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Biologics and hypereosinophilic syndromes: knowledge gaps and controversies

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Abstract

Hypereosinophilic syndromes (HES) are a heterogeneous group of disorders defined by blood and/or tissue hypereosinophilia and clinical manifestations attributable to the eosinophilia. Although various clinical subtypes of HES have been described, the general approach to therapy in all subtypes has focused on the reduction of blood and tissue eosinophilia to improve symptoms and halt disease progression. Until recently, this typically involved the use of corticosteroids and/or other immunosuppressive or cytotoxic drugs with significant toxicity. Whereas imatinib, the first targeted therapy approved for treatment of HES, has dramatically changed the prognosis of patients with primary (myeloid) forms of HES, it is ineffective in patients with other HES subtypes. For these non-myeloid patients with HES, the development of eosinophil-targeting biologics (most notably, mepolizumab, the first biologic approved for the treatment of HES) has been transformative. Nevertheless, important issues remain with respect to the efficacy and safety of these biologics in the treatment of the varied subtypes of HES. Moreover, with the increasing number of commercially available biologics with direct or indirect effects on eosinophils, questions related to the choice of initial biologic, potential reasons for biologic failure, and treatment options in the setting of incomplete response are becoming increasingly common.

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Keywords

eosinophil; mepolizumab; reslizumab; benralizumab; dupilumab; targeted therapy

Introduction

Hypereosinophilic syndromes (HES) are defined by the presence of sustained blood (>1.5 × 10^9 cells/L) or tissue hypereosinophilia (HE) and presumed or proven eosinophil-mediated organ or tissue involvement[1]. This definition encompasses a wide range of disorders, including idiopathic HES, primary myeloid neoplasms, overlap disorders (e.g., eosinophilic granulomatosis with polyangiitis (eGPA) and eosinophilic gastrointestinal disorders (EGIDs)) and secondary causes of eosinophilia (e.g., medication reactions, neoplasms, parasitic (particularly helminth) infections, and inborn errors of immunity) which can be clinically indistinguishable from idiopathic HES[2]. The diversity of disorders encompassed by this umbrella definition necessitates a staged and rational approach to diagnosis that can adapt to new mechanistic insights and diagnostic advances[3]. To this end, a consensus conference that included a wide variety of experts from different medical subspecialities proposed clinical subtypes of HES[1] (Table 1). Although imperfect, these clinical subtypes have been shown to associate with HES response to a variety of conventional and targeted therapies[4–6].

In this *Clinical Commentary*, we explore the use of biologic agents for the treatment of lymphocytic, overlap and idiopathic variants of HES in the context of a clinical case. The discussion will be divided into sections addressing the choice of initial biologic, potential reasons for biologic failure, and treatment options in the setting of incomplete response and conclude with a summary of the current knowledge gaps and unmet needs. Although the use of targeted biologics as an adjunct to definitive therapy of associated HES has been reported (e.g., in the setting of drug reaction with eosinophilia and systemic symptoms (DRESS)[8] or inborn errors of immunity[9]), this is a complex issue and beyond the scope of this review.

The general approach to therapy in HES has centered on reduction of eosinophil counts in the blood and tissues, as this tends to mirror improvement in symptoms and halt disease progression. Historically, except for associated HES, in which definitive treatment is focused on addressing the underlying condition (i.e., anthelmintic treatment for parasitic infection or chemotherapy for malignancy), glucocorticoids were the first line agent used irrespective of the clinical subtype. Although initially effective in up to 85% of patients, glucocorticoid therapy is associated with significant long-term toxicity and failure rates. Second line agents, including cytotoxic and immunosuppressive therapies, pose similar challenges with high rates of treatment interruption due to lack of efficacy and/or side effects. In myeloid HES, the identification of specific mutations driving the eosinophilia and the development of therapeutics that specifically target these mutations have dramatically altered the approach to treatment. The most striking example of this is, without doubt, *FIP1L1::PDGFRA*-positive HES, a disorder with mortality rates as high as 30% within 5 years of diagnosis despite conventional therapy, but with near 100% response rates to imatinib and cure achievable in up to 80% of patients. Although therapies targeting other drivers of myeloid HES

exist, myeloid neoplasms account for only 15–20% of HES diagnoses. Clearly, effective therapeutics with improved safety profiles are needed for patients with non-myeloid forms of HES.

Given the key role of IL-5 in the differentiation, activation, and survival of eosinophils, the first biologic therapies developed for the treatment of eosinophilic disorders targeted the IL-5/IL-5 receptor axis. Mepolizumab and reslizumab, humanized monoclonal antibodies to IL-5, bind and neutralize free IL-5 preventing interaction with its cognate receptor on eosinophils. In contrast, benralizumab, an afucosylated humanized monoclonal antibody to IL-5-receptor receptor alpha (IL-5Rα), both prevents IL-5 from binding its receptor and targets eosinophils for antibody-dependent cell cytotoxicity (ADCC). Whereas all 3 drugs are Food and Drug Administration (FDA)-approved for other indications and used off-label to treat patients with HES, only mepolizumab is currently approved for all subtypes of HES. Of note, benralizumab was shown to be effective in a phase 2 trial in patients with treatment-refractory *PDGFRA*-negative HES[7], prompting a phase 3 trial that is ongoing (NCT04191304). The availability of these, as well as newer biologics that interfere with eosinophil migration to the tissues (dupilumab, tralokinumab) and block ILC2 secretion of IL-5 (tezepelumab) is exciting and may provide additional therapeutic options for patients with HES.

Case: A 33-year-old woman presented with hypereosinophilia (HE; absolute eosinophil count (AEC) of 3.7×10^9/L, asthma, chronic rhinosinusitis with polyps (CRSwNP), aspirin exacerbated respiratory disease, intermittent rash, and biopsy-proven eosinophilic esophagitis (EoE) and gastritis (EoG). She was treated with prednisone (60 mg orally daily) and swallowed crushed budesonide (9 mg orally daily) with initial improvement, but symptoms recurred with tapering of the prednisone below 7.5 mg orally daily. Despite her initial response, her inability to taper the prednisone below 10 mg daily prompted discussion of steroid-sparing agents including clinical trial options.

Choice of an Initial Biologic

The number of eosinophil-targeting biologics that are commercially available for the treatment of eosinophil-associated disorders continues to increase (Table 2). Consequently, the question of which biologic to choose is becoming more difficult, especially in patients with HE (defined as AEC $>1.5 \times 10^9$/mL) and an eosinophilic diagnosis for which a biologic therapy other than mepolizumab is approved and potentially preferred. The above-described patient with idiopathic HES, asthma, CRSwNP, and EGID exemplifies this situation. Whereas mepolizumab is FDA-approved for the treatment of HES, has an excellent safety profile, and would appear to be the logical choice, clinical trials have failed to show efficacy of anti-IL-5 therapy (mepolizumab or reslizumab) in reducing symptoms in EoE[10] and a recent study comparing different biologics for the treatment of CRSwNP suggests that mepolizumab may be inferior to dupilumab for this indication[11]. In contrast, dupilumab is the only biologic approved for the treatment of EoE and has shown efficacy in reducing symptoms and improving pathology in phase 2 trials in EoG, but reports of blood eosinophilia and rare eosinophilic complications in patients without HE treated with dupilumab[12] raise concern for its use in patients with HES. Finally, benralizumab is

approved for asthma and showed efficacy in reducing eosinophilia and improving clinical symptoms in a phase 2 trial in HES that included 7 patients with gastrointestinal (GI) involvement[7,13] but appears to be relatively ineffective for the treatment of CRSwNP[11].

Whereas the most important consideration when choosing among biologic therapies is clearly the likelihood of a clinical response, this can be particularly difficult in patients with HES due to the variability of clinical responses in patients with different clinical subtypes and/or different patterns of organ involvement and the paucity of data addressing these issues. With respect to clinical subtype, limited data suggest that patients with myeloid HES are unlikely to respond to mepolizumab, reslizumab, benralizumab, dupilumab, or omalizumab, and that responses may be suboptimal in patients with lymphocytic variant HES[6,7,14,15]. Conversely, specific organ system involvement appears to be a major determinant of response to individual biologics in patients with HES. The most convincing data for this come from the randomized, placebo-controlled trials of mepolizumab in HES: patients with skin involvement receiving mepolizumab 750 mg intravenously (iv) monthly were less likely to achieve steroid-reduction than patients with other clinical manifestations[16] and patients with skin involvement receiving mepolizumab 300 mg subcutaneously (sc) monthly in the phase 3 trial demonstrated no improvement in HES-related symptom burden compared to those receiving placebo[17]. Although data addressing organ-specific activity of the other eosinophil-targeting biologics in patients with HES are extremely limited[15], differential effects are likely based on comparisons between existing studies of individual biologics in single organ eosinophil-associated disorders.

Unlike conventional therapies for HES, the side effect profiles of currently available biologics are excellent. Whether increased production of eosinophils in patients with HES will lead to an increase in eosinophilic complications in drugs that block eosinophil transit to the tissues (e.g., dupilumab, tralokinumab) remains to be seen. Additional factors to consider when choosing a biologic for a patient with HES include cost, convenience (i.e., route and frequency of administration), and effects on comorbid atopic disorders, such as food allergy, that may not be driven by eosinophils.

Case (continued): After completing participation in a clinical trial (Patient 5,[18]) the patient resumed prednisone monotherapy. Approximately one year later, she tapered prednisone and began benralizumab 30 mg sc monthly. This led to dramatic improvement in her sinus and pulmonary symptoms. After 3 months, the frequency of benralizumab dosing was decreased to every other month. The patient felt that her symptoms were not as well-controlled on this dose, and she complained of fatigue, hair loss and joint pain that she attributed to the biologic. Benralizumab therapy was discontinued.

Lack of Response to Biologic Treatments

There are multiple reasons for lack of response to a specific biologic treatment in a patient with HES. These include variability in pharmacokinetics or pharmacodynamics, development of anti-drug antibodies (ADA) that limit drug efficacy[19], and/or involvement of other cell types or pathways. While clinical trials report mean response data, some individuals may require higher or more frequent dosing strategies (e.g., in the case

of obesity, variable drug metabolism, or incompletely bound targets). With respect to the development of ADA, a recent systematic review and meta-analysis reported that benralizumab was associated with a higher incidence of neutralizing anti-drug antibody development in patients with asthma (5.81% with every 4 week dosing) than the other biologics studied[19]. Although data in HES is limited, 1/19 (5%) of patients receiving benralizumab in the phase 2 trial in HES developed neutralizing antibodies and clinical relapse[7], suggesting that the risks of ADA development in HES are likely to be similar to those in other disorders. Finally, in some patients with HES, cells and/or pathways other than eosinophils and IL-5 may be involved in disease pathogenesis. This is likely the case in EoE, for example, where depletion of eosinophils has proven to be insufficient in significantly reducing clinical symptoms[10] and other type 2 cytokines (including IL-4 and IL-13), and cells (such as mast cells and epithelial cells) have been implicated. In such circumstances, one could consider *adding* a different biologic (vs. switching to a different biologic), or targeting upstream factors (e.g., thymic stromal lymphopoietin (TSLP), IL-33) to address several cytokines simultaneously.

It is also important to define the goals of treatment. Beyond lowering eosinophil counts, additional outcomes such as improving patient-reported symptoms, corticosteroid reduction or withdrawal, and prevention of exacerbations need to be considered. For example, in the licensing trial for eGPA, despite sustained reduction of blood eosinophils below 0.5 $\times 10^9$/L in all but one patient receiving mepolizumab 300 mg sc monthly, only 53% experienced remission as defined by the Birmingham Vasculitis Activity Score and a prednisone dose of ≤4 mg[20]. While the goal is response across all clinical domains (i.e., super-responders), some patients may be partial responders and may warrant continued clinical treatment with a specific therapy. Lastly, it is important to ascertain whether there is active inflammation or whether symptoms may be due to tissue damage from previous eosinophilic inflammation since some manifestations such as neuropathy or cardiomyopathy can persist despite effective treatment. Finally, it is important to question whether the disease and/or symptoms are related to the HE at all.

Case (continued): Following discontinuation of benralizumab, the patient's AEC rose transiently to 0.5 $\times 10^9$/L before returning to the normal range. She reported that she felt well with minimal symptoms on only her maintenance inhaler and that both her pulmonologist and otolaryngologist concurred. She remained in remission for approximately one year at which point she began to note a gradual decline in her sense of smell and return of sinus and pulmonary symptoms. She developed recurrent GI symptoms, rash, and rhinosinusitis. AEC at this time was increased at 1.1 $\times 10^9$/L. Over the course of the next month, her symptoms worsened and her AEC rose to a peak of 4.7 $\times 10^9$/L. Endoscopy revealed eosinophilic duodenitis (>90 eosinophils/high power field). She was started on mepolizumab 300 mg sc monthly with improvement in her pulmonary and GI symptoms and resolution of peripheral eosinophilia (AEC 0.1 $\times 10^9$/L) but continued to experience loss of smell and sinusitis requiring intermittent prednisone therapy.

The Nuts and Bolts of Treatment Changes

As discussed above, the question of when to change or add a biologic depends both on the goals of treatment and the likely reason(s) for a lack of the expected response. Balancing patient expectations is also essential. Outside of clinical trials, patients may discontinue biologic therapy on their own due to a lack of perceived benefit or because of clinical symptoms attributed to the biologic. Conversely, they may inappropriately stop or taper the dose of a concomitant medication in the setting of response to the biologic. Although patients may wish to manage their condition with injections alone, it may not be practical and re-introduction or addition of non-biologics may be needed. Finally, it might not be possible to switch to a second biologic that is not covered by insurance, is unaffordable or for which there is not FDA approval for the patient's indication.

Despite the large number of studies examining real-world biologic use in asthma (reviewed in[21]), there is no consensus regarding the definition of treatment failure or when to switch or add biologics. Considering the rarity and heterogeneity of HES, it is unlikely that collection of data sufficient to inform a consensus approach is even feasible. Nevertheless, some conclusions can be drawn from existing data. Of the 121 patients sequentially enrolled in a multicenter retrospective study of off-label biologics use for the treatment of HES, 101/110 (92%) experienced some degree of clinician-defined symptomatic improvement on a biologic and 86/103 (77%) were able to taper other HES therapies[15]. As expected, the likelihood of a hematologic response (reduction of the AEC to $<1.0 \times 10^9$/L) was greatest for eosinophil targeting therapies (i.e., mepolizumab, reslizumab and benralizumab). The study population was comprised of patients with varied clinical HES subtypes (58 idiopathic, 16 lymphocytic variant, 46 overlap, and 1 myeloid) and clinical manifestations. Overall, patients with lymphocytic variant or myeloid HES were least likely to demonstrate a clinical response. In addition, some HES associated symptoms responded better to biologic therapy than other. For example, response rates were high for pulmonary symptoms (67–100% depending on the biologic, excluding alemtuzumab which did not improve pulmonary symptoms in the 2 patients treated) but negligeable for renal involvement (0–33%). Of note, 24 patients switched biologics due to lack of efficacy, of which 13 experienced clinical improvement. Although this study was limited by its retrospective design and relatively small and heterogenous patient cohort, it does suggest that switching biologics is a reasonable approach in patients receiving a biologic with a suboptimal clinical response. That said, the question of when to add a second biologic rather than switch biologics remains unanswered.

Many patients with HES have residual symptoms despite overall improvement with a given biologic therapy and maximal adjunct therapy. When the biologic most likely to be effective for the treatment of persistent symptoms in a patient with HES is less likely to suppress peripheral eosinophilia than the original biologic (e.g., dupilumab or omalizumab), dual biologic therapy provides a potential solution. Unfortunately, data on dual biologic use in HES is limited to six patients in the previously mentioned multicenter retrospective study of biologics in HES, who were reported as receiving dual biologics (mepolizumab with omalizumab, n=4; mepolizumab with benralizumab, n=1; and mepolizumab with reslizumab, n=1) with no other information provided[15], 2 patients with eGPA included

in a case series of 25 patients with severe asthma on dual biologic therapy (omalizumab with mepolizumab for 25. months and benralizumab with dupilumab for 6 months)[22], and 2 patients with HES included in a case series of patients with inflammatory or allergic diseases on dual biologics (mepolizumab with dupilumab for 24 months and omalizumab with mepolizumab for 1 month). Although no adverse events are described in any of these cases, information is limited and the potential risks of long-term blockade of multiple cell types or pathways unknown.

Conclusions and Unmet Needs

The introduction of biologics for the treatment of eosinophil-associated diseases has substantially improved therapeutic options for HES, often supplanting the need for systemic corticosteroids. To date, biologics targeting the IL-5-IL5R axis (Table 2) have an excellent safety profile. As evidenced by EoE, however, for which IL-5 directed therapies have not been effective and dupilumab has been, the immunopathophysiologies that underlie the diverse forms of HES remain poorly understood and likely differ among the various clinical subtypes of HES. The centrality of eosinophils as the targeted primary mediators of disease manifestations in some forms of HES (including eGPA) and the criticality of IL-5 in these varied disorders remain to be delineated.

As noted above in the case-based discussion, several unresolved issues remain with respect to the use of biologics in HES. Increased dosing of anti-IL5 monoclonal antibodies might be considered not only based on BMI but also on whether higher doses are needed in some forms of HES. Effects on other cells that may express IL-5 receptors[23] are unknown. Whether neutralizing antibodies against biologics develop and limit their benefits is a concern. Eosinophils are more than effectors of disease and have diverse potential roles in tissue sites and host homeostasis and responses[24,25]. Whether there may be untoward effects on homeostatic function, such as metabolism and tumor immunity[26], as a consequence of long-term eosinophil suppression remains to be monitored. Moreover, the underlying pathophysiologies of the varied disorders encompassed by the term “HES” remain poorly understood, and new insights are needed to help define the role of eosinophils in the context of these differing forms of HES.

The varied subtypes of HES are a heterogenous group of uncommon diseases linked by the presence of blood and/or tissue hypereosinophilia. Nevertheless, the role of eosinophils in the clinical manifestations of a particular type of HES may vary depending on the underlying pathophysiology necessitating different approaches when targeted therapies are used in place of broader systemic drugs, like corticosteroids. Moreover, concomitant atopic or immunologic disorders may require additional and/or alternative therapies. Many biologics that directly or indirectly affect eosinophils are already commercially available (Table 2) and more (e.g., anti-IL-33, anti-eotaxin) are in clinical development. Going forward, clinical trials and collective long term clinical experience, perhaps in the form of an HES patient registry, will be essential for several reasons, including 1) providing agents for patients with HES who do not meet requirements for already approved indications, 2) detecting unanticipated toxicities in patients with HES (eosinophilic complications with

dupilumab, for example), and 3) helping us understand the pathophysiologies of HES and HES subtypes.

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Conflict of Interest:

Drs. Klion and Khoury have no conflicts of interest to disclose.

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Abbreviations

ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
AEC	absolute eosinophil count
CRSwNP	chronic rhinosinusitis with nasal polyposis
DRESS	drug reaction with eosinophilia and systemic symptoms
EGID	eosinophilic gastrointestinal disorders
eGPA	eosinophilic granulomatosis with polyangiitis
EoE	eosinophilic esophagitis
EoG	eosinophilic gastritis
FDA	Food and Drug Administration
GI	gastrointestinal
HE	hypereosinophilia
HES	hypereosinophilic syndrome
IL	interleukin
ILC	innate lymphoid cell
PDGFRA	platelet-derived growth factor receptor alpha
SC	subcutaneously
TSLP	thymic stromal lymphopoeitin

References

1. Valent P, Klion AD, Roufosse F, Simon D, Metzgeroth G, Leiferman KM, et al. Proposed refined diagnostic criteria and classification of eosinophil disorders and related syndromes. Allergy 2023;78:47–59. [PubMed: 36207764]
2. Klion AD. How I treat hypereosinophilic syndromes. Blood 2015;126:1069–77. [PubMed: 25964669]
3. Khoury P, Bochner BS. Consultation for elevated blood eosinophils: clinical presentations, high value diagnostic tests, and treatment options. J Allergy Clin Immunol Pract 2018;6:1446–53. [PubMed: 30197068]
4. Khoury P, Abiodun AO, Holland-Thomas N, Fay MP, Klion AD. Hypereosinophilic syndrome subtype predicts responsiveness to glucocorticoids. J Allergy Clin Immunol Pract 2018;6:190–5. [PubMed: 28757367]
5. Khoury P, Desmond R, Pabon A, Holland-Thomas N, Ware JM, Arthur DC, et al. Clinical features predict responsiveness to imatinib in platelet-derived growth factor receptor-alpha-negative hypereosinophilic syndrome. Allergy 2016;71:803–10. [PubMed: 26797802]
6. Kuang FL, Fay MP, Ware J, Wetzler L, Holland-Thomas N, Brown T, et al. Long-Term Clinical Outcomes of High-Dose Mepolizumab Treatment for Hypereosinophilic Syndrome. J Allergy Clin Immunol Pract 2018;6:1518–1527.e5. [PubMed: 29751154]
7. Kuang FL, Legrand F, Makiya M, Ware J, Wetzler L, Brown T, et al. Benralizumab for PDGFRA-Negative Hypereosinophilic Syndrome. N Engl J Med 2019;380:1336–46. [PubMed: 30943337]
8. Gschwend A, Helbling A, Feldmeyer L, Mani-Weber U, Meincke C, Heidemeyer K, et al. Treatment with IL5-/IL-5 receptor antagonists in drug reaction with eosinophilia and systemic symptoms (DRESS). Allergo J Int 2022;1–8.
9. Adatia A, Allen CJ, Wald J, Richards CD, Waserman S, Nair P. Benralizumab for Prednisone-Dependent Eosinophilic Asthma Associated With Novel STAT3 Loss of Function Mutation. Chest 2021;159:e181–4. [PubMed: 34022014]
10. Dellon ES, Spergel JM. Biologics in eosinophilic gastrointestinal diseases. Ann Allergy Asthma Immunol 2023;130:21–7. [PubMed: 35738437]
11. Cai S, Xu S, Lou H, Zhang L. Comparison of different biologics for treating chronic rhinosinusitis with nasal polyps: A network analysis. J Allergy Clin Immunol Pract 2022;10:1876–1886.e7. [PubMed: 35272073]
12. Wechsler ME, Klion AD, Paggiaro P, Nair P, Staumont-Salle D, Radwan A, et al. Effect of dupilumab on blood eosinophil counts in patients with asthma, chronic rhinosinusitis with nasal polyps, atopic dermatitis, or eosinophilic esophagitis. J Allergy Clin Immunol Pract 2022;10:2695–709. [PubMed: 35636689]
13. Kuang FL, De Melo MS, Makiya M, Kumar S, Brown T, Wetzler L, et al. Benralizumab completely depletes gastrointestinal tissue eosinophils and improves symptoms in eosinophilic gastrointestinal disease. J Allergy Clin Immunol Pract 2022;10:1598–1605. [PubMed: 35283330]
14. Roufosse F, de Lavareille A, Schandené L, Cogan E, Georgelas A, Wagner L, et al. Mepolizumab as a corticosteroid-sparing agent in lymphocytic variant hypereosinophilic syndrome. J Allergy Clin Immunol 2010;126:828–835.e3. [PubMed: 20810155]
15. Chen MM, Roufosse F, Wang SA, Verstovsek S, Durrani SR, Rothenberg ME, et al. An International, Retrospective Study of Off-Label Biologic Use in the Treatment of Hypereosinophilic Syndromes. J Allergy Clin Immunol Pract 2022;10:1217–28. [PubMed: 35181548]
16. Rothenberg ME, Klion AD, Roufosse FE, Kahn JE, Weller PF, Simon H-U, et al. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. N Engl J Med 2008;358:1215–28. [PubMed: 18344568]
17. Roufosse F, Butterfield J, Steinfeld J, Bentley JH, von Maltzahn R, Kwon N, et al. Mepolizumab therapy improves the most bothersome symptoms in patients with hypereosinophilic syndrome. Front Med (Lausanne) 2023;10:1035250.

18. Panch SR, Bozik ME, Brown T, Makiya M, Prussin C, Archibald DG, et al. Dexpramipexole as an oral steroid-sparing agent in hypereosinophilic syndromes. Blood 2018;132:501–9. [PubMed: 29739754]
19. Chen M-L, Nopsopon T, Akenroye A. Incidence of Anti-Drug Antibodies to Monoclonal Antibodies in Asthma: A Systematic Review and Meta-Analysis. J Allergy Clin Immunol Pract 2023;11:1475–1484.e20. [PubMed: 36716995]
20. Wechsler ME, Akuthota P, Jayne D, Khoury P, Klion A, Langford CA, et al. Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. N Engl J Med 2017;376:1921–32. [PubMed: 28514601]
21. Shah PA, Brightling C. Biologics for severe asthma-Which, when and why? Respirology 2023;
22. Lommatzsch M, Suhling H, Korn S, Bergmann K-C, Schreiber J, Bahmer T, et al. Safety of combining biologics in severe asthma: Asthma-related and unrelated combinations. Allergy 2022;77:2839–43. [PubMed: 35585763]
23. Gorski SA, Lawrence MG, Hinkelman A, Spano MM, Steinke JW, Borish L, et al. Expression of IL-5 receptor alpha by murine and human lung neutrophils. PLoS ONE 2019;14:e0221113.
24. Wechsler ME, Munitz A, Ackerman SJ, Drake MG, Jackson DJ, Wardlaw AJ, et al. Eosinophils in Health and Disease: A State-of-the-Art Review. Mayo Clin Proc 2021;96:2694–707. [PubMed: 34538424]
25. Weller PF, Spencer LA. Functions of tissue-resident eosinophils. Nat Rev Immunol 2017;17:746–60. [PubMed: 28891557]
26. Blomberg OS, Spagnuolo L, Garner H, Voorwerk L, Isaeva OI, van Dyk E, et al. IL-5-producing CD4+ T cells and eosinophils cooperate to enhance response to immune checkpoint blockade in breast cancer. Cancer Cell 2023;41:106–123.e10. [PubMed: 36525971]

Table 1.

Clinical subtypes of HES.

Clinical Subtype of HE/HES	Definition	Comments
Myeloid	Suspected or proven eosinophilic myeloid neoplasm	*FIP1L1::*PDGFRA is the most common molecular abnormality (80%) and responds to imatinib mesylate therapy; treatment should be directed at the underlying molecular driver
Lymphocytic variant	Clonal and/or phenotypically aberrant T cell-driven	T cell production of IL-5 and other type 2 cytokines is thought to be the driver of the eosinophilia; most common aberrant phenotype is $CD3^{-}CD4^{+}$
Overlap	Single organ eosinophilic disorders and recognized/distinct eosinophilic syndromes	Examples include eosinophilic gastrointestinal disorders, eosinophilic granulomatosis with polyangiitis and eosinophilic fasciitis; therapy dictated by organ involvement
Associated	Secondary to a defined cause	Examples include parasitic infection, neoplasms, drug hypersensitivity and inborn errors of immunity. Therapy should be directed at underlying cause.
Familial	Present in multiple family members over several generations	Most cases described are autosomal dominant and associated with a benign course in the absence of therapy
Idiopathic	Meets criteria for HES and does not fit any of the other categories	Variable presentation and severity

Table 2.

Commercially available biologics that affect eosinophils

Agent	Approved Indications*	Target	Route of Administration	Frequency of Administration	Boxed warnings and eosinophil-related concerns	Efficacy Considerations
Mepolizumab	HES EGPA Asthma CRSwNP	IL-5	subcutaneous (autoinjectors available)	3 injections monthly (HES, EGPA) 3 injections monthly 1 injection monthly (asthma)	None	Likely ineffective in MHES; may have decreased efficacy in LHES and in patients with dermatologic manifestations[6,14,17]
Reslizumab	Asthma	IL-5	intravenous	1 infusion monthly	Boxed warning: anaphylaxis (0.3% of patients in placebocontrolled studies in asthma)	Little to no data in HES but likely similar to mepolizumab
Benralizumab	Asthma	IL-5R	subcutaneous (autoinjectors available)	1 injection monthly x3 months, then every 8 weeks	None	Likely ineffective in MHES; LHES patients may have increased relapse rate[7]
Omalizumab	Asthma	IgE	subcutaneous	1–3 injections every 2–4 weeks	Boxed warning: anaphylaxis (0.2% of patients in post-marketing studies); progression to EGPA has been reported in some patients with asthma	Limited data suggest poor efficacy in HES[15]
Dupilumab	Asthma CRSwNP Atopic dermatitis Eosinophilic esophagitis Prurigo nodularis	IL4R	subcutaneous (autoinjectors available)	1 injection every 1–4 weeks depending on indication	Transient increase in blood eosinophilia (peak AEC >1.50 × 10^9/L in 6.3–35.9% of patients depending on the trial) and rare, but reported, eosinophilic complications[12]	Limited data suggest some efficacy in idiopathic and overlap HES[15]
Tralokinumab	Atopic dermatitis	IL-13	subcutaneous	4 injections followed by 2 injections every 2 weeks	Transient increase in AEC to >5.0 × 10^9/L reported in 1.2% (compared to 0.3% in placebo) per package insert	No data in HES
Tezepelumab	Asthma	TSLP	subcutaneous (autoinjectors available)	1 injection every 4 weeks	None	No data in HES
Alemtuzumab	Chronic lymphocytic leukemia	CD52	intravenous	1 infusion daily	Boxed warnings: bone marrow suppression, infusion reactions, opportunistic infections	Some efficacy in LHES although relapse is common