

Biologic Agents for the Treatment of Hypereosinophilic Syndromes



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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 $1.5 \times 10^9/L$ 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

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

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 (hyper-eosinophilia [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 1).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-PDGFR*. Other fusions and point mutations in *PDGFR* 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 *PDGFR*-positive patients before the discovery of *FIP1L1-PDGFR* (Table 1). 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

TABLE I. Diagnostic evaluation of HE

Test	Comment
All patients with HE	
Complete blood count*	
Routine chemistries, including liver function tests*	
Quantitative serum immunoglobulin levels, including IgE	
Serum troponin,* echocardiogram	If abnormal, consider cardiac MRI as this may show characteristic features of eosinophilic involvement
Pulmonary function tests*	
Chest/abdomen/pelvis CT*	To assess for splenomegaly, lymphadenopathy, occult neoplasms, and pulmonary infiltrates
Bone marrow biopsy, including cytogenetics*	Recommended in all patients with AEC > 5.0 × 10 ⁹ /L and features of M-HES or L-HES
Biopsies of affected tissues (if possible)*	
Other testing as indicated by history, signs, and symptoms	May include parasitic serologies, antineutrophil cytoplasmic antibodies, and HIV
Serum tryptase and B12 levels	Markedly elevated in myeloid HES. Vitamin B12 levels are elevated because of aberrant B12 binding proteins on granulocytes
<i>FIP1L1/PDGFR</i> A analysis by FISH or RT-PCR	Peripheral blood testing is sufficient
T- and B-cell receptor rearrangement studies	
Lymphocyte immunophenotyping by flow cytometry*	Minimum of CD3, CD4, CD8, and CD19/20 staining to assess for aberrant lymphocyte populations and B-cell lymphoproliferative disorders
Patients with features of M-HES	
Additional testing for <i>BCR-ABL1</i> , <i>PDGFRB</i> , <i>JAK2</i> , <i>FGFR1</i> , and <i>KIT</i> mutations by FISH, PCR, or other methods as appropriate	Testing should be guided by clinical and/or bone marrow findings
Patients with evidence of L-HES	
Consider PET scan,* lymph node biopsy*	
EBV viral load	

AEC, Absolute eosinophil count; CT, computed tomography; EBV, Epstein-Barr virus; FISH, fluorescence in situ hybridization; HE, hypereosinophilic; HES, hypereosinophilic syndrome; L-HES, lymphocytic variant HES; M-HES, myeloid variant HES; MRI, magnetic resonance imaging; PDGFR, platelet-derived growth factor receptor; PET, positron emission tomography.

Adapted with permission from Klion.³

*Results substantially affected by GC therapy. Consider obtaining before treatment if clinically stable.

most affected family members remain asymptomatic despite long HE, treatment is generally not indicated. In the event of progression to HES, these patients would need to be classified with respect to clinical phenotype and treated accordingly.

Idiopathic HES

Idiopathic HES is the term used for patients with HES who do not fit into any of the above categories.

GENERAL APPROACH TO TREATMENT

The overall goals of therapy in all patients with HES are to reduce the absolute eosinophil count (AEC), improve signs and symptoms, and prevent progression of disease. Although these 3 outcomes are linked in most patients, the target AEC can vary depending on the severity of the clinical manifestations and the toxicity of the therapies required to suppress the eosinophilia. Patients with HE and no evidence of clinical manifestations (hypereosinophilia of unknown significance and familial HES) typically do not require therapy, but should be followed closely for evidence of progression to HES.

Systemic GC therapy is considered first line in all patients with HES except: (1) patients with associated HES due to an identified treatable secondary cause (such as a helminth infection, drug hypersensitivity, or neoplasm); (2) patients with a known mutation in *PDGFRA* or *PDGFRB*, who should be treated with imatinib mesylate (see below); and (3) patients with overlap syndromes, such as EGID, who may respond to topical GC therapy. In a multicenter retrospective study of 188 patients with HES, GC response rates approached 85% at 1 month.² However, >40% of subjects ultimately discontinued GC therapy because of the lack of efficacy, intolerance, or other reasons, and the dose required to suppress eosinophilia varied widely. A more recent retrospective study of GC responsiveness in *PDGFR* mutation-negative HES demonstrated that clinical subtype was the single best predictor of the minimum GC dose required to suppress eosinophilia and symptoms.¹⁰ Although preliminary, these data suggest that alternative and/or GC-sparing therapies should be considered early in patients with M-HES or L-HES.

Imatinib mesylate is the only FDA-approved drug for the treatment of HES and has radically changed the prognosis of patients with *PDGFR*-associated disease, especially those with the *FIP1L1-PDGFR*A fusion. Response rates approach 100% in most series, and recent data suggest that imatinib therapy may be curative in some patients.¹¹ Although uncommon, imatinib resistance and severe imatinib toxicity leading to discontinuation of therapy do occur. In this setting, second-line tyrosine kinase inhibitors that target *PDGFR* should be initiated.

As a general rule, the addition of a second-line agent, most commonly hydroxyurea, IFN- α , or imatinib, should be considered for *PDGFR* mutation-negative patients with HES who require >10 mg of prednisone daily (or equivalent). Unfortunately, there is little published data to guide selection of a particular agent in this setting. Consequently, the choice of second-line therapy has traditionally been based on a combination of factors, including side effect profiles, ease of administration, and patient and/or physician preferences (Table II). A recent study of imatinib treatment in *PDGFR* mutation-negative HES found a 50% response rate in patients with M-HES

TABLE II. Conventional treatment approaches based on HES clinical subtypes

HES clinical subtype*	Secondary classification	First-line therapy	Second-line agents
Myeloid variant (11%)	<i>PDGFR</i> -associated MN Idiopathic HES with myeloid features (M-HES)* Other myeloid neoplasms presenting as HES	Imatinib GCs Varied	Other tyrosine kinase inhibitors with activity against <i>PDGFR</i> Imatinib Varied
Lymphocytic variant (11%)		GC	IFN- α Alternatives: other T-cell active therapies
Single-organ overlap (32%)	EGID EGPA Other	Topical GC, diet Systemic GC $\pm$ cyclophosphamide Varied	Systemic GC Methotrexate, azathioprine, rituximab
Associated (10%)		Treat underlying disease	
Familial (1%)		Observation	
Idiopathic (35%)		Systemic GC	Hydroxyurea or IFN- α

EGID, Eosinophilic gastrointestinal disorder; EGPA, eosinophilic granulomatosis with polyangiitis; GC, glucocorticoid; M-HES, myeloid variant hypereosinophilic syndrome; MN, Myeloid neoplasm; *PDGFR*, platelet-derived growth factor receptor.

*Percentages taken from National Institutes of Health HES cohort (n = 415) as of January 2017.

compared with 0% in those with GC-resistant HES without myeloid features, suggesting that clinical subtype is a useful predictor of imatinib response.¹¹ Although data are lacking for other second-line therapies, it would seem reasonable to preferentially select agents that have an effect on T cells, such as IFN- α or cyclosporine, for the treatment for patients with L-HES. A general approach to the use of conventional therapies for HES by clinical subtype is given in Table II.

BIOTHERAPEUTICS FOR HES

Despite the wide variety of commercially available immunomodulatory and cytotoxic agents, a significant proportion of patients with HES are treatment refractory or experience treatment-related toxicity.² Monoclonal antibodies that target eosinophils, either directly or indirectly by blocking mediators involved in eosinophil production, migration, or apoptosis, provide a promising alternative (see a recent review).¹² Although none of these agents is FDA approved for HES, several, including alemtuzumab, omalizumab, mepolizumab, and reslizumab, have been studied in patients with HES and are approved for other indications. Table III provides a summary of completed and ongoing phase 2 or phase 3 clinical trials of biologics on HES, grouped by clinical subtype.

Alemtuzumab

After 2 promising case reports of remission with alemtuzumab (anti-CD52) treatment in patients with treatment-refractory HES,^{26,27} alemtuzumab was used to treat 11 subjects with treatment-refractory idiopathic HES or CEL-NOS.²⁸ Although 10 subjects achieved complete hematologic remission, 7 subjects experienced relapse with discontinuation of therapy and 3 developed significant complications related to immunosuppression. Reinstitution of therapy was successful in some cases, but sustained remission required long-term administration.²⁹ Given the significant side effect profile associated with the long-term use of this agent, alemtuzumab is rarely used for HES.

Omalizumab

Omalizumab is FDA approved for use in asthma and chronic idiopathic urticaria and is well tolerated in most patients.

Consistent with prior studies, pooled analysis of data from 5 placebo-controlled studies of omalizumab treatment for moderate-to-severe asthma (n = 2,236) demonstrated a significant decrease in AEC in patients who received omalizumab and improved clinical outcomes with reduced AEC regardless of the therapy received.³⁰ An open-label study of 9 patients with EGID also showed a significant decrease in AEC and symptomatic improvement with omalizumab therapy, although the reduction in tissue eosinophilia failed to reach statistical significance.³¹ Finally, despite promising results from a small open-label trial of omalizumab treatment for eosinophilic esophagitis (EoE) in which 5 of 15 subjects demonstrated complete histopathologic remission and improved symptoms,³² these findings were not replicated in a placebo-controlled trial.²⁴ Of note, response in the open-label trial was associated with a normal AEC. These data suggest that omalizumab may be useful in selected patients with allergen-driven eosinophilic disease, but is unlikely to be useful in the most patients with HES.

Anti-IL-5 (mepolizumab and reslizumab)

Mepolizumab and reslizumab are humanized monoclonal antibodies to IL-5, a growth factor crucial for eosinophil maturation and activation, initially developed for use in asthma. After several small clinical trials demonstrated the efficacy of mepolizumab and reslizumab in selected patients with HES,^{16,33,34} a multicenter placebo-controlled trial of mepolizumab (750 mg intravenously [IV] monthly) was conducted in 84 GC-responsive patients with *PDGFRA*-negative HES. Mepolizumab therapy was well tolerated and had a significant GC-sparing effect with 84% of patients achieving the primary endpoint of ≤ 10 mg prednisone daily for ≥ 8 consecutive weeks.^{13,15} Of note, 3 of 7 (86%) patients with L-HES met the primary endpoint compared with 23 of 24 (96%) of those with a normal T-cell profile ($P = \text{NS}$) and a significantly lower proportion of patients with L-HES achieved an AEC $< 600/\mu\text{L}$ for the duration of the study,¹⁴ suggesting that high levels of IL-5 production by the T-cell clone may decrease drug efficacy. Although baseline IL-5 levels were not predictive of response in the trial, subjects entered the trial with AEC $< 1000/\mu\text{L}$ on prednisone and the majority had undetectable serum IL-5 levels. The GC-sparing effect of mepolizumab was sustained for up to 302 weeks (mean exposure

TABLE III. Clinical trials of biologics for the treatment of HES by clinical subtype*

HES subtype	Drug	Design	Patient population	Dose	Outcome	Reference
PDGFRA-negative HES	Mepolizumab	Ph 2 DBPC	Adults with GC-sensitive HES controlled on 20-50 mg prednisone (n = 85)	750 mg IV monthly	Met primary endpoint: proportion of subjects achieving prednisone dose ≤ 10 mg/d $\times$ 8 wk	13,14
		Ph 2 OL	Adults with GC-sensitive HES controlled on 20-50 mg prednisone (n = 78)	750 mg IV; variable frequency	N/A	15
		CUP	Prior participation in clinical trial of mepolizumab for HES OR Refractory, life-threatening HES	300 mg sc-700 mg IV; variable frequency	Ongoing	NCT00244686
	Reslizumab	Ph 3 DBPC	GC-responsive adults and children ≥ 12 y old with AEC ≥ 1000 on stable therapy (estimated n = 120)	300 mg sc monthly	Ongoing	NCT02836496
		Ph 2 OL	Adults with HES refractory to or intolerant of conventional therapy (n = 4)	1 mg/kg single dose	2 of 4 subjects had reduction in eosinophilia	16
Overlap (EGPA)	Benralizumab	Ph 2 DBPC/OL	Adults with HES and AEC ≥ 1000 despite background therapy (n = 20)	30 mg sc monthly	Recently completed	NCT02130882
	Mepolizumab	Ph 2 OL	Adults with active disease and on stable prednisolone dose > 12.5 mg for at least 1 wk (n = 7)	750 mg IV monthly	Met primary endpoint: percentage of subjects attaining remission	17
		Ph 2 OL	Adults with EGPA requiring ≥ 10 mg/d prednisone (n = 7)	750 mg IV monthly	Met primary endpoint: decreased prednisone dose at the end of treatment phase	18
		Ph 3 DBPC	Adults with relapsing probable or definite EGPA requiring ≥ 7.5 mg/d prednisone (n = 136)	300 mg sc monthly	Met coprimary endpoints: accrued duration of remission and proportion of subjects in remission at weeks 36 and 48	19
	Reslizumab	Ph 2 OL	Adults with probable or definite EGPA on ≥ 5 mg/d of prednisone (estimated n = 10)	3 mg/kg monthly	Ongoing	NCT02947945
	Benralizumab	Ph 2 OL	Adults with probable or definite EGPA on ≥ 5 mg/d of prednisone (estimated n = 10)	30 mg sc monthly	Ongoing	NCT03010436
	Rituximab	Ph3 DBPC	Adults with newly diagnosed or relapsing EGPA (estimated n = 108)	No details	Ongoing	NCT02807103
Overlap (EGID)	Mepolizumab	Ph 2/3 OL	Adults with active EoE (peak eos > 20 /hpf) (n = 4)	750 mg IV monthly $\times$ 3 doses	Reduced blood and tissue eosinophils, improved symptoms (n = 4)	20
		Ph 2 DBPC	Adults with active EoE (peak eos > 20 /hpf) (n = 11)	750 mg IV weekly $\times$ 2 doses, then monthly $\times$ 2 if no response	Reduced blood and tissue eosinophils, no change in symptoms	21

	Ph 2 DB	Children with active EoE (peak eos > 20/hpf) (n = 59)	0.55 mg/kg, 2.5 mg/kg, 10 mg/kg IV monthly × 3 doses	Reduction of tissue eosinophils, no significant effect on symptoms	22
Reslizumab	Ph 2 DBPC	Children with active EoE (peak eos > 24/hpf) (n = 226)	1-3 mg/kg monthly × 4 doses	Met one coprimary endpoint (reduction of tissue eosinophils), but symptoms improved in both drug and placebo groups	23
Omalizumab	Ph 2 OL	Adults with active EoE (peak eos > 15/hpf) and serum IgE 30-700 IU/mL who failed steroid therapy (n = 30)	0.016 mg/kg/IgE (IU/mL) every 2-4 wk × 16 wk	Did not meet primary endpoints: reduction in tissue eosinophilia and dysphagia score	24
Dectrecumab (QAX576, anti-IL-13)	Ph 2 DBPC	Symptomatic adult subjects with EoE who failed elimination diets (n = 23)	6 mg/kg IV every month × 3 mo	Did not meet primary endpoint: proportion with ≥75% reduction in tissue eosinophils	25
RPC4046 (anti-IL-13)	Ph 2 DBPC	Adult subjects with EoE with symptoms (estimated n = 100)	First dose IV, followed by low- and high-dose subcutaneous injections weekly × 16 wk, then open-label extension	Recently completed	NCT02098473
Dupilumab (anti-IL4Rα antagonist)	Ph 2 DBPC/OL	Adult subjects with EoE with symptoms (n = 47)	No details	Ongoing; enrollment complete	NCT02379052

AEC, Absolute eosinophil count; CUP, compassionate use program; DBPC, double-blind placebo-controlled; EGID, eosinophilic gastrointestinal disorder; EGPA, eosinophilic granulomatosis with polyangiitis; EoE, eosinophilic esophagitis; eos, eosinophils; GC, glucocorticoid; HES, hypereosinophilic syndrome; hpf, high power field; IV, intravenously; OL, open label; PDGFR, platelet-derived growth factor receptor; sc, subcutaneously.

*This list is based on unpublished data from a search of [ClinicalTrials.gov](https://clinicaltrials.gov) and EudraCT on August 4, 2017, using the search terms “hypereosinophilic syndrome” or “eosinophilic disorders” and includes only phase 2 and 3 clinical trials.

251 weeks) in a subsequent open-label extension.¹⁵ Although both mepolizumab (Nucala; 100 mg subcutaneously [sc] monthly) and reslizumab (Cinqair; 3 mg/kg IV monthly) are FDA approved as add-on maintenance therapy of severe eosinophilic asthma, the approved dosing is lower than that used in any of the trials in HES to date, and the treatment of HES is specifically excluded in the package inserts for both drugs.

To date, more than 200 patients with HES, including prior participants in mepolizumab trials and patients with life-threatening, treatment-refractory HES, have been enrolled in a compassionate use observational study of mepolizumab at doses ranging from 300 mg sc to 700 mg IV monthly.³⁵ This larger cohort should provide an opportunity to explore the effects of mepolizumab in GC-responsive and -refractory HES, including dosing and predictors of response. A multicenter placebo-controlled trial of mepolizumab 300 mg sc in HES has recently begun enrollment and will also begin to address some of these questions (unpublished data, <https://clinicaltrials.gov: NCT02836496>).

Mepolizumab has also been used in 2 clinical trials in patients with EGPA (including probable EGPA/overlap HES). In a pilot open-label study of monthly mepolizumab at 750 mg IV, a GC-sparing effect was observed in all 7 subjects (overall decrease in mean GC dose of 61% after 4 months).¹⁸ This prompted a multicenter placebo-controlled trial of mepolizumab (300 mg sc monthly) as a GC-sparing agent in 136 patients with EGPA.¹⁹ Both primary endpoints, total accrued weeks in remission and the proportion of patients in remission at weeks 36 and 48, were met, although 47% of mepolizumab-treated patients with EGPA never achieved disease remission. The characteristics of these patients have yet to be fully characterized, although possible explanations include contributions of noneosinophil-driven manifestations, incomplete tissue depletion of eosinophils, and inadequate dosing.

Both mepolizumab and reslizumab have been used in clinical trials in EGID. In a pilot study in 4 adult patients with treatment-refractory eosinophilic gastritis and/or enteritis and peripheral eosinophilia, single-dose reslizumab (1 mg/kg IV) led to a reduction in the AEC and symptom improvement in all 4 subjects.³⁶ In a subsequent double-blind placebo-controlled trial in 226 children with EoE, reslizumab significantly reduced esophageal eosinophilia compared with placebo at all doses tested (1, 2, and 3 mg/kg IV monthly for 4 months), but did not significantly improve symptoms over placebo.²³ Similar results were observed with mepolizumab (750 mg or 0.55–10 mg/kg IV monthly) in 3 separate studies in children and adults with EoE.^{20–22}

In summary, high-dose mepolizumab (and likely reslizumab) appears to be effective in GC-sensitive HES, including idiopathic HES, L-HES, and EGPA/HES overlap. Data on M-HES are unavailable at this time, although the compassionate use mepolizumab program likely includes patients in this subgroup. The data from studies in EGID suggest that anti-IL-5 therapy may be less effective in EoE than in other forms of HES. Potential reasons for this include incomplete tissue depletion of eosinophils, involvement of cells other than eosinophils in disease pathogenesis, and the contribution of structural abnormalities to symptoms.

Other FDA-approved monoclonal antibodies

The utility of other biologic therapies recently approved for the treatment of allergic and inflammatory conditions, including dupilumab (anti-IL4R α), brodalumab (anti-IL17R), and secukinumab (anti-IL17), in treating HES remains to be seen.

BIOTHERAPEUTICS ON THE HORIZON

Anti-IL-5R α (benralizumab)

IL-5R is expressed on mature eosinophils, mast cells, and basophils, and their precursors. It is a heterodimer composed of an α chain (unique to IL-5) and a β chain (common to IL-3R and granulocyte-macrophage colony-stimulating factor receptor). Benralizumab (anti-IL-5R α) is an afucosylated monoclonal antibody that binds the IL5R α chain, recruits natural killer cells via its F $_c$ chain, and causes eosinophil cell death by antibody-mediated cytotoxic killing. Like anti-IL-5, it was developed to treat eosinophilic asthma and has been shown in 2 multicenter placebo-controlled trials to be safe and effective in reducing asthma exacerbations and improving forced expiratory volume in 1 second.^{37,38}

There are a number of theoretical advantages and disadvantages of benralizumab therapy over anticytokine (IL-5) therapy. Theoretical advantages include the lack of interference from high IL-5 levels, targeting eosinophil precursors and complete depletion of tissue-resident eosinophils. Moreover, benralizumab may be effective in M-HES where eosinophils may be IL-5 independent, but retain IL-5R on their surface. Potential disadvantages include the observation that in untreated patients, as AEC increases, IL-5R α expression decreases, and soluble IL-5R α levels increase.³⁹ This could lead to decreased efficacy in patients with the highest AECs (ie, patients with HES). Factors that affect cytotoxic cell function, including CD16 polymorphisms, could also affect drug efficacy. Finally, although not observed in the asthma trials to date, eosinophil lysis in the setting of enhanced killing could complicate therapy in patients with high-grade eosinophilia. A double-blind, placebo-controlled trial of benralizumab for treatment-refractory HES has just completed enrollment (NCT02130882) and should help address some of these questions.

Anti-Siglec-8

Sialic acid-binding immunoglobulin-like lectin 8 (Siglec-8), an inhibitory receptor highly expressed on mature eosinophils, mast cells, and basophils, is another promising target.⁴⁰ Crosslinking of Siglec-8 with anti-Siglec antibodies induces apoptosis of human eosinophils *in vitro* that is enhanced in the presence of cytokines that normally promote eosinophil survival (including IL-5), providing a theoretical advantage to the use of such antibodies in the treatment of patients with HES.⁴¹ Siglec-8 antibody also inhibits degranulation of human mast cells,⁴¹ a potential advantage in the treatment of EGID and other HES subtypes, where tissue mast cells may be pathogenic. Two anti-Siglec-8 antibodies are currently in clinical trials: AK001, an IgG4 antibody expected to induce eosinophil apoptosis, is in a phase 2 trial for moderate-to-severe nasal polyposis (unpublished data, <https://clinicaltrials.gov: NCT02734849>) and AK002, an afucosylated antibody that both induces eosinophil apoptosis and targets cells expressing Siglec-8 for enhanced ADCC, is in a phase 1 trial for indolent systemic mastocytosis (unpublished data, <https://clinicaltrials.gov: NCT02808793>).

CONCLUSIONS

As our understanding of the mechanisms driving eosinophilia in HES increases, the approach to therapy has become increasingly complex. In this regard, novel antieosinophil biologics have the potential to be effective across HES subgroups without off-target effects. Conversely, in eosinophilic disorders in which other cells or processes play a role, clinical improvement may be

incomplete but provide insight into disease pathogenesis. Although the heterogeneous nature of the clinical presentations of HES has made the development of a uniform assessment tool challenging, complicating the endpoints for clinical trials, the future for patients with eosinophilic-associated diseases is promising as new therapeutics become available to test hypotheses suggested by clinical experience.

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