

Approach to the Therapy of Hypereosinophilic Syndromes

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With the introduction of new diagnostic methods and treatment modalities, it has become increasingly clear that hypereosinophilic syndromes (HES) are a heterogeneous group of disorders for which a single approach to treatment is insufficient. This situation is best exemplified by the group of patients now recognized as having chronic eosinophilic leukemia (CEL) on the basis of an interstitial deletion in chromosome 4 leading to the formation of the fusion tyrosine kinase FIP1L1/PDGFRA (F/P) [1]. Typically, this subgroup of patients is refractory to corticosteroid therapy, and before the availability of the tyrosine kinase inhibitor, imatinib, had extremely high morbidity and mortality [2]. Although corticosteroid therapy remains the first-line therapy for patients fulfilling the diagnostic criteria of HES who do not have F/P-positive CEL, the choice of a second-line agent depends on a number of factors, including the type of HES, the patient's concomitant therapies and medical history, cost, and patient preference. Sequential trials of several agents alone or in combination may be necessary to optimize treatment for an individual patient. Unfortunately, some patients who have HES are unresponsive to or intolerant of all currently available agents. With the development of new therapies specifically targeting eosinophils, including monoclonal antibodies directed at interleukin-5 (IL-5), the treatment algorithm is likely to change dramatically in the next several years.

General principles of treatment

Establishing the correct diagnosis is necessarily the first step in determining appropriate treatment for patients assumed to have HES. For this

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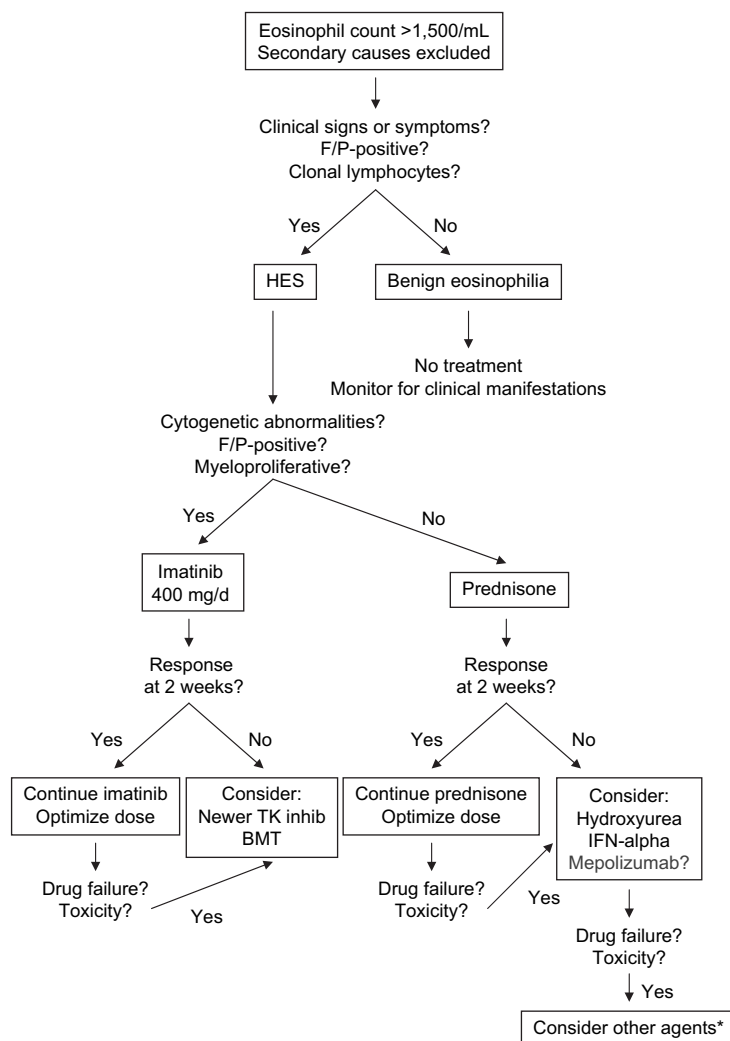
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purpose, the original diagnostic criteria of Chusid [3] continue to be useful with minor modifications. First, the patient should have a peripheral eosinophil count higher than 1500/ μ L. Although most would agree that this count should be documented on more than one occasion, a delay in treatment for the 6 months required to make the diagnosis using Chusid's criteria could prove fatal in patients who have aggressive disease, particularly those who have F/P-positive CEL. Next, secondary causes of eosinophilia, such as parasitic infection and drug hypersensitivity, should be excluded. Finally, signs and symptoms of organ involvement by eosinophilic infiltration should be demonstrated. This last criterion deserves special mention, because there are individuals who have marked eosinophilia with counts higher than 1500/ μ L sustained over many years who do not develop end-organ involvement. These individuals do not require specific therapy but should be followed closely, particularly in the first 5 years following the identification of marked eosinophilia, because the onset of signs or symptoms could herald the development of true HES. The initial evaluation of all patients who have sustained unexplained eosinophilia with counts higher than 1500/ μ L, regardless of the presence of symptoms or an abnormal physical examination, should include a bone marrow examination with cytogenetics, molecular or fluorescent in situ hybridization (FISH) testing for F/P, and assessment of lymphocyte clonality to identify occult CEL, lymphoma, or lymphocytic-variant HES (L-HES).

Regardless of the etiology of HES, the primary goal of treatment is to reduce tissue eosinophilia and eosinophil-mediated tissue damage. Although peripheral eosinophilia provides an inexpensive and accessible measure of treatment response in HES, the absolute eosinophil count does not predict reliably the extent of tissue involvement. Furthermore, some patients progress despite eosinophil counts below the 1500/ μ L threshold. A number of other potential markers of disease progression have been proposed, including serum levels of eosinophil granule proteins and surface expression of eosinophil activation markers; however, none have been validated to date. Consequently, patients need to be followed closely for clinical evidence of disease activity on therapy. In addition, because cardiac involvement may be relatively asymptomatic until irreversible damage has occurred, serial echocardiograms should be performed every 6 to 12 months in all patients. The need for and frequency of other testing, including assessment of pulmonary function and CT of the chest and/or abdomen, should be tailored to the clinical manifestations of the individual patient.

Myeloproliferative hypereosinophilic syndrome

Once the diagnosis of HES has been confirmed, it is important to identify patients who have evidence of myeloproliferative HES, because treatment for this subset of patients is markedly different from that for patients who have other types of HES (Fig. 1). For the purposes of treatment, patients



* See Table 1

Fig. 1. Treatment algorithm for HES. BMT, bone marrow transplantation; F/P, FIP1L1/*PDGFRA*; IFN, interferon; TK inhib, tyrosine kinase inhibitors.

who have myeloproliferative HES can be divided into two categories: (1) patients who have cytogenetic or molecular evidence of *PDGFRA*-associated CEL and (2) patients who have features of myeloproliferative disease of unknown etiology. Features of myeloproliferative HES include the presence of dysplastic eosinophils or eosinophil precursors on peripheral blood smear, elevated serum B₁₂ levels, anemia and/or thrombocytopenia, hepatosplenomegaly, bone marrow biopsy with increased cellularity,

myelofibrosis and/or the presence of increased numbers of spindle-shaped mast cells, and elevated serum tryptase levels [2].

Imatinib is first-line treatment for F/P-positive disease and should be considered for all HES with myeloproliferative features, because successful therapy has been reported in patients lacking the F/P mutation [1,4]. Early treatment is essential, because structural damage from endomyocardial fibrosis is irreversible [2]. Mild side effects of imatinib therapy are common but rarely lead to discontinuation of therapy. These side effects include myelosuppression, elevated transaminase levels, nausea, vomiting, edema, muscle cramps, arthralgias, diarrhea, and skin rashes. Acute eosinophilic myocarditis has been reported following initiation of imatinib therapy in three patients who had HES [4,5]. In view of this finding, it has been suggested that a screening serum troponin level be obtained before imatinib therapy in patients who have eosinophilia and that corticosteroid therapy be initiated if the serum troponin level is elevated [5]. Congestive heart failure, possibly caused by a toxic effect of imatinib on heart muscle cells, has been reported in 0.7% of 1100 patients who had chronic myeloid leukemia (CML) treated with imatinib in an international phase III study (compared with 0.9% of those taking interferon and cytarabine) [6]. This side effect seems to be most common in patients who have other cardiac risk factors, such as advanced age or a prior history of cardiac disease. Because imatinib therapy is likely to be prolonged (possibly lifelong), oligospermia has been reported in a patient receiving imatinib for HES [7], and the majority of patients who have imatinib-responsive HES are young men, male patients should be counseled to consider storing sperm before the initiation of therapy.

Because the initial response to imatinib is rapid, a failure of response to 400 mg daily after 1 to 2 weeks is indicative of drug failure. Although many patients, especially those who have the F/P mutation, ultimately respond to doses of imatinib as low as 100 mg weekly, some patients do not achieve molecular remission on low-dose therapy [8]. Furthermore, data from CML suggest that the magnitude of the molecular response is a predictor of relapse and disease progression [9]. Thus, it seems prudent to use high-dose therapy (400 mg daily) initially to achieve molecular remission and then to decrease the dose slowly while following closely for evidence of molecular relapse by reverse transcriptase polymerase chain reaction or FISH. In the author's experience, patients who are F/P negative but have features of myeloproliferative disease have a less dramatic response to imatinib and often require higher doses to maintain hematologic and clinical remission (Klion AD, unpublished data). Once the eosinophil count has decreased, repeat bone marrow examination should be performed to exclude occult leukemia in all F/P-negative patients [10].

Imatinib resistance has been reported in F/P-positive CEL [1,11]. All cases reported to date have been caused by a T6741 mutation in *PDGFR*A similar to the most common imatinib-resistance mutation in CML. Thus,

alternative tyrosine kinase inhibitors with activity against imatinib-resistant CML, including dasatinib, nilotinib, and sorafenib, are likely to be effective in F/P-positive patients and should be considered in patients who develop imatinib resistance or side effects necessitating discontinuation of imatinib therapy. The side-effect profiles of these agents are, in general, less favorable than that of imatinib and preclude their use as first-line agents. Nonmyeloablative allogeneic bone marrow transplantation has been used successfully in patients who have HES [12] and is the only curative therapy for this disease. Despite improvements in recent years, however, morbidity and mortality of the procedure itself remain a problem. Consequently, bone marrow transplantation should be reserved for patients who have progressive disease despite chemotherapy.

Idiopathic hypereosinophilic syndrome

Although corticosteroids have been used as therapy for HES for many decades and remain the first-line treatment for most patients who do not have F/P-associated disease, little is known about the most appropriate dosing regimen. An initial dose of 1 mg/kg or 40 mg/d or higher has been recommended and would seem most appropriate for patients who have evidence of severe symptoms or life-threatening complications [13]. In corticosteroid-responsive patients, symptomatic improvement and resolution of eosinophilia are extremely rapid, often occurring within 24 hours of initiation of therapy. Once a response is obtained, the dose can be decreased gradually to minimize side effects. Some patients, including those who have episodic eosinophilia and angioedema (Gleich's syndrome), can be managed with intermittent short courses of steroids.

Because corticosteroid-induced bone loss occurs early (even within the first 6 months) and can be observed in patients receiving doses as low as 5 mg/d, a baseline measurement of bone mineral density and supplementation with calcium and vitamin D is recommended for all patients for whom the duration of glucocorticoid treatment is anticipated to be 3 months or longer [14]. A bisphosphonate should be added unless contraindicated, because its efficacy in preventing and treating steroid-induced osteoporosis has been demonstrated in several large randomized, controlled clinical trials [14]. Prophylaxis against *Pneumocystis* pneumonia should be instituted for patients requiring long-term, high-dose corticosteroid therapy.

Despite a dramatic initial response to corticosteroids in the majority of patients with HES, most patients ultimately experience significant drug-related toxicities, and alternative therapies must be considered. Although a wide variety of therapies have been used to treat steroid-refractory and steroid-intolerant HES (Table 1), hydroxyurea and interferon-alpha are the most commonly used agents available for second-line therapy (for a detailed discussion, see the article by Butterfield in this issue). Of note, both hydroxyurea and interferon-alpha have a slow onset of action (1–2 weeks)

Table 1
Summary of treatment options for hypereosinophilic syndromes

Treatment	Indications	Dose	Comments
Corticosteroids	First-line therapy unless <i>PDGFRA</i> -associated	Varied	Initial dose ≥ 40 mg daily with slow taper to lowest effective dose
Hydroxyurea	Second-line therapy	1–3 g/d	Slow onset of action (1–2 weeks)
Vincristine	Consider for counts $> 100,000/\text{mm}^3$	1–2 mg intravenously	For rapid reduction of eosinophilia; not for chronic therapy
Other cytotoxic agents (including cyclophosphamide, 6-thioguanine, methotrexate, cytarabine, 2-CDA)	Consider for refractory HES unresponsive to corticosteroids, hydroxyurea, IFN- α	NA	Myeleran and 6-mercaptopurine have been consistently ineffective in published studies
IFN- α	Second-line therapy	1–2 MU/d subcutaneously	Slow onset of action (1–2 weeks); pegylated IFN- α seems to have comparable efficacy
Anti-IL-5 antibody	Research indication to date	NA	Currently unavailable except in clinical trials or for compassionate use (mepolizumab, GlaxoSmithKline [Philadelphia, PA])
Other immuno-modulatory therapy (including alemtuzumab, cyclosporine, IVIG)	Consider for refractory disease	NA	Little published data
Imatinib mesylate	First-line therapy for <i>PDGFRA</i> -associated and myeloproliferative variant; consider for other refractory disease	100–400 mg/d	With corticosteroids if cardiac involvement; not useful in lymphocytic variant
Bone marrow transplantation	<i>PDGFRA</i> -associated and imatinib-resistant F/P-negative patients who have disease progression despite aggressive therapy	NA	Nonmyeloablative

Abbreviations: HES, hypereosinophilia syndrome; IFN- α , interferon-alpha; IL-5, interleukin 5; IVIG, intravenous immunoglobulin; MU, million units; NA, not applicable.

Adapted from Klion AD, Bochner BS, Gleich GJ, et al. Approaches to the treatment of hypereosinophilic syndromes: a workshop summary report. *J Allergy Clin Immunol* 2006;117:1295.

and should not be used as single agents for severe, progressive disease. Monoclonal anti-IL-5 antibody therapy seems to be a promising alternative, particularly for steroid-responsive patients experiencing drug toxicity [15–17]; however, it is currently available only for research use.

A number of factors should be considered in the choice of second-line therapy, including cost, ease of administration, the toxicity profile, and patient preference. Hydroxyurea is an alkylating agent with cytotoxic activity on developing cells in the bone marrow. Doses used to treat HES typically range from 1 to 3 g/d. Advantages of hydroxyurea include its low cost and oral route of administration. The most common dose-limiting toxicities are hematologic (anemia, thrombocytopenia, and neutropenia) and gastrointestinal. Idiosyncratic fever reactions necessitating drug discontinuation also have been reported [18]. The major disadvantage of hydroxyurea is that monotherapy rarely achieves a complete response [19].

The utility of interferon- α in the treatment of HES has been documented in numerous case series beginning in the early 1990s [20], and sustained remissions following discontinuation of therapy have been reported [21]. A wide variety of doses and regimens have been used, with efficacy demonstrated in some cases at doses as low as 0.5 million units every other day. The major disadvantages of interferon therapy are cost, the need for subcutaneous administration, and its side effect profile, which leads to drug discontinuation in a majority of patients. The most common side effects are flulike symptoms, gastrointestinal complaints, myalgias, cytopenias, and depression. Less commonly, development or exacerbation of autoimmune phenomena, including autoimmune thyroiditis and retinopathy, can occur. Administration of hydroxyurea at low doses (500–1000 mg/d) in combination with interferon seems to potentiate the therapeutic effect and can be used in situations of dose-limiting toxicity [22]. Interferon should be avoided in patients who have a significant history of depression because it can markedly exacerbate symptoms despite antidepressant therapy.

Numerous other treatment options exist for patients who do not respond to therapy with corticosteroids (see Table 1), although which treatment, if any, is likely to be effective in a given patient is unpredictable. In general, agents with the least toxicity should be tried first. Care should be taken to start agents one at a time and to evaluate the response to one agent completely before moving on to the next. Given the favorable side-effect profile and dramatic clinical improvement in patients who respond, a short (1- to 2-week) trial of imatinib is an attractive choice for patients who have steroid-unresponsive idiopathic HES, although the likelihood of response in patients who do not have myeloproliferative features is likely to be low. Because imatinib therapy is quite expensive (approximately \$2400/mo at a dose of 400 mg/d) and is not without toxicity, therapy should be discontinued if a response is not evident within 2 weeks.

Clearly, new approaches to the therapy of HES are needed. Although a number of agents targeting cytokine and chemokine receptors on

eosinophils are in preclinical development, only monoclonal anti-IL-5 antibody has been tested in patients who have HES. Two different antibodies, mepolizumab and reslizumab, were developed independently by GlaxoSmithKline (Philadelphia, Pennsylvania) and Schering-Plough Research Institute (Kenilworth, New Jersey), respectively. Both were shown in early small clinical trials to be safe and effective in lowering blood eosinophil counts in patients who had HES [15,23]. More recently, a multicenter, randomized, double-blind, placebo-controlled trial of mepolizumab was conducted to assess the steroid-sparing effects of mepolizumab in 85 patients who had F/P-negative HES. Consistent with the results of the prior studies, mepolizumab was effective in reducing corticosteroid requirements in more than 80% of patients who had steroid-responsive, F/P-negative HES [17]. An open-label extension study is underway currently to assess long-term effects of mepolizumab in this group of patients.

Lymphocytic-variant hypereosinophilic syndrome

Although steroids are the initial treatment of choice for patients who have L-HES, there are some notable differences in the choice of a second-line agent and the approach to the monitoring of therapy in these patients as compared with patients who have true idiopathic HES. First, because clonal T cells are the primary cause of the eosinophilia in L-HES, therapies targeting eosinophils or eosinophil precursors, such as hydroxyurea and imatinib, would be expected to have little effect on the underlying cause of the disease. In fact, imatinib has been administered to several patients who had L-HES without response [24,25]. Interferon-alpha, on the other hand, has been shown to inhibit *in vitro* proliferation and IL-5 production by clonal T cells from such patients [26] and has shown clinical efficacy in this subgroup of patients. Because interferon also was found to prolong survival of CD3⁺/CD4⁺ clonal T cells in these studies, the authors suggest that interferon not be used as monotherapy in patients who have L-HES but be used in association with a proapoptotic agent, such as corticosteroids. Other agents that target T cells and/or IL-5, including cyclosporine A, alemtuzumab (anti-CD52 antibody), mepolizumab, and reslizumab (anti-IL5 antibodies) would be logical choices for therapy in patients who have L-HES refractory to corticosteroids.

Additional monitoring of therapy in L-HES should include periodic assessment for lymphadenopathy and/or increasing lymphocytosis (every 3–4 months), quantification of aberrant T cells (twice yearly), and karyotyping (yearly), because these patients can progress to lymphoma [27].

Summary

Although recent advances in the understanding of the pathogenesis of HES have altered the approach to therapy in some groups of patients,

most notably those who have myeloproliferative disease, a standardized approach to treatment is lacking for most patients who have HES, largely because HES is extremely uncommon, and patients do not present to a single subspecialty for care. As new therapies become available, well-designed, multicenter trials to address the safety and efficacy of these agents in this heterogeneous group of patients will become increasingly important.

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