

Treatment of Hypereosinophilic Syndromes—The First 100 Years

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Treatment of the hypereosinophilic syndrome (HES) has advanced rapidly and prevention of end organ damage previously associated with the disorders is now possible in most patients who have had a timely diagnosis. Tried and true medications such as prednisone, hydroxyurea, and interferon- α continue to play a valuable role in treating HES and their cost is modest. Newer medications included pegylated forms of IFN- α and IFN- α 2b, first- and second-generation tyrosine kinase inhibitors (imatinib mesylate, nilotinib), and monoclonal antibodies to interleukin (IL)-5 and CD52. The combination of better understanding of HES and better medications now provide the clinician with an improved ability to control unregulated proliferation of eosinophils.

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It has been nearly 100 years since the first case of eosinophilic leukemia was reported by Stillman. When it is remembered that for approximately the first 50 of the subsequent 100 years there was very little advancement in the understanding of the mechanism(s) causing eosinophilia or in the treatment of eosinophilia, it is remarkable that we have progressed as far as we have to date. No commercially available drugs have been tested in double-blind placebo-controlled trials to determine their effectiveness in treating the hypereosinophilic syndromes (HES). Nonetheless, the clinician faced with a hypereosinophilic patient now has a variety of therapeutic “arrows in the quiver” about which there has accumulated a degree of clinical experience in the management of HES. These “arrows” include tried and true agents such as glucocorticoids, hydroxyurea, and interferon- α (IFN- α), as well as newer agents such as monoclonal antibodies directed against interleukin (IL)-5 and against CD52, as well as first- and second-generation tyrosine kinase inhibitors. Each of these agents has its own advantages and side effects, and it remains an ongoing challenge to the clinician to use our “arrows” to achieve their greatest therapeutic advantage while avoiding unnecessary side effects.

GLUCOCORTICOIDS

The initial reports of response of eosinophilic patients to treatment, primarily to glucocorticoids (GC), appeared before the terms and definitions that are currently employed to define HES, most notably those of Hardy and Anderson (1968),¹ Chusid (1975),² and Parrillo et al (1978).³ These reports, therefore, must be viewed with some caution, because it is difficult to be certain that all of these cases would meet our current criteria for HES. By the mid 20th century, a confluence of clinical experience and laboratory data predictably led to the use of adrenocorticotropin (ACTH) and GC to treat hypereosinophilia. GC subsequently became the mainstay of treatment for the next 30 years and continues to have wide use today.

In Vitro Effects of GC

Eosinophils possess approximately 7.5–11,000 high-affinity ($K_d = 15.3 \pm 0.6$ nmol/L dexamethasone) GC receptor sites per cell,^{4,5} and the lack of detectable receptors correlates with GC resistance, both in vitro and in vivo.⁴ One of the most important effects of GC is to inhibit the production and effect of eosinophil-active cytokines, including granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-5, derived from various cellular sources, on eosinophil survival, chemotaxis, and activation.^{6–9} The inhibitory activity of dexamethasone and methylprednisolone can be overcome by incubation of eosinophils with increasing concentrations of GM-CSF, IL-3, or IL-5.⁸ In vitro studies have also generally shown that, on balance, dexamethasone and mometasone increase apoptosis of eosinophils from normal volunteers.⁹ Studies of GC effects on eosinophil colony formation have given a mixed pic-

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ture of the ability, as well as the mechanism(s), of these agents to inhibit eosinophil colony growth.

Clinical Experience With GC

Clinical experience with ACTH and GC in the treatment of HES greatly exceeds that of any other agent used in this disorder. Cortisone administration to normal volunteers results, reliably, in an eosinopenia that reaches a nadir 4 hours after administration.¹⁰ Similarly, it was subsequently noted nearly 30 years later in six HES patients that good responders to GC all showed a profound and prolonged eosinopenic response 4 to 12 hours after challenge with a single dose of prednisone (60 mg).¹¹ Beginning with the report of Rothstein et al in 1953,¹² the decade of the 1950s saw the initial reports of successful use of corticotropin for reducing eosinophil numbers and improving clinical symptoms in eosinophilic patients.^{13–15} During the 1960s the use of corticotropin for hypereosinophilia was supplanted by that of GC. However, doses of GC, treatment durations, and success rates were not uniform. With the publication criteria for HES in 1968 by Chusid et al,² it became possible to compare treatment responses for patients meeting specific diagnostic requirements. In the landmark publication by Parrillo et al, it was reported that prednisone, 60 mg/d or 1 mg/kg/d for 1–2 weeks gave a good (38%) or partial (31%) eosinopenic effect and that this response could be maintained with burst or every-other-day regimens.³ Although the original recommendation for prednisone use entailed a change to every-other-day treatment for 3 months and subsequent tapering over the course of 1 year after an initial favorable response to daily treatment, with the advent of alternative medications for treating HES, current practice generally does not include such protracted treatment with GC, with a more rapid reduction generally possible in those responding well. In a recent review of treatment responses in HES, GC monotherapy induced complete or partial responses at 1 month in 85% of patients, with most patients remaining on a maintenance dose of ~10 mg/d for 2 months to 20 years.¹⁴

Clinical Correlates of a Good Response to GC

In addition to a prolonged eosinopenic response, patients with a favorable response to GC were more likely to have episodic severe angioedema and lacked findings of hepatosplenomegaly.³ An elevated serum IgE level ($2,338 \pm 684$ IU/mL for responders *v* 51 ± 27 IU/mL for nonresponders) has also traditionally been felt to characterize GC responders^{3,15}; however, this finding has been called into question by a recent multicenter review of HES cases that showed the percentage of patients with elevated IgE was comparable in GC responders (57%) and in non-responders (31%), $P = .09$.¹⁴ Of interest, this study showed that serum thymus

and activation-related chemokine (TARC) levels were significantly elevated in GC responders compared with non-responders (979 pg/mL *v* 242 pg/mL; $P = .01$). Patients resistant to the effects of GC, as might be expected, have had the opposite of the favorable findings, many of which are now well-recognized criteria of the myeloproliferative forms of HES (M-HES).¹⁶ These include lack of eosinopenic response to prednisone, elevated vitamin B₁₂ levels, folate deficiency, basophilia >3%, bone marrow chromosomal abnormalities, low leukocyte alkaline phosphatase scores, the presence of hepatosplenomegaly, congestive heart failure, substantial leukocytosis, and the presence of myeloblasts in the peripheral blood.³

GC and Childhood HES

Children with HES experience many of the same complications as adults do with this disorder, and GC can be effective treatment for them.¹⁷ GC alone are not effective in all children with HES. Additional or alternative agents may be warranted for children with leukocyte counts >100,000/ μ L, for those with associated myelodysplastic syndrome, and for those positive for the *FIP1L1-PDGFR* fusion.¹⁸ Prolonged low-dose prednisone can be effective treatment for some children with HES,¹⁹ and interestingly, several reports confirm the ability to eventually discontinue use of GC in some children with HES.²⁰

GC Use in L-HES

GC are currently the first-line treatment for the lymphocytic variant of HES (L-HES) in which there is a polyclonal expansion of eosinophils in response to overproduction of IL-5 by T cells bearing abnormal surface phenotypes, most frequently CD3⁺CD4⁺ or CD3⁺CD4⁺CD8⁺.²¹

Specific Organ System Responses to GC

Global reduction of the total eosinophil count in theory should improve or prevent organ system damage from toxic eosinophil constituents. This effect is in part due to the fact that eosinophils largely reside in the body's tissues, and the finding of elevated circulating eosinophil numbers is simply a reflection of the transit of eosinophils from their site of production in the bone marrow to the final destination in the tissues. It has been estimated that the ratio of tissue to blood eosinophils is approximately 200–300:1. Success or failure of organ system response to treatment of HES depends to a great deal on the degree of organ damage that has already occurred prior to institution of treatment. For example, once cardiac involvement in HES has progressed beyond the inflammatory/necrotic and thrombotic stages and has resulted in endomyocardial fibrosis, administration of GC, though important in prevention of progressive tissue damage, is less

likely to result in regression of cardiac changes.²² With these caveats in mind, there are numerous reports of clinical control of organ system complications of HES by timely use of GC.

Vascular Complications

Thromboembolic complications of HES have been difficult to control despite adequate anticoagulation. Control of HES-associated disseminated intravascular coagulation, though, has been reported using a combination of GC and low molecular weight heparin²³ or GC plus cyclosporine.²⁴

Cardiac Complications

The heart itself is a primary target of eosinophils. One general principle that recurs in the reports of treatment successes in HES-associated cardiac involvement is that control of eosinophilia is crucial to long-lasting successful management, regardless of whatever other medical and/or surgical measures are administered. Treatment of heart failure in patients with early heart disease, as well as acute episodes of heart failure, with bedrest, diuretics, and prednisolone 40–60 mg/d has been successful. Moreover, regular doses of prednisolone appeared to prevent progression of heart involvement from the acute necrotic stage to the later thrombotic stage.²⁵ Clinical studies of acute eosinophilic heart disease show GC-induced hemodynamic improvement (left ventricular ejection fraction increase from 18.3% to 29.6%²⁶ and from 37% to 60%,²⁷ scintigraphic (201-Tl myocardial perfusion scan),²⁶ improvement of endomyocardial biopsy specimens,²⁷ improved electrocardiogram findings, and disappearance of eosinophilic cationic protein deposition.²⁷ Timely treatment with GC has also been effective at reversing clinical and biopsy abnormalities in necrotic stage eosinophilic myocarditis due to severe hypersensitivity myocarditis. These findings lend credence to the concept that treatment of the heart during the early, “necrotic” stage can positively influence treatment outcomes in eosinophilic heart disease.

The need for surgical replacement of cardiac valves damaged by HES has fallen off during recent years as we have learned to avoid this complication by earlier prevention of unregulated eosinophil proliferation. Surgical replacement of mitral and aortic valves damaged by HES has also emphasized the need to control ongoing eosinophilia in addition to replacing the physically damaged valves. This is especially important because mechanical valves are inherently thrombogenic and HES patients already have a thrombotic tendency. Prosthetic valve obstruction can rapidly occur when treatment of eosinophilia is ignored or delayed. Treatment with prednisone, prednisone plus hydroxyurea, or (unspecified) chemotherapy has prevented recurrent prosthetic valvular obstruction, and persistent chest pain

following valve replacement²⁸ and has improved transvalvular gradients.

Neurologic Complications

Neurologic dysfunction resulting from HES can be a serious problem. Central nervous system (CNS) abnormalities can result from emboli to the CNS causing stroke and transient ischemic episodes but may also be manifested by encephalopathy with behavioral disturbances and upper motor neuron signs. Peripheral neuropathy (sensory polyneuropathy, mononeuritis multiplex, and radiculopathy) occurs in about 50% of patients. Pulse intravenous methylprednisolone sodium succinate 1 g/d for 5 days has proven effective at treating encephalopathic features of HES.²⁹ Resolution of left hemiplegia and regression of diffuse gadolinium enhancement and periventricular nodular lesions, and normalization of peripheral eosinophilia have occurred with prednisolone treatment, initial dose 1 mg/kg/d, tapered thereafter over 20 months.³⁰ GC have also proven effective at treating HES-associated peripheral neuropathy. Combined treatment with prednisolone and cyclophosphamide was required for symptomatic control of a child who presented with HES and generalized myasthenia gravis.³¹

Dermatologic Complications

Dermatologic features of HES are numerous, commonly including erythematous macules, papules, plaques, wheals, nodules, and in severe cases incapacitating mucosal ulcers.³² Skin manifestations may be the only features of HES in an otherwise asymptomatic patient.³² Similar to management of the other complications of HES, control of hypereosinophilia applies to management of dermatologic features as well. Examples of dermatologic manifestations that resolve or improve with the use of GC alone include angioedema, and pruritic erythematous papules.³² Case reports have documented additional examples of improvement from GC use in HES including (1) a patient with elevated serum IL-5 levels and expression of eotaxin by lesional dermal endothelial cells³³; (2) a hypereosinophilic woman with betamethasone-responsive bullous changes and profound swelling as the only manifestations of HES³⁴; and (3) a patient with deflazacort-responsive solar urticaria as the presenting sign of HES.³⁵

Gastrointestinal Complications

At times it can be difficult to distinguish HES with limited (gastrointestinal) organ involvement from primary eosinophilic gastroenteritis, a disorder in which eosinophil infiltration has been reported in most intra-abdominal organs. GC administration has proven effective for treatment of cholestatic liver disease,³⁶ chronic active hepatitis,³⁷ and sclerosing cholangitis associated with HES.³⁸

HYDROXYUREA

Hydroxyurea was the first major advance for the treatment of HES patients with poor prognostic signs (very high leukocyte counts, congestive heart failure, splenomegaly, presence of myeloblasts in the peripheral blood) who were resistant to treatment with GC alone.³ Many of these unfavorable signs are now included among the characteristic findings of patients with the myeloproliferative form of HES.²¹ Hydroxyurea is well absorbed following oral administration, entering cells by passive diffusion and readily entering the cerebrospinal fluid. In vivo, hydroxyurea is converted into a free radical nitroxide that intracellularly quenches the tyrosyl free radical at the active site of the M2 protein subunit of ribonucleotide reductase, inactivating the enzyme, inhibiting DNA synthesis without affecting RNA or protein synthesis, and synchronizing the surviving fraction of cells in S phase until they are killed.³⁹ Hydroxyurea may kill up to 80% of S-phase pleuripotential hematopoietic stem cells.⁴⁰ This ability has taken on added significance because of the recent finding that the *FIP1L1-PDGFR*A mutation is present in multiple lineages, suggesting that for these patients their disease represents an early multipotent progenitor cell/stem cell disorder.⁴¹

Prior to the first large-scale study of hydroxyurea use in HES in 1978,³ the success of combined vincristine plus hydroxyurea to maintain control of eosinophilic leukemia, and the ability of a combination of prednisone plus hydroxyurea to control eosinophilia in one patient with endomyocardial pathology were reported. The landmark study by Parillo et al in 1978³ demonstrated that seven of eight HES patients who had failed treatment with prednisolone, with six of the eight having at least one poor prognostic sign and evidence of cardiac involvement, responded to the addition of hydroxyurea. The remaining two subjects experienced a partial response.

When hydroxyurea is used as a single agent to treat HES, the doses required can lead to cytopenias. Hence, hydroxyurea has generally been used in combination with other agents. Suggested doses have ranged from 1.0 to 2.0 g/d, beginning at a dose of 0.5–1.0 g/d and thereafter gradually advancing the daily dose by 0.5 g every 2 to 4 weeks, depending on the urgency of the clinical situation, the total eosinophil count and the clinical and hematologic responses. The dose of hydroxyurea can be reduced when the total leukocyte count falls to below $10 \times 10^9/L$.⁴²

Improvement in clinical status has been reported when hydroxyurea has been used in combination with GC and with IFN- α . In a series of seven patients the combination of IFN- α and hydroxyurea resulted in control of myeloproliferative hypereosinophilia.⁴³ Addition of hydroxyurea to a program of prednisone and aspirin

resulted in disappearance of abnormal hyperintense T2-weighted magnetic resonance imaging (MRI) of the cerebellar hemispheres and clinical improvement in one HES patient with recurrent dizziness, asthenia, and malaise.⁴⁴ In another case report, GC plus hydroxyurea has caused improvement of cardiac complications of HES (reduction of ventricular wall thickness, disappearance of mitral regurgitation, and MRI-documented reduction of myocardial infiltration and cavity obliteration). Control of HES pulmonary and neurologic abnormalities associated with the presence of aberrant T cells and elevated serum IL-2 and IL-15 levels, but normal levels of IL-3, IL-5, and GM-CSF, was achieved in another patient by addition of hydroxyurea to a program of prednisone. Abnormal T cells were no longer detectable and elevated cytokine levels returned to normal after 2 months.

INTERFERON-ALPHA

Nearly simultaneous case reports in 1990 first documented that IFN- α was an effective treatment for HES patients with disease resistant to prednisone and hydroxyurea.^{44–46} These initial observations have been confirmed in subsequent reports in which IFN- α has proven effective in HES patients resistant to a variety of medications used individually and in combination (Table 1).

In Vitro Effects of IFN- α

Although a functional receptor for IFN- α is present on eosinophils taken from patients with various eosinophilic disorders, there is a wide range (20% to 86%) of receptor-positive cells.⁴⁷ The beneficial clinical effects of IFN- α are supported by in vitro and in vivo studies. Pre-incubation of eosinophils with IFN- α inhibits release of toxic eosinophil-derived neurotoxin and eosinophil cationic protein by cells stimulated with IgA or IgE immune complexes,⁴⁷ and in clinical trials serum levels of eosinophil major basic protein decreased in patients treated with IFN- α .

IFN- α also regulates eosinophils through several effects on eosinophil active cytokine production. By promoting development of Th₁-helper lymphocytes, IFN- α can inhibit differentiation and tissue migration of eosinophils through the effects of IFN- γ .⁴⁸ Additionally both IFN- α and IFN- γ have been shown to decrease viability and increase apoptosis of umbilical cord mononuclear cell-derived eosinophils, and the combination of tissue necrosis factor alpha (TNF- α) and IFN- γ can induce differentiation of the EoL-1 eosinophil line into a non-eosinophil lineage. Finally, in a variety of experimental systems, IFN- α has been shown to inhibit production or gene expression of IL-5, GM-CSF, TNF- α , and IL-13, cytokines that are important in the migra-

Table 1. Actions of IFN- α in HES

Action	Potential Effect in HES
<i>Effects on eosinophil granule protein levels</i>	
Reduced release of EDN, ECP in vitro ⁴⁷	Decreased levels of toxic eosinophil granule proteins in circulation and tissues with reduction of tissue damage
Reduced MBP levels in HES patients taking IFN- α ⁵⁰	
<i>Effects on eosinophilopoiesis</i>	
Inhibition of eosinophil colony growth ⁸¹	Direct inhibition of eosinophilopoiesis; interruption of autocrine loop in which eosinophil production of IL-5 activates and increases survival of eosinophils
<i>Effects on cytokine production</i>	
Promotion of development of Th1 T-helper lymphocytes ^{48,82–84}	IFN- α from Th1 cells inhibits differentiation and migration of eosinophils; IFN- α and IFN- α decrease viability, increase apoptosis of umbilical cord mononuclear cell-derived eos
Reduced gene expression of IL-5, GM-CSF, TNF- α , IL-13 in peripheral blood mononuclear cells ⁸⁵	TNF- α plus IFN- α induce EoL-1 cells to non-eosinophil monocyte/macrophage cells Reduced TNF- α , IL-13–induced VCAM and ICAM-1 expression on endothelium with reduced transmigration of eosinophils to sites of activation/inflammation in HES; reduced IL-5, GM-CSF–induced eosinophil activation, proliferation and survival
Reduced production of IL-5, GM-CSF (several model systems) ^{85–87}	Reduced eosinophil activation, proliferation and survival
<i>Effects on chromosomal abnormalities</i>	
Multiple reports of effectiveness of IFN- α alone (or in combination) in HES with chromosomal abnormalities including chromosome 5, the sites of genes coding for eosinophil-active cytokines IL-3, IL-5, GM-CSF ^{52,88–91}	Complete or major cytogenetic and clinical remissions

Abbreviations: HES, hypereosinophilic syndrome; EDN, eosinophil-derived neurotoxin; ECP, eosinophil cationic protein; MBP, eosinophil major basic protein; IFN, interferon; IL, interleukin; GM-CSF, granulocyte-macrophage colony-stimulating factor; TNF, tumor necrosis factor; VCAM, vascular cellular adhesion molecule; ICAM, intracellular adhesion molecule.

tion, proliferation, activation, and survival of eosinophils.⁴⁹

Clinical Effects of IFN- α

There are numerous examples of beneficial organ system responses resulting from control of eosinophilia by IFN- α . Resolution or improvement of hepatomegaly, splenomegaly, and hepatosplenomegaly are commonly reported.⁴⁵ IFN- α was the first agent to successfully control HES-associated incapacitating mucosal ulcers,⁵⁰ and is also effective in the treatment of the more common dermatologic findings of pruritic papules, nodules, and plaques. Examples of cardiac and cardiorespiratory responses include enhanced cardiovascular function, improved congestive heart failure, reversal of electrocardiographic changes, partial resolution of a left ventricular obliterative mass, resolution of pulmo-

nary infiltrates, reduction in restrictive lung defect,⁴⁵ and control of asthma symptoms. PEG-intron, a long-acting preparation of IFN- α that can be administered once per week has also been effective in the treatment of HES.⁵¹

IFN- α was the first medication to result in cytogenetic remission in HES patients having chromosomal abnormalities. As a single agent, IFN- α has reduced nullisomy Y findings to 15% of cells in one HES patient with this abnormality, has effected clinical and cytogenetic remission in a patient with a 46, XY, t(5;9)(q32;q33) abnormality, and in a patient with a complex chromosomal translocation 46, XY,t(3;9;5)(q25;q34;q33) who also had elevated blood IL-5 levels.⁵² A patient with a unique [t(4;7)(q11;p13)] aberration and a patient with trisomy 8 have also experienced karyotypic remissions.

HUMANIZED MONOCLONAL ANTIBODIES

Mepolizumab

Mepolizumab is a humanized IgG1 kappa, non-complement fixing, monoclonal antibody that binds IL-5⁵³ and prevents its binding to the IL-5 receptor alpha chain. IL-5 is an eosinophil growth and differentiation factor.⁵⁴ It is therefore a good target for the therapy of HES. It was found to be beneficial not only to patients with L-HES, but also to patients with myeloproliferative HES harboring the *FIP1L1-PDGFR*A mutation.⁵⁵ Studies to evaluate the safety of mepolizumab in primates have been published as early as 2001.⁵⁶

The theoretical benefit of eliminating the eosinophil growth and differentiation factor (IL-5), is very clear.^{55,57} The first international, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of mepolizumab was reported in 2008.⁵⁸ It showed the ability of mepolizumab to reduce blood eosinophil count to less than 600 eosinophils per microliter in 95% of patients with steroid-responsive L-HES receiving mepolizumab, as compared with 45% of patients receiving placebo ($P < .001$).⁵⁸ Mepolizumab was corticosteroid-sparing. Rates of adverse events were similar in treated and placebo groups. Response was comparable in patients with and without L-HES.

The pharmacokinetics of mepolizumab have been evaluated in clinical studies at doses of 0.05–10 mg/kg. Mepolizumab was eliminated slowly, with mean initial and terminal phase half-life values of approximately 2 and 20 days, respectively. Peripheral blood eosinophil levels decreased after intravenous mepolizumab. The estimated maximal decrease in eosinophil count was approximately 85% from baseline.⁵⁹ Mepolizumab has not yet been approved by the US Food and Drug Administration (FDA) as a therapeutic agent for HES, but it is available for compassionate use in life-threatening, treatment-refractory disease.

Reslizumab

Reslizumab (previously known as SCH55700) is another humanized IgG4 anti-IL-5 monoclonal antibody designed for the treatment of eosinophilia and eosinophil-mediated disorders.⁶⁰ It is currently in phase III studies for the treatment of eosinophilic esophagitis.⁶¹ Early studies evaluating this monoclonal antibody showed improvement of eosinophilia and clinical symptoms in six of eight of patients with peripheral eosinophilia for as long as 12 weeks. However, this was followed by an increase in eosinophil counts above baseline levels, accompanied by an exacerbation of symptoms.⁶² More studies are needed for further evaluation of the therapeutic potential of this antibody.

Alemtuzumab

Alemtuzumab is another IgG1 humanized monoclonal antibody approved by the FDA in 2001 for use in

the treatment of chronic myeloid leukemia.⁶¹ It has been employed in the therapy of eosinophilic disorders, namely, HES, resistant to other therapeutic modalities. Alemtuzumab is an anti-CD52 antibody.^{63–69} In 1996, CD52 expression on the surface of eosinophils was first identified.⁷⁰ This finding led to the few case reports cited above of the use of alemtuzumab for the treatment of eosinophilic disorders. The side effects of alemtuzumab include reactivation of cytomegalovirus requiring other therapy and a reported orbital lymphoma responsive to therapy.⁶⁸

MEDI-563

MEDI-563 is a humanized monoclonal antibody against the IL-5 receptor alpha chain.⁷¹ It was found to reduce the peripheral blood eosinophil count and to deplete basophils after administration.^{71,72} The reduction in eosinophils was dose-dependent.⁷¹ Ongoing studies are evaluating its role in the treatment of bronchial asthma.⁷² Its potential role as an HES therapeutic agent cannot be ignored.

TYROSINE KINASE INHIBITORS

Imatinib Mesylate

Imatinib mesylate (Gleevec) is a first-generation tyrosine kinase inhibitor. It is reported to selectively inhibit the Abelson Bcr/Abl, Kit, and platelet-derived growth factor receptors alpha and beta (PDGFRA and PDGFRB).⁷³ Multiple reports have shown its efficacy in the treatment of patients with myeloid HES. Those HES patients with the PDGFRA-associated disease susceptible to control by imatinib mesylate.^{16,74,75} Only about 10% to 20% of patients with HES have this mutation and almost all of them are males.⁷⁵ The starting dose of imatinib mesylate is 100 mg/d or 400 mg/d orally. The side effects of imatinib include the rare occurrence of acute myocardial necrosis. The response in women is lower than in men (86% *v* 18%), and resistance mutations in the kinase domain of *FIP1L1-PDGFR*A have been described.

Nilotinib

Nilotinib is a second-generation tyrosine kinase inhibitor. It was reported to induce a remission in patients with *FIP1L1-PDGFR*A who were either resistant or intolerant to therapy with imatinib mesylate.^{76,77}

Sorafenib

Sorafenib is another second-generation tyrosine kinase inhibitor. It has been used for the treatment of patients with myeloproliferative HES resistant to imatinib mesylate.^{78,79}

Table 2. Patient Monthly Treatment Cost for HES*

Medication	Dose/Frequency	Cost
Prednisone	40 mg/d	\$110
	10 mg/d	\$109
Hydroxyurea	500 mg/d	\$120
	2,000 mg/d	\$157
Interferon alfa 2A (Roferon-A)†	3 MU 3x/wk	\$998
	5 MU 5x/wk	\$2,037
PegIntron (PEG-Interferon alfa 2B)	150 µg/wk	\$3,160
	120 µg/wk	\$3,022
	80 µg/wk	\$2,891
	50 µg/wk	\$2,766
Pegasys (PEG-IFN-α 2A)	180 µg/0.5 mL/wk	\$3,074
Mepolizumab	750 mg/mo IV	Investigational
Reslizumab	3 mg/kg body weight once a month IV	Investigational
Alemtuzumab	30 mg biweekly then 30 mg every 3 wks	\$4,882
MEDI-563	0.3–3 mg/kg body weight phase I trial	Investigational
Imatinib mesylate	400 mg/d	\$6,439
	100 mg/d	\$1,865
	100 mg/wk	\$249
Nilotinib	400 mg orally twice daily	\$5,329
Sorafenib	400 mg orally twice daily	\$10,333
Dasatinib	70 mg twice daily	\$10,068

Abbreviation: IV, intravenous.

*Source: Mayo Clinic Pharmacy.

†Roferon-A has been discontinued by the manufacturer.

Dasatinib

The efficacy of dasatinib *in vitro* suggests that it will be of benefit in clinical use in myeloproliferative HES.⁸⁰

COST COMPARISONS

Although the efficacy and tolerability of medications used for control of HES are of primary concern, the cost of treatment remains an important consideration for all patients as treatment will be lifelong. Table 2 lists the monthly and annual costs of the medications commonly used for control of HES. For patients not responsive to or intolerant of prednisone and hydroxyurea, the cost of treatment increases substantially, although low-dose imatinib mesylate that can be effective in *FIP1L1-PDGFR*A-positive HES patients is also quite cost-effective. While much clinical attention has been directed to the newer tyrosine kinase inhibitors and monoclonal antibodies their annual cost may be prohibitive for patients.

CONCLUSIONS

The last half century has witnessed an extraordinary increase in our ability to understand and control hypereosinophilia.

The medications outlined above have been lifesaving for many, and newer agents promise even better results for future patients. With each successive generation of medications, our treatment options have become more focused and effective. Monoclonal antibodies and tyrosine kinase inhibitors are at the cutting edge of current therapy, yet older therapies are still important arrows in our “therapeutic quiver” to control difficult HES. Ineffective agents for HES including antihistamines, anabolic steroids, 6-mercaptopurine, 6-thioguanine, and busulfan are no longer considered in therapeutic decision-making. Other agents such as vincristine have seen limited use in pediatric HES and for initial control of extreme hypereosinophilia. Lastly, cyclophosphamide and methotrexate, two agents that have previously been ineffective in HES, have found promising roles as single agents to control L-HES associated with T-cell non-Hodgkin lymphoma.

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