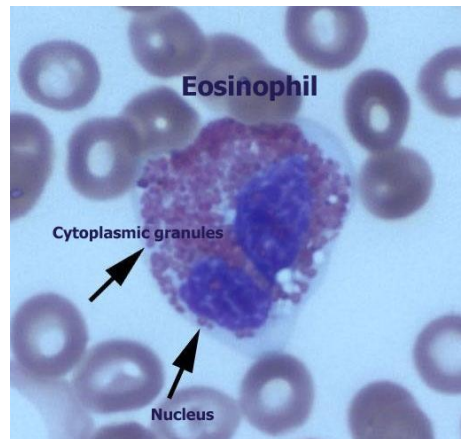


Hypereosinophilic Syndrome (HES)

What is an Eosinophil?

An eosinophil is a type of white blood cell that plays an important role in the human immune system. For example, it helps us fight off certain types of infections like parasites. Many different problems can cause high numbers of eosinophils in the blood, including allergies, asthma, some gastrointestinal disorders, parasitic infection, some blood/bone marrow diseases, certain cancers, and other problems. When eosinophils occur in higher than normal numbers in the blood, without a known cause and for a sustained period of time (more than 6 months), an innate disorder of eosinophils may be present.



Eosinophil, Courtesy of Dr. Margaret Collins

Normally, there are less than 3% eosinophils circulating in the blood vessels because they migrate quickly into the tissues and organs of the body. The highest concentration of eosinophils is usually found in the gastrointestinal tract. There is a complex series of chemical events that determine the levels of eosinophils in the blood and tissues. The proper balance and function of these events determine eosinophil production, their activity, and their time to die.

Eosinophil production is governed by several chemicals in blood called cytokines, including interleukin 3 (IL-3), interleukin 5 (IL-5), and granulocyte-macrophage colony-stimulating factor (GM-CSF). Cytokines have many functions. They mediate and regulate immunity, inflammation, and hematopoiesis (production of blood cells) and different cytokines are produced in high amounts in different diseases. IL-5 appears to be the most important and specific cytokine that is responsible for the production and activity of eosinophils. Cytokines bind to specific chemicals on the surface of cells, called membrane receptors, that initiate the cascade of changes in other chemicals inside the cell leading toward the change in cell's behavior, including higher activity and multiplication. Many of the membrane receptors and intracellular chemicals belong to a class of chemicals called tyrosine kinases.

What is HES?

HES is a group of disorders in which there are very high numbers of eosinophils found in the blood, for prolonged period of time (more than six months) for which a cause cannot be found. The continuous presence of high number of eosinophils in blood can

eventually cause multiple organ tissue damage as these eosinophils infiltrate different tissues and cause inflammation. HES can affect any organ in the body, including the stomach and intestines, the heart, lungs, skin and other organs.

Since many different problems can cause high numbers of eosinophils in the blood, higher than normal blood eosinophil number alone does not mean an individual has, or will develop, HES. Criteria has been developed that must be fulfilled for an individual to be diagnosed with HES.

Criteria for Diagnosis of HES

1. Peripheral blood eosinophilia (high numbers of eosinophils in the blood); more than 1500 eosinophils/ μ l, for at least six months' duration
2. End-organ (heart, lungs, GI tract, brain, skin, etc) involvement with eosinophil tissue infiltration (invasion) and injury
3. Exclusion of known other causes for the eosinophilia such as parasitic infections and certain bone marrow/blood diseases.

A bone marrow biopsy may be recommended in a patient fulfilling these criteria and suspected of having HES.

Standard Treatments for HES

Treatment goals include decreasing blood eosinophil numbers, preventing organ damage, and slowing disease progression. Treatments vary based on organs involved and disease severity, as well as on the presence of other medical problems a patient may have.

Systemic steroids are often needed to treat HES with organ involvement or with systemic symptoms, like severe rash, fluid retention, and similar. Steroids are very effective for controlling eosinophil numbers in blood and most patients can be maintained on oral steroid medication (called prednisone) for long period of time with good control of the disease. However, the blood eosinophils and disease symptoms generally return once steroids have been stopped. Long-term steroid use (especially when used in high doses) has, unfortunately, been associated with side effects.

Interferon alpha (IFNa) is used for a variety of diseases including infections (like hepatitis) and malignancies (like certain types of leukemia). IFNa has been shown to be effective in HES by suppressing the symptoms related to the disease. Toxicity, however, is a major obstacle to the use of this therapy. IFNa is commonly injected into the fatty tissue under the skin 3-5 times a week. Upon the initiation of therapy most patients experience influenza-like symptoms such as fever, chills, muscle aches, headaches, and joint pain. Other side effects of IFNa are low blood counts and elevated liver enzymes that require careful monitoring. These side effects usually lessen over time, but other toxicities can manifest themselves in various forms after long-term therapy. Overall experience with IFNa in myeloproliferative diseases is that about 25-30% of patients require discontinuation of therapy due to side effects. New long-acting forms of IFNa (pegylated interferons) have been developed over last few years and are now approved

as therapy for hepatitis. These medications are administered only once a week and may, therefore, be better tolerated.

Cyclosporine is a potent medication that suppresses the immune system and it is used primarily to prevent organ rejection in people who have had organ transplants. In some patients with HES there might be evidence that the immune cells have a role in supporting the diseases existence (so called T cells) and cyclosporine may have a role as therapy in such cases.

Anti-neoplastic agents provide an alternative approach to therapy of advanced cases of HES. These are chemotherapeutic agents that may control the disease. They are used to treat many malignancies and are not specific for eosinophilic disorders. They are potent medications that kill cells that grow the fastest (eosinophils in HES) but may potentially have harmful side effects and are reserved only for more severe cases. Careful monitoring while taking these medications is essential. Chemotherapeutic agents that have been used in HES include: Hydroxyurea, Methotrexate, Etoposide, Cyclophosphamide, Vincristine, and Cladribine.

New therapies for HES

As a result of cell growth research, scientists have been able to develop a group of therapeutic agents known as **tyrosine kinase inhibitors**. By blocking the ability of tyrosine kinases to function, these compounds provide a valuable tool for controlling malignant cell growth. The novel approach for treating HES is to “target” specific receptors on the eosinophil surface in order to interrupt their unregulated replication. PDGF-R (platelet derived growth factor receptor) is a receptor that is tyrosine kinase involved with the maintenance of normal blood cell production, skin pigment production, formation of female ova and male sperm, and the growth and activity of certain white blood cells involved in allergy and immune response. Alteration in PDGF-R tyrosine kinase activity is known to be responsible for disease onset and progression in some patients with HES. Therefore, medications (tyrosine kinase inhibitors) were developed to interfere with this process.

Gleevec (Imatinib Mesylate) is a tyrosine kinase inhibitor that is known to inhibit PDGF-R. Gleevec was developed for and is currently approved by the Food and Drug Administration for use as a treatment for Chronic Myelogenous Leukemia (CML); in this disease it blocks the activity of one other tyrosine kinase and is very effective therapy. Gleevec may eliminate disease in select HES patients, those having alteration in PDGF-R tyrosine kinase activity. Therefore, it is mandatory that HES patients be tested for this abnormality; there are 2 ways this can be accomplished, either using PCR test for FIP1L1-PDGFRa gene rearrangement, or using FISH test for CHIC2 gene deletion. Most HES patients do not have PDGF-R alteration, and some patient without it may still respond to Gleevec therapy, by improving signs and symptoms of the disease. Gleevec is given at a starting dose of 100 mg orally daily, with a dose escalation up to 400 mg after one month if no response is observed. Other tyrosine kinase inhibitors are being evaluated as therapy for HES patients.

Dasatinib is a tyrosine kinase inhibitor that was recently approved for therapy of CML patients failing Gleevec. It may affect many different tyrosine kinases and is being evaluated in a clinical study for HES patients not responding to standard therapies.

Nilotinib is another tyrosine kinase inhibitor that is also being developed for CML patients losing a response to Gleevec, but is not approved yet. This agent too is being evaluated in a clinical study for HES patients not responding to standard therapies.

Mepolizumab is an investigational medication for HES, not yet approved. It is a medication given intravenously monthly, that binds to IL-5 which is primary cytokine responsible for eosinophil growth. This therapy is being evaluated in clinical trials for patients with HES and other eosinophilic diseases and the initial results are encouraging.

Alemtuzumab is a monoclonal antibody reactive with several cell populations carrying a particular molecule termed CD52. Recent reports have shown the usefulness of alemtuzumab (anti-CD52) for the treatment of two female HES patients with cutaneous manifestations, one with a CD3⁺ CD4⁺ T-cell population [30,31]. Although this medication carries a black box warning because of hematological toxicity, infusion reactions and opportunistic infections, it may have a place in the treatment of certain HES patients who are resistant to other therapies.

Several clinical studies with new medications for HES are currently underway in the USA. Go to www.clinicaltrials.gov and enter “**Hypereosinophilic Syndrome**” to find active studies. Clinical trials include:

1. Dasatinib clinical study is currently accruing HES patients at the MD Anderson Cancer Center, Houston, Texas. More details can be found at: <http://www.mdanderson.org/diseases/mpd/> under ‘Clinical Trials’
2. Nilotinib clinical study is open at many centers in the USA, including MD Anderson Cancer Center in Houston, Texas. http://www.amn107.com/clinical_en.jsp
3. Mepolizumab clinical study is accessible at many academic centers in the USA. <http://www.clinicaltrials.gov/ct/show/NCT00244686>

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