Published in final edited form as:

J Allergy Clin Immunol Pract. 2017 ; 5(6): 1502–1509. doi:10.1016/j.jaip.2017.08.001.

Biologic agents for the treatment of hypereosinophilic syndromes

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Abstract

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 interferon- α , are initially effective in reducing eosinophilia and symptoms in a majority of patients with platelet-derived growth factor (PDGFR) mutation-negative HES, 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 HES patients 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.

Keywords

Hypereosinophilic Syndrome; Monoclonal Antibody; Interleukin 5

Introduction

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 eosinophilia¹. Conventional therapies include glucocorticoids (GC), hydroxyurea, interferon- α , imatinib and other commercially available immunomodulatory and suppressive therapies. Although these agents are effective in reducing eosinophilia and controlling symptoms in many patients, resistance and drug-

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related toxicities lead to discontinuation of therapy in a significant proportion of cases². 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 pre-clinical 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, two monoclonal antibodies, mepolizumab (Nucala; GlaxoSmithKline) and reslizumab (Cinqair; Teva Pharmaceuticals), that target interleukin-5 (IL-5), the cytokine critical for eosinophil maturation and activation, recently received FDA approval for treatment of eosinophilic asthma. A third monoclonal antibody, benralizumab (AstraZeneca/MedImmune), that depletes eosinophils by binding to IL-5 receptor 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 is available and the theoretical efficacy of those that are in clinical or pre-clinical 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 (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 treatment³. 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 *FIPIL1-PDGFR*A. Other fusions and point mutations in *PDGFR*A have also been described. Defined mutations driving HES can also occur in other tyrosine kinases, including *PDGFR*B, *FGFR1*, *KIT*, and *JAK2*. Some patients have a clinical phenotype with myeloid features

similar to what was described in *PDGFRA*-positive patients prior to the discovery of *FIPIL1-PDGFRA* (see Table 2). 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 since CEL-NOS is typically treatment refractory and most often requires bone marrow transplantation.

Lymphocytic variant HES

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/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 EGID, eosinophilic fasciitis and chronic eosinophilic pneumonia, and multisystem eosinophilic disorders with a distinct clinical phenotype, such as 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}. Since most affected family members remain asymptomatic despite lifelong 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 three 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 (HE_{US} and familial HES) typically do not require therapy, but should be followed closely for evidence of progression to HES.

Systemic glucocorticoid (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 eosinophilic gastrointestinal disease (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 month². However, >40% of subjects ultimately discontinued GC therapy due to 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 (Khouri et al. *J Allergy Clin Immunol In Pract* 2017, in press). 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 *FIPIL1-PDGFR*A fusion. Response rates approach 100% in most series, and recent data suggest that imatinib therapy may be curative in some patients¹⁰. 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, addition of a second-line agent, most commonly hydroxyurea, interferon- 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/physician preferences (Table 2). A recent study of imatinib treatment in *PDGFR*-mutation negative HES found a 50% response rate in patients with M-HES compared to 0% in those with GC-resistant HES without myeloid features, suggesting that clinical subtype is a useful predictor of imatinib response¹⁰. Although data is lacking for other second-line therapies, it would seem reasonable to preferentially select agents that have an effect on T cells, such as interferon- 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 2.

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 toxicity². Monoclonal antibodies that target eosinophils, either directly or indirectly by blocking mediators involved in eosinophil production, migration or apoptosis, provide a promising alternative (see recent review)¹¹. 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.

Alemtuzumab

After two promising case reports of remission with alemtuzumab (anti-CD52) treatment in patients with treatment-refractory HES^{12,13}, alemtuzumab was used to treat 11 subjects with treatment-refractory idiopathic HES or CEL-NOS¹⁴. 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 administration¹⁵. Given the significant side effect profile associated with 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=2236) demonstrated a significant decrease in AEC in patients who received omalizumab and improved clinical outcomes with reduced AEC regardless of the therapy received¹⁶. 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 significance¹⁷. Finally, despite promising results from a small open-label trial of omalizumab treatment for eosinophilic esophagitis (EoE) in which 5/15 subjects demonstrated complete histopathologic remission and improved symptoms¹⁸, these findings were not replicated in a placebo-controlled trial¹⁹. 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^{20–22}, a multicenter, placebo-controlled trial of mepolizumab (750 mg 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 10mg prednisone daily for 8 consecutive weeks^{23,24}. Of note, 3/7 (86%) patients with L-HES met the primary endpoint compared to

23/24 (96%) of those with a normal T cell profile ($p=NS$) and a significantly lower proportion of L-HES patients achieved an $AEC < 600/\mu L$ for the duration of the study²⁵, 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 $AEC < 1000/\mu L$ 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 251 weeks) in a subsequent open-label extension (14). Although both mepolizumab (Nucala®; 100mg 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 treatment of HES is specifically excluded in the package inserts for both drugs.

To date, more than two hundred 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 300mg sc to 700mg IV monthly (Duncan et al, ATS 2015 poster; NCT00244686). 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 multi-center placebo-controlled trial of mepolizumab 300mg sc in HES has recently begun enrollment and will also begin to address some of these questions (<https://clinicaltrials.gov: NCT02836496>).

Mepolizumab has also been used in two 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)²⁶. This prompted a multicenter placebo-controlled trial of mepolizumab (300mg sc monthly) as a GC-sparing agent in 136 patients with EGPA²⁷. 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 EGPA patients never achieved disease remission. The characteristics of these patients have yet to be fully characterized, although possible explanations include contributions of non-eosinophil 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/enteritis and peripheral eosinophilia, single dose reslizumab (1 mg/kg IV) led to reduction in the AEC and symptom improvement in all 4 subjects²⁸. In a subsequent double-blind placebo controlled trial in 226 children with EoE, reslizumab significantly reduced esophageal eosinophilia compared to placebo at all doses tested (1, 2 and 3 mg/kg IV monthly for 4 months), but did not significantly improve symptoms over placebo²⁹. 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^{30–32}.

In summary, high dose mepolizumab (and likely reslizumab) appear to be effective in GC-sensitive HES, including idiopathic HES, L-HES and EGPA/HES Overlap. Data on M-HES is 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-5 receptor (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 GM-CSFR). Benralizumab (anti-IL-5R α) is an afucosylated monoclonal antibody that binds the IL5R α chain, recruits natural killer (NK) 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 two multi-center placebo-controlled trials to be safe and effective in reducing asthma exacerbations and improving FEV1^{33,34}.

There are a number of theoretical advantages and disadvantages of benralizumab therapy over anti-cytokine (IL-5) therapy. Theoretical advantages include 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 increase³⁵. This could lead to decreased efficacy in patients with the highest AECs (i.e. HES patients). 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 target³⁶. 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 HES³⁶. Siglec-8 antibody also inhibits degranulation of human mast cells³⁷, 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 Phase 2 trial for moderate to severe nasal polyposis ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02734849): NCT02734849) and AK002, an afucosylated antibody that both induces eosinophil apoptosis and targets cells expressing Siglec-8 for enhanced ADCC, is in Phase 1 trial for indolent systemic mastocytosis ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02808793): 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 anti-eosinophil 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.

Acknowledgments

This work was supported by the Division of Intramural Research, National Institute of Allergy and Infectious Disease, National Institutes of Health

Abbreviations

AEC	Absolute eosinophil count
CEL-NOS	chronic eosinophilic leukemia-not otherwise specified
CT	computer-assisted tomography
EBV	Epstein-Barr virus
EGID	Eosinophilic gastrointestinal disorders
EGPA	Eosinophilic granulomatosis with polyangiitis
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
GC	glucocorticoid
GM-CSF	granulocyte-macrophage stimulating factor
HE	hypereosinophilia
HE_{US}	hypereosinophilia of unknown significance
HES	hypereosinophilic syndrome

HIV	human immunodeficiency virus
IL	interleukin
IL-5R	IL-5 receptor
L-HES	lymphocytic variant HES
M-HES	myeloid HES
NK	natural killer cell
PDGFR	platelet-derived growth factor receptor
PET	positron emission tomography
RT-PCR	reverse transcriptase polymerase chain reaction
Siglec	Sialic acid-binding immunoglobulin-like lectin

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Table 1**Diagnostic Evaluation of Hypereosinophilia**

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, as well as 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, anti-neutrophil cytoplasmic antibodies, and HIV
Serum tryptase and B12 levels	Markedly elevated in myeloid HES. Vitamin B12 levels are elevated due to 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	

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

Adapted from Klion A "How I treat hypereosinophilic syndromes" in *Blood* (2015) 126(9) 1069–77.

Table 2

Conventional Treatment Approaches based on HES Clinical Subtypes

HES Clinical Subtype [*]	Secondary Classification	First-line therapy	Second-line Agents
Myeloid-variant (11%)	PDGFR-associated MN	Imatinib	Other tyrosine kinase inhibitors with activity against PDGFR
	IHES with myeloid features (MHES) [*]	Glucocorticoids	Imatinib
	Other myeloid neoplasms presenting as HES	Varied	Varied
Lymphocytic-variant (11%)		GC	Interferon- α . Alternatives: other T cell active therapies
Single Organ Overlap (32%)	EGID	Topical GC, diet	Systemic GC
	EGPA	Systemic GC $\pm$ cyclophosphamide	Methotrexate, azathioprine, rituximab
	Other	Varied	
Associated (10%)		Treat underlying disease	
Familial (1%)		Observation	
Idiopathic (35%)		Systemic GC	Hydroxyurea or interferon- α

^{*} Percentages taken from NIH HES cohort (n=415) as of January 2017.

Table 3

Clinical Trials of Biologics for the Treatment of HES*

HES subtype	Drug	Design**	Patient population	Dose	Outcome	Reference
<i>PDGFRA</i> -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/day × 8 weeks	23,25
		Ph 2 OL	Adults with GC-sensitive HES controlled on 20–50 mg prednisone (n=78)	750 mg iv; variable frequency	N/A	24
		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
		Ph 3 DBPC	GC-responsive adults and children 12 years old with AEC 1000 on stable therapy (estimated n=120)	300 mg sc monthly	Ongoing	NCT02836496
	reslizumab	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	20
	benralizumab	Ph 2 DBPC/OL	Adults with HES and AEC 1000 despite background therapy (n=20)	30mg sc monthly	Recently completed	NCT02130882
Overlap (EGPA)	mepolizumab	Ph 2 OL	Adults with active disease and on stable prednisolone dose > 12.5 mg for at least one week (n=7)	750mg IV monthly	Met primary endpoint: percentage of subjects attaining remission	38
		Ph 2 OL	Adults with EGPA requiring 10 mg/day prednisone (n=7)	750mg IV monthly	Met primary endpoint: decreased prednisone dose at the end of treatment phase	26
		Ph 3 DBPC	Adults with relapsing probable or definite EGPA requiring 7.5mg/day prednisone (n=136)	300mg sc monthly	Met co-primary endpoints: accrued duration of remission and proportion of subjects in remission at week 36 and 48	27
	Reslizumab	Ph 2 OL	Adults with probable or definite EGPA on 5 mg/day of prednisone (estimated n=10)	3 mg/kg monthly	Ongoing	NCT02947945
	Benralizumab	Ph 2 OL	Adults with probable or definite EGPA on 5 mg/day of prednisone (estimated n=10)	30mg sc monthly	Ongoing	NCT03010436

HE's subtype	Drug	Design**	Patient population	Dose	Outcome	Reference
	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)	750mg IV monthly × 3 doses	Reduced blood and tissue eosinophils, improved symptoms (n=4)	32
		Ph 2 DBPC	Adults with active EoE (peak eos > 20/hpf) (n=11)	750mg IV weekly × 2 doses, then monthly × 2 if no response	Reduced blood and tissue eosinophils, no change in symptoms	31
		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	30
	Reslizumab	Ph 2 DBPC	Children with active EoE (peak eos > 24/hpf) (n=226)	1 to 3 mg/kg monthly × 4 doses	Met one co-primary endpoint (reduction of tissue eosinophils), but symptoms improved in both drug and placebo groups	29
	Omaliuzumab	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 weeks × 16 weeks	Did not meet primary endpoints: reduction in tissue eosinophilia and dysphagia score	19
	Dectrecumab (QAX576, anti-IL-13)	Ph 2 DBPC	Symptomatic adult EoE subjects who failed elimination diets (n=23)	6 mg/kg IV every month × 3 months	Did not meet primary endpoint: proportion with 75% reduction in tissue eosinophils	39
	RPC4046 (anti-IL-13)	Ph 2 DBPC	Adult EoE subjects with symptoms (estimated n=100)	1 st dose IV, followed by low and high dose sc injections weekly × 16 weeks, then open label extension	Recently completed	NCT02098473
	Dupilumab (anti-IL4Rα antagonist)	Ph 2 DBPC/OL	Adult EoE subjects with symptoms (n=47)	No details	Ongoing; enrollment complete	NCT02379052

* Note: this list is based on 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.

** DB – double-blind, PC – placebo-controlled; OL – open-label, CUP – compassionate use program