rare autosomal dominant condition, likely due to dysregulation of IL-5 expression.[8,9] Because