Workshop summary

Approaches to the treatment of hypereosinophilic syndromes: A workshop summary report

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Hypereosinophilic syndromes are a heterogeneous group of uncommon disorders characterized by the presence of marked peripheral blood eosinophilia, tissue eosinophilia, or both, resulting in a wide variety of clinical manifestations. Although corticosteroids are the first-line therapy for many of these disorders, approaches to the treatment of patients who do not tolerate or are unresponsive to corticosteroids are poorly standardized. A multidisciplinary group of 37 clinicians and scientists participated in a workshop held in May 2005 in Bern, Switzerland to discuss current and future approaches to therapy for 3 eosinophil-mediated disorders: hypereosinophilic syndrome, Churg-Strauss syndrome, and eosinophil-associated gastrointestinal disease. The goal of the workshop was to summarize available data regarding treatment of these disorders to identify the most promising therapies and approaches for further study. There was consensus among all of the participants that the identification of markers of disease progression to assess treatment responses is a research priority for all 3 disorders. Furthermore, the need for newer therapeutic strategies and novel drugs, as well as multicenter trials to assess all treatment modalities, was emphasized. (J Allergy Clin Immunol 2006;117:1292-302.)

Key words: Eosinophil, hypereosinophilic syndromes, Churg-Strauss syndrome, eosinophil-associated gastrointestinal disease, treatment

Hypereosinophilic syndromes (HESs), including idiopathic hypereosinophilic syndrome (IHES), platelet-derived growth factor receptor α (PDGFRA)–associated HES, lymphocytic variant HES (L-HES), familial hypereosinophilia, Churg-Strauss Syndrome (CSS), and eosinophil-associated gastrointestinal disease (EGID), are a heterogeneous group of uncommon disorders that are characterized by marked eosinophilia in the peripheral blood, tissues, or both, often without an identifiable cause. Although corticosteroids are the first-line treatment for many of these disorders, therapy for patients whose symptoms cannot be maintained with low doses of corticosteroids is poorly standardized, in large part because of the low prevalence of these disorders and the lack of published series comparing different agents. Recent advances in our understanding of the causes of eosinophilic disorders coupled with the availability of new agents targeting specific components of the immune response have already changed our approach to therapy in some cases (eg, the use of imatinib in PDGFRA-associated HES), highlighting the need for a rational therapeutic approach.

A 2-day workshop was convened on May 25 and 26, 2005, in Bern, Switzerland, in conjunction with the biannual meeting of the International Eosinophil Society to discuss (1) the state of currently available therapies for 3 eosinophil-mediated disorders (HES, CSS, and EGID),

Abbreviations used
ANCA: Anti-neutrophil cytoplasmic antibody
CSS: Churg-Strauss syndrome
EE: Eosinophilic esophagitis
EGID: Eosinophil-associated gastrointestinal disease
FIP1L1: Fip1-like 1
HES: Hypereosinophilic syndrome
IHES: Idiopathic hypereosinophilic syndrome
L-HES: Lymphocytic variant hypereosinophilic syndrome
PDGFRA: Platelet-derived growth factor receptor α

taking into account recent developments in diagnostic testing and advances in the understanding of the pathogenesis of hypereosinophilic conditions, and (2) novel strategies for the treatment of eosinophilic disorders (for agenda, see the Web site at http://www.pharmacology. unibe.ch/eos2005).

The workshop was funded by the Office of Rare Diseases Research of the National Institutes of Health, GlaxoSmithKline (Philadelphia, Pa), and the American Partnership for Eosinophilic Disorders. Thirty-seven clinicians and scientists from varied disciplines with expertise in the treatment of eosinophilic disorders participated in the discussions. There was consensus among all of the participants that the identification of markers of disease progression to assess treatment responses is a research priority for all 3 of the disorders. Furthermore, the need for newer therapeutic strategies and novel drugs, as well as multicenter trials to assess all treatment modalities, was emphasized.
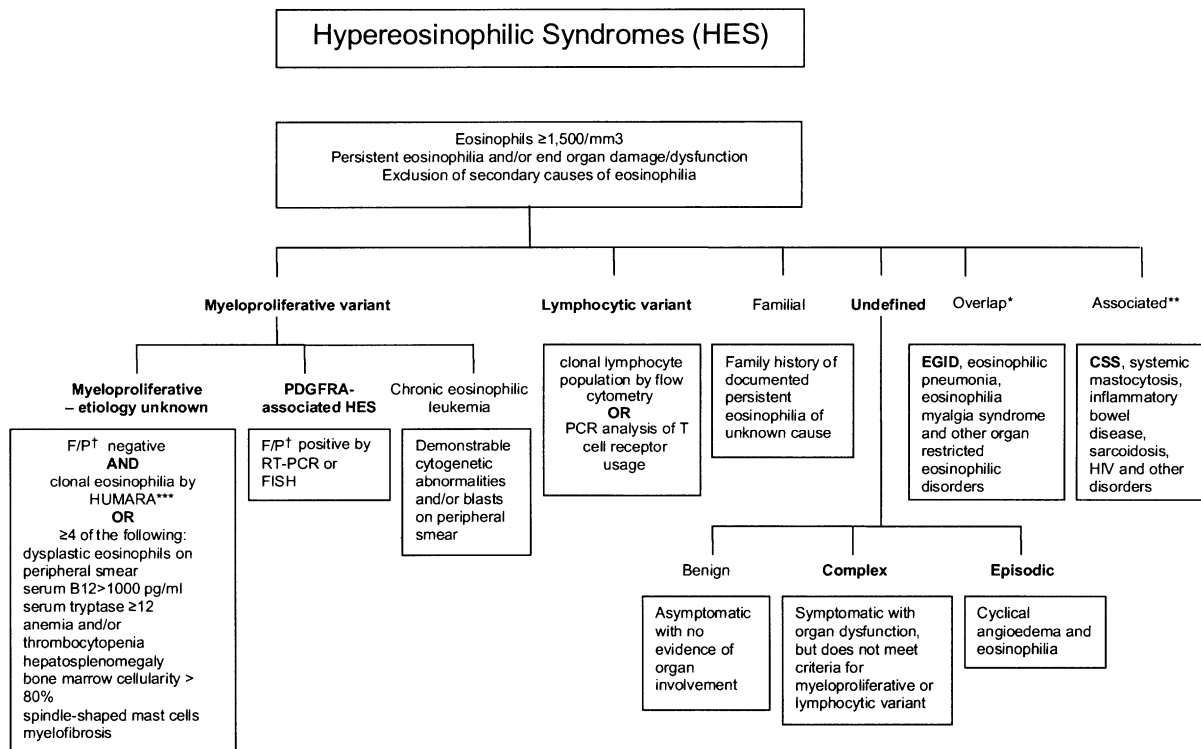
DIAGNOSIS

Central to any discussion of therapy for eosinophilic disorders is the differential diagnosis of the eosinophil-associated conditions. In the past, many of these conditions were lumped together as IHES, defined by the following: (1) the presence of eosinophilia (>1500 eosinophils/mm^3 for at least 6 months) that remains unexplained despite a comprehensive evaluation for known causes of eosinophilia (including parasitic helminth infections, HIV, drug hypersensitivity, nonhematologic malignancies, lymphomas, and primary allergic disorders) and (2) evidence of organ dysfunction directly attributable to the eosinophilia or otherwise unexplained in the clinical setting.[1] In addition, IHES was distinguished from other idiopathic eosinophilic disorders that involved limited organs, such as the eosinophilic pneumonias, EGID, and eosinophilic cystitis.[2] More recently, the heterogeneous group of disorders defined by Hardy and Anderson have begun to be reclassified, as clinical subtypes have been recognized and new molecular and immunologic markers are described.[3,4] Currently recognized subtypes include PDGFRA-associated HES, L-HES, chronic eosinophilic leukemia, and familial eosinophilia (Fig 1). Indeed, the term *idiopathic* is no longer a useful modifier of the

term *hypereosinophilic syndrome*, and there was a general consensus to use the term *hypereosinophilic syndrome* to define these heterogeneous conditions associated with high-grade peripheral eosinophilia often accompanied by eosinophilic infiltration of organ tissue. From a diagnostic point of view, many of the entities can now be reliably distinguished from other conditions associated with high-grade eosinophilia through a combination of routine and specialized testing.[4]

In some instances better clinical definition has guided treatment options, the most dramatic being the use of imatinib in the PDGFRA-associated HES.[5] Unfortunately, for the majority of individuals with HES, no definitive basis underlying their disease has been identified. Moreover, there are known clinical entities (CSS, EGID, and systemic mastocytosis) that can be associated both with marked peripheral eosinophilia and tissue-organ dysfunction or damage that must be distinguished from HES as the approach to therapy differs. With the knowledge that treatment options for many of the eosinophil-associated conditions are targeting underlying defects, the HES Working Group examined approaches to therapy of HES and 2 defined entities (CSS and EGID) that can present in a manner that is difficult to distinguish clinically from HES.

CSS is associated with significant peripheral eosinophilia, constitutional symptoms, and eosinophilic tissue infiltration but is different from HES in that it is a complex disease characterized by the presence of eosinophilic vasculitis that might involve multiple organ systems.[6] Previously referred to as allergic angiitis and granulomatosis,[7] the hallmark diagnostic criteria of CSS include eosinophilic vasculitis in addition to one or more of the following: asthmatic airway obstruction, pulmonary infiltrates, sinusitis, and neuropathy.[8] Although the cause of this disorder that affects 4 to 6 subjects per million per year[9] is unknown, CSS has both allergic and autoimmune features. These include increased numbers of circulating T cells, the presence of immune complexes, and increased serum levels of rheumatoid factor, IgE, and eosinophil cationic protein. Anti-neutrophil cytoplasmic antibodies (ANCAs) are present in about 50% of patients with CSS, but there is no direct evidence for a pathogenic role for ANCAs in patients with CSS.[10] Of note, there is increasing recognition that some patients given diagnoses of chronic eosinophilic pneumonia are either exhibiting early manifestations of CSS or will ultimately progress to CSS.

Primary eosinophil-associated gastrointestinal disorders (now referred to by the acronym EGID) are defined as disorders that affect the gastrointestinal tract with eosinophil-rich inflammation in the absence of known causes of eosinophilia (eg, drug reactions, parasitic infections, and malignancy).[11] Patients with EGID have a variety of problems, including failure to thrive, abdominal pain, irritability, gastric dysmotility, vomiting, diarrhea, and dysphagia. Although the incidence of primary EGID has not been rigorously calculated, a miniepidemic of these diseases (especially eosinophilic esophagitis [EE]) has been noted over the last decade, with estimated

Mechanisms of asthma and allergic inflammation

FIG 1. Classification of HESs. Specific syndromes discussed at the workshop are indicated in bold. *Incomplete criteria, apparent restriction to specific tissues-organs. **Peripheral eosinophilia $\geq$1500/mm^3 in association with a defined diagnosis. †Presence of the *FIP1L1/PDGFRA* mutation. ***Clonality analysis based on the digestion of genomic DNA with methylation-sensitive restriction enzymes followed by PCR amplification of the CAG repeat at the human androgen receptor gene (*HUMARA*) locus at the X chromosome. *FISH*, Fluorescence *in situ* hybridization.

prevalences of EE as high as 1:2500 among children[12] and 1:4000 among adults.[13] Although the cause of EGID remains unproved, several lines of evidence support an allergic cause with environmental and genetic components.[12,14] These include the finding that many patients with EGID are atopic and/or have evidence of food and aeroallergen hypersensitivity as defined by means of skin prick testing, allergen-specific IgE testing, and/or delayed skin patch testing and the observation that institution of an allergen-free diet often ameliorates the symptoms and might even induce remission of EGID.

TREATMENT OF HES

HES treatment outcomes: Indicators of clinical response

Although peripheral blood eosinophilia, the hallmark of HES, is an inexpensive and accessible measure with which to follow the response to treatment, the relationship between the absolute eosinophil count and eosinophil-mediated tissue damage is not consistent. Clearly there are subgroups of patients with eosinophil counts greater than 1500/mm^3 who show no evidence of clinical disease, as well as symptomatic patients with HES and normal eosinophil counts on therapy. Although a number of potential markers of disease progression, including serum levels of

eosinophil granule proteins and surface expression of eosinophil activation markers, granule proteins, or both have been suggested, none has been validated to date. Subtypes of HES for which specialized laboratory parameters might be useful to monitor the response to therapy include PDGFRA-associated HES (presence of the abnormal fusion gene, serum tryptase levels, or both[5,15]) and L-HES (numbers of phenotypically aberrant lymphocytes, development of abnormal cytogenetics, or both[16,17]). In most cases of HES, however, the current approach to the monitoring of therapy remains inexact based on a combination of clinical manifestations and absolute eosinophil counts.

Corticosteroids

Corticosteroids have been used for decades in the treatment of HES and, with the exception of PDGFRA-associated HES, remain the first-line treatment for most patients (for a summary of treatment options for HES, see Table I). Adjunctive corticosteroids are also indicated, when initiating imatinib in patients with PDGFRA-associated HES and evidence of myocarditis, as suggested by electrocardiographic or echocardiographic assessment or by the presence of an increased serum troponin level.[18] For non–PDGFRA-associated HES, the most appropriate initial corticosteroid dose and the duration of steroid therapy have not been studied, but it seems prudent to start

TABLE I. Summary of treatment options for HES

Diagnosis	Treatment	Indications	Dose	Comments
HES	Corticosteroids	First-line therapy unless *FIP1L1/PDGFRA*-positive	Varied	Initial dose ≥40 mg daily with slow taper to lowest effective dose
	Hydroxyurea	Second-line therapy	1-3 g/d	Slow onset of action (1-2 wk)
	Vincristine	Consider for counts >100,000/mm³, including in children	1-2 mg intravenously	For rapid reduction of eosinophilia, not for chronic therapy
	Other cytotoxic agents (including cyclophosphamide, 6-thioguanine, methotrexate, cytarabine, 2-CDA)	Consider for refractory HES unresponsive to corticosteroids, hydroxyurea, IFN-α	NA	Myeleran and 6-mercaptopurine have been consistently ineffective in published studies
	IFN-α	Second-line therapy	1-2 mU sq daily	Slow onset of action (1-2 wk), pegylated IFN-α appears to have comparable efficacy
	Anti–IL-5 antibody	Research indication to date	≤750 mg/kg monthly	Currently unavailable except in clinical trials or for compassionate use (mepolizumab; GlaxoSmithKline)
	Other immunomodulatory therapy (including alemtuzumab, cyclosporine, IVIG)	Consider for refractory disease	NA	Little published data
	Imatinib mesylate	First-line therapy for *FIP1L1/PDGFRA*-positive and myeloproliferative variant, consider for other refractory disease	100-400 mg daily	With corticosteroids if cardiac involvement, not useful in lymphocytic variant
	Bone marrow transplant	*FIP1L1/PDGFRA*-positive and imatinib resistant *FIP1L1/PDGFRA*-negative with disease progression despite conventional therapies	NA	Nonmyeloablative

CDA, Chlorodeoxyadenosine; *NA*, not applicable; *IVIG*, intravenous immunoglobulin.

with a moderate to high dose (≥40 mg of prednisone equivalent) and to taper very slowly while following the eosinophil count closely. Using this approach, most, but not all, patients will respond initially, and some will have their symptoms maintained on low doses of corticosteroids for long periods. For those patients requiring long-term corticosteroid treatment, evaluation of bone density, adjunctive therapies to prevent bone loss, and, in some cases, prophylaxis against opportunistic infection (notably *Pneumocystis* species–induced pneumonia) must be considered.

Predictors of a prolonged response to corticosteroid therapy include episodic angioedema, a profound and sustained eosinopenic response 4 to 12 hours after challenge with 60 mg of prednisone, an increased serum IgE level, and the lack of hepatosplenomegaly.[2] Over time, the toxicities of corticosteroid therapy become limiting in most patients, and alternative therapies must be considered.

Cytotoxic agents

A number of cytotoxic therapies have been used for the management of corticosteroid-refractory HES. Of these, hydroxyurea has been the most extensively studied at doses of 1 to 3 g/d.[19] As the dose increases, hematologic and gastrointestinal side effects become common, however, limiting the utility of hydroxyurea monotherapy in the treatment of HES. Low-dose (500 mg daily) hydroxyurea appears to act synergistically with IFN-α to lower the eosinophil count without increasing side effects and has

been useful in some cases.[20] More recently, successful treatment of a single patient with a combination of hydroxyurea and imatinib has been reported. Hydroxyurea, a drug that acts by suppressing bone marrow eosinophilopoiesis, cannot be used to decrease the eosinophil count acutely because a therapeutic effect is generally not achieved for up to 2 weeks.

Vincristine at a dose of 1 to 2 mg administered intravenously can be efficacious in rapidly decreasing eosinophilia in patients with extremely high eosinophil counts ($>100,000/mm^3$) and might be useful in the treatment of children with aggressive disease who are unresponsive to other therapies.[21] Prolonged vincristine use can be complicated by peripheral neuropathy, which is at times difficult to distinguish from underlying HES-associated neuropathies. Of the remaining cytotoxic agents for which there are published data, myeleran and 6-mercaptopurine have been consistently ineffective in the treatment of HES. Cyclophosphamide, 6-thioguanine, methotrexate, cytarabine, and 2-chlorodeoxyadenosine have each been tried in a small number of cases, with variable results.

Immunomodulatory therapy

In some patients with corticosteroid-refractory HES or intolerable side effects of corticosteroid treatment, immunomodulatory agents with effects on type 2 cytokine (eg, IL-4 and IL-5) production and T-cell proliferation, which include IFN-α, cyclosporine, and alemtuzumab, have been shown to have a therapeutic effect. Of these, IFN-α is the only one for which sufficient clinical data are available.[20] Stable responses can often be achieved with relatively low doses of IFN-α (1-2 million U/d) and might persist for prolonged periods of time. Because the effects of IFN-α on eosinophil numbers in the peripheral blood might not become evident for several weeks, escalation to an effective dose could require several months. Rarely, patients have remained in remission for extended periods of time after cessation of IFN-α therapy, suggesting that IFN-α might be curative in a small subset of individuals.

Even at low doses, systemic toxicity is common with IFN-α therapy and can be dose limiting. Low-dose hydroxyurea (500 mg daily) appears to potentiate the effect of IFN-α on suppressing eosinophilia without increasing toxicity and can be used in these situations. Monotherapy with IFN-α should be used with caution in L-HES, where in vitro data have demonstrated an inhibitory effect of IFN-α on spontaneous apoptosis of clonal $CD3^-CD4^+$ T cells.[22] In this instance the addition of corticosteroids should be considered because of their proapoptotic effect on the pathogenic T cells. It should be noted, however, that clinical data supporting the in vitro studies are not yet available. Although there are no published data regarding the use of pegylated IFN-α (0.5-1 μg/kg once weekly) in HES, responses appear to be similar to the standard IFN-α formulation, with pegylated IFN-α being better tolerated (J. Butterfield, G. Gleich, and M. E. Rothenberg, personal communication).

Monoclonal antibody therapy

Monoclonal anti–IL-5 antibody therapy for HES has a number of unique advantages related to the specificity of IL-5 for the eosinophil lineage. Preliminary studies with 2 different anti–IL-5 antibodies, SCH55700 (Schering-Plough, Deerfield, Ill) and mepolizumab (GlaxoSmithKline), demonstrated dramatic and prolonged decreasing of peripheral eosinophil counts in response to a single dose of antibody in a majority of patients with HES, regardless of the underlying cause or baseline IL-5 level.[23-25] These responses were sustained for up to a year after multiple infusions of anti–IL-5 in some patients. The therapy is extremely well tolerated, although a rebound in symptoms and eosinophilia associated with an increase in serum IL-5 levels was noted in one study as drug levels decreased.[26] The safety and efficacy of anti–IL-5 therapy as a corticosteroid-sparing agent in HES is currently being assessed in a large, double-blind, placebo-controlled study of mepolizumab.

The monoclonal anti-CD52 antibody alemtuzumab has been used successfully to treat 2 patients with HES, one of whom had a clonal population of T cells, and might provide an alternative therapy for patients with HES refractory to other therapies.[27,28]

Imatinib mesylate

Imatinib mesylate is a tyrosine kinase inhibitor with activity against several receptor tyrosine kinases, including the fusion kinase FIP1L1/PDGFRA, which is responsible for PDGFRA-associated HES. Consequently, few experts would disagree with the use of imatinib as first-line therapy in patients in whom the FIP1L1/PDGFRA fusion gene has been demonstrated or in selected patients with the characteristic clinical and laboratory features of this myeloproliferative subtype of HES (eg, male sex, tissue fibrosis, and increased serum B12 and tryptase levels). Imatinib response rates in FIP1L1/PDGFRA-positive patients approach 100%, with only 2 reported cases of acquired drug resistance, both associated with a T6741 substitution in the ATP-binding domain of PDGFRA.[5,29-31] Imatinib is the only commercially available tyrosine kinase inhibitor with activity against PDGFRA at the present time; however, additional agents now in development are likely to be effective in PDGFRA-associated HES. One of these, PKC412 (Novartis, Basel, Switzerland), has already been demonstrated to be effective against the T6741 resistance mutation in vitro.[32]

Clinical responses to imatinib in FIP1L1/PDGFRA-positive patients are rapid, with normalization of eosinophil counts generally occurring within 1 week of initiation of treatment and reversal of signs and symptoms within 1 month. The exception is cardiac involvement, which is irreversible unless treatment is begun before fibrosis leads to permanent anatomic alterations.[30] Although side effects of imatinib therapy are generally mild and rarely lead to discontinuation of therapy, acute cardiac decompensation has been observed in at least one patient at the onset of treatment with imatinib and has led to the recommendation

that patients with evidence of potential cardiac involvement (eg, increased troponin levels) be pretreated with corticosteroids.[18]

Doses of imatinib as low as 100 mg daily appear to be effective in controlling symptoms and eosinophilia in most instances, but some patients will continue to have molecular evidence of the *FIP1L1/PDGFRA* mutation at this dose.[30] In view of the data from chronic myelogenous leukemia, which suggests that clinical relapse is more common in patients with detectable residual disease,[33] it might be prudent to begin imatinib treatment at 400 mg to achieve molecular remission and then to decrease the dose slowly, following closely for evidence of molecular relapse by means of RT-PCR or fluorescence *in situ* hybridization.

The utility of imatinib therapy in hypereosinophilic patients without a demonstrable *FIP1L1/PDGFRA* mutation remains controversial, although some patients have demonstrated a response. In general, these responses have been slower and have required higher imatinib doses than those in patients with PDGFRA-associated disease. This suggests the existence of other, as yet to be determined, tyrosine kinase–based mutations in this disease. Imatinib does not appear to be useful in treating patients with L-HES and should not be used as first-line therapy in these patients.

Bone marrow transplantation

Nonmyeloablative allogeneic bone marrow transplantation has been used successfully in several patients with HES.[34] Although the toxicities of bone marrow transplantation have improved considerably in recent years, the morbidity and mortality of the procedure itself remain a problem. Consequently, this treatment modality should be reserved for patients with *FIP1L1/PDGFRA*-positive disease who become resistant to or are unable to tolerate imatinib therapy or *FIP1L1/PDGFRA*-negative patients with progressive end-organ damage once standard therapies have been exhausted. Early HLA typing to identify potential donors is recommended if transplantation is to be considered a treatment option.

TREATMENT OF CSS

Treatment outcomes: Indicators of clinical response

Management of CSS involves quelling active inflammation, suppressing the immune response, and managing disease-specific manifestations, such as asthma and sinusitis. Whereas current therapies cannot cure the disease, CSS-targeted therapies seek to minimize tissue and organ damage and prevent relapses. A variety of CSS therapies can dramatically alter the course of CSS: 50% or fewer of those who are untreated die within 3 months of diagnosis, whereas treated subjects have a 6-year survival of more than 70%.

Because untreated CSS has such a high mortality and is associated with significant morbidity, it is critical to establish a diagnosis early, to treat aggressively, and to assiduously assess response to therapy. Blood eosinophil levels and nonspecific markers of inflammation, such as the erythrocyte sedimentation rate and C-reactive protein level, might correlate with symptomatic improvement and response to therapy; there is, however, often a lack of concordance between blood eosinophilia, erythrocyte sedimentation rate, and C-reactive protein levels and progression of eosinophilic vasculitis. Similarly, ANCA titers are poor markers of therapeutic response.[35] Although the persistence of ANCA favors relapse (and the reoccurrence of ANCA might precede relapse), the absence of ANCA does not exclude relapse. Moreover, ANCA levels are not correlated with severity of disease. Plasma levels of eosinophil-derived cationic proteins, such as eosinophil cationic protein and major basic protein, have yet to demonstrate utility in monitoring disease activity. Because there are currently no gold standard biochemical or molecular markers of either vascular endothelial damage or eosinophilic tissue infiltration, clinicians should assess therapeutic response in patients with CSS by monitoring clinical symptoms and laboratory indices and assessing specific organ involvement by using tools, such as echocardiography (to assess decrements in the ejection fraction), pulmonary function testing, nerve conduction studies, and electromyograms.

Corticosteroids

Corticosteroids (starting at 1 mg/kg and tapering over 3 to 6 months) are the cornerstone of CSS therapy and result in rapid clinical remission in more than 90% of subjects with CSS (for a summary of treatment options for CSS, see Table II). Approximately 25% of corticosteroid-responsive subjects experience relapses, often in the setting of corticosteroid tapering, with an increasing eosinophil count heralding the relapse. Inhaled corticosteroids, often used in combination with long-acting bronchodilators, might relieve asthma symptoms and modulate airway inflammation, but they are rarely a complete substitute for oral corticosteroid therapy. Thus most patients require lifelong, low-dose oral corticosteroids. Side effects, including weight gain, osteoporosis, easy bruising, hyperglycemia, depression, and risk of infection, might limit the benefits of corticosteroid therapy in some patients.

Cytotoxic therapy

Because myocardial, gastrointestinal, renal (increased creatinine values or proteinuria) and central nervous system involvement all portend a poor prognosis,[35] treatment with higher doses of corticosteroids or the addition of a cytotoxic agent, such as cyclophosphamide, is warranted in the minority of patients with CSS who are unresponsive to standard doses of corticosteroids. Although survival does not differ between corticosteroid-treated patients managed with or without cyclophosphamide, the addition of cyclophosphamide in patients with involvement of at least 2 extrapulmonary organs is associated with a significantly reduced incidence of relapse and an improved clinical response to treatment. In general, cyclophosphamide should be prescribed for at least 4 months to prevent

TABLE II. Summary of treatment options for Churg-Strauss vasculitis

Diagnosis	Treatment	Indications	Dose	Comments
Churg-Strauss vasculitis	Corticosteroids	First-line therapy	1 mg/kg with taper over 3-6 mo	Corticosteroid monotherapy controls most patients' symptoms acutely but only rarely induces lifelong remission
	Cyclophosphamide	In addition to corticosteroids for treatment of refractory disease, relapse, or acute disease with involvement of ≥2 extrapulmonary organs	Monthly intravenous or daily oral	Monthly intravenous administration is better tolerated, no difference in survival but decreased incidence of relapse with addition of cyclophosphamide
	Other cytotoxic agents (including azathioprine, methotrexate)	Consider as alternative corticosteroid-sparing agents for maintenance therapy, treatment of relapse, or both	Escalate dose as tolerated based on side effects	Little published data, high rate of relapse with methotrexate
	Immunomodulatory agents (including IFN-α, mycophenolate mofetil, TNF blockers, and IVIG)	Consider as alternative corticosteroid-sparing agents for maintenance therapy, treatment of relapse, or both	NA	Little data to support use in CSS, leukoencephalopathy reported in 2/12 patients treated with long-term IFN-α
	mAbs (including anti–IL-5, anti-IgE [omalizumab])	Unknown	NA	No published data in CSS and uncertain efficacy for the underlying vasculitis, anti-IgE therapy reduces exacerbations and symptoms in severe asthma
	Routine asthma management	Should be used as adjuvant therapy in all patients with asthma symptoms	Variable	Leukotriene modifier use in CSS is controversial, although data to date do not support a causative role for these agents in the development of CSS

IVIG, Intravenous immunoglobulin; *NA,* not applicable.

relapses and should be considered as first-line add-on therapy in patients who experience relapses. Both daily oral formulations and monthly intravenous infusions of cyclophosphamide are effective in preventing relapses, but monthly regimens are better tolerated.[36] Cyclophosphamide is also effective as a corticosteroid-sparing agent in more benign forms of CSS.

Because cyclophosphamide is associated with an increased susceptibility to infection, the development of cytopenias, malignancy, and hemorrhagic cystitis, other cytotoxic agents (eg, azathioprine) with a more favorable side-effect profile should be considered for maintenance therapy.[37]

Immunomodulatory agents

When CSS relapses occur despite corticosteroids, cytotoxic agents, or both or if patients are unable to effectively taper corticosteroid dosing, a number of immunomodulatory agents might be effective. Although there is a scientific rationale for each of these therapies, there have been only small case series or brief reports of each, and no large randomized, prospective clinical trials have been performed.

IFN-α has been shown to inhibit eosinophil production and release of eosinophil cationic protein and eosinophil-derived neurotoxin and has efficacy in other eosinophilic syndromes, such as HES and eosinophilic cellulitis. In CSS there have been several reports of reduction of eosinophil counts and disease activity in response to IFN-α, and a recent small, prospective, open-label trial of IFN-α (3 million U subcutaneously 3 times/wk) in treatment-refractory patients showed promising results, with a complete or partial remission (diminished eosinophil count and reduction in maintenance corticosteroids) in 8 patients with marked eosinophilia despite corticosteroids (median dose, 20 mg/d) and cytotoxic therapy (cyclophosphamide or methotrexate).[38] Unfortunately, although IFN-α was well tolerated and effective for induction of remission, patients followed beyond 12 months continued to have relapses. In view of these results and a recent report of leukoencephalopathy in 2 of 12 patients with CSS who received IFN-α for 4 or more years,[39] maintenance IFN-α therapy for CSS remains controversial.

A number of other immunomodulatory agents, including methotrexate, cyclosporine, mycophenolate mofetil, and TNF-α blockers (eg, etanercept), are effective in the

TABLE III. Summary of treatment options for eosinophilic gastrointestinal disorders

Diagnosis	Treatment	Indications	Dose	Comments
Eosinophilic gastroenteritis	Dietary therapy	Consider as first-line therapy, especially in children	NA	Elemental diet more effective but less practical than specific allergen avoidance
	Corticosteroids, topical	Chronic therapy, especially in patients refractory to diet changes	Varied	Delivery systems limit broad applicability
	Corticosteroids, systemic	Primarily useful for acute therapy	Varied depending on age but generally 1-2 mg/kg	
	Anti–IL-5 antibody	Research indication to date	NA	Currently unavailable except in clinical trials or for compassionate use (mepolizumab; GlaxoSmithKline)
	Anti-IgE therapy	Research indication to date	NA	
	Other therapies (including lactobacillus, cromolyn, azathioprine)	Consider for patients refractory to standard therapies	Varied	Little published data, ketotifen and leukotriene inhibitors appear to be of limited utility

NA, Not applicable.

treatment of some patients with non-CSS, ANCA-associated vasculitides and asthma. Of these agents, the best data with respect to use in the treatment of CSS exist for methotrexate. Remission is achieved in a majority of patients with methotrexate-treated CSS; however, almost half experience relapses within a year.[40] Intravenous immunoglobulin therapy has also been attempted in CSS but has been largely unsuccessful without concomitant plasmapheresis.

Monoclonal antibody therapies

Despite the recent availability of mAbs against IL-5, IgE, and a wide range of receptors and cytokines involved in allergy and inflammation, there are no published reports of mAb therapy for CSS. Theoretically, because of the association between CSS and asthma and the prominence of allergic features in patients with CSS, omalizumab, an mAb to IgE with proved efficacy in asthma, might play an adjuvant role in CSS management, improving CSS airway symptoms and thereby allowing for corticosteroid withdrawal. Alternatively, mepolizumab, an antibody to IL-5 that has been shown to decrease eosinophilia in the blood and tissues of patients with HES, might be useful in preventing eosinophilic vasculitis.

TREATMENT OF EGIDs
Treatment outcomes: Indicators of clinical response

Patients with EGID require chronic therapy, and disease symptoms and pathology generally return when therapy is discontinued. In the case of EE, in which a high rate of esophageal strictures and remodeling changes in the esophagi of adult patients has been reported, therapy has been advocated to control the inflammation, irrespective of clinical symptoms.[13] Whether this holds true for other forms of EGID, such as eosinophilic colitis and eosinophilic gastritis, remains uncertain.

Endoscopic analysis is always required to assess the degree of gastrointestinal disease. It is not uncommon for the endoscopic appearance of the gastrointestinal tract of patients with EGID to be normal, and thus microscopic evaluation of biopsy samples is essential and is the gold standard for diagnosis and monitoring. Furthermore, the disease often has patchy involvement, necessitating multiple endoscopic biopsy specimens from each intestinal segment. Differentiation of EGID from the normal condition relies on several factors, including (1) eosinophil quantification, (2) the location of eosinophils (eg, their presence in abnormal positions, such as the surface or crypt epithelium or the crypt lumen), and (3) associated pathologic abnormalities (eg, epithelial hyperplasia in the case of EE).[11] However, it is important to note that eosinophils normally exist in most portions of the intestinal tract distal to the esophagus, although the normal numbers of eosinophils present in these tissues have not been defined. Unless patients present with peripheral blood eosinophilia, monitoring peripheral blood eosinophil levels is usually not helpful. Monitoring noninvasive markers of disease activity (eg, eosinophil cationic proteins in the blood or stool) has not yet been studied.

Dietary therapy

Although difficult from a practical standpoint (ie, when patients are sensitized to many allergens), a trial of specific food antigen and aeroallergen avoidance is often indicated for patients with EGID (for a summary of treatment options for EGID, see Table III). Unfortunately, the results

with this approach are often unsatisfactory.[11,41] In contrast, an elemental diet with an amino acid–based formula has been shown to improve symptoms in most patients with EGID. In a study of 346 children and adolescents with EE who were started on an elemental diet, the average time to clinical improvement was rapid (8.5 ± 3.6 days), and the number of eosinophils was decreased in the esophageal biopsy specimens of most patients.[42] Although food can generally be reintroduced slowly after 1 month, patients on elemental diets might require placement of a gastrostomy tube to achieve adequate caloric support. The mechanism by which elemental diets work has not been determined, but it is reasonable to consider that this approach is effective because it removes exposure to food allergens. Alternatively, perhaps, an elemental diet has a general immunosuppressive effect on gastrointestinal immune responses.

Corticosteroids

Corticosteroids (systemic or topical) have also been used with satisfactory results in all forms of EGID. Systemic corticosteroids are used for acute exacerbations, whereas topical preparations are used to provide long-term control. Topical therapy can be administered by formulating beclomethasone for gastric delivery, by using commercially available budesonide for the distal small intestine, or by having patients use an asthma metered-dose inhaler (without a spacer) and swallow the dose to promote deposition on the esophageal mucosa. A number of uncontrolled open-label studies in both adults and children have demonstrated the efficacy of topical agents in EE. In addition to improving symptoms in a majority ($\leq 80\%$) of patients, there is a decrease in eosinophils and $CD3^+CD8^+$ T cells in the esophageal mucosa and reversal of epithelial hyperplasia after 2 to 3 months of swallowed fluticasone (880 μg/d in divided doses).[41,43] Rarely, prolonged courses of systemic corticosteroids might be necessary to control disease.

Monoclonal antibody therapies

A number of humanized mAbs that interfere with various aspects of T_H2-mediated inflammation have been approved (omalizumab, anti-IgE; daclizumab, anti-CD25) or are in clinical trials (mepolizumab, anti–IL-5). Of these, only anti–IL-5 antibody and anti-IgE antibody have been used in patients with EGID, both with promising results. In a small trial of 4 subjects with EGID and peripheral eosinophilia, administration of the anti–IL-5 antibody SCH55700 at a dose of 1 mg/kg led to resolution of peripheral eosinophilia in all subjects and a moderate decrease in tissue eosinophilia but no improvement in symptoms.[26] A single patient with EE treated with the anti–IL-5 antibody mepolizumab at a dose of 10 mg/kg had a more marked decrease in tissue eosinophilia and dramatic improvement in dysphagia and vomiting.[25] Additional studies with mepolizumab are currently underway.

Anti-IgE antibody therapy is also currently being studied in patients with EGID in a pilot study of omalizumab. Preliminary data show a dramatic decrease in allergen-specific basophil activation, a 25% decrease in peripheral eosinophilia, and improvements in symptom scores in response to omalizumab therapy (C. Prussin, personal communication).

Immunomodulatory therapy

Although there are good rationales for the use of other immunomodulatory therapies in EGID, including suplatast tosilate (an orally active downregulator of IL-4 and IL-5 production and allergen-dependent IgE synthesis that is approved for treatment of allergic disorders in Japan), mycophenolate mofetil (an inosine monophosphate dehydrogenase inhibitor widely used for prophylaxis of organ rejection in patients undergoing solid organ transplantation), and oral lactobacillus, the efficacy of these drugs in the treatment of EGID is anecdotal. Of note, treatment with lactobacillus, which alters the intestinal flora, has been shown in 2 controlled studies of children with atopic dermatitis to decrease skin manifestations, with a concomitant decrease in serum levels, urine levels, or both of eosinophil granule proteins. Whereas tacrolimus has been proposed as a potential therapy for EGID, it should be used with caution, if at all, because of its association with gut eosinophilia in some patients undergoing transplantation.

Other therapies

A variety of other agents have been used in small numbers of patients with EGID, with varied success. Based on numerous case reports and unpublished data, blockers of mast cell activation (oral cromolyn sodium at a dose of 200 mg 4 times daily 30 minutes before meals for eosinophilic gastroenteritis and cromolyn metered-dose inhaler, 2 puffs twice daily swallowed [not inhaled and without a spacer], for EE) are sometimes helpful in EGID with minimal side effects. In contrast, the mast cell stabilizer ketotifen appears to have limited utility. Leukotriene inhibitors have been studied in a small case series, but they do not appear to decrease esophageal eosinophil levels in patients with EE. Successful use of azathioprine (1-2 mg/kg) as a corticosteroid-sparing agent has been reported in 2 corticosteroid-dependent patients with EE and as adjunctive therapy in 5 patients with other forms of EGID, although formal studies of this or other corticosteroid-sparing agents are lacking.

POTENTIAL NOVEL APPROACHES TO THE TREATMENT OF EOSINOPHILIC DISORDERS
Transcription factors

The role of transcription factors in regulating or facilitating selective eosinophil development compared with other bone marrow–derived hematopoietic lineages is exceedingly complex. Nevertheless, current data from both mouse and human studies suggest that a handful of transcription factors are critical in eosinophilopoiesis,[44] such that the commitment and terminal differentiation of

eosinophils from myeloid progenitors requires concomitant expression of C/EBPα, PU.1, and a moderate level of GATA-1, with no expression of FOG-1 (friend of GATA-1). Consistent with this, eosinophils do not develop at all in GATA-1 or C/EBPα knockout mice, and eosinophil terminal differentiation is significantly impaired in PU.1 knockout mice.[45] Although these findings suggest a number of potential targets for elimination of the eosinophil lineage, the involvement of many of these transcription factors in hematopoietic pathways other than eosinophilopoiesis has hindered the development of this approach in the treatment of eosinophilic disorders in human subjects.

Tyrosine kinase inhibitors other than imatinib

It is now known that at least 4 translocations other than that involving FIP1L1 and PDGFRA (BCR-PDGFRα [4q12], ETV6-PDGFRβ [5q33], ZNF198-FGFR1 [8p11] and PCM1-JAK2 [t(8;9)(p22;p24)]) result in gain-of-function biology that tyrosine kinase inhibitors should effectively antagonize. Indeed, on the heels of imatinib's success in treating chronic myelogenous leukemia, HES, and other disorders, there are additional tyrosine kinase inhibitors in development or already in clinical trials, including AMN107, PKC412, SU5614, SU11248, and MLN518. Some of these are more potent than imatinib, work against imatinib-resistant mutations, or both.[32] As many as 20 or more inhibitors in this category are in development, and it is anticipated that a much broader array of tyrosine kinase inhibitors that block ABL, ARG, KIT, PDGFR, PKC, FLT3, NTRK, and VEGFR signaling might soon be available.

Other possible therapeutic targets on the eosinophil surface

On the basis of current knowledge about the eosinophil surface phenotype,[46] there are many ways in which drugs could potentially inhibit hematopoiesis, adhesion, migration, and survival of eosinophils or actively induce their apoptosis as ways of reducing eosinophil numbers in diseased organs. Several adhesion-related targets could be considered, including LFA-1 (efalizumab), PSGL1, L-selectin, and a variety of chemokine receptors, especially CCR3, CRTH2, the H4 histamine receptor, C3aR, C5aR, cysteinyl leukotriene 1, and the platelet-activating factor receptor.

Whereas anti–IL-5 is working its way through clinical trials as a selective antieosinophil agent, modulation of other cytokine receptors, including CD116/CD135 (GM-CSFR) and others that regulate eosinophil survival or apoptosis (IL-3 receptor, IL-9 receptor, IL-13 receptor, TNF-α receptor, IFN-γ receptor, TRAIL, and nerve growth factor receptor), could possibly be used to reduce eosinophil survival. Already the list of proapoptotic eosinophil agents includes corticosteroids, lidocaine, TGF-β, IL-12, and Fas (CD95), as well as cross-linking of CD30, CD45, CD69, CD137, and Siglec-8.[47] With the exception of IL-5 receptor–targeted therapies, many of these other surface molecules are also found on other leukocytes, but some, such as CCR3, CRTH2, and Siglec-8, are limited to cell types related to allergic inflammation, such as mast cells, basophils, and T_H2 cells. Therefore targeting these receptors, although not necessarily specific enough to treat hypereosinophilic disorders, might be a useful approach for treating allergic disorders.

CONCLUSION

Despite a number of important advances in our understanding of the causes of HES, CSS, and EGID, the relative lack of large prospective trials addressing different treatment modalities and markers of treatment response continues to impair our ability to formulate a rational approach to therapy for these disorders, particularly in those patients for whom corticosteroids are ineffective or have unacceptable toxicity. To this end, the need for multicenter cooperation cannot be overemphasized. The collaborative interactions of a core group of clinicians with expertise in eosinophilic disorders and summarization of currently available data, initiated at the 2005 Workshop, are the first steps in this process.

Plans are currently underway to reconvene and expand this multidisciplinary group of clinical and basic scientists in eosinophil biology at the next meeting of the International Eosinophil Society in Salt Lake City in 2007.

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