

Management of Hypereosinophilic Syndromes



Florence Roufosse, MD, PhD

KEYWORDS

- Idiopathic hypereosinophilic syndrome
- *FIP1L1-PDGFR α* -associated myeloid neoplasm
- Lymphocytic variant hypereosinophilic syndrome • Corticosteroid
- Imatinib mesylate • Hydroxyurea • Interferon- α • Targeted therapy

KEY POINTS

- Clinical manifestations in a patient with persistent hypereosinophilia may be related to underlying disease, organ damage and dysfunction provoked by eosinophils, or both. Pathologic assessment is key to establishing a direct role for eosinophils in signs and symptoms, thereby defining a hypereosinophilic syndrome.
- Most patients presenting with hypereosinophilia have an underlying disease or condition driving polyclonal eosinophil expansion. Many of these conditions are treatable, and the causal relationship with hypereosinophilia is confirmed when posttreatment eosinophil counts return to normal. Corticosteroid treatment often effectively reduces eosinophil counts if the response to specific treatment is delayed or the underlying disease is untreatable.
- Clonal hypereosinophilia is infrequent but must be identified, because prognosis is poor in the absence of the therapy with the tyrosine kinase inhibitor imatinib mesylate (for *FIP1L1-PDGFR α* -positive patients), cytoreductive agents, or allogeneic stem cell transplantation.
- Idiopathic hypereosinophilic syndrome qualifies patients with persistent unexplained hypereosinophilia associated with eosinophil-mediated damage. Most patients respond to first-line corticosteroid treatment, but use of second-line agents (most commonly hydroxyurea and interferon- α) is often necessary to reduce the toxicity of long-term maintenance therapy.

INTRODUCTION

Hypereosinophilia (HE) is not uncommon, and may be discovered in a variety of settings, from the asymptomatic patient undergoing a routine checkup in the general

Disclosure Statement: F. Roufosse has received consultancy fees from GlaxoSmithKline. Department of Internal Medicine, Hôpital Erasme, Institute for Medical Immunology, Université Libre de Bruxelles, 808 Route de Lennik, Brussels 1070, Belgium
E-mail address: florence.roufosse@erasme.ulb.ac.be

Immunol Allergy Clin N Am 35 (2015) 561–575

<http://dx.doi.org/10.1016/j.iac.2015.05.006>

immunology.theclinics.com

0889-8561/15/\$ – see front matter © 2015 Elsevier Inc. All rights reserved.

practitioner's office to the patient with acute life-threatening eosinophil-mediated end-organ damage in the intensive care unit. Between these extremes, the most frequent situation is that of a symptomatic patient with signs and symptoms of organ and system involvement (eg, respiratory, cardiovascular, digestive, neurologic, cutaneous) presenting to the relevant specialist. The tasks of the physician are to determine whether the HE itself is contributing to damage and disease manifestations (thereby defining a hypereosinophilic syndrome [HES]), identify the cause of the patient's HE if possible, and finally treat the cause, deleterious hypereosinophilic state, or both.

This article proposes a practical approach to these different facets of HES management and has been designed to address questions encountered in routine practice. Most of what follows concerns the typical symptomatic hypereosinophilic patient whose life is not in immediate danger, allowing for stepwise investigations followed by initiation of adapted therapy. Management of patients with acute life-threatening disease is different, initially focusing on rapid therapeutic control of eosinophilia, and is addressed in [Table 1](#). The etiologic workup of persistent HE is covered by Ogbogu and Curtis, and novel therapies for eosinophilic disorders are addressed by Bochner, both elsewhere in this issue. Furthermore, several recent reviews discuss HES management with a more classic layout,¹⁻⁴ and complement the content of this article.

ASSESSMENT FOR THE PRESENCE OF EOSINOPHIL-MEDIATED COMPLICATIONS

Activated eosinophils are prone to infiltrate various tissues and release a wide array of mediators, inducing organ or system damage and dysfunction, as developed in detail by Weller and Akuthota elsewhere in this issue. According to the currently accepted definition, diagnosis of a HES can be proposed in the presence of documented persistent HE (ie, in routine practice: [1] blood eosinophil count greater than $1.5 \times 10^9/L$ on at least 2 occasions, ideally at minimum 1 month apart, and/or [2] tissue eosinophilia that is considered excessive by the pathologist) and organ damage or dysfunction attributable to tissue eosinophils.⁵ The major difference from previous definitions is that identification of an underlying disease responsible for HE (eg, lymphoma, parasitic infection) is no longer incompatible with a diagnosis of HES, reflecting that the deleterious effects of eosinophils on tissue may be indistinguishable, whatever the cause of HE. Indeed, an important defining feature that has been maintained over time pertains to the direct and predominant involvement of eosinophils in organ damage.

When a symptomatic patient is found to have HE, signs and symptoms may be due to an underlying disease, eosinophils, or both. Establishing that eosinophils are responsible for clinical manifestations is important in guiding therapeutic decisions, and requires a thorough and systematic evaluation that can be conducted in the outpatient clinic in most cases. Hospitalization is indicated in the presence of life-threatening complications, or if the patient is acutely ill.

A careful clinical examination and routine blood testing are crucial first steps toward the identification of signs, symptoms, and markers of organ damage and dysfunction. Findings will guide additional studies, including radiologic and isotopic imaging, endoscopies, and biopsies (see Ref.⁴ and article by Weller and Akuthota elsewhere in this issue).

Pathologic Assessment for Hypereosinophilic Syndrome

Establishing that eosinophils contribute to disease mostly relies on the ability to demonstrate their presence in damaged tissues, and all efforts should be made to do so. Biopsies and fluid sampling for cytology (eg, pleural fluid, bronchoalveolar

Table 1

General management of hypereosinophilic syndrome and treatment of acute life-threatening presentations

Condition	Recommendation	Comments
General measures		
<i>Management of specific manifestations of eosinophil-mediated damage</i>		
- Intravascular/cardiac thrombus - Embolic stroke, acute arterial occlusion - Heart failure - Structural cardiac damage (fibrosis)	- Heparin, warfarin, thrombectomy - Fibrinolysis - ACE inhibitor, diuretic - Surgery: Valve repair or replacement, thrombectomy, endocardectomy, transplantation	Eosinophilia should be controlled
<i>Prevention/treatment of complications of long-term corticosteroid treatment</i>		
- Osteoporosis - Hypertension - Diabetes - Gastritis, peptic ulcer	- Calcium, vitamin D supplementation, biphosphonates - Antihypertensive(s) - Antidiabetic(s) - Proton pump inhibitor	Bone density scan at baseline
Acute presentation with life-threatening hypereosinophilic syndrome		
- Urgent evaluation and treatment - Initial rapid evaluation	- Hospitalisation, intensive care unit - Blood sampling - Thoracic (abdominal) imaging (radiograph, CT) - Echocardiogram - Bone marrow smear/biopsy	- Stop all unnecessary medications (drug allergy, DRESS) - CBC+differential, blood smear, routine chemistry, troponin, vitamin B12, tryptase, IgE, IgG, IgM, ANCA, FISH/PCR for FIP1L1-PDGFRα, T cell phenotyping, TCR rearrangement studies - If tests suggest possible MP disease or lymphoma
- Hemodynamic instability, hypoxia - Risk of prior exposure to <i>S. Stercoralis</i>	- Inotropic support, medical treatment for heart failure, mechanical ventilation - Ivermectin 200 microg/kg 2 d	Draw blood for serology (larvae in stools, BALF)
<i>Eosinophil-lowering therapy</i>		
- First-line - CS-resistance and MP features - Very marked HE (eg, >100 G/L) - No response to above	- Prednisone 15 mg/kg IV - Imatinib mesylate 400–600 mg - Vincristine 1–2 mg/m² IV - Initiate second-line agents for HES - HLA typing	- Check for response within 4–6 h - With 1 mg/kg PDN; response within days - Few reports, mostly children; response within hours - See Table 2, idiopathic HES; eventually combination therapy - For future ASCT

Abbreviations: ACE, angiotensin-converting enzyme; ANCA, anti-neutrophil cytoplasmic antibodies; ASCT, allogeneic stem cell transplantation; BALF, bronchoalveolar fluid; CBC, complete blood count; CS, corticosteroid; CT, computed tomography; DRESS, drug reaction with eosinophilia and systemic symptoms; FISH, fluorescent in situ hybridization; HE, hypereosinophilia; HES, hypereosinophilic syndrome; HLA, human leukocyte antigen; Ig, immunoglobulin; IV, intravenous; MP, myeloproliferative; PCR, polymerase chain reaction; PDN, prednisone; Rx, treatment; TCR, T-cell receptor.

lavage, stools, ascites, urine, cerebrospinal fluid, synovial fluid) should be guided by clinical manifestations and by results of blood tests and imaging studies. The presence of eosinophils or Charcot-Leyden crystals is revealed by appropriate staining (hematoxylin-eosin, May-Grunwald-Giemsa, Wright-Giemsa). Readily accessible sites for biopsy include skin and soft tissue (eg, fascia, muscle), lungs, and the upper and lower digestive tract. Liver, kidney, peripheral nerve, and heart can also be biopsied, whereas sites less amenable to pathologic assessment include the brain, most of the small intestine, and large vessels. Hence, in a patient with multiple systemic manifestations, biopsies should first be attempted at the most accessible and safest sites.

Shortcomings of Pathology in the Evaluation of the Hypereosinophilic Patient

Biopsies for HES diagnosis may be disappointing, because of either sampling error or extensive eosinophil degranulation. For example, eosinophils infiltrating the deeper layers of the intestinal wall (submucosa, muscularis propria or serosa), will not be detected in superficial biopsies.^{6,7} Deeper (or surgical) biopsies may be more rewarding, but generally, medical imaging will show a thickened and contrast-enhanced intestinal wall; ascites may suggest serosal involvement. In a hypereosinophilic patient with abdominal complaints, these indirect signs may be considered sufficient evidence of eosinophil-mediated digestive involvement.

In other instances, eosinophils that were indeed present in a biopsied tissue may have largely degranulated before the procedure, leaving behind rare intact cells in the presence of extracellular granule proteins that escape detection by routine stains. Positive immunohistologic staining for eosinophil cationic protein (ECP), major basic protein (MBP),^{8,9} or eosinophil protein X (EPX),¹⁰ conducted by expert hands and interpreted carefully, may be sufficient to conclude that a patient has HES. However, to date it remains unknown as to how long these products remain detectable or whether their presence can be held responsible for ongoing damage, namely in a treated patient with normal blood eosinophil counts.

On the other hand, eosinophils may indeed be detected in biopsies within mixed inflammatory infiltrates, but their contribution to damage remains uncertain. For example, in bullous pemphigoid (BP), the major pathogenic mechanism consists in binding of autoantibodies to basal epidermal cells. Whether nearby eosinophils truly contribute to local damage through their procoagulant properties remains speculative.¹¹ Similarly, in eosinophilic granulomatosis with polyangiitis (EGPA), it is not clear whether necrotizing vasculitis is a direct consequence of the eosinophilia that can be observed within vessel walls or is related to antineutrophil cytoplasmic antibodies.¹² By contrast, eosinophils clearly play a role in the pulmonary infiltrates and eosinophilic cardiomyopathy that complicate the course of this disease.

Evaluation of Eosinophil-Mediated Damage Using Methods Other than Histology

It is noteworthy that, for certain eosinophil-mediated complications, highly specific abnormalities shown by imaging studies may be considered sufficient evidence for HES. Combined endothelial toxicity and procoagulant effects of activated eosinophils are responsible for characteristic damage involving the heart, brain, and blood vessels.¹³ Endomyocardial fibrosis, mitral valve entrapment and regurgitation, and intraventricular (often apical) thrombus formation detected by an echocardiogram or cardiac MRI generally obviate an endomyocardial biopsy in a hypereosinophilic patient.¹⁴ The presence of multiple bilateral ischemic brain lesions in watershed areas (best appreciated using diffusion-weighted imaging combined with MRI)¹⁵ or thrombosis of large vessels^{16,17} is also characteristic.

Are There Surrogate or Predictive Markers for Eosinophil-Mediated Damage?

It must be underlined that eosinophils are not necessarily deleterious, and it is well known that the extent and severity of organ damage are not correlated with the degree of HE. Thorough evaluation of a hypereosinophilic patient may indeed fail to show the slightest indication that eosinophils are causing damage.

To spare patients the inconvenience of invasive investigations, efforts have been made to identify markers that reliably reflect or predict eosinophil-mediated complications. A recent study has shown that expression of the activation markers CD25, CD69, and HLA-DR by eosinophils, and serum levels of eotaxin and various cytokines (interleukin [IL]-5, IL-9, IL-13, IL-17) are comparable in symptomatic patients with HES and in asymptomatic patients with persistent unexplained and uncomplicated HE (hypereosinophilia of undetermined significance, or HE_{US}).¹⁸ Serum levels of eosinophil degranulation products may be more promising markers to distinguish quiescent from activated eosinophils.¹⁹ Serum cationic proteins seem to correlate with disease severity in HES, but their quantification is challenging and unavailable in routine practice settings. Development of more reliable methods for simultaneous measurement of ECP, MBP, EPX, and eosinophil-derived neurotoxin is in progress.²⁰

DIAGNOSTIC EVALUATION OF HYPEREOSINOPHILIA

The search for an underlying cause of HE, developed in detail by Ogbogu and Curtis elsewhere in this issue, is conducted simultaneously with assessment for eosinophil-mediated damage. In most patients, an underlying disease or condition (eg, drug allergy, parasitic infections, or cancer) is found after clinical examination and a limited series of relatively routine investigations. When these first-line investigations are negative, further testing is warranted. Diagnostic evaluation of HE is therefore conducted in a stepwise manner, first ruling out more common causes, then pursuing with more elaborate second-line tests to detect rare but specific treatable conditions such as *FIP1L1-PDGFR α* -associated myeloid neoplasms. The requirement for bone marrow biopsy with cytogenetic testing is guided by results of first-line investigations. Indications include the presence of myeloproliferative features or T-cell abnormalities (clonality, aberrant phenotype), to rule out a (chronic) myeloid neoplasm or T-cell lymphoma.

Establishing a Link Between a Given Condition or Disease and Hypereosinophilia

Identification of certain causes of HE is straightforward and can be achieved rapidly and unequivocally. For example, the presence of numerous *Strongyloides stercoralis* larvae in stools from a patient who has traveled to an endemic area and has typical digestive, respiratory, and cutaneous complaints indicates an active parasitic infection causing HE. This finding should put an end to diagnostic evaluations and prompt anthelmintic therapy with subsequent evaluation for therapeutic success. Likewise, detection of a CHIC2 deletion by fluorescent in situ hybridization and/or a *FIP1L1-PDGFR α* fusion by polymerase chain reaction in blood or bone marrow of a hypereosinophilic patient is sufficient for diagnosis of myeloid neoplasm and initiation of imatinib mesylate (IM) before irreversible damage occurs.

In other situations, the cause of HE can be inferred from a characteristic clinical presentation with a high degree of certainty. Development of a generalized rash associated with fever and elevated liver enzymes in a patient who has recently initiated anticonvulsant therapy is more than likely to represent drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.²¹ Five to 8 weeks after the incident, a

positive lymphocyte transformation test in the presence of the drug in soluble form will help identify the offending agent in most cases.^{22,23}

In many instances, however, etiologic workup leads the clinician to hypothesize that a given condition could be driving HE, and proving this assumption may take some time. Trichinellosis, for example, may present with largely nonspecific clinical manifestations, and resolve spontaneously over a variable period of time. A positive serology does not necessarily indicate an active infection, but in the absence of an alternative diagnosis for a symptomatic hypereosinophilic patient, treatment for trichinellosis should be administered, with subsequent evaluation to ensure that eosinophils have dropped durably and symptoms have disappeared. The time frame for normalization of eosinophil counts remains undefined, but may be months to years. Similarly, in patients with drug allergy, it may take weeks or months for HE to regress after drug withdrawal.

In conditions where HE is an uncommon complication, the clinician should also refrain from drawing hasty conclusions. For example, the discovery of lung cancer during etiologic workup may or may not be related to HE. The presence of abundant eosinophils within the tumor biopsy may suggest a causal role, which will only be confirmed if curative surgery²⁴ or successful chemotherapy/radiotherapy is followed by normalization of eosinophil counts (or if normal counts are maintained in a patient who received prior corticosteroid treatment). Investigating the production of eosinophilopoietic/eosinophilotactic factors, such as IL-5 or granulocyte-macrophage colony stimulating factor by tumor cells, is not feasible in routine practice.²⁴

An increasingly common diagnostic shortcut is taken when abnormal T-cell phenotyping and T-cell receptor (TCR) gene rearrangement studies are misinterpreted, leading to the erroneous diagnosis of lymphocytic variant HES (L-HES).^{25,26} First, T-cell lymphoma should be suspected and investigated thoroughly in these circumstances. Second, the relevance of abnormal phenotypes should be explored with the help of clinicians and biologists with expertise. Only the CD3⁺CD4⁺ T-cell subset has repeatedly been shown to overproduce IL-5 in vitro, clearly establishing a direct role in eosinophil expansion.²⁷ For other phenotypes (eg, CD3⁺CD4⁺CD7⁺, CD3⁺TCR α/β ⁺CD4⁺CD8⁺), or in the presence of an isolated clonal TCR gene rearrangement pattern, production of eosinophilopoietic cytokines should be demonstrated before concluding that the patient has L-HES.

TREATMENT OF HYPEREOSINOPHILIC SYNDROMES ASSOCIATED WITH A KNOWN UNDERLYING CONDITION

In most situations where HE is reactive (secondary) and judged deleterious, systemic corticosteroid therapy represents the most effective and rapid means of reducing eosinophils. By contrast, primary HE that can accompany various myeloid neoplasms (including *FIP1L1-PDGFR α* -associated disease) is typically corticosteroid resistant, and treatment should target the underlying hematologic disorder or cytogenetic abnormality.

Decision on Whether to Treat the Underlying Condition, the Hypereosinophilia, or Both

Once a disease causing HE has been identified and a role for eosinophils in at least part of the clinical manifestations has been established, the most appropriate therapeutic strategy must be adopted. In practice, eradicating HE by treating the underlying condition is a logical, but not always applicable, strategy. Indeed, the condition itself may or may not warrant treatment; if treated, a response may be observed more or less rapidly, if at all. Furthermore, HE per se may or may not jeopardize the function of target organs in the short term; in the latter case, signs and symptoms may or may not be tolerable. Sometimes, the therapeutic agent(s) used to treat the underlying

disease may also be effective in reducing eosinophilia. Whether to specifically treat HE in a specific situation is guided by these considerations, as illustrated in the following paragraphs describing the approach to selected clinical conditions.

Situations whereby the underlying condition is the major focus of treatment include most infections (eg, helminth infection, scabies) and cancer. Successful treatment using agents that have no direct effect on eosinophils typically results in resolution of HE and accompanying HES.²⁴ If treatment fails (eg, metastatic lung cancer refractory to chemotherapy), management of the HES with corticosteroids may improve the patient's quality of life.²⁸

The approach to drug allergy depends on the clinical presentation and the complexity of comorbidities and their treatment. Patients with severe, potentially life-threatening complications of HE, such as DRESS syndrome, cardiomyopathy, or pulmonary hypersensitivity, should be hospitalized for surveillance and treatment. Certain drugs are more likely culprits than others (eg, antiepileptics, sulfonamides, allopurinol, clozapine), and should be withdrawn in all cases. Systemic corticosteroid treatment may accelerate eosinophil apoptosis and clearance from target organs, although this strategy may increase the risk of infectious complications.²⁹ For less severe drug reactions in patients on multiple medications, there is time for sequential withdrawal and/or replacement by compounds with different chemical compositions while verifying the impact on blood eosinophil levels. The use of drugs considered essential to the well-being of a patient and causing asymptomatic HE may eventually be pursued, provided eosinophil-mediated complications are monitored.

Other instances in which it is justified to withhold therapy directed against the condition causing HE include disorders for which treatment has an unacceptable risk/benefit balance or is nonexistent. For example, Wells syndrome with marked eosinophilia and flame figures in a skin biopsy was the presenting feature of nodal B-cell lymphocytic lymphoma in an elderly patient.³⁰ Because of her age and the indolent nature of the hematologic disease, lymphoma was not treated, and her debilitating eosinophil-mediated cutaneous condition responded well to oral corticosteroids. Another more complex example is that of a young patient with congenital CARD9 deficiency complicated by invasive *Trichophyton rubrum* infection, who developed marked and persistent HE as the infection progressed, with abundant subcutaneous eosinophilic infiltrates and marked pruritus (Roufousse F, unpublished observation, 2013). Elevated eosinophil counts were observed in 9 of 10 patients with CARD9 mutations and dermatophytosis, including this patient,³¹ suggesting that eosinophil expansion may result from deficient CARD9 signaling or a T-helper 2 polarized immune response to fungal invasion. No treatment is currently available for this congenital immunodeficiency, and the benefits of treating HE must be weighed carefully against the risk of further impairing the immune response.

Finally, certain autoimmune or T-cell-driven disorders associated with HE require immunosuppressive or cytotoxic therapy that also targets eosinophils. Examples include T-cell lymphoma, BP, inflammatory bowel disease, and graft-versus-host disease. Recurrence of HE may herald a disease flare. Management of EGPA has been reviewed recently³² and is not covered herein.

Specific Management of Myeloid Neoplasms

Most cases of myeloid neoplasm are associated with the *FIP1L1-PDGFR*A fusion gene. Because this represents a particularly aggressive form of chronic HE, with high rates of morbidity and mortality,³³ treatment is mandatory, regardless of the clinical presentation. The tyrosine kinase inhibitor (TKI) IM is approved by the Food and Drug Administration for this indication, and is used as first-line treatment because practically all patients respond³⁴ (Table 2). Eosinophil counts typically drop within

Table 2
Management of hypereosinophilic syndrome (HES) variants

Condition	Recommendation	Comments
<i>Eosinophil-lowering therapy</i>		
<i>Idiopathic HES</i>		
- Initial therapy - Second-line agents (for CS-resistant patients or those with unacceptable CS-toxicity)	- PDN 1 mg/kg/d - Hydroxyurea, up to 2 g/d - IFNα, 1–2 10^6 U/2d; then increase to 10–14 10^6 U/wk - Imatinib mesylate 400–800 mg/d - Mepolizumab 750 mg IV monthly^b - Alemtuzumab 30 mg IV or sc, 3/wk - Other agents	- Dose can be lower if symptoms mild; RR 85% - Response within 2 wk; taper to lower maintenance dose - Progressive dosing to reduce flu-like symptoms; side effects often dose-limiting; Pegylated-IFN possible option - Most effective in CS-refractory patients and/or with MP features - RR 84% if CS-responsive; not commercialised (compassionate use) - Only for very severe cases; induces marked immunosuppression - Case reports: CSA, MTX, CTX, ARA-C, 2CDA, VCR, fludarabine
Treatment-refractory severe HES	ASCT	Only curative treatment for HES
<i>FIP1L1-PDGFRα+ CEL</i>		
- Initial therapy - Cardiac involvement present - Maintenance - Imatinib-resistance (primary or secondary)	- Imatinib mesylate 100–400 mg/d - PDN 0.5–1 mg/kg/d for first 1–2 wk - Imatinib mesylate 100 mg/d - Expert referral, HLA-typing - Alternative TKI, ASCT	- Eosinophil counts decrease within days in almost all cases Goal: molecular remission (within weeks to months) - To prevent acute heart failure - Lower dosing may be effective (100 mg/wk) - High morbidity/mortality; at risk for blastic transformation - Durable response toTKI unlikely

Lymphocytic variant HES

- | | | |
|----------------------------------|--|---|
| • Initial therapy | • PDN 0.5–1 mg/kg/d then taper | • High RR (90%); maintenance often 10–25 mg/d |
| • Second-line agents | • IFN α : see idiopathic HES | • High RR (87%); acts on eosinophils and pathogenic T cells |
| | • CSA 2–5 mg/kg/d | • Adapt dose to trough (response rate may be >50%) |
| | • Mepolizumab 750 mg IV monthly ^b | • RR equivalent to idiopathic HES |
| • Progression to T cell lymphoma | • (R-)CHOP, ASCT | • Poor response to classical chemotherapy |

Follow-Up^a

Idiopathic HES	3–4 mo	Monitoring of disease activity ^c and iatrogenic complications
	6 mo	Once disease has been stabilised with Rx for 18–24 mo
FIP1L1-PDGFR α myeloid neoplasm	3 mo	See above + Cytogenetic remission (FISH or PCR)
	6 mo	Once cytogenetic remission has been maintained 18–24 mo
Lymphocytic variant HES	3–4 mo	See above + T cell phenotyping, abs T cell counts; FDG-PET if
	6 mo	new or evolving lymph node enlargement ^d

Abbreviations: 2CDA, cladribine; ARA-C, cytarabine; ASCT, allogeneic stem cell transplantation; CEL, chronic eosinophilic leukemia; CS, corticosteroid; CSA, cyclosporin A; CTX, cyclophosphamide; FDG, ¹⁸F-fluorodeoxyglucose; FISH, fluorescent in situ hybridization; IFN- α , interferon- α ; MP, myeloproliferative; MTX, methotrexate; PCR, polymerase chain reaction; PDN, prednisone; (R-)CHOP, (rituximab-) cyclophosphamide-hydroxydaunorubicin-vincristine-prednisone; RR, response rate; TKI, tyrosine kinase inhibitor; VCR, vincristine.

^a Patient must first be stabilised with treatment; during this period and depending on the presentation, the interval between visits is shorter (daily, weekly, monthly).

^b Recent studies in asthma show efficacy of sub-cutaneous and lower dosing regimens.

^c Eosinophil counts, chemistry for relevant target organs (troponin, liver enzymes), physical examination, and eventual functional/imaging studies as appropriate.

^d Increased hypermetabolism of lymph nodes, spleen may suggest progression to lymphoma.

days, and clinical manifestations of reversible damage regress, but disappearance of the *FIP1L1-PDGFR*A fusion gene (ie, the goal of therapy) typically takes longer.³⁴ Remission can then be maintained with a lower dose^{34,35} with regular monitoring for molecular relapse. Tolerance is generally excellent, and patients are often maintained in molecular remission for years with continuous treatment. Recent data show that some patients remain in remission even after prolonged interruption of IM,³⁴ suggesting they may be cured.

Rare cases of *FIP1L1-PDGFR*A-associated myeloid neoplasm with primary or secondary resistance to IM have been reported, and switching to other TKIs (nilotinib, ponatinib, sorafenib) should be attempted, although chances of success are lower.^{1,36–38} Such patients should be referred to centers with expertise for allogeneic stem cell transplantation (ASCT).³⁹

In a small proportion of patients with persistent HE, a chromosomal rearrangement other than the *FIP1L1-PDGFR*A fusion is identified or bone marrow blasts are increased (remaining <20%). These patients meet criteria for chronic eosinophilic leukemia (CEL),⁵ and should also be referred for appropriate management. Patients with less common rearrangements involving *PDGFR*A or *PDGFR*B and various fusion partners may respond extremely well to IM.^{40,41}

SPECIFIC MANAGEMENT OF LYMPHOCYTIC VARIANT HYPEREOSINOPHILIC SYNDROME

L-HES is an indolent and benign lymphoproliferative disorder that generally responds to oral corticosteroid therapy.⁴² However, patients often require second-line agents for corticosteroid-sparing purposes (see [Table 2](#)). Interferon- α ,⁴² mepolizumab,⁴³ and cyclosporin A⁴² are the most effective, and isolated responses to hydroxyurea and alemtuzumab have been reported. Modalities for administering these agents are discussed in the section on idiopathic HES.

It is essential that patients with L-HES be monitored for the development of peripheral T-cell lymphoma, as malignant progression may be observed, generally after several years of stable disease.^{27,42} However, the existence of enlarged hypermetabolic lymph nodes should not be interpreted as evidence for malignancy, as this is relatively frequent in L-HES during the benign phase.⁴² New or enlarged lymph nodes developing during treatment should be biopsied to detect lymphoma. Patients who do develop lymphoma generally fail to respond to conventional chemotherapy with CHOP (cyclophosphamide-hydroxydaunorubicin-vincristine-prednisone)-like regimens, but can be cured by ASCT.⁴⁴

TREATMENT OF SYMPTOMATIC AND UNEXPLAINED HYPEREOSINOPHILIA

From a practical standpoint, when eosinophil-mediated organ damage or dysfunction occurs in the absence of a detectable cause or condition associated with HE (ie, idiopathic HES, including organ-restricted eosinophilic disorders), eosinophil-targeted treatment is justified to control symptoms, restore vital organ function, and prevent further deterioration with development of irreversible damage. Although controlling eosinophilia is the therapeutic end point, eosinophils need not necessarily be strictly maintained within the normal range, and the benefits of tighter eosinophil control must be weighed against iatrogenic complications of therapy. Indeed, idiopathic HES is a chronic inflammatory disease, and with the exception of ASCT none of the current treatment options are curative, so they must be administered on a long-term basis.

Several agents are available for treatment of idiopathic HES, as discussed here and in [Table 2](#). To limit toxicity and improve tolerance, treatment should be tapered

progressively to the lowest effective dose once remission is achieved. Disease activity may fluctuate spontaneously, so it is worthwhile to repeatedly attempt dose tapering after an initial failure to control disease with low-dose treatment. Combination therapy with 2 or more agents may allow further dose reductions and decrease toxicity. Notwithstanding these precautions, regular monitoring for treatment-induced toxicity is essential, with implementation of preventive and therapeutic measures as appropriate (see [Table 1](#)).

Corticosteroid Treatment

First-line treatment with an oral corticosteroid is effective in most cases.⁴⁵ Initial prednisone (PDN) dosing depends on the severity of clinical manifestations and is generally between 20 and 60 mg/d. Eosinophil counts may drop within hours, and when clinical remission is achieved treatment can be tapered progressively. Some patients with organ-restricted disease such as eosinophilic gastroenteritis, chronic eosinophilic pneumonia, or Wells syndrome experience prolonged remissions after corticosteroid withdrawal, whereas others flare within days or weeks and require prolonged maintenance treatment. Most patients with multisystem HES also require continuous treatment, with a median daily maintenance dose of PDN of 10 mg.⁴⁵

In the absence of an initial response to corticosteroid, higher doses can be administered (eg, 15 mg/kg/d intravenously), but this approach is unlikely to produce a durable decrease in eosinophils, and a second-line agent should be considered without delay. Patients less likely to respond to corticosteroid include those with features of myeloproliferative disease (high serum vitamin B12 and/or tryptase levels, anemia, thrombocytopenia, circulating leukocyte precursors, organomegaly, bone marrow fibrosis).

Corticosteroid-Sparing Agents and Second-Line Treatment

Patients who fail to respond to corticosteroid or those who experience significant toxicity with maintenance treatment (PDN >10 mg/d) require second-line agents, most of which were inspired from the treatment of chronic myeloproliferative neoplasms (see [Table 2](#)).

The most commonly used and least expensive agent for idiopathic HES is hydroxyurea. A prospective study showed that initial combination therapy with relatively high doses of PDN (1 mg/kg) and hydroxyurea (2 g) controlled disease in 15 of 15 patients; remission was maintained with hydroxyurea alone (0.5–1 g/d) after progressive tapering of both compounds.⁴⁶

Interferon- α is a more expensive and less well tolerated alternative for patients who do not respond to corticosteroids and hydroxyurea. Roughly half of patients with HES respond, but treatment is often interrupted because of poor tolerance.⁴⁵ Besides flu-like symptoms, side effects that should be monitored include depression, hepatotoxicity, autoimmunity, and thyroid gland dysfunction. Pegylated interferon may have equivalent efficacy and be better tolerated, and has been used both as switch-over treatment from nonpegylated forms of interferon- α and as initial treatment.⁴⁷

IM is a second-line alternative for corticosteroid-refractory patients and those with features of chronic myeloproliferative disease.⁴⁸ Although rare cases have been reported with a dramatic and rapid response, most patients with idiopathic HES fail to respond at all, and those who do generally require higher doses⁴⁹ (and more time) to respond than those with *FIP1L1-PDGFR α* -positive disease. Dose-related side effects include rash, cytopenias, fluid retention, and hepatotoxicity. The very few data available for other TKIs is not promising.⁵⁰

Case reports mention use of various immunosuppressive and cytotoxic agents (see [Table 2](#)) to treat idiopathic HES, with variable results. One study showed a high response rate to the monoclonal anti-CD52 antibody, alemtuzumab, in 10 of 12 patients with severe refractory disease (9 idiopathic HES, 3 CEL with abnormal cytogenetics), but treatment had to be repeated and was associated with opportunistic infections and secondary malignancy.⁵¹

Novel monoclonal antibodies directed against IL-5, such as mepolizumab,⁵² or its receptors, such as benralizumab, are extremely promising for idiopathic HES, as developed by Bochner elsewhere in this issue, but are not yet approved for use other than in the setting of investigational trials.

Finally, ASCT is an option for patients with treatment-refractory and life-threatening HES. Reduced intensity conditioning regimens have been administered successfully to patients with significant disease-related morbidity.⁵³

SUMMARY AND FUTURE CONSIDERATIONS

With the recognition more than 40 years ago that chronic HE could be deleterious and the subsequent identification of pathogenic mechanisms underlying HE in specific disease variants, management of patients has improved significantly, resulting in less morbidity and better survival. However, because most available therapeutic agents for HES deplete eosinophils through nonspecific mechanisms, long-term iatrogenic toxicity and treatment-refractory disease remain subjects of concern. This situation reflects gaps in our current understanding of pathogenesis in most cases, most obviously for idiopathic HES but also for L-HES, in which the underlying T-cell disorder remains poorly characterized.

Future developments toward tailored therapy and better patient outcome include (1) identification of biomarkers that would reliably distinguish harmful from innocuous eosinophils, to avoid overtreating some patients; (2) identification of biomarkers that reflect ongoing eosinophil-mediated damage, to adapt treatment to disease activity; (3) wider access to more targeted eosinophil-specific agents currently in development for asthma, such as anti-IL-5 (receptor) antibodies, and others (see article by Bochner elsewhere in this issue); and (4) further understanding of molecular mechanisms and perturbed signaling pathways driving eosinophilia, for the development of therapy targeting upstream triggers of disease.

REFERENCES

1. Cogan E, Roufosse F. Clinical management of the hypereosinophilic syndromes. *Expert Rev Hematol* 2012;5(3):275–89.
2. Simon HU, Klion A. Therapeutic approaches to patients with hypereosinophilic syndromes. *Semin Hematol* 2012;49(2):160–70.
3. Klion A. Hypereosinophilic syndrome: current approach to diagnosis and treatment. *Annu Rev Med* 2009;60:293–306.
4. Klion A. How I treat hypereosinophilic syndromes. *Blood* 2015. [Epub ahead of print].
5. Valent P, Klion AD, Horny HP, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. *J Allergy Clin Immunol* 2012;130(3):607–12.
6. Mungan Z, Attila T, Kapran Y, et al. Eosinophilic jejunitis presenting as intractable abdominal pain. *Case Rep Gastroenterol* 2014;8(3):377–80.
7. Talley NJ, Shorter RG, Phillips SF, et al. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. *Gut* 1990;31(1):54–8.

8. Cantarini L, Volpi N, Carbotti P, et al. Eosinophilia-associated muscle disorders: an immunohistological study with tissue localisation of major basic protein in distinct clinicopathological forms. *J Clin Pathol* 2009;62(5):442–7.
9. Wright BL, Leiferman KM, Gleich GJ. Eosinophil granule protein localization in eosinophilic endomyocardial disease. *N Engl J Med* 2011;365(2):187–8.
10. Nair P, Ochkur SI, Protheroe C, et al. The identification of eosinophilic gastroenteritis in prednisone-dependent eosinophilic bronchitis and asthma. *Allergy Asthma Clin Immunol* 2011;7(1):4.
11. Marzano AV, Tedeschi A, Berti E, et al. Activation of coagulation in bullous pemphigoid and other eosinophil-related inflammatory skin diseases. *Clin Exp Immunol* 2011;165(1):44–50.
12. Khoury P, Grayson PC, Klion AD. Eosinophils in vasculitis: characteristics and roles in pathogenesis. *Nat Rev Rheumatol* 2014;10(8):474–83.
13. Roufosse F. L4. Eosinophils: how they contribute to endothelial damage and dysfunction. *Presse Med* 2013;42(4 Pt 2):503–7.
14. Kleinfeldt T, Nienaber CA, Kische S, et al. Cardiac manifestation of the hypereosinophilic syndrome: new insights. *Clin Res Cardiol* 2010;99(7):419–27.
15. Grigoryan M, Geisler SD, St Louis EK, et al. Cerebral arteriolar thromboembolism in idiopathic hypereosinophilic syndrome. *Arch Neurol* 2009;66(4):528–31.
16. Todd S, Hemmaway C, Nagy Z. Catastrophic thrombosis in idiopathic hypereosinophilic syndrome. *Br J Haematol* 2014;165(4):425.
17. Ponsky TA, Brody F, Giordano J, et al. Brachial artery occlusion secondary to hypereosinophilic syndrome. *J Vasc Surg* 2005;42(4):796–9.
18. Chen YY, Khoury P, Ware JM, et al. Marked and persistent eosinophilia in the absence of clinical manifestations. *J Allergy Clin Immunol* 2014;133(4):1195–202.
19. Confalonieri M, Tacconi F, De Amici M, et al. Benign idiopathic hypereosinophilia: a feeble masquerader or a smouldering form of the hypereosinophilic syndrome? *Haematologica* 1995;80(1):50–3.
20. Makiya MA, Herrick JA, Khoury P, et al. Development of a suspension array assay in multiplex for the simultaneous measurement of serum levels of four eosinophil granule proteins. *J Immunol Methods* 2014;411:11–22.
21. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: part I. Clinical perspectives. *J Am Acad Dermatol* 2013;68(5):693.e1–14.
22. Jurado-Palomo J, Cabanas R, Prior N, et al. Use of the lymphocyte transformation test in the diagnosis of DRESS syndrome induced by ceftriaxone and piperacillin-tazobactam: two case reports. *J Investig Allergol Clin Immunol* 2010;20(5):433–6.
23. Kano Y, Hirahara K, Mitsuyama Y, et al. Utility of the lymphocyte transformation test in the diagnosis of drug sensitivity: dependence on its timing and the type of drug eruption. *Allergy* 2007;62(12):1439–44.
24. Pandit R, Scholnik A, Wulfekuhler L, et al. Non-small-cell lung cancer associated with excessive eosinophilia and secretion of interleukin-5 as a paraneoplastic syndrome. *Am J Hematol* 2007;82(3):234–7.
25. Christoforidou A, Kotsianidis I, Margaritis D, et al. Long-term remission of lymphocytic hypereosinophilic syndrome with imatinib mesylate. *Am J Hematol* 2012;87(1):131–2.
26. d'Elbee JM, Parrens M, Mercie P, et al. Hypereosinophilic syndrome—lymphocytic variant transforming into peripheral T-cell lymphoma with severe oral manifestations. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2013;116(3):e185–90.
27. Roufosse F, Cogan E, Goldman M. Lymphocytic variant hypereosinophilic syndromes. *Immunol Allergy Clin North Am* 2007;27(3):389–413.

28. Lo CH, Jen YM, Tsai WC, et al. Rapidly evolving asymptomatic eosinophilia in a patient with lung adenocarcinoma causes cognitive disturbance and respiratory insufficiency: case report. *Oncol Lett* 2013;5(2):495–8.
29. Funck-Brentano E, Duong TA, Bouvresse S, et al. Therapeutic management of DRESS: a retrospective study of 38 cases. *J Am Acad Dermatol* 2015;72(2):246–52.
30. Spinelli M, Frigerio E, Cozzi A, et al. Bullous Wells' syndrome associated with non-Hodgkin's lymphocytic lymphoma. *Acta Derm Venereol* 2008;88(5):530–1.
31. Lanternier F, Pathan S, Vincent QB, et al. Deep dermatophytosis and inherited CARD9 deficiency. *N Engl J Med* 2013;369(18):1704–14.
32. Greco A, Rizzo MI, De Virgilio A, et al. Churg-Strauss syndrome. *Autoimmun Rev* 2015;14(4):341–8.
33. Vandenbergh P, Wlodarska I, Michaux L, et al. Clinical and molecular features of FIP1L1-PDGFRA (+) chronic eosinophilic leukemias. *Leukemia* 2004;18(4):734–42.
34. Legrand F, Renneville A, Macintyre E, et al. The spectrum of FIP1L1-PDGFR α -associated chronic eosinophilic leukemia: new insights based on a survey of 44 cases. *Medicine* 2013;92(5):e1–9.
35. Helbig G, Moskwa A, Hus M, et al. Durable remission after treatment with very low doses of imatinib for FIP1L1-PDGFR α -positive chronic eosinophilic leukaemia. *Cancer Chemother Pharmacol* 2011;67(4):967–9.
36. Savage N, George TI, Gotlib J. Myeloid neoplasms associated with eosinophilia and rearrangement of PDGFRA, PDGFRB, and FGFR1: a review. *Int J Lab Hematol* 2013;35(5):491–500.
37. Metzgeroth G, Erben P, Martin H, et al. Limited clinical activity of nilotinib and sorafenib in FIP1L1-PDGFR α positive chronic eosinophilic leukemia with imatinib-resistant T674I mutation. *Leukemia* 2012;26(1):162–4.
38. Al-Riyami AZ, Hudoba M, Young S, et al. Sorafenib is effective for imatinib-resistant FIP1L1/PDGFR α T674I mutation-positive acute myeloid leukemia with eosinophilia. *Leuk Lymphoma* 2013;54(8):1788–90.
39. Halaburda K, Prejzner W, Szatkowski D, et al. Allogeneic bone marrow transplantation for hypereosinophilic syndrome: long-term follow-up with eradication of FIP1L1-PDGFR α fusion transcript. *Bone Marrow Transpl* 2006;38(4):319–20.
40. Curtis CE, Grand FH, Musto P, et al. Two novel imatinib-responsive PDGFRA fusion genes in chronic eosinophilic leukaemia. *Br J Haematol* 2007;138(1):77–81.
41. Cheah CY, Burbury K, Apperley JF, et al. Patients with myeloid malignancies bearing PDGFRB fusion genes achieve durable long-term remissions with imatinib. *Blood* 2014;123(23):3574–7.
42. Lefevre G, Copin MC, Staumont-Salle D, et al. The lymphoid variant of hypereosinophilic syndrome: study of 21 patients with CD3-CD4 $^{+}$ aberrant T-cell phenotype. *Medicine* 2014;93(17):255–66.
43. Roufousse F, de Lavareille A, Schandene L, et al. Mepolizumab as a corticosteroid-sparing agent in lymphocytic variant hypereosinophilic syndrome. *J Allergy Clin Immunol* 2010;126(4):828–35.
44. Bergua JM, Prieto-Piiego E, Roman-Barbera A, et al. Resolution of left and right ventricular thrombosis secondary to hypereosinophilic syndrome (lymphoproliferative variant) with reduced intensity conditioning allogeneic stem cell transplantation. *Ann Hematol* 2008;87(11):937–8.
45. Ogbogu PU, Bochner BS, Butterfield JH, et al. Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy. *J Allergy Clin Immunol* 2009;124(6):1319–25.

46. Dahabreh IJ, Giannouli S, Zoi C, et al. Management of hypereosinophilic syndrome: a prospective study in the era of molecular genetics. *Medicine* 2007; 86(6):344–54.
47. Butterfield JH, Weiler CR. Use of pegylated interferon in hypereosinophilic syndrome. *Leuk Res* 2012;36(2):192–7.
48. Cools J, DeAngelo DJ, Gotlib J, et al. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med* 2003;348(13):1201–14.
49. Butterfield JH. Success of short-term, higher-dose imatinib mesylate to induce clinical response in FIP1L1-PDGFRalpha-negative hypereosinophilic syndrome. *Leuk Res* 2009;33(8):1127–9.
50. Hochhaus A, le Coutre PD, Kantarjian HM, et al. Effect of the tyrosine kinase inhibitor nilotinib in patients with hypereosinophilic syndrome/chronic eosinophilic leukemia: analysis of the phase 2, open-label, single-arm A2101 study. *J Cancer Res Clin Oncol* 2013;139(12):1985–93.
51. Strati P, Cortes J, Faderl S, et al. Long-term follow-up of patients with hypereosinophilic syndrome treated with Alemtuzumab, an anti-CD52 antibody. *Clin Lymphoma Myeloma Leuk* 2013;13(3):287–91.
52. Rothenberg ME, Klion AD, Roufosse FE, et al. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med* 2008;358(12):1215–28.
53. Sauvage D, Roufosse F, Sanoussi I, et al. Treatment-refractory hypereosinophilic syndrome responding to fludarabine in a 12-year-old boy. *Leuk Lymphoma* 2015; 25:1–3.