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EXPERT REVIEWS

Clinical management of the hypereosinophilic syndromes

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Hypereosinophilic syndromes (HESs) are rare disorders characterized by marked hypereosinophilia that is directly responsible for organ damage or dysfunction. Different pathogenic mechanisms have been discovered in patient subgroups leading to the characterization of myeloproliferative and lymphocytic disease variants. In the updated terminology, idiopathic HES is now restricted to patients with HES of undetermined etiology. The practical clinical approach of patients with the different HES variants is reviewed herein, focusing on specific diagnostic tools and therapeutic options. Corticosteroids, hydroxyurea and IFN-α remain the classical agents for treatment of most patients with HESs. The specific role of therapeutic compounds that have become available more recently, namely, tyrosine kinase inhibitors and IL-5 antagonists, is discussed.

Keywords: anti-IL-5 • chronic eosinophilic leukemia • hypereosinophilic syndrome • imatinib • lymphocytic variant hypereosinophilic syndrome

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Learning objectives

Upon completion of this activity, participants will be able to:

- Assess the diagnostic process for hypereosinophilic syndrome
- Analyze the use of corticosteroids and hydroxyurea for hypereosinophilic syndrome
- Evaluate new treatments for hypereosinophilic syndrome
- Distinguish the best marker to gauge treatment efficacy in cases of hypereosinophilic syndrome

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Defining criteria & classification of hypereosinophilic syndromes: past & present

The term 'hypereosinophilic syndrome(s)' (HESs) initially referred to the association of marked peripheral blood eosinophilia and eosinophilic tissue infiltrates with ensuing damage and/or dysfunction [1,2]. The term 'idiopathic' referred to the exclusion of under-lying diseases known to cause hypereosinophilia, whose diagnosis is relatively straightforward using clinical judgment and readily available ('first-line') diagnostic tools (e.g., drug allergy, parasitic infections, cancer, lymphoma and myeloproliferative disorders). At that time, well-defined immune-mediated systemic inflammatory disorders such as Churg–Strauss vasculitis (CSS) or inflammatory bowel disease were excluded from this entity, although the etiology and pathobiology of (eventual) associated eosinophilia was also unknown.

Subsequently, in a workshop summary report published in 2006, the definition of HESs was extended to include such disorders as organ-restricted eosinophilic disease associated with blood eosinophilia such as Carrington's disease (chronic eosinophilic pneumonia) and eosinophilia–myalgia syndrome [3]. Indeed, from a practical standpoint, when the clinician is faced with a patient presenting marked hypereosinophilia and various target-organ manifestations, it is appropriate to consider all the diseases covered by this larger definition. Use of 'second-line' diagnostic tools (i.e., those recommended after the exclusion of obvious causes of hypereosinophilia) was integrated, in order to distinguish the pathogenic disease variants described well after the term HES was introduced (i.e., lymphocytic variant HES [L-HES] [4,5] and myeloproliferative forms of HES including *FIP1L1-PDGFRA (F/P)*-associated disease [6]), from HES of unknown etiology. This latter disease subgroup was classified as 'undefined' rather than 'idiopathic', and in addition to patients presenting with various eosinophil-mediated complications ('complex undefined HES'), patients with persistent hypereosinophilia but no evidence of end-organ damage were included in the classification scheme ('benign undefined HES'), in order to draw attention to the fact that such patients require regular follow-up for timely detection of eosinophil-mediated complications justifying therapeutic intervention. Finally, a small subgroup of patients with familial HES, driven by an as of yet unknown inherited gene defect, was distinguished from the other etiological subgroups.

To address some of the imperfections of prevailing definitions, and to clarify some practical issues, the same group proposed an updated working definition of HESs in 2010 [7]: blood eosinophilia of greater than 1500/μl on at least two occasions, or evidence of prominent tissue eosinophilia associated with symptoms and 'marked' blood eosinophilia; and exclusion of secondary causes of eosinophilia, such as parasitic or viral infections, allergic diseases, drug-induced or chemical-induced eosinophilia, hypocorticism and neoplasms [7]. By comparison with the criteria of Chusid *et al.* [1], the most important differences of the proposed working definition can be outlined as follows:

- The arbitrary level of 1500 eosinophils/ml^2 is no longer necessary in the presence of marked eosinophilic tissue infiltration with tissue damage or organ dysfunction;
- Blood hypereosinophilia must be confirmed, but the 6-month duration of disease is no longer required. Indeed, nowadays, marked hypereosinophilia in a symptomatic patient with organ involvement must be treated without delay to prevent irreversible organ damage;
- Signs and/or symptoms of organ involvement are not mandatory in the new criteria since some patients may be asymptomatic at presentation, and either remain so, or develop symptoms related to tissue eosinophil infiltration. It is currently impossible to predict the outcome in a given asymptomatic patient, so all patients warrant follow-up;
- The prior requirement that the trigger of eosinophilia be unknown for diagnosis of HES has been removed, and HES variants with known pathogenic mechanisms are well identified as separate entities within the classification scheme.

In parallel with these evolving concepts, rapid progress has been made in the fields of hematology and cytogenetics with regard to the molecular mechanisms of clonal hypereosinophilia. The terms 'chronic eosinophilic leukemia' (to designate F/P-associated disease as well as other forms of clonal eosinophilia) and 'idiopathic hypereosinophilic syndrome' are mutually exclusive in the hematological community, as reflected in the current WHO classification [8]. In the same line, this classification scheme excludes patients with clonal (phenotypically aberrant) T cells from the group 'idiopathic HES' (I-HES).

Thus, with increased understanding of mechanisms underlying hypereosinophilia, the terminology, classification and diagnostic algorithms pertaining to patients with marked peripheral blood and tissue eosinophilia have evolved and diverged among the different medical subspecialities, paradoxically resulting in increasing confusion in this field. A pluridisciplinary working group was convened in May 2011 with the goal of developing a consensual framework for definition and classification of eosinophilic disorders. In this proposal [9], the term HES is restricted to patients with hypereosinophilia (blood and/or tissue) of any cause (reactive, neoplastic or idiopathic) with end-organ damage directly attributable to eosinophils. In the absence of eosinophil-mediated complications, the proposed terminology is 'hypereosinophilia of undetermined significance'. This paper also provides a detailed enumeration of the mutations described in association with clonal hypereosinophilia, which will not be covered in the present review.

We propose to limit the scope of the present review to clinical management of patients with HESs as defined by Simon *et al.* in 2010 but excluding those with well-defined diseases and specific treatment strategies, such as Churg–Strauss vasculitis or Crohn's disease [7,10].

Diagnostic approach to patients with HESs

The 'first-line' set of diagnostic investigations that should be conducted in hypereosinophilic patients has been reviewed elsewhere [11,12] and will not be detailed herein. When these tests have failed to identify underlying diseases, and hypereosinophilia persists, further 'second-line' investigations must be performed, both to identify patients with specific HES variants and to evaluate the consequences of prolonged hypereosinophilia *per se* (Table 1).

Taking into account clinical, biological and cytogenetic features, and evidence of clonal eosinophilia on the one hand, or evidence that eosinophilic expansion is driven by Th2 cytokine-secreting T cells on the other hand, myeloproliferative HES and L-HES variants may be identified. Nevertheless, in up to 75% of patients, the cause of hypereosinophilia remains undefined and the term I-HES remains appropriate. The characteristics of the different HES variants are summarized in Figure 1, and their prevalence, pathogenesis, clinical characteristics and prognosis have been reviewed elsewhere [12–15].

The clinical manifestations of HES are variable from one patient to another, depending on target-organ involvement by eosinophils. Organ damage and/or dysfunction is the consequence of eosinophil release of various mediators, whose nature and functions have been enumerated in great detail by Valent *et al.* in the previous issue of this journal [9]. Although virtually any tissue or organ can be affected in HES, major tissue targets include the skin, lungs, digestive tract, heart and nervous system [16]. The frequency of specific organ involvement is variable from one study to another depending on the clinical subspecialty of the authors. A high prevalence of cardiovascular (58%) and neurologic (54%) involvement was reported by Weller and Bubley in 1994 [16]. The patients in this review were collected from three previously published retrospective studies on American, British and French cohorts, and it is believed that these early studies included more severe cases referred to tertiary centers. In the most recent survey of 188 patients with HES, cardiovascular and neurologic manifestations were present in only 20% [17]. In this study, dermatologic manifestations were the most prevalent at initial presentation (37%) and in the course of the disease (69%). Of note, cardiac manifestations are uncommon in patients with L-HES [13]. The frequency of organ involvement in HES patients, and specifically in L-HES, is summarized in Table 2.

Treatment of HES

Choice of therapy for patients with HES should be guided by the following considerations: the relative urgency of lowering blood and tissue eosinophil levels in a new patient depending on the existence of preoccupying and progressive end-organ damage, preventing the development of irreversible complications of sustained hypereosinophilia, weighing the side effects of therapeutic agents against the expected benefit of maintenance treatment and choosing the most appropriate agent(s) for a given patient on the basis of underlying mechanisms of disease, if known. We will first describe the agents that can be used to treat HES, then address treatment options and issues pertaining to specific clinical presentations and finally enumerate several general considerations that are important for optimal care of patients with HES.

Therapeutic agents for patients with HES

Corticosteroids

Corticosteroids (CSs) represent the most widely used group of molecules for treatment of HES. A recent multicenter retrospective study reported that 81% (163 out of 188) of patients with HES received CS as initial therapy [17]. Of patients receiving CS monotherapy, 85% experienced a partial or complete response at 1 month after the initiation of treatment. In the majority of CS responders, the eosinophil-lowering effect is very rapid, generally within hours [18]; an observation that remains unexplained.

There are some indications that certain patient groups are more or less likely to respond to CS. Indeed, the long-held belief that elevated serum IgE is predictive of a favorable response to CS [19] was recently challenged by the observation that IgE levels did not differ significantly between CS responders and nonresponders in a large, multicenter, retrospective study [17]. By contrast, serum levels of the chemokine TARC (produced by various cell types in

Table 1. Recommended evaluation of patients with hypereosinophilic syndromes.

HES variant identification		
Variation	*Routine tests*	*Specialized laboratories*
M-HES	Complete blood count with differential serum tryptase and vitamin B12 RT-PCR and/or FISH (CHIC2) for detection of *FIP1LI-PDGFRA* rearrangement (blood and bone marrow) Karyotype Bone marrow aspirate (biopsy): cellularity, increased CD34, dysplasic changes, increased reticulin staining, atypical mast cells Evaluation for organomegaly	Search for other fusion genes involving PDGFRA and PDGFRB (diagnosis of PDGFR overexpression using generic RQ-PCR analysis) JAK2 mutations
L-HES	T-cell phenotyping (at minimum CD3, CD4 and CD8; blood) TCR gene rearrangement analysis by PCR (blood and bone marrow) Serum IgE, IgG, IgA and IgM Karyotype FDG-PET/CT scan (for T-cell lymphoma)	T-cell phenotyping (CD2, CD5, CD6, CD7, CD25, CD27, CD45RO and TCR Vβ panel) Serum TARC T-cell cytokine production (flow cytometry, ELISA, PCR)
Detection of eosinophil-mediated organ involvement†		
Organ	*In all patients*	*In symptomatic patients*
Cardiac	Serum troponin T, NT-proBNP, CK Electrocardiogram Echocardiogram	Cardiac MRI
Digestive, hepatic–splenic, pancreatic	Liver enzymes, lipase Abdominal CT	Endoscopy with biopsies
Pulmonary	Chest x-ray and CT Pulmonary function tests	Lung biopsy Bronchoalveolar lavage
Neurological		Brain MRI with DWI (or brain CT with contrast) Electroencephalogram Nerve conduction studies
Skin		Skin biopsy
Vascular		Angiography
Kidney, urinary tract	Urea, creatinine, urine dip-stick	Kidney/bladder biopsy Eosinophiluria

†Beyond thorough physical examination.
CK: Creatine kinase; CT: Computed tomography; DWI: Diffusion-weighted imaging; FDG: Fluorodeoxyglucose; HES: Hypereosinophilic syndrome; L-HES: Lymphocytic variant HES; M-HES: Myeloproliferative variant-HES; RQ: Real-time quantitative.

response to IL-4 in the setting of certain Th2-driven disorders) were shown to be significantly higher in CS responders, and very elevated TARC levels like those encountered in patients with L-HES (>10,000 pg/ml) were only observed among responders. Patients with L-HES do indeed generally respond to CS therapy; although the doses required to control disease are very variable and may be elevated. Importantly, CS treatment may in some cases [20] (but not all [21]) reduce the absolute counts of abnormal $CD3^-CD4^+$ T cells, perhaps through a proapoptotic effect on the $CD3^-CD4^+$ T cells as observed *in vitro* [Schandené L, Unpublished Data]. Another common belief is that patients with underlying myeloproliferative disease respond less well to CS [22]. In the retrospective series of Ogbogu *et al.*, 11 out of 18 patients with $F/P)^{pos}$ chronic eosinophilic leukemia (CEL) received CS monotherapy early in their management (prednisone [PDN]-equivalent doses ranging from 30 mg to 2 mg/kg), and all interrupted treatment due to lack of efficacy [17] [Ogbogu P, Unpublished Data].

Recommended starting doses are typically 0.5–1 mg PDN/kg body weight, daily. However, patients with non-life-threatening disease complications and tolerable manifestations can start with lower doses. The PDN dose required to maintain disease control is highly variable from one patient to another and even for a given patient over time. In the large retrospective study mentioned above, the median maximal dose given was 40 mg daily, and the median maintenance dose was 10 mg [17]. When such doses are administered on a long-term basis, patients experience a number of well-known side effects justifying introduction of CS-sparing second-line agents. The most commonly administered agents used in combination with CS are hydroxyurea (HU) and IFN-α [17,19].

Hydroxyurea

HU is the most commonly used second-line agent for treating HES, generally at doses between 0.5 and 2 g/day. Clinical

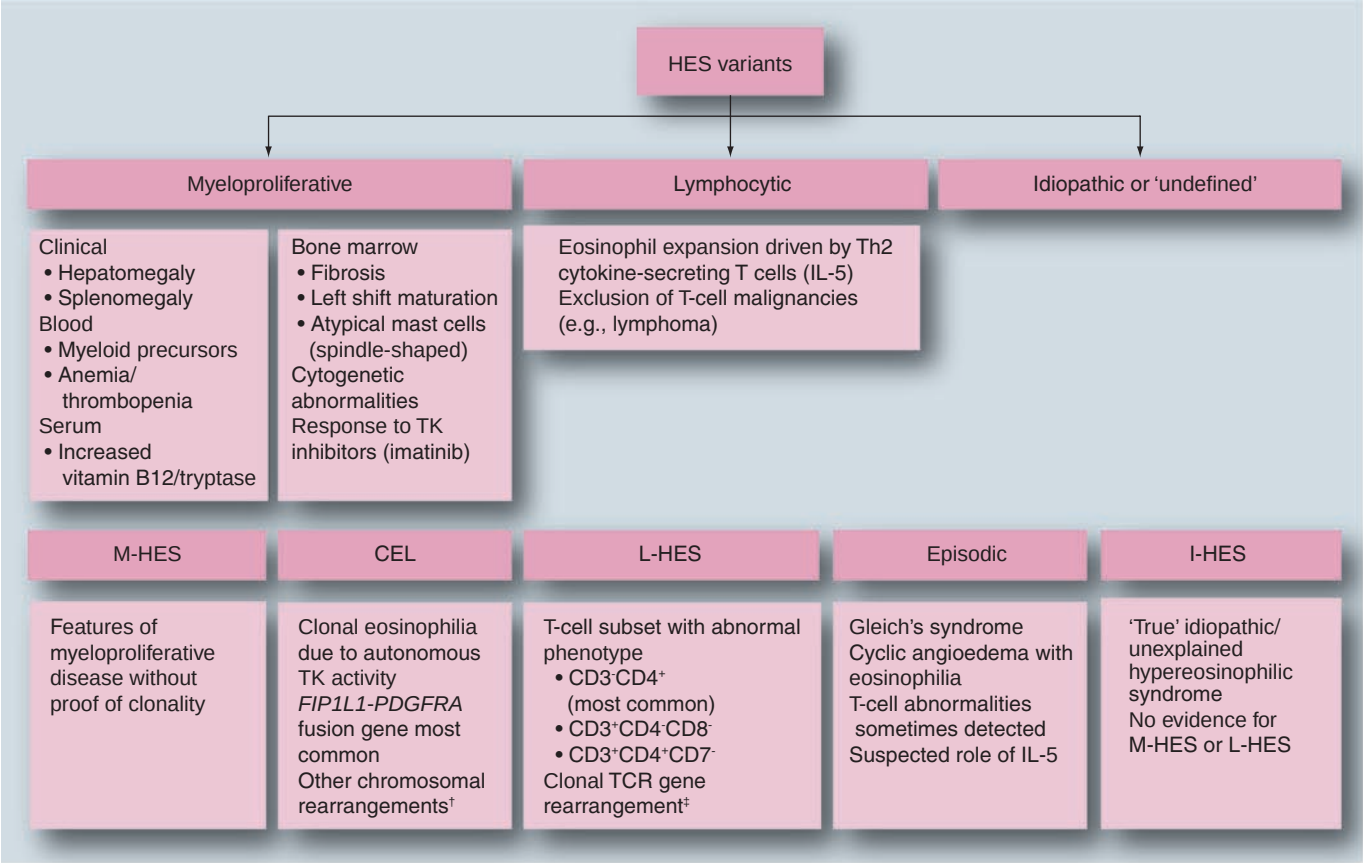

Figure 1. Classification and characteristics of hypereosinophilic syndrome variants (defined according to [7]**).** HES patients can be subdivided into three pathogenic subgroups: myeloproliferative, lymphocytic and undefined or idiopathic forms. In myeloproliferative forms, a number of clinical, biological and molecular features indicate that eosinophilia is clonal, although this can be formally demonstrated only in a minority of cases, which are best qualified as chronic eosinophilic leukemia. The remaining patients are said to 'presumably' have a primary myeloproliferative disorder. It is anticipated that further molecular advances will increase the proportion of patients with well-defined clonal eosinophilia. In lymphocytic forms, polyclonal hypereosinophilia is driven by eosinophilopoeitic cytokines that are produced by abnormal (often clonal) T-cell subsets. These subsets most frequently bear a $CD3^-CD4^+$ phenotype. In idiopathic HES, which remains the largest patient subgroup, neither clinical characteristics nor molecular investigations are indicative of a primary myeloproliferative disorder or cytokine-driven eosinophilia. In episodic angioedema (Gleich's syndrome), eosinophilia may be cytokine driven or idiopathic. Familial HES, a rare pathogenic variant, is not included in this figure.
†For more details see [9].
‡The detection of circulating clonal T cells by PCR is not a sufficient condition to allow diagnosis of a lymphocytic variant.
CEL: Chronic eosinophilic leukemia; HES: Hypereosinophilic syndrome; I-HES: Idiopathic HES; L-HES: Lymphocytic variant HES; M-HES: Myeloproliferative variant HES; TK: Tyrosine kinase.

efficacy is delayed due to the fact that it acts centrally while leaving peripheral eosinophils intact, so this agent is not to be used as an acute eosinophil-lowering agent. HU is rarely used alone to induce disease remission; it is most beneficial when it is combined with other agents. In one single-center prospective study, combined therapy with HU (2000 mg/day) and PDN (1 mg/kg/day) was administered to 15 treatment-naive patients with F/P^{neg} HES [23]; nine had a complete response and six had a partial response. Doses of both agents were then tapered progressively, and in all patients, maintenance therapy with HU alone (500–1000 mg daily in the majority of cases) was sufficient to ensure disease control. The overall response rate to this treatment combination was lower (69%) in the large multicenter retrospective study of Ogbogu *et al.* [17]. The most likely explanation for the observed difference in response rates is the prospective nature of the study by Dahabreh *et al.*, with a pre-established dosing protocol wherein HU was administered at a dose of 2 g/day, whereas the median maximum daily dose in the retrospective study was 1 g/day [23]. Approximately, 10% (18 out of 188) of patients in this latter study received HU monotherapy at one point, and a complete response was observed in a third of patients (six out of 18). Notably, three-quarters of patients receiving HU alone or in combination with another agent interrupted this agent (49 out of 64), with a similar proportion doing so either because of lack of efficacy (23 out of 49 patients or 47%) or because of treatment-related side effects (21 out of 49 patients/43%).

The most common dose-limiting side effects are related to central hematological and gastrointestinal toxicity, which are more

Table 2. Frequency of organ involvement in hypereosinophilic syndrome.

	Series			
	HES		L-HES	
	Weller and Bubley (1994) [16]	Ogbogu *et al.* (2009) [17]	Roufosse *et al.* (2007) [13]†	
			CD3⁻CD4⁺	*Other phenotypes*
Number of patients	105	188	35	21
Cutaneous (%)	58	69	94	67
Cardiac‡ (%)	56	20	12	6
Neurological (%)	54	21	0	0
Digestive (%)	23	38	9	6
Pulmonary (%)	49	44	9	17
Splenic (%)	43	10	9	17
Hepatic (%)	30	NM	0	0
Ocular (%)	23	NM	0	0
Raynaud's (%)	NM	NM	12	0
Angioedema (%)	NM	NM	31	5

The 105 patients of the Weller and Bubley study [16] is the compilation of American [81], French [82] and British [83] series published between 1982 and 1989. Ogbogu and colleagues' series represents the largest published study of patients with different HES variants.
†In addition to the 38 patients reported by Roufosse *et al.* [13], nine patients from references [77,84–89] and nine unpublished patients referred to our center were also included.
‡In Weller and Bubley's series, cardiac and vascular involvement are considered together.
HES: Hypereosinophilic syndrome; L-HES: Lymphocytic variant HES; NM: Not mentioned.

prevalent at daily doses above 1 g/day. It has proven useful in individual cases to associate low-dose HU with other compounds such as IFN-α [19], combining efficacy while reducing side effects of each molecule.

In the prospective study wherein the large majority of patients responded to maintenance therapy with HU alone, they were classified as truly 'I-HES', with complications involving mainly the lungs, skin, gastrointestinal tract and nervous system [23]. Although HU would not be the first choice for patients with L-HES on theoretical grounds, it effectively lowered eosinophil levels and associated symptoms in one patient with a $CD3^-CD4^+$ clone [24] and abolished an abnormal T-cell clone in another patient with CS-resistant HES associated with IL-2 and IL-15 overproduction [25].

Overall, HU is an easily obtained and inexpensive agent that appears efficacious in a satisfactory proportion of patients with HES, but its use at doses required to induce remission may be precluded by poor tolerance. It is best used in combination with CS, or eventually IFN-α, and should not be used alone as a first-line agent in patients suffering serious complications of disease, because of its slow action.

IFN-α

IFN-α was introduced in the management of HES in the 1990s, on the basis of similarities with chronic myeloid leukemia (CML) [26,27]. The first reports showed disease control in patients who were refractory to CS and HU [28]. Small series and case reports showed encouraging responses to treatment in terms of disease control, and some patients even experienced durable remission after treatment interruption, suggesting that IFN-α may be curative in some cases [29]. This molecule is now relatively commonly used for treating patients with HES and was given to a quarter of the patients included in the large retrospective study [17].

Like HU, the effects of IFN-α are delayed, both because of its mechanisms of action and recommended progressive dosing imposed by poor tolerance. Treatment with IFN-α is indeed generally introduced progressively, over several weeks or months, because of poor initial tolerance, essentially related to flu-like symptoms. As patients become accustomed to a given dose, the amount of IFN-α per subcutaneous injection is increased by small increments until a response is observed. The median maximal weekly dose administered to patients was 14 million units in the study by Ogbogu *et al.* [17]. However, the majority of patients had to interrupt treatment with IFN-α, and poor tolerance was the most common explanation. Although flu-like symptoms tend to improve, severe depression with suicidal ideation, fatigue, myalgia, induction of autoantibodies or exacerbation of autoimmune disease (including autoimmune thyroiditis and psoriasis), myelosuppression and increased liver transaminases may develop over time. Another drawback of this treatment modality is the requirement for several subcutaneous injections a week; one study has shown that IFN-α can be replaced by pegylated-IFN-α, which only requires a single weekly injection and appears as effective as the native form [19]. This immunomodulatory agent targets both eosinophils and T cells, making it an interesting choice for all disease variants. Many IFN-α responders reported in the literature present a number of features suggestive of myeloproliferative disease, but these reports pre-date description of the F/P fusion. It is noteworthy that some of these patients had karyotype abnormalities that disappeared during treatment [30]. In one series of patients with F/P^{pos} CEL, IFN-α generally combined with HU produced only partial responses and had to be interrupted in all cases because of side effects [22]. We have observed a clear-cut CS-sparing effect of IFN-α in two patients with $CD3^{-/dim}CD4^+$ clones, with a progressive decrease in absolute numbers of circulating abnormal T cells over time, and eventually complete disappearance of these cells in one patient who has remained in remission more than 5 years after treatment interruption [Roufosse F, Unpublished Data]. *In vitro*, IFN-α is known to inhibit proliferation of CD4 T cells [31] and has been shown to inhibit IL-5 production by $CD3^-CD4^+$ cells [32], but it also inhibits their death by apoptosis to a similar degree as IL-2 [33], leading us to recommend this agent in association with CS for patients with L-HES.

Overall, IFN-α represents a therapeutic option for patients with F/P^{neg} HES, irrespective of disease presentation, but HES is not a recognized indication, making it expensive and difficult to obtain in many countries. Furthermore, side effects are common and are the most common cause of treatment interruption.

Imatinib mesylate & other kinase inhibitors

Imatinib mesylate (IM) is a small molecule tyrosine kinase inhibitor (TKI) that targets the inactive conformation of fusion genes involving *abl*, *c-kit*, *PDGFRA* and *PDGFRB*, occupying the ATP-binding site and interfering with downstream phosphorylation [34]. This drug, which is commonly used to treat patients with CML, was administered to a small group of patients with HES, showing remarkable efficacy in four out of five cases [35]. On the basis of this very encouraging observation, a search for the target kinase driving disease in patients with HES was undertaken, and this led to the discovery of the F/P fusion in a subgroup of patients [6]. Since then, several other fusion genes involving imatinib targets (PDGFRA and PDGFRB) have been reported in patients with CEL, presenting clinically as HES. Whereas the *PDGFRA* rearrangements are usually cytogenetically undetectable, *PDGFRB* rearrangements generally occur in the setting of readily detectable chromosomal translocations.

The tyrosine kinase activity of the F/P fusion is over 100-fold more sensitive to IM than the CML-associated bcr-abl fusion *in vitro*, explaining that F/P^{pos} CEL patients respond to lower doses of this agent. In addition, response to treatment is both rapid (generally within a week) and dramatic in terms of controlling eosinophil levels and most clinical manifestations, with the exception of irreversible cardiac damage (endomyocardial fibrosis and valvular alterations) and sequelae of thromboembolic events [22,36]. Cytogenetic remission is achieved in the majority of patients with the F/P fusion, although this takes longer (within a period ranging from 1 month to over a year) [36,37]. However, interruption of IM after cytogenetic remission results in reappearance of the fusion gene, which precedes recurrence of hypereosinophilia [37,38]. Although reintroduction of imatinib has consistently reinduced molecular remission in such cases, one study has shown that the dose required to maintain remission may be higher than the dose that initially achieved this end point. These observations suggest that a contingent of F/P^{pos} stem cells persists during treatment with imatinib and that emergence of imatinib-resistant subclones may be favored by temporary withholding of treatment. For this reason, some experts recommend pursuing daily treatment with at least 100 mg, despite the fact that one group has reported prolonged clinical and molecular remission with only 100 mg IM a week (median 29 months, range 3–61 months, for 11 patients) [39]. Although prolonged remission has been observed in some patients with CML despite interruption of therapy with imatinib, suggesting that CML may eventually be cured with TKIs [40], similar observations have not yet been reported in F/P^{pos} CEL. This agent is therefore not to be considered as curative and should be pursued indefinitely; long-term observation of patients with different treatment regimens will hopefully help determine the optimal approach to maintenance therapy.

Development of secondary resistance during ongoing treatment with IM has been reported in four F/P^{pos} patients, due to the appearance of a T674I point mutation in the PDGFR-α ATP-binding site [6,41]. More recently, primary resistance to IM has been reported as well [42]. One patient with F/P^{pos} CEL who did not respond to a daily dose of 400 mg IM was shown to have a double S601P/L629P mutation. This mutant was also resistant to sorafenib. An additional F/P^{pos} patient with primary resistance to IM was reported in the retrospective study of Ogbogu *et al.* [17], but the mechanisms were not reported.

There is no doubt that IM represents first-line therapy for patients with F/P^{pos} CEL, and because of the reported occurrence of other cytogenetic rearrangements involving imatinib-sensitive kinases in rare patients with unexplained hypereosinophilia [43–45], it is worthwhile to try IM in F/P^{neg} patients with features of myeloproliferative disease (Figure 1). In most cases, F/P^{neg} patients receiving a trial with IM either do not respond or present an incomplete and transient response with higher doses of imatinib than F/P^{pos} patients [46]. In a recent study, four out of eight F/P^{neg} CS-resistant patients responded to IM, three of which responded within a week and were successfully maintained in remission with a daily dose of 100 mg [47]. The only clinical parameters showing statistically significant differences between the IM responders versus nonresponders in this study were lower age and higher percentage of eosinophils in peripheral blood in the former group. Both of the patients reported to have splenomegaly responded to IM within days. Of note, one CS-dependent patient with F/P^{neg} HES and poor tolerance to HU and IFN-α responded to a daily imatinib dose of 800 mg, which allowed CS tapering; disease remission was then maintained despite tapering of the daily imatinib dose to 100 mg [48]. This patient had no features of myeloproliferative disease with the exception of increased serum tryptase. Imatinib has not shown efficacy in patients with L-HES associated with well-characterized phenotypic abnormalities [49,50]. One group has recently reported the case of a F/P^{neg} HES patient with a clonally expanded but phenotypically normal CD4 T-cell population, whose eosinophil levels decreased in response to imatinib 400 mg/day, although no effect on the clone itself was observed [51]. No evidence for cytokine-driven hypereosinophilia was provided in this study, so no conclusions can be drawn regarding efficacy of imatinib in L-HES.

Because of the low dosing required for patients with F/P^{pos} CEL, IM is generally well tolerated, and side effects are rarely observed. However, development of acute congestive heart failure shortly after initiation has been reported in a few patients [52], presumably related to release of cytotoxic mediators by eosinophils within the myocardium. This complication is associated with increased serum troponin levels, which should therefore be monitored in patients initiating therapy with IM, and regresses with CS treatment. In order to avoid this complication, it is recommended to administer PDN (1 mg/kg/day) at the initiation of imatinib administration.

TKIs other than IM have been tested *in vitro* on cells transfected with the F/P fusion gene versus its T674I mutant form, and *in vivo*, on a murine bone marrow transplant model of F/P-associated disease [53]. Although nilotinib and sorafenib are effective on both the native fusion gene and the T674I mutant [54,55], a recent study has shown disappointing clinical efficacy of these agents in CEL patients with mutant F/P [56]. In another report, increasing the dose of nilotinib to 800 mg/day successfully controlled disease in one such

patient [57]. One patient with T674I-mutated F/P presented an initial response to sorafenib, but disease recurred as a second D842V mutation developed, conferring resistance to all inhibitors studied so far [58]. Similarly, activity of the mutated S601P form responsible for primary resistance was not inhibited by sorafenib *in vitro* [42].

Dasatinib has also shown efficacy *in vitro*, similar to IM, on the native fusion expressed by the EOL-1 cell line [59]. PKC412 is a structurally unrelated molecule derived from staurosporine, known to inhibit PKC, FLT3, KDR, PDGFRA and PDGFRB. This compound inhibits activity of the native F/P fusion and its mutated form, both *in vitro* and *in vivo* [53].

Overall, IM is effective in the large majority of patients with F/P^{pos} disease, with an excellent safety profile related to the low dosing required to maintain prolonged remission.

Antibodies targeting IL-5

Monoclonal anti-IL-5 antibodies target eosinophils by binding to IL-5 and preventing its ligation to the IL-5R α-chain expressed on the eosinophil membrane. Anti-IL-5 was first shown to decrease eosinophil levels rapidly in a dose-dependent manner in patients with asthma [60]. In addition to eosinophil-lowering effects, treatment with anti-IL-5 also affects eosinophil functions, namely, by decreasing sensitivity to eotaxin *in vitro* [61].

Several open-label studies evaluating effects of intravenous anti-IL-5 monoclonal antibody in HES patients showed a rapid decline of blood eosinophil counts within days after administration, associated with improvement of a range of clinical manifestations, correlating with significant reductions of eosinophil numbers in the skin and esophagus of patients with eosinophilic dermatitis and severe eosinophilic esophagitis, respectively [62,63]. Eosinophil depletion and clinical benefit in response to anti-IL-5 treatment can be surprisingly long lasting, persisting 3 months after the last infusion in three-quarters of patients in one open-label study [61]. However, eosinophilia eventually recurs in the absence of repeated infusions, and in one study, rebound hypereosinophilia was observed in six patients [64]. Like other treatments for HES, anti-IL-5 is therefore only suspensive and must be administered repeatedly for maintenance of clinical remission.

Efficacy of mepolizumab, a monoclonal anti-IL-5 antibody, as a CS-sparing agent in CS-responsive F/P^{neg} HES patients was recently confirmed in the setting of a randomized, double-blind, placebo-controlled clinical trial [65]. In this study, patients were stabilized under CS monotherapy (daily dose ranging from 20 to 60 mg PDN equivalent) and then randomized to receive intravenous mepolizumab 750 mg versus saline solution, every 4 weeks for a period of 36 weeks. The daily PDN dose required to stabilize disease and eosinophil levels could durably be tapered down to a predefined threshold value (i.e., daily PDN dose of 10 mg or less) in a significantly higher proportion of patients in the active treatment arm (36 out of 43 patients/87%, vs 18 out of 42 patients/43% in the placebo arm), and the difference between treatment arms was even more marked in patients requiring more than 30 mg PDN at baseline (ten out of 13 patients/77% in the active treatment arm, vs one out of 12 patients/8% in the placebo arm), indicating that the benefit of treatment with mepolizumab is particularly marked in patients with more severe disease. Furthermore, almost half of the patients receiving mepolizumab were durably tapered off CS until the end of the study. Exploratory investigations conducted during this trial identified a subset of patients with L-HES, and their response to IL-5-targeted therapy was compared with that of patients with normal T-cell phenotyping studies [66]. Mepolizumab showed similar efficacy in both groups in terms of CS-sparing, although a lower proportion of patients with L-HES maintained eosinophil levels below 600/µl throughout the study.

Mepolizumab was shown to be well tolerated and safe in this short-term study, and the long-term safety has recently been assessed in a 5-year open-label extension study, the results of which will be known shortly. The dosing frequency required to maintain disease control has also been analyzed in this prolonged study. Unfortunately, although clearly a very efficient and safe CS-sparing therapeutic alternative for patients with HES, mepolizumab has not yet been commercialized and is currently available only to patients with life-threatening disease who are refractory or intolerant to at least three other recognized HES active agents, in the setting of a compassionate use trial [101].

A humanized monoclonal antibody directed against the IL-5 receptor α chain and engineered to enhance its antibody-dependent cell-mediated cytotoxicity (MEDI-563) [67] has been shown to display potent proapoptotic activity on *in vitro* cultured eosinophils and has recently been investigated in a Phase I study conducted on patients with asthma [68]. This study has shown a very profound eosinophil-depleting effect 24 h after intravenous administration of anti-IL-5Rα, which subsists for more than 12 weeks in virtually all patients. Importantly, this approach may more effectively target tissue-dwelling eosinophils with reduced membrane expression of IL-5Rα than anti-IL-5 antibodies, because cytotoxicity is relatively independent of the density of targeted receptors, whereas IL-5 inhibition may be circumvented by the presence of other eosinophilopoietic factors. MEDI-563 has not been evaluated in patients with HES.

Other cytotoxic & immunomodulatory agents

Besides HU and IFN-α, several other agents have been used as maintenance therapy for individual patients with HES. Reports on administration of cytotoxic agents such as cyclophosphamide, methotrexate, busulfan and chlorambucil are scarce and arouse little if any enthusiasm for further assessment of their effectiveness in the setting of clinical trials. Vincristine has also successfully induced disease regression in acute settings; case reports of this agent mostly concern children [69,70]. Other agents enumerated in the retrospective study by Ogbogu *et al.* include cyclosporine A, azathioprine and dapsone [17]. Overall, cyclosporin and methotrexate appear to be the most commonly administered. However, they are discontinued in the majority of patients either because of a lack of efficacy or poor tolerance [17]. In one study, two patients classified as L-HES with significant disease-related morbidity were given cyclophosphamide and methotrexate, respectively, and experienced complete clinical remission, although the T-cell clone remained detectable [50]. Similarly, we observed persistence of $CD3^{-}CD4^{+}$ T cells in one L-HES patient treated with fludarabine, although an initial temporary clinical response was observed [Roufosse F, Unpublished Data].

Alemtuzumab, a monoclonal antibody directed against CD52 that is expressed by eosinophils and T cells, has also shown benefit in some patients with HES refractory to other agents [71–73]. Most alemtuzumab responders reported so far have I-HES, although one of the first patients reported had a clonal $CD3^{-}CD4^{+}$ T-cell subset [71], indicating that patients with L-HES requiring high-dose CS may benefit from a trial with this agent. However, toxicity is a matter of concern, essentially due to profound and prolonged T-cell depletion and occurrence of opportunistic infections, namely severe CMV reactivations. It is therefore reasonable to reserve alemtuzumab only for patients with significant disease complications, who are refractory to standard therapies. Effects of alemtuzumab on eosinophil levels are observed within days to weeks, and the duration of the effect after treatment discontinuation varies, with some patients experiencing remissions for several months, whereas others relapse more quickly [72,74]. Continued therapy is necessary to maintain remission. The dosing regimens reported so far are similar to those used for patients with chronic lymphocytic leukemia. However, a recent study conducted on patients with Sezary's syndrome showed that low-dose alemtuzumab was as effective as the standard dosing regimen (10 vs 15 mg on alternate days), with decreased toxicity [75]. Maintenance therapy was tailored for each patient on the basis of regular immunological monitoring of Sezary cell counts. This approach may be of interest for patients with L-HES, in whom phenotypically aberrant T-cell subset can be monitored in peripheral blood.

Allogeneic stem cell transplantation

HES patients who are refractory to classical therapy and who present progressive life-threatening end-organ damage may be candidates for allogeneic stem cell transplantation. Potential indications for this procedure may include patients with F/P-associated disease [22,76] who are intolerant to or no longer respond to imatinib and patients initially presenting L-HES who develop peripheral T-cell lymphoma, as eradication of malignant T cells is not easily achieved using classical chemotherapeutic regimens [13,77]. Given the high rates of treatment-related morbidity and mortality, stem cell transplantation should not be considered as a standard treatment option for patients with HES other than the situations described above.

General considerations pertaining to optimal patient management

Choosing the correct treatment strategy for patients with HESs is critical for preventing complications due to the disease itself and to therapeutic agents, and therefore for improving overall outcome. Recommendations for the management of specific disease presentations are summarized in Table 3. Several general considerations that are useful for patient care are given below.

Disease biomarkers

Eosinophil counts in peripheral blood are currently the major biomarker used to follow disease activity and response to treatment. However, eosinophil levels are of little help for predicting which patients will develop significant disease-related complications, and there are no predictive markers for preferential targeting of specific organs. Among patients with benign disease at presentation, that is, no apparent complications of hypereosinophilia, it is currently impossible to distinguish those who will remain asymptomatic from those who will develop complications. Careful clinical assessment at regular intervals, together with blood tests investigating occult organ involvement (e.g., troponin and liver enzymes), are therefore essential to optimal patient care.

The utility of serum levels of eosinophil cationic proteins, namely MBP1, ECP and EDN, as biomarkers of disease activity has not been prospectively assessed; furthermore, these tests are not standardized and not readily available and can therefore not be recommended. At the tissue level, activated degranulated eosinophils may be difficult to detect with classical hematoxylin–eosin staining. Some investigators recommend staining for cationic proteins in parallel, and a recent report using a new antibody directed against eosinophil peroxydase suggests that this may be a more reliable and specific marker of eosinophil degranulation, at least in the gut [78].

Serum TARC levels may represent an interesting marker of disease activity in patients with L-HES. Although this has not been investigated prospectively in this setting, evidence along this line has been produced for other diseases, namely Churg–Strauss syndrome and cutaneous T-cell lymphoma [79,80]. Measurement of serum TARC is reproducible and straightforward but is not performed in routine laboratories.

Goals of maintenance therapy

Once clinical and biological remission of disease has been achieved with an agent or combination of agents, treatment must be tapered so that disease control is maintained using the lowest possible doses. Indeed, patients with HES are often overtreated and exposed to unjustified treatment-related toxicity. The requirement for lower maintenance doses than those initially required to induce disease control is a typical observation in HES management. The aims of maintenance therapy, and hence, what is meant by 'disease control is maintained', vary depending on the clinical presentation. Different levels of disease control include normalization of blood eosinophil levels, clearance of eosinophilic infiltrates in biopsied tissues, control of clinical signs and symptoms, and resolution of abnormalities observed in imaging and functional studies. Molecular remission, relevant only in a minority of patients with a demonstrated cytogenetic defect, is the aim of therapy in this subgroup.

Regarding blood eosinophil levels, the degree of eosinophil control will be more stringent for a patient with cardiac complications than for a patient with skin lesions as the only manifestation of HES. In the latter case, persistent mild hypereosinophilia is acceptable provided that the patient is comfortable, and regular assessment excludes the development of other end-organ complications of HES. Similarly, a patient with isolated lung involvement who complains of cough and dyspnea and whose lung computed tomography shows pulmonary infiltrates can pursue the CS dose that clears symptoms and computed tomography abnormalities, even if the blood eosinophil level remains slightly above normal. We would recommend strict control of eosinophil levels within normal limits in the following situations: eosinophil-related cardiac damage (or existence of

Table 3. Therapeutic management of specific clinical presentations.

Clinical situation	Associated findings	Comments	Treatment
Newly diagnosed symptomatic patient with evidence of acute life-threatening complications involving vital organs	Heart failure, thromboembolic complications, respiratory distress, focal/diffuse CNS involvement (splinter hemorrhages)	Goal is rapid control of eosinophil level to prevent irreversible damage or death If possible, perform routine blood assessments in Table 1, and parasite serologies/stool examination before treatment	First-line: CS 1 mg/kg PDN equivalent orally (15 mg/kg mPDN intravenous if no rapid response) Consider adding imatinib 400 mg daily if myeloproliferative features (high serum vitamin B12 and/or tryptase, splenomegaly, abnormal CBC)
	Thromboembolic complications (arterial embolism, intracavitary thrombus)	Difficult to control; high recurrence rate despite anticoagulant therapy	Warfarin Defibrotide may have contributed to disappearance of cardiac thrombus in one case [77]
	Possible exposure to strongyloides stercoralis	Based on travel history/habitat Do not wait for results of serology Anthelmintic treatment required to avoid hyperinfestation	Ivermectin 200 µg/kg on day 1 and 15
	CS-resistant disease	Combined therapy	CS, HU, IFN-α, imatinib
	Presents in children	A few case reports show response to vincristine	First-line: CS CS-resistant disease: vincristine
Asymptomatic patient or 'hypereosinophilia of undetermined significance'	Thorough evaluation shows no evidence for eosinophil-mediated complications (and no underlying molecular disorder)	Assessment for end-organ involvement and possible underlying disease must be repeated at regular intervals	No specific treatment
Symptomatic I-HES	Various signs and symptoms related to eosinophilic tissue infiltration	For example, cough, dyspnea, abdominal pain, vomiting, diarrhea, signs of heart involvement, peripheral neuropathy	First-line: oral CS Start dose: 1 mg/kg PDN equivalent Tapered to the lowest possible dose maintaining remission
		For example, isolated cutaneous involvement, mild general symptoms (e.g., myalgia, arthralgia)	Start dose: ≤0.5 mg/kg PDN equivalent No specific treatment if manifestations well tolerated and provided regular assessments are performed for end-organ damage/dysfunction
	CS responders, with maintenance dose >10 mg daily and/or poor CS tolerance	Combined therapy	CS, HU, IFN-α, mepolizumab (only available on compassionate use basis if other agents have failed and complication(s) considered life threatening)
	CS-resistance and/or features typically encountered in myeloproliferative disease	In F/P^{neg} patients, IM is generally not or only transiently effective at higher doses Small subset of patients with probable cytogenetic rearrangement involving IM-target kinase showing dramatic response	Trial with imatinib 400 mg daily In absence of hematological response after 2–4 weeks, stop imatinib
	Patients refractory to all the above agents, with severe complications		Alemtuzumab, SCT

CBC: Complete blood count; CEL: Chronic eosinophilic leukemia; CS: Corticosteroid; F/P: FIP1L1-PDGFRA; HES: Hypereosinophilic syndrome; HU: Hydroxyurea; I-HES: Idiopathic HES; IM: Imatinib mesylate; L-HES: Lymphocytic variant HES; mPDN: Methylprednisolone; PDN: Prednisone; SCT: Stem cell transplantation; TKI: Tyrosine kinase inhibitor.

Table 3. Therapeutic management of specific clinical presentations (cont.).

Clinical situation	Associated findings	Comments	Treatment
F/P^{pos} CEL (most frequent cytogenetic abnormality observed in patients with CEL)	Overt cardiac complications and/or elevated serum troponin	Hematological response to IM observed within days Risk of acute heart failure at treatment initiation	First-line: imatinib, start at 400 mg daily and taper when molecular remission is achieved Combined with CS 1 mg/kg PDN equivalent orally during the first week
	No cardiac involvement Various disease presentations	Even asymptomatic patients should be treated	Imatinib can be started at 100 mg daily
	IM resistance	Referral to expert center for molecular characterization and treatment	Other TKI: sorafenib, midostaurin (nilotinib)
	TKI refractory		IFN-α or allogeneic SCT
CEL with other cytogenetic rearrangements involving PDGFR (rare)		Referral to expert center for molecular characterization	Imatinib
L-HES	Few symptoms (self-limiting urticaria or episodic angioedema)	Regular assessment for disease progression (risk of lymphoma)	No treatment Intermittent CS therapy
	Chronic and debilitating disease-related manifestations		First-line: CS, start at 0.5–1 mg/kg PDN daily Taper to lowest dose maintaining remission
	CS responders, with maintenance dose >10 mg daily and/or poor CS tolerance	*In vitro* studies show that IFN-α prolongs survival of clonal T cells; CS enhance apoptosis Mepolizumab is an effective CS-sparing agent in L-HES, although eosinophil control is less tight than in patients with I-HES	IFN-α combined with CS Mepolizumab infusions every 1–3 months
	CS- and IFN-α-resistant disease with serious complications or malignant progression	Marked and prolonged treatment-induced T-cell depletion favors opportunistic infections	Alemtuzumab Allogeneic SCT

CBC: Complete blood count; CEL: Chronic eosinophilic leukemia; CS: Corticosteroid; F/P: FIP1L1-PDGFRA; HES: Hypereosinophilic syndrome; HU: Hydroxyurea; I-HES: Idiopathic HES; IM: Imatinib mesylate; L-HES: Lymphocytic variant HES; mPDN: Methylprednisolone; PDN: Prednisone; SCT: Stem cell transplantation; TKI: Tyrosine kinase inhibitor.

unrelated heart disease); thromboembolic complications; and CNS involvement. Regarding imaging studies, it is important to note that certain abnormalities may not be reversible because they reflect structural damage to the organ; this is typically the case of endomyocardial fibrosis, which persists despite prolonged control of eosinophil levels.

Patients with predominant lung involvement & sinusitis

Hypereosinophilic patients with predominant lung involvement (associating dyspnea and pulmonary infiltrates) can present with chronic sinusitis as well. In the absence of anti-neutrophil cytoplasmic antibody and clinical evidence of vasculitic complications, there are no features allowing a clear-cut distinction between anti-neutrophil cytoplasmic antibody-negative CSS, idiopathic hypereosinophilic syndrome and even chronic eosinophilic pneumonia. Furthermore, symptoms related to eosinophilic tissue infiltration may be erroneously interpreted as evidence of vasculitis. Although such patients commonly respond to CS, it is often necessary to introduce second-line CS-sparing agents; and here, the choice between HU (the least expensive and most easily obtained second-line agent for I-HES) and azathioprine or methotrexate (more commonly used as second-line agents in patients with CSS) is problematic. Clearly, prospective clinical trials addressing the choice of second-line agents are warranted here.

Expert commentary

With better understanding of the pathogenic role played by eosinophils in organ damage and mechanisms resulting in hypereosinophilia, management of patients with HES has evolved since the introduction of this term in medical language and prognosis has improved. Attention first focused on preventing irreversible and life-threatening complications, by rapid therapeutic lowering of blood eosinophil counts using CSs and other immunomodulatory or cytotoxic agents. A

major advance was made with the discovery of the cryptic F/P fusion responsible for clonal eosinophil expansion through autonomous tyrosine kinase activation. The outcome of these patients, who had significant disease-related morbidity and mortality, and who were most resistant to classical treatment, has improved drastically with the introduction of IM. For the majority of patients, however, molecular mechanisms of disease remain unknown, and therapeutic approaches have changed little over time, relying on long-term administration of various combinations of CSs, HU and IFN-α, all of which are associated with significant toxicity. Targeting IL-5 with monoclonal antibodies was recently proven a well-tolerated, safe and effective CS-sparing agent for F/P^{neg} HES. Although this represents a new leap forward for patients, anti-IL-5 has not been approved for clinical use so far.

Five-year view

Besides patients with F/P^{pos} CEL, much progress remains to be made for optimal management of patients with HES. This is indeed a chronic and unpredictable disorder, occurring in relatively young patients and requiring long-term treatment. Because molecular mechanisms underlying disease are unknown, targeted therapy is not available; current agents have significant toxicity and may in some cases be more deleterious than the disease itself. Expectations for the near future include the following features: identification of biomarkers reflecting eosinophil activation and predicting the occurrence of serious target-organ damage; development and dissemination of tools and biomarkers to detect increased tyrosine kinase activity associated with clonal eosinophil expansion and thereby to facilitate the identification of patients likely to respond to imatinib; identification of the pathophysiological mechanisms involved in I-HES, which still represents the majority of patients; and identification and validation of biomarkers for facilitating diagnosis of T-cell driven HES and for detection of T-cell malignancy. Such advances would improve the management of HESs, through avoiding unnecessary exposure of patients with a low likelihood of developing complications to treatment-associated morbidity and favoring more rapid introduction of appropriate and tailored therapy targeting upstream disease mechanisms. Perhaps by then, therapies targeting IL-5 will have proven their efficacy in other eosinophilic conditions and will be made available to patients with HESs.

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Key issues

- The term hypereosinophilic syndrome (HES) now refers to patients with hypereosinophilia of any cause with end-organ damage directly attributable to eosinophils. In the absence of eosinophil-mediated complications, the proposed terminology is 'hypereosinophilia of undetermined significance'. In this review, HES developing in the setting of underlying diseases readily diagnosed with first-line evaluations (e.g., parasitic infections and Hodgkin's lymphoma) has not been covered.
- Eosinophil counts in peripheral blood are currently the major biomarker used to follow disease activity and response to treatment in patients with HESs, but are of little help for predicting which patients will develop significant disease-related complications.
- Prior to treatment initiation, evaluation for disease variants and detection of eosinophil-mediated complications are essential for guiding choice of therapy.
- Only corticosteroids (CSs; initial dose 1 mg prednisone/kg or intravenous methylprednisolone 15 mg/kg for severe life-threatening disease) and imatinib mesylate (IM) are currently available as agents able to lower eosinophils rapidly (within hours or days).
- The majority of patients with HES respond to CSs, but long-term treatment is complicated by substantial toxicity, and effective CS-sparing agents are often needed.
- Overall, hydroxyurea (500 mg to 2 g/day) is an easily obtained and inexpensive agent that is best used in combination with CSs, or eventually IFN-α, and should not be used alone as a first-line agent in patients suffering serious complications of disease because of its slow action.
- IFN-α represents a therapeutic option both for patients with lymphocytic variant HES and for patients with idiopathic HES but is limited by poor tolerance.
- IM (400 mg/day) represents first-line therapy for patients with FIP1L1-PDGFRA (F/P)^{pos} chronic eosinophilic leukemia, and it is worthwhile to try IM in F/P^{neg} patients with features of myeloproliferative disease; it is recommended to associate prednisone (1 mg/kg/day) at the initiation of imatinib administration.
- Patients with F/P^{pos} chronic eosinophilic leukemia who do not initially respond to IM or who develop resistance during treatment should be referred to an expert center for thorough molecular characterization of the mutation conferring imatinib resistance.
- Mepolizumab, an anti-IL-5 antibody, has been proven a safe and effective CS-sparing agent for patients with F/P^{neg} HES, in the first randomized, placebo-controlled clinical trial ever conducted in patients with HESs. This compound is currently not commercially available.
- Alemtuzumab is considered only for patients with significant disease complications, who are refractory to standard therapies, because its toxicity is not justified in the majority of cases.

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Activity Evaluation
Where 1 is strongly disagree and 5 is strongly agree

	1	2	3	4	5
1. The activity supported the learning objectives.					
2. The material was organized clearly for learning to occur.					
3. The content learned from this activity will impact my practice.					
4. The activity was presented objectively and free of commercial bias.					

1. You are seeing a 52-year-old woman referred to your clinic for suspected hypereosinophilic syndrome (HES). What should you consider regarding the diagnostic approach to HES?
   - ☐ **A** Hypereosinophilia must be present for at least 6 months prior to diagnosis and treatment
   - ☐ **B** The cause of HES remains undefined in 75% of patients
   - ☐ **C** The most common organ involved in HES is the liver
   - ☐ **D** Cardiac manifestations are most common in cases of lymphocytic variant HES (L-HES)

2. You decide to begin treatment for this patient. What should you consider regarding initial therapy for HES?
   - ☐ **A** Corticosteroids can reduce eosinophilia after 1–2 weeks of treatment
   - ☐ **B** Elevated serum IgE levels predict a good response to treatment with corticosteroids
   - ☐ **C** The dose of corticosteroid required to maintain disease control is highly variable
   - ☐ **D** Hydroxyurea is best employed as a solo agent

3. The patient has a poor response to initial therapy. What else should you consider regarding treatment for HES?
   - ☐ **A** Flu-like symptoms associated with IFN-α worsen with time on the medication
   - ☐ **B** Imatinib mesylate is limited by its slow onset of action
   - ☐ **C** Imatinib mesylate is the first-line therapy for F/P^{pos} chronic eosinophilic leukemia
   - ☐ **D** The efficacy of treatment with anti-IL-5 dissipates as soon as the medication is withdrawn

4. Which of the following is the most important biomarker to follow to gauge this patient's response to treatment?
   - ☐ **A** Eosinophil counts from the peripheral blood
   - ☐ **B** The eosinophilic cationic protein MBP1
   - ☐ **C** The eosinophilic cationic protein ECP
   - ☐ **D** The eosinophilic cationic protein EDN