

Hypereosinophilic Syndrome: An Update

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Hypereosinophilic syndrome (HES) is a rare disorder that is characterized by persistent and marked eosinophilia combined with organ system dysfunction. HES has substantial clinical heterogeneity but can be fatal without treatment, especially in patients who present with a myelodysplastic variant of the disorder. Although the pathophysiology of HES is poorly defined, dysregulation of cytokines (interleukin 5 [IL-5], IL-3, granulocyte-macrophage colony-stimulating factor [GM-CSF]) responsible for the maturation of eosinophils is a primary feature. Of these cytokines, IL-5 appears to have the greatest role in the regulation of eosinophil maturation. There is no Food and Drug Administration-approved treatment for HES as yet; current strategies are designed to lower blood eosinophils and attempt to limit end-organ damage. Historically, corticosteroids and cytotoxic agents have been the mainstays of therapy, with biological response modifiers such as interferon-alpha also effective in some patients. However, despite improvements in survival, available agents have significant limitations in terms of efficacy, tolerability, and long-term toxicity. More recently, new agents directed at specific targets in the pathogenesis of HES have been developed. These include imatinib mesylate, a tyrosine kinase inhibitor, and more recently, mepolizumab, an anti-IL-5 monoclonal antibody. In a small case series of patients, these agents have been shown to produce hematological and clinical responses in patients with HES, although they may be effective in different subsets of patients. These targeted therapies have the potential to improve clinical outcomes and to further the understanding the pathophysiology of this difficult-to-treat condition. *Am. J. Hematol.* 80:148–157, 2005. © 2005 Wiley-Liss, Inc.

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INTRODUCTION

Hypereosinophilic syndrome (HES) is a term used to describe a wide variety of eosinophilic disorders without a known etiology [1]. The hallmark characteristics of this syndrome are a persistent eosinophilia combined with unexplained organ-system dysfunction [2,3]. HES has substantial clinical heterogeneity and a highly variable prognosis [4]. As late as the 1970s, HES was associated with an extremely poor prognosis with a mean survival duration of 9 months and a 3-year survival rate of only 12% [5]. Recent advances in the management of HES, including earlier diagnosis and improved management of cardiac sequelae, have extended survival in HES patients. For example, among 40 patients with HES from France,

Lefebvre et al. reported 80% survival at 5 years and 42% survival at 10 and 15 years [6].

Despite improvements in survival among patients with HES, the disease remains difficult to manage.

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Treatment strategies are aimed at symptom control and limiting end-organ damage by lowering blood eosinophils. There is no U.S. Food and Drug Administration (FDA)-approved drug indicated for the treatment of this syndrome, and currently used agents, such as corticosteroids and cytotoxic chemotherapy, have significant limitations in terms of efficacy and safety. Therefore, there is a pressing need to develop new therapeutic agents with improved efficacy, safety, and tolerability profiles. This article presents an overview of the epidemiology, pathogenesis, and clinical presentation of HES, which is followed by a review of current management approaches and a discussion of emerging treatment strategies.

DIAGNOSIS OF HES

HES is a heterogeneous group of disorders whose common feature is persistent eosinophilia with organ-system dysfunction related either to infiltration of eosinophils or secondary to eosinophil-associated damage to tissue [5]. In 1975, Chusid et al. established empirical diagnostic criteria for idiopathic HES that remain in use today: (1) blood eosinophilia exceeding 1,500/ μ L for more than 6 consecutive months with signs and symptoms of hypereosinophilic disease; (2) absence of an underlying cause of hypereosinophilia despite extensive diagnostic evaluation; and (3) organ damage or dysfunction as a result of local release of the toxic contents of eosinophils [5]. Typical frequencies of organ involvement are shown in Table I.

Because there is no specific diagnostic test for HES, the diagnosis of the syndrome is one of exclusion [7,8]. Hypereosinophilia is a common clinical finding that can be secondary to a number of disorders, such as parasitic disease, allergy, drug reactions, and malignant or vasculitic diseases [4,8,9]. The diagnosis of HES is further complicated by a large number of diseases reported in the medical literature that have

identical clinical and histological presentations: Churg Strauss, hypersensitivity vasculitis, Loffler syndrome (Loffler's endocarditis syndrome), PIE syndrome (pulmonary infiltrates with eosinophilia), eosinophil leukemia, myeloproliferative disorders with predominant eosinophilia, and some chromosomal translocations with pre-leukemic states [1,5].

Distinguishing HES from eosinophilic leukemia is particularly problematic, but the differential diagnosis of these diseases has prognostic and therapeutic implications [4,7]. In general, patients with chronic eosinophilic leukemia have specific cytogenetic abnormalities [7]. The presence of increases in blast cells, hepatomegaly, splenomegaly, anemia, and thrombocytopenia also favors diagnosis of eosinophilic leukemia [7]. However, with the recent identification of the abnormal fusion of the *FIP1L1* and *PDGFRA* genes in some HES patients, it has been proposed that there can be overlap between eosinophilic leukemia and classic HES (of the myeloproliferative type).

Three recently defined subtypes of HES have been described: myeloproliferative, lymphocytic, and idiopathic variants [4]. The myeloproliferative subtype is usually characterized by chromosomal abnormality, tyrosine kinase involvement, elevated levels of dysplastic mast cells in the bone marrow, as well as mast cell products in the circulation (serum tryptase), elevated levels of vitamin B₁₂, and splenomegaly. Tyrosine kinase involvement is due to a rearrangement of genes that code for tyrosine kinases, thus altering the activity or regulation of the production of the resultant proteins. The lymphocytic subtype is characterized by an abnormal T cell (aberrant phenotype) and is associated with increased Th2 lymphocyte production of interleukin 5 (IL-5), interleukin 3 (IL-3), and granulocyte-macrophage colony-stimulating factor (GM-CSF). The pathogenic T cells often have a variety of abnormal surface markers, such as the α chain of the IL-2 receptor and the class II major histocompatibility complex molecule HLA-DR antigen [10]. The clonal proliferation of these aberrant lymphocytes is often associated with progression to lymphoma [4]. Idiopathic HES is a subtype of the disease that is not associated with a specific chromosomal or clonal abnormality.

Clinically distinguishing characteristics of the subtypes of HES are shown in Table II. Testing to differentiate among the subtypes of HES is not widely available. Flow cytometry can be used to identify phenotypically aberrant subsets of T cells; however, these abnormalities are often very discrete and difficult to identify because they may result in slight alterations of staining intensity for surface antigens [4]. It is likely that further advances in the understanding of the pathophysiology of HES will result

TABLE I. Frequency of Organ Involvement Observed in Three Large Series of Patients*

Organ system	Frequency (<i>N</i> = 105)
Hematologic	100%
Cardiovascular	58%
Cutaneous	56%
Neurologic	54%
Pulmonary	49%
Splenic	43%
Hepatic	30%
Ocular	23%
Gastrointestinal	23%

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TABLE II. Clinically Distinguishing Characteristics of the Sub-types of Hypereosinophilic Syndrome (HES)

Myeloproliferative HES	Lymphocytic HES
Cardiac complications	Cutaneous manifestations (pruritus, eczema, erythroderma, urticaria, angioedema)
Anemia and/or thrombocytopenia	Increased serum immunoglobulin E levels
Abnormal leukocyte alkaline phosphatase score	Increased interleukin-5-producing T-cell population with cytogenetic changes
Increased serum vitamin B ₁₂	Polyclonal hypergamma-globulinemia
Chromosomal abnormalities	
Hepatomegaly, splenomegaly	
Splenomegaly	

in the replacement of HES with terminology for more well-defined hematological disorders that can be identified with specific tests.

EPIDEMIOLOGY OF HES

There are no published data regarding the incidence/prevalence of HES, although the syndrome is considered rare in adults and very rare in children [11]. An informal estimate of prevalence was derived using the National Hospital Discharge Survey, a stratified random sample of discharges from hospitals in the United States. As an upper bound for prevalence, there were approximately 6,000 discharges with at least one discharge diagnosis falling under the International Classification of Diseases rubric for eosinophilia (288.3; including allergic, hereditary, idiopathic, and secondary forms) in 2000 (based on 47 occurrences in the sample population). To further refine the estimate, the complete array of diagnoses for all discharges in 1999 and 2000 were reviewed by one of us (J.W.), which revealed that about one-third of patients with eosinophilia had comorbid diagnoses compatible with HES. This refinement suggested a prevalence of about 2,000 cases (i.e., 33% of 6,000 total eosinophilia discharges) in the U.S. However, because HES is under-diagnosed by primary care physicians, this estimate likely represents a several-fold underestimation of the prevalence of the syndrome. Approximately 60% of patients with HES have aggressive infiltrative disease at initial diagnosis, with the remainder having a less aggressive disease. Because high blood eosinophilia often occurs in several other more common idiopathic disorders, such as eosinophil-associated gastrointestinal disorders, the true prevalence of HES, using a broad definition that includes these disorders, may be much higher.

A similar approach to that above that might possibly capture nonhospitalized patients (by selecting all patients with eosinophilia [288.3] as a diagnosis and reviewing concomitant diagnoses) was used in a separate evaluation of a U.S. claims database. Application of the rates from this dataset to the overall U.S. population gave an estimate of 785 inpatients and 2,011 outpatients (ratio of outpatients to inpatients = 2.5). If this ratio is applied to the discharge estimate, it suggests about 5,000 patients with HES. These data are consistent with the above suggestion that the prevalence of HES may be higher than the one based purely on hospital discharges. By contrast, prevalence of chronic myeloid leukemia in the U.S. is between 14,500 and 16,000 cases in the year 2000 [12].

The age of onset of HES is variable, occurring anywhere from early childhood to extreme old age, although the majority (70%) of patients have onset between 20 and 50 years of age [5,6,11,13]. The majority of patients (approximately three-quarters) described in reports from Europe and North America were Caucasian, and males were more likely to be afflicted than females, with male/female ratios ranging from 4:1 to 9:1 [2,5,6,13].

PATHOGENESIS AND CLINICAL MANIFESTATIONS OF HES

Pathogenesis

Because of the clinical heterogeneity of patients with HES, it is likely that there are multiple mechanisms involved in the pathophysiology of the disease. The eosinophil is formed in the bone marrow where it spends about 8 days maturing, under the regulation of the transcription factors GATA-1, GATA-2, and c/EBP. Notably, GATA-1 and GATA-2 over-expression are sufficient signals for promoting eosinophil development in avian, murine, and human systems. Additionally, mice with a targeted genetic deletion in the high-affinity GATA site present in the GATA-1 promoter are selectively deficient in the eosinophil lineage. These transcription factors provide “instructional” signals that cooperate with the “permissive” eosinophil growth factors IL-3, IL-5, and granulocyte-macrophage colony stimulating factor (GM-CSF). These three four-helix bundle cytokines bind to cell-surface receptors composed of an alpha chain and a beta chain. The alpha chain is specific for the individual cytokine (i.e., IL-5R α is the alpha chain that specifically binds IL-5, GMR α specifically binds GM-CSF, and IL-3R α specifically binds IL-3). The beta chain is shared by all 3 receptors, and is termed β c (for common beta chain) and is the signal-transducing unit [14].

IL-5 is the most specific to the eosinophil lineage and is responsible for the selective expansion of eosinophils and their release from the bone marrow. Signal transduction following IL-5 binding (Fig. 1) proceeds along multiple pathways, including the Janus kinase-signal transducers and activators of transcription (JAK-STAT) pathway, which induces regulation of gene transcription, the Ras-Raf pathway with subsequent mitogen-activated protein (MAP) kinase activation and phosphoinositol-3 kinase (PI3K) activation with subsequent activation of protein kinase B (PKB), which enhances cell survival [15].

Following IL-5 signaling, eosinophils subsequently relocate into the peripheral circulation for 8–12 hr and finally traffic to specific tissues, predominantly the gastrointestinal tract, under the regulation of the chemokine eotaxin-1. The critical role of IL-5 in the production of eosinophils is best demonstrated by genetic manipulation of mice. Overproduction of IL-5 by a variety of approaches including transgenic over-expression results in profound eosinophilia, and deletion of the IL-5 gene causes a marked reduction of eosinophils in the blood, lungs, and gastrointestinal tract after allergen challenge.

The exact etiology of HES is unknown; however, the process probably involves a dysregulation of

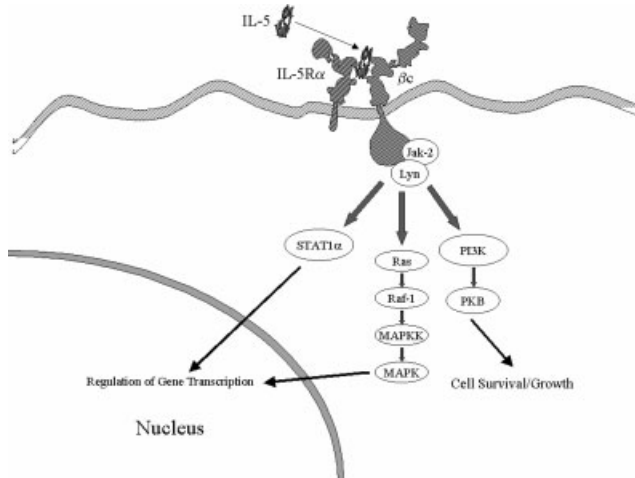


Fig. 1. Signal transduction in eosinophils induced by interleukin-5 (IL-5). IL-5 binds to a heterodimeric cell-surface receptor comprised of an alpha chain specific for IL-5 (IL-5R α) and a beta chain that is shared with the IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF) receptors (β c). The β c chain is activated upon binding and receptor aggregation, and via the Jak and Lyn kinases activates downstream effector pathways, including STAT1 α , with effects on gene transcription, the Ras-Raf-1-MAP kinase pathway, also affecting gene transcription, and the PI3K-PKB pathway, with effects on cell survival and growth. Abbreviations: MAP, mitogen-activated protein; PI3K, phosphoinositol-3 kinase; PKB, protein kinase B.

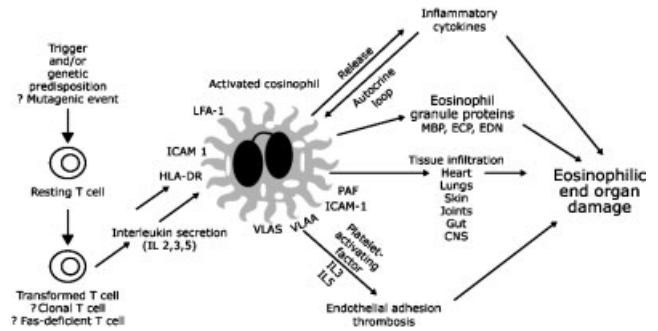


Fig. 2. Diagrammatic pathogenetic model of the idiopathic hypereosinophilic syndrome. Abbreviations: MBP, major basic protein; EcCP, eosinophilic cationic protein; EDN, eosinophil derived neurotoxin; PAF, platelet-activating factor. Integrins: LFA-1, leucocyte function activation; ICAM-1, intercellular adhesion molecule; VCAM-1, vascular cell adhesion molecule; VLA4 and VLA6, very late antigen.

IL-3, IL-5, and/or GM-CSF (Fig. 2) [3,4]. Overproduction of one or more of these cytokines is sufficient to induce blood and tissue eosinophilia by stimulating bone marrow generation of eosinophils, migration of eosinophils into the bloodstream, and increasing the survival of eosinophils [4,11]. While IL-3 and GM-CSF have activities on other hematopoietic lineages, IL-5 is highly specific for the eosinophil/basophil lineage [16]. Evidence suggests that IL-5 is the major cytokine implicated in HES and other eosinophilic diseases, indicating a unique role for this cytokine [3,7,16]. Although mastocytes, basophils, and eosinophils are all sources of IL-5, T-lymphocytes are the primary source of IL-5 [4,17]. These are usually classified as Th2 cells, and they tend to skew the immune system toward atopic/allergic immune responses characterized by production of IgE and certain IgG subclasses as well as eosinophil activation. Interestingly, the role of IL-5 differs in the murine and human immune systems. In the murine system, IL-5 receptors are present on lymphocytes, and it is known to act as a growth and differentiation factor on B cells. In humans, IL-5 receptor expression is limited to eosinophils and basophils, and effects on lymphocytes are not directly produced.

Although the exact mechanism of eosinophil-related tissue damage is not known, eosinophil accumulation appears to have pathological consequences. Eosinophils have direct cytotoxicity through the local release of toxic substances including cationic proteins, enzymes, reactive oxygen species, pro-inflammatory cytokines, and arachidonic acid-derived factors [4,18]. The degree of end-organ damage is heterogeneous, and there is often not a correlation between the level or duration of eosino-

philia and the severity of organ damage [3]. Many patients exhibit the involvement of multiple organ systems, and end-organ damage is most frequently seen in the heart, lungs, liver, nervous system, skin, and digestive tract (Fig. 2) [2–4]. In particular, cardiac involvement is the major cause of the morbidity and mortality associated with HES [3].

Clinical Manifestations

Patients may present with various nonspecific symptoms: weakness, fatigue, cough, dyspnea, myalgias, angioedema, rash, fever, and diarrhea [2,3,8]. The spectrum of clinical presentations ranges considerably, from those with asymptomatic disease to those with leukemia (Table II).

An intermediate hypersensitivity-type presentation is characterized by angioedema, hypergammaglobulinemia, elevated levels of serum IgE, and circulating immune complexes. Patients with this presentation are less likely to develop heart disease, have a benign clinical course, and typically respond well to steroids [9]. The intermediate infiltrative-type presentation is characterized by splenomegaly, thrombocytopenia, elevated levels of serum vitamin B₁₂, vacuolated eosinophils, and eosinophils with smaller granules than normal. These patients are at increased risk for endomyocardial fibrosis (cause of greatest morbidity) or frank leukemia with blast cells [9].

Considerable heterogeneity exists among patients with HES, and various subdivisions of the disease have been recently recognized. The syndrome of episodic angioedema associated with eosinophilia was first described in the 1980s [19], and the nodules, eosinophilia, rheumatism, dermatitis, and swelling (NERDS) syndrome was recognized later [20]. A variety of other diseases, such as eosinophilic gastroenteritis [21] and eosinophilic pneumonia, satisfy the criteria for HES and may respond to the same treatments.

Markers of poor prognosis in HES include the presence of anemia, thrombocytopenia, white blood cell count greater than 100,000 cells/cm³, abnormal marrow and/or basophils, elevated serum levels of vitamin B₁₂, serum tryptase, and abnormal levels of leukocyte alkaline phosphatase [2,5]. Cardiac involvement is also associated with a poor clinical outcome [2,5,22]. Indeed, prior to the introduction of current treatment protocols, the majority of deaths in patients with HES were a result of cardiac complications and thromboembolic events [5,13]. Development of congestive heart failure was often secondary to vascular and valvular damage [5,13].

MANAGING HES

Goals of Therapy

Currently, there is no FDA-approved treatment or universally effective therapy for HES, and there is no cure. The three primary goals for the management of HES are the following: (1) reduction of peripheral and tissue levels of eosinophils; (2) prevention of end-organ damage; and (3) prevention of thromboembolic events in patients at risk [2,9,23]. Early diagnosis and intervention are necessary to prevent disease progression and end-organ damage, and chronic maintenance therapy is usually required [3].

The classic management algorithm developed by the National Institutes of Health (NIH) is a step-by-step escalation of therapy that is dependent on the degree of eosinophilia and the clinical status of the patient [2]. Patients without progressive organ system dysfunction typically do not require specific treatment; however, these patients should be monitored closely [2]. For those with mild disease that is limited to the skin, symptomatic treatment combined with close follow-up is indicated [2,3]. In contrast, patients with vital organ involvement require more intense treatment [2,3]. Chronic maintenance therapy has been recommended (as opposed to aggressive treatment designed to produce a “remission”) as a more effective method of preventing the development of end-organ damage [3].

TREATMENT OPTIONS

Corticosteroids

Corticosteroids are considered first-line therapy for symptomatic treatment of patients with HES (Table III) [3,9,23]. High-dose prednisone is typically initiated at a dose of 1 mg/kg/day (≈ 60 mg) because it rapidly decreases eosinophil levels [3,9]. Once eosinophilia is properly controlled, the drug can be tapered progressively [9]. Patients who will respond to corticosteroid therapy can usually be identified early in the course of therapy, often on the first day [9]. If eosinophilia is not controlled with high-dose corticosteroids, maintenance therapy with these agents is unlikely to be of value [3]. Characteristics of corticosteroid-refractory patients include splenomegaly and cardiac or neurologic dysfunction at presentation [24]. In an NIH series of patients, 6/16 (38%) had a good response (symptoms/signs of disease disappeared or clearly improved) to prednisone and another 5 (31%) had a partial response (symptoms/signs stabilized or a definite slowing of disease progression) [22].

TABLE III. Treatment Options for Hypereosinophilic Syndrome*

Treatment	Mechanism of action	Side effects
Corticosteroids	Inhibit the production of cytokines and chemokines Induce apoptosis in eosinophils	Osteoporosis Myopathy Diabetes Cushingoid phenotype Cataracts Growth suppression
Cytotoxic agents (hydroxyurea, vincristine, cyclophosphamide, busulfan, methotrexate, chlorambucil)	Impede DNA synthesis Inhibit bone marrow-derived cells	Leukopenia Anemia Thromocytopenia
Biological response modifiers Interferon-alpha	Inhibits chemotaxis Decreases the secretion of cytokines	Flu-like symptoms GI effects (nausea, vomiting, diarrhea) CNS effects (fatigue, headache, depression, irritability, anxiety, nervousness, insomnia) Myalgia Arthralgia Alopecia
Cyclosporine	Suppresses the production of activated T cells	Nephrotoxicity Hepatotoxicity CNS effects (convulsions, tremor, headache, paresthesia) CV effects (hypertension, cramps)
Targeted therapy Imatinib mesylate	Inhibits tyrosine kinase	GI intolerance Abnormal liver function tests Myelosuppression Rash Edema Weight gain
Mepolizumab	Anti-interleukin-5 monoclonal antibody Arrests eosinophil maturation within the bone marrow	Fatigue Headache

*Abbreviations: CNS, central nervous system; CV, cardiovascular; GI, gastrointestinal.

Corticosteroids appear to act at least partially through an inhibition of the production of various cytokines and chemokines involved in the maturation and activation of eosinophils. They may induce apoptosis in eosinophils by interfering with the ability of IL-5, IL-3, and GM-CSF to promote the development of eosinophils [3,4]. Corticosteroids may also promote the redistribution of eosinophils from the blood to the spleen and lymph nodes [3,4] and decrease levels of eosinophil chemoattractants such as the chemokine eotaxin.

The primary limitations associated with corticosteroid therapy are the well-known adverse effects that occur with their long-term use (e.g., osteoporosis, myopathy, diabetes, Cushingoid phenotype, cataracts, etc. and growth suppression in children). Because of these effects, corticosteroids are not favored for use in pediatric patients or for maintenance therapy.

Cytotoxic Agents

Until recently, cytotoxic agents were considered second-line therapy in corticosteroid-refractory patients and were typically used in patients who continued to have end-organ involvement despite the use of corticosteroids (Table III) [3,4]. The mechanism of action of cytotoxic agents is the inhibition of bone marrow-derived cells by impeding DNA synthesis. Hydroxyurea is the most commonly used cytotoxic agent, along with vincristine, cyclophosphamide, busulfan, methotrexate, and chlorambucil. However, there are only case reports describing the use of the various cytotoxic agents. For example, in the NIH series, 6 of 8 patients (primarily corticosteroid-refractory) achieved a good response to hydroxyurea, with the other 2 having a partial response [22]. Hematological response to hydroxyurea is typically not observed until 7–14 days after the initiation of therapy, reflecting the turnover of circulating eosinophils [3,4].

Because cytotoxic treatment does not specifically target eosinophils but affects all rapidly dividing cells, adverse events can be serious and the tolerability profiles of these drugs tend to be quite poor [3]. In particular, hematological adverse events (e.g., leukopenia, anemia, thrombocytopenia) are among the most commonly reported side effects. Among cytotoxic agents, vincristine has the least effect on bone marrow and may, therefore, be of use in patients with poor bone marrow reserve [13].

Biological Response Modifiers

Based on its demonstrated efficacy in chronic myelogenous leukemia and multiple myeloma, interferon-alpha ($IFN\alpha$) has recently been evaluated in the treatment of patients with HES (Table III) [3,4,25]. $IFN\alpha$ is a biological response modifier with a number of direct actions on eosinophils, such as the inhibition of chemotaxis and the decreased production of hydrogen peroxide and peroxidase in response to stimulus [23]. $IFN\alpha$ also has indirect effects on the growth factors and cytokines that regulate eosinophil proliferation; for example, inhibiting the secretion of GM-CSF, granulocyte colony-stimulating factor (G-CSF), and $IL-1\beta$ from the bone marrow and decreasing the production of $IL-5$ by $CD3^-CD4^+$ cells [4,23].

Treatment with $IFN\alpha$ is associated with clinical, biological, and cytogenetic remission in some HES patients [4], and its effects can be long lasting (up to 5 years) [23,26]. In most cases, $IFN\alpha$ has been used in highly variable dosing regimens to treat patients with the myeloproliferative type of HES who had failed to respond to treatment with standard therapies. In most patients, treatment with $IFN\alpha$ has produced both clinical improvement and decreases in the circulating levels of eosinophils [23,26]. Based on these encouraging results, $IFN\alpha$ is now considered the treatment of choice in corticosteroid-refractory patients.

One of the potential limitations associated with $IFN\alpha$ therapy is that the drug may prolong survival of clonal $CD3^-CD4^+$ cells by inhibiting spontaneous apoptosis, thereby providing these cells with a selective advantage [4]. Although this is a theoretical concern, there is no evidence that this is important in clinical practice. Other disadvantages are that $IFN\alpha$ therapy is inconvenient because it requires frequent injections and adverse events frequently occur, particularly during the initial stages of treatment. The most common adverse events include fatigue, headache, fever, chills, flu-like symptoms, myalgia, arthralgia, nausea, vomiting, diarrhea, depression, irritability, anxiety, nervousness, insomnia, and alopecia [9]. These adverse effects can be significant,

affecting the patients' quality of life as well as their ability to remain on long-term therapy.

Cyclosporin has been used occasionally in patients with HES, usually in combination with corticosteroids (Table III) [3,27]. The use of this agent is based on its ability to suppress the production of activated T cells, possibly by interference with the anti-apoptotic effects of $IL-2$ [9,27]. In one small series, cyclosporin was effective in decreasing eosinophils and ameliorating clinical symptoms while decreasing the need for corticosteroids [27]. However, cyclosporin is associated with substantial adverse effects (e.g., nephrotoxic, central nervous system, and cardiovascular effects), and its use requires monitoring of serum concentrations of the drug.

Imatinib Mesylate

Imatinib mesylate is a tyrosine kinase inhibitor that blocks signal transduction via tyrosine kinase oncoproteins including bcr-abl (a constitutively activated tyrosine kinase arising from a gene translocation between the *bcr* and *c-abl* genes) and receptors for stem cell factor (c-kit) and platelet-derived growth factor receptor (PDGFR) [28,29]. The drug is approved for use in chronic myelogenous leukemia and gastrointestinal stromal tumors and is currently available in 80 countries. The rationale for the use of imatinib mesylate in HES is based on the constitutive activation of tyrosine kinases as a key element in the pathogenesis of myeloproliferative diseases (Table III). The efficacy of imatinib mesylate has been evaluated in several case reports and small series of patients with HES [30–35]. Early reports suggested that this drug is primarily effective among patients with normal $IL-5$ serum levels [32]; however, results from a subsequent series of patients suggest that elevated $IL-5$ serum levels are not useful in distinguishing responders from nonresponders [35]. In another study, elevated serum tryptase levels identified a subset of patients with the myeloproliferative subtype of HES who had tissue fibrosis, poor prognosis, and were responsive to treatment with imatinib [33,34]. In the largest series, 9 of 11 patients treated with imatinib mesylate had responses that lasted more than 3 months [31]. A chromosomal analysis revealed the presence of a novel constitutively activated tyrosine kinase in 5 of the 9 responders, suggesting that this kinase is the target of imatinib mesylate [31]. In these patients, a deletion in chromosome 4 brought together a DNA sequence homologous to yeast protein FIP1 (FIP1L1) and the gene for the cytoplasmic domain of the PDGFR α receptor, producing the *FIP1L1-PDGFR α* fusion gene. In another study

conducted in 7 patients with the myeloproliferative variety of HES and with the *FIPILI-PDGFR*A fusion gene present, treatment with imatinib mesylate caused serum tryptase levels to decline to normal levels [33,34]. At the same time, detectable *FIPILI-PDGFR*A transcripts disappeared in 5 of 6 patients. Although the eosinophilia resolved and clinical improvement was observed in all patients, cardiac abnormalities due to hypereosinophilia remained despite treatment.

Therapy with imatinib mesylate is pharmacologically suitable for patients with the *FIPILI-PDGFR*A gene; however, approximately 40% of the patients with HES who respond to treatment with the drug also lack the fusion gene, indicating the involvement of other activated tyrosine kinases in these patients [36]. Furthermore, it is likely that HES patients with classical symptoms as described by Chusid et al. [5] are also responsive to the drug [37]. Thus, although recent reports describe impressive improvement in patients with HES, imatinib mesylate is only effective in some patients, only male patients thus far, those with overactive tyrosine kinases. An even more important problem is that resistance to therapy may develop with time [31].

Notably, the *FIPILI-PDGFR*A α gene rearrangement is a novel clonal abnormality that is not evident on standard karyotyping; therefore, patients with this abnormality should be classified by World Health Organization criteria as having chronic eosinophilic leukemia (CEL) rather than HES [38]. However, because both HES and CEL are associated with the *FIPILI-PDGFR*A gene fusion, and some patients with either disease respond to treatment with imatinib mesylate, the WHO classification scheme for differentiating between CEL and HES may need to be revised [36].

Adverse events associated with imatinib mesylate include gastrointestinal intolerance, abnormal liver function tests, myelosuppression, rash, edema, and weight gain [39]. In addition, the long-term efficacy of imatinib mesylate remains to be established, as well as the ability of the drug to reverse eosinophil-related organ damage. In addition, imatinib has not yet been approved for pediatric usage. Clinical trials with lower doses of imatinib mesylate are currently underway, and side-effect issues should be less of a problem.

Limitations Associated With Current Therapy

Despite recent advances, there remains a limited understanding of the pathogenesis of HES. This lack of understanding means that there is currently no specific target for therapy, and current treatment regimens

are either not effective in a large proportion of patients, do not produce a sustainable response, or cannot be tolerated for long-term maintenance therapy. The adverse effects associated with current therapies also make them undesirable for long-term treatment. Consequently, there is a need for a safe, effective, and well-tolerated therapy that allows for effective long-term management of the disease. This is particularly true for those with aggressive disease where current regimens produce limited survival benefit.

FUTURE STRATEGIES FOR MANAGING HES: TARGETING IL-5

Because IL-5 has a crucial role in the maturation, growth, and survival of eosinophils, an agent that targets this cytokine has therapeutic potential in the treatment of HES. Mepolizumab is a fully humanized anti-IL-5 monoclonal antibody that produces rapid, marked, and sustained reductions in eosinophil counts (Table III) [40–42]. The effect of mepolizumab appears to be due to the Arresting of eosinophil maturation within the bone marrow [42]. Notably, mepolizumab decreases eosinophils without altering the distribution and activation status of lymphocytes [40].

Data evaluating mepolizumab in the treatment of HES are limited, and only a few small series have been reported [43–45]. Plotz et al. described 3 patients who received intravenous infusions of mepolizumab (750 mg) for treatment of corticosteroid-resistant HES that was characterized by eosinophilic dermatitis and increased levels of IL-5 [45]. Skin symptoms (e.g., pruritus) disappeared within 1 week, and blood eosinophil counts returned to normal within 24 hr [45]. In another series involving 4 patients with a broad spectrum of eosinophil-associated disorders including HES, mepolizumab produced declines in peripheral eosinophil counts that were sustained for at least 8 weeks after the last dose and were associated with improvements in clinical status and quality of life [43]. Mepolizumab was very well tolerated in these case series, with only mild adverse events noted [45]. No positive titers for antibodies to mepolizumab (either anti-framework or anti-idiotypic) for up to 16 weeks post-dose have been detected, and no cases of anaphylaxis or serum sickness have been reported [46]. Further trials are required to assess the long-term efficacy and safety of mepolizumab in patients with HES.

A different monoclonal antibody to IL-5, SCH55700, was investigated in 4 patients with HES resistant to conventional treatment [47]. In 2 patients, a single 1 mg/kg dose of SCH55700 caused the eosinophil counts to decrease to normal within 48 hr after receiving the drug. Response to the drug was not

correlated with serum IL-5 levels or the presence or absence of the *FIP1L1/PDGFRA* mutation. The eosinophil counts remained low for up to 12 weeks, then rebound eosinophilia occurred. Monthly treatment with SCH55700 decreased the eosinophilia and improved symptoms. This provides further evidence that anti-IL-5 treatment may be useful for treating HES, regardless of the specific etiology.

CONCLUSIONS

HES is a heterogeneous disease syndrome and is characterized by a variety of disease patterns. Controlling the eosinophilia in blood and tissue is important in order to prevent end organ damage from eosinophils. Despite improvements in medical management, HES remains a serious condition with a poor prognosis for the majority of patients. Currently available therapies for HES are not adequate; an effective, safe, and tolerable treatment option is required to minimize the morbidity and mortality associated with HES. A better understanding of eosinophil biology and HES pathogenesis has resulted in new therapies directed at novel targets. New agents, such as imatinib mesylate and mepolizumab, target specific abnormalities associated with HES and have the potential to improve clinical outcomes in HES.

REFERENCES

- Hardy WR, Anderson RE. The hypereosinophilic syndromes. *Ann Intern Med* 1968;68(6):1220–1229.
- Fauci AS, Harley JB, Roberts WC, et al. NIH conference. The idiopathic hypereosinophilic syndrome. Clinical, pathophysiologic, and therapeutic considerations. *Ann Intern Med* 1982;97(1):78–92.
- Weller PF, Bubley GJ. The idiopathic hypereosinophilic syndrome. *Blood* 1994;83(10):2759–2779.
- Roufousse F, Cogan E, Goldman M. The hypereosinophilic syndrome revisited. *Annu Rev Med* 2003;54:169–184.
- Chusid MJ, Dale DC, West BC, Wolff SM. The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. *Medicine (Baltimore)* 1975;54(1):1–27.
- Lefebvre C, Bletry O, Degoulet P, et al. Prognostic factors of hypereosinophilic syndrome. Study of 40 cases. *Ann Med Interne (Paris)* 1989;140(4):253–257.
- Bain BJ. Hypereosinophilia. *Curr Opin Hematol* 2000;7(1):21–25.
- Spry CJF. Idiopathic hypereosinophilic syndrome. In: Makino S, Fukuda T, editors. *Eosinophils: biological and clinical aspects*. Boca Raton, FL: CRC; 1993. p 403–419.
- Roufousse F, Bartholome E, Schandene L, et al. The idiopathic hypereosinophilic syndrome: clinical presentation, pathogenesis and therapeutic strategies. *Drugs Today (Barc)* 1998;34(4):361–373.
- Simon HU, Plotz SG, Dummer R, Blaser K. Abnormal clones of T cells producing interleukin-5 in idiopathic eosinophilia. *N Engl J Med* 1999;341(15):1112–1120.
- Assa'ad AH, Spicer RL, Nelson DP, Zimmermann N, Rothenberg ME. Hypereosinophilic syndromes. *Chem Immunol* 2000;76:208–209.
- SEER Cancer Statistics Review, 1975–2001. Retrieved 4 August 2004 from http://seer.cancer.gov/csr/1975_2001/
- Spry CJ, Davies J, Tai PC, et al. Clinical features of fifteen patients with the hypereosinophilic syndrome. *Q J Med* 1983;52(205):1–22.
- Chaiken IM, Williams WV. Identifying structure-function relationships in four-helix bundle cytokines: towards de novo mimetics design. *Trends Biotechnol* 1996;14(10):369–375.
- Wong CK, Ip WK, Lam CW. Biochemical assessment of intracellular signal transduction pathways in eosinophils: implications for pharmacotherapy. *Crit Rev Clin Lab Sci* 2004;41(1): 79–113.
- Sanderson CJ. Interleukin-5, eosinophils, and disease. *Blood* 1992;79(12):3101–3109.
- Wardlaw AJ. Eosinophils in the 1990s: new perspectives on their role in health and disease. *Postgrad Med J* 1994;70(826):536–552.
- Gleich GJ. Mechanisms of eosinophil-associated inflammation. *J Allergy Clin Immunol* 2000;105(4):651–663.
- Gleich GJ, Schroeter AL, Marcoux JP, et al. Episodic angioedema associated with eosinophilia. *N Engl J Med* 1984;310(25):1621–1626.
- Butterfield JH, Leiferman KM, Gleich GJ. Nodules, eosinophilia, rheumatism, dermatitis and swelling (NERDS): a novel eosinophilic disorder. *Clin Exp Allergy* 1993;23(7):571–580.
- Rothenberg ME. Eosinophilic gastrointestinal disorders (EGID). *J Allergy Clin Immunol* 2004;113(1):11–28; quiz 29.
- Parrillo JE, Fauci AS, Wolff SM. Therapy of the hypereosinophilic syndrome. *Ann Intern Med* 1978;89(2):167–172.
- Yoon TY, Ahn GB, Chang SH. Complete remission of hypereosinophilic syndrome after interferon-alpha therapy: report of a case and literature review. *J Dermatol* 2000;27(2):110–115.
- Schooley RT, Flaum MA, Gralnick HR, Fauci AS. A clinicopathologic correlation of the idiopathic hypereosinophilic syndrome. II. Clinical manifestations. *Blood* 1981;58(5):1021–1026.
- Butterfield JH, Gleich GJ. Interferon-alpha treatment of six patients with the idiopathic hypereosinophilic syndrome. *Ann Intern Med* 1994;121(9):648–653.
- Baratta L, Afeltra A, Delfino M, et al. Favorable response to high-dose interferon-alpha in idiopathic hypereosinophilic syndrome with restrictive cardiomyopathy—case report and literature review. *Angiology* 2002;53(4):465–470.
- Zabel P, Schlaak M. Cyclosporin for hypereosinophilic syndrome. *Ann Hematol* 1991;62(6):230–231.
- Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med* 2001;344(14): 1038–1042.
- Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001;344(14):1031–1037.
- Ault P, Cortes J, Koller C, et al. Response of idiopathic hypereosinophilic syndrome to treatment with imatinib mesylate. *Leuk Res* 2002;26(9):881–884.
- 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):1201–1214.
- Gleich GJ, Leiferman KM, Pardanani A, Tefferi A, Butterfield JH. Treatment of hypereosinophilic syndrome with imatinib mesylate. *Lancet* 2002;359(9317):1577–1578.
- Klion AD, Noel P, Akin C, et al. Elevated serum tryptase levels identify a subset of patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome associated with tissue fibrosis, poor prognosis, and imatinib responsiveness. *Blood* 2003;101(12):4660–4666.
- Klion AD, Robyn J, Akin C, et al. Molecular remission and reversal of myelofibrosis in response to imatinib mesylate treatment in patients with the myeloproliferative variant of hypereosinophilic syndrome. *Blood* 2004;103(2):473–478.

35. Pardanani A, Reeder T, Porrata LF, et al. Imatinib therapy for hypereosinophilic syndrome and other eosinophilic disorders. *Blood* 2003;101(9):3391–3397.
36. Gotlib J, Cools J, Malone JM 3rd, Schrier SL, Gilliland DG, Coutre SE. The FIP1L1-PDGFRalpha fusion tyrosine kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia: implications for diagnosis, classification, and management. *Blood* 2004;103(8):2879–2891.
37. Leiferman KM, Gleich GJ. Hypereosinophilic syndrome: case presentation and update. *J Allergy Clin Immunol* 2004;113(1):50–58.
38. Bain B, Pierre R, Imbert M, et al. Chronic eosinophilic leukaemia and the hypereosinophilic syndrome. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. World Health Organization classification of tumours: pathology and genetics of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC Press; 2001. p 29–31.
39. Gleevec [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp.; 2003.
40. Buttner C, Lun A, Spletstoesser T, et al. Monoclonal anti-interleukin-5 treatment suppresses eosinophil but not T-cell functions. *Eur Respir J* 2003;21(5):799–803.
41. Gnanakumaran G, Babu KS. Technology evaluation: mepolizumab, GlaxoSmithKline. *Curr Opin Mol Ther* 2003;5(3):321–325.
42. Menzies-Gow A, Flood-Page P, Sehmi R, et al. Anti-IL-5 (mepolizumab) therapy induces bone marrow eosinophil maturational arrest and decreases eosinophil progenitors in the bronchial mucosa of atopic asthmatics. *J Allergy Clin Immunol* 2003;111(4):714–719.
43. Garrett JK, Jameson SC, Thomson B, et al. Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. *J Allergy Clin Immunol* 2004;113(1):115–119.
44. Koury MJ, Newman JH, Murray JJ. Reversal of hypereosinophilic syndrome and lymphomatoid papulosis with mepolizumab and imatinib. *Am J Med* 2003;115(7):587–589.
45. Plotz SG, Simon HU, Darsow U, et al. Use of an anti-interleukin-5 antibody in the hypereosinophilic syndrome with eosinophilic dermatitis. *N Engl J Med* 2003;349(24):2334–2339.
46. Data on file. King of Prussia, PA: GlaxoSmithKline; 2003.
47. Klion AD, Law MA, Noel P, et al. Safety and efficacy of the monoclonal anti-interleukin-5 antibody SCH55700 in the treatment of patients with hypereosinophilic syndrome. *Blood* 2004;103(8):2939–2941.