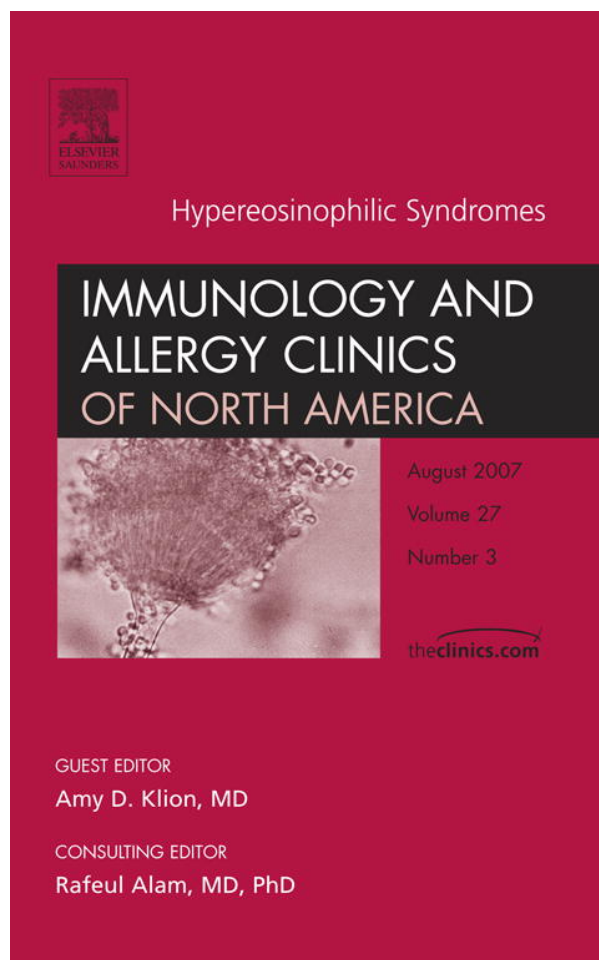




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Novel Approaches to Therapy of Hypereosinophilic Syndromes

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The hypereosinophilic syndromes (HES) are a heterogeneous group of disorders that are characterized by the presence of marked blood and tissue eosinophilia resulting in a variety of clinical manifestations. Three criteria, established by Chusid and colleagues [1], define HES: (1) sustained blood eosinophilia of greater than 1500/mL for longer than 6 months; (2) apparent etiologies for eosinophilia must be absent; and (3) patients must have signs of organ involvement. Known causes of eosinophilia include parasitic helminth infections, HIV, allergic disorders, and malignancies. There has been recent progress in our understanding of the pathogenesis of at least some HES subgroups. For instance, T-cell clones expressing interleukin (IL)-5 have been identified as a cause of HES in some patients [2–5]. In other patients, mutations in hematopoietic stem cells largely contribute to the development of HES [6,7]. Currently, such patients are still considered as suffering from HES, although the cause of eosinophilia can be explained.

Corticosteroids are the first-line treatment for most patients, but the most appropriate dose and the duration of therapy have not been evaluated. Usually, patients are treated with a high dosage (>40 mg of prednisone equivalent) initially, and the dosage is reduced gradually. Using this approach, most, but not all, patients who have HES respond. Patients receiving long-term treatment have increased risks for developing opportunistic infections (eg, *Pneumocystis* species-induced pneumonia) and bone loss.

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Corticosteroid-mediated adverse effects often become limiting, and the use of alternative therapies must be considered. Cytotoxic therapies might be used in corticosteroid-refractory HES. For instance, hydroxyurea has been applied successfully at dosages of 1 to 3 g/d [8]; however, these treatments are associated with unwanted hematologic and gastrointestinal effects. Recently, therapeutic progress has been made, particularly in those patients in whom our understanding of the pathogenesis of the disease has improved. This article summarizes these new pharmacologic approaches to the therapy of HES.

Interferon- α

Low-dose (1–3 million U/d) interferon- α has been reported to control HES for prolonged periods of time [9]. In contrast to corticosteroids, eosinophil numbers do not decline rapidly, but a reduction can be expected within 2 to 4 weeks. The antieosinophil effect of interferon- α might be the consequence of its effect on the T helper 1 (Th1)-T helper 2 (Th2) balance [10]; however, interferon- α receptors also are present on eosinophils [11], suggesting that clinical benefits also can be due to the direct effects on eosinophils. It is unclear when eosinophils activate the interferon- α receptor gene during maturation, but it is likely that it occurs late, during terminal differentiation, as observed in neutrophils [12]. Therefore, the effects of interferon- α in patients with mutations in hematopoietic stem cells associated with HES might be limited.

Because interferon- α , even at low doses, has multiple unwanted systemic effects (Box 1), it often is used only in corticosteroid-refractory HES [10]. Interferon- α has been reported to break corticosteroid resistance [10] or, at the least, to act synergistically with corticosteroids in treatment outcomes [9]. Interferon- α has been lifesaving for patients with intractable HES that was resistant to corticosteroids. Interferon- α also has been reported to act synergistically with low-dose hydroxyurea [9].

Anti-interleukin-5 monoclonal antibody

Eosinophil development from hematopoietic stem cells is regulated mainly by IL-5 and, to a lesser extent, IL-3 and granulocyte/macrophage colony-stimulating factor (GM-CSF) [13]. Because IL-5 seems to contribute to the pathogenesis of some HES subgroups [14], it represents a logical therapeutic target for these diseases. Preliminary open-label studies in the treatment of HES with anti-IL-5 monoclonal antibody (mAb) from two companies were encouraging; the treatment reduced blood eosinophil numbers into the normal range within 48 hours [15,16]; however, tissue eosinophilia was reduced by only 50% [15]. Nevertheless, clinical improvement was seen in patients who had HES in association with anti-IL-5 mAb therapy, and the drug was tolerated well.

Box 1. Adverse effects of antieosinophil therapies*Low-dose interferon- α*

Flulike symptoms
Nausea
Lack of appetite
Depression
Fatigue
Elevated liver transaminases
Myelosuppression

Imatinib

Nausea
Diarrhea
Rash
Edema
Muscle cramps
Elevated liver transaminases
Myelosuppression
Acute cardiac decompensation?

Mepolizumab

Upper respiratory tract infection
Myalgia

Alemtuzumab

Flulike symptoms (first day only)
Infections
Myelosuppression

Following these initial reports, a randomized, double-blind, placebo-controlled study was conducted with an anti-IL-5 mAb (mepolizumab). Eighty-five patients who had HES without evidence of a Fip1-like 1 (FIP1L1)-platelet-derived growth factor receptor α (PDGFRA) gene fusion (see later discussion) were randomized [17]. This study demonstrated a significant corticosteroid-sparing effect of mepolizumab, which suggests that corticosteroid-mediated morbidity can be reduced by this antibody therapy. Notably, approximately 50% of the mepolizumab-treated patients no longer required any corticosteroids. Therefore, mepolizumab represents the first drug specifically targeting eosinophils that showed clinical usefulness in an eosinophil-based disorder.

Mepolizumab only partially depleted eosinophils from tissues in patients suffering from bronchial asthma [18], eosinophilic dermatitis [15], or eosinophilic esophagitis (A. Straumann and H-U. Simon, unpublished data). The reduction of eosinophil numbers in inflamed tissues is rarely more than

50%, a finding that is independent of the underlying disease. In all of these clinical studies, the dose of mepolizumab was 750 mg, which resulted in a rapid decline of blood eosinophil numbers to normal levels. We recently conducted a mepolizumab study in patients who had eosinophilic esophagitis that confirmed these findings. Increasing the dose to 1500 mg did not lead to increased reductions of eosinophil numbers within the epidermal layer of the esophagus (A. Straumann and H.-U. Simon, unpublished data). Because eosinophils are not depleted from inflamed tissues, it remains to be shown whether mepolizumab is able to prevent, or at least to reduce, end-organ pathology associated with HES.

Mepolizumab seems to be tolerated well [17]. The incidence of adverse effects in mepolizumab-treated patients was in the same range as with placebo, with two exceptions. In the randomized, double-blind, placebo-controlled study of mepolizumab treatment for HES, 21% of the mepolizumab-treated patients developed respiratory infections compared with 10% in the placebo group. In addition, myalgia occurred more frequently with mepolizumab (19% compared with 7% with placebo; see [Box 1](#)); however, the latter adverse event also might have been due to the reduction of the corticosteroid dose.

Imatinib

Imatinib, a tyrosine kinase inhibitor, is an effective drug in PDGFRA-associated HES. In this HES subgroup, a gene fusion occurs between FIP1L1 and PDGFRA as the result of an 800-kilobase interstitial deletion on chromosome 4q12 [6,19]. The gene fusion has been identified in eosinophils as well as in multiple other hematopoietic lineages, including neutrophils, monocytes, lymphocytes, and mast cells, suggesting that PDGFRA-associated HES is actually an eosinophilic leukemia that arises from a mutation in a pluripotent hematopoietic stem cell. The imatinib response rate in these patients is nearly 100%, with only a few cases of acquired drug resistance due to a T674I mutation in PDGFRA [6,20]. The reduction in blood eosinophils is seen within 1 week of initiation of therapy. Generally, clinical improvement is seen within 1 month. Low-dose (100 mg/d) imatinib is usually sufficient to control eosinophilia and symptoms. Side effects of imatinib therapy generally are mild and rarely lead to discontinuation of therapy (see [Box 1](#)) [21].

The use of imatinib in patients who have HES, in which PDGFRA does not play a role, is controversial. Imatinib does not seem to be useful in treating patients in whom cytokine-producing T cells are the underlying cause of HES; however, it was reported that some FIP1L1/PDGFRA-negative patients who had HES responded to imatinib [6,22]. This raises the possibility that such patients have a rearrangement, mutation, or at least overexpression of a gene encoding a tyrosine kinase. It is likely that most, if not all, patients who have HES and are responsive to imatinib actually suffer

from eosinophilic leukemia or chronic myeloid leukemia associated with eosinophilia [7,23].

Other tyrosine kinase inhibitors

Despite the fact that imatinib treatment results in rapid, complete, and durable responses in FIP1L1-PDGFR α positive patients, some of the patients may relapse during imatinib therapy. Four patients have been described who developed resistance to imatinib; in all patients, the resistance was due to a T674I mutation within the kinase domain of FIP1L1-PDGFR α [6,20,24,25]. Despite the fact that FIP1L1-PDGFR α is extremely sensitive to imatinib, the FIP1L1-PDGFR α (T674I) mutant is highly resistant to imatinib, and increasing the dosage of imatinib cannot overcome resistance [6].

PKC412 [26], nilotinib (AMN107) [27,28], and sorafenib (BAY43-9006, Nexavar) [29] are small-molecule kinase inhibitors, with a different structure than imatinib, which show activity against PDGFR α and are under clinical development. The staurosporine derivative PKC412 originally was identified as an inhibitor of protein kinase C (PKC); it subsequently was shown to inhibit tyrosine kinases as well, including KDR, KIT, FLT3, and PDGFR [30]. PKC412 has shown activity in mast cell leukemia with the D816V KIT mutation [31] and is being tested in clinical trials for the treatment of acute myeloid leukemia with the FLT3 mutation [32]. Using in vitro and in vivo models, it was shown that PKC412 inhibits FIP1L1-PDGFR α and the imatinib resistant T674I mutant [26].

Nilotinib (AMN107) was rationally designed as a novel BCR-ABL inhibitor based on modeling of the binding of imatinib to the ABL kinase domain. Similar to imatinib, nilotinib interferes with tyrosine kinase activity by binding to the ATP-binding pocket when the kinase is in an inactive conformation. Nilotinib, however, inhibits proliferation of BCR-ABL transformed cells with a higher potency than does imatinib. In addition, nilotinib is active against several imatinib-resistant BCR-ABL mutants [33]. Nilotinib also inhibits the proliferation of cell lines transformed by activated KIT and PDGFR. Based on these observations, nilotinib also was tested for its activity against FIP1L1-PDGFR α and ETS variant gene 6 (ETV6)-PDGFR β and was found to inhibit these activated kinases at low nanomolar concentrations [28]. In addition, nilotinib showed at least some activity against the imatinib-resistant FIP1L1-PDGFR α (T674I) mutant [27].

Sorafenib (BAY43-9006, Nexavar) was developed as a BRAF inhibitor and was approved recently by the US Food and Drug Administration for the treatment of renal cell carcinoma [34]. More detailed analysis of the specificity of sorafenib revealed that it also had potent activity against RET and PDGFR family kinases. This was confirmed by in vitro studies using cell lines expressing activated FLT3, ETV6-PDGFR β , and FIP1L1-PDGFR α [29,35]. Sorafenib also showed potent activity against the

imatinib-resistant FIP1L1-PDGFR α (T674I) mutant [29], which was confirmed recently in vivo by treatment of a FIP1L1-PDGFR α (T674I)-positive chronic eosinophilic leukemia patient with sorafenib (E. Lierman, J. Cools, and P. Vandenberghe, unpublished data).

These inhibitors might be suitable for patients who do not tolerate imatinib or have developed imatinib resistance as a result of the T674I mutation in PDGFR α . It remains to be investigated whether some of these inhibitors could be combined to prevent the development of resistance, especially in patients who have chronic eosinophilic leukemia in blast crisis.

Anti-CD52 monoclonal antibody

CD52 is a glycosyl-phosphatidyl-inositol-linked glycoprotein expressed by leukocytes, including T and B cells, as well as eosinophils. An anti-CD52 mAb (alemtuzumab) has been developed that is being used increasingly for the prevention or treatment of acute allograft rejection in organ transplant recipients [36] and in the treatment of chronic lymphocytic leukemia [37]. Alemtuzumab was used in the treatment of two patients who had HES [38,39]. One patient suffered from a clonal T-cell disease associated with HES. The primary cellular target of this antibody in HES remains to be determined. Alemtuzumab treatment increases the risk for opportunistic infections (see Box 1) [40].

Bone marrow transplantation

Attempts to treat HES with allogeneic hematopoietic stem cell transplantation have been reported since 1988 [41–49]. Because HES are a heterogeneous group of uncommon disorders, these reports only represent cases or small series of patients. Clearly, in such a situation, it is difficult to establish a transplantation standard. Because of the high treatment-associated mortality, stem cell transplantation is reserved for patients suffering from aggressive HES that are resistant to drug treatment. In the case of imatinib failure in PDGFR α -associated HES, allogeneic hematopoietic stem cell transplantation represents a confirmed curative option [50].

Summary

There has been recent progress in the understanding of the pathogenesis of HES. This has led to the distinction of subgroups in which the underlying cause has been identified. Consequently, promising new treatment options became available. For instance, the prognosis of PDGFR α -associated HES is poor because of cardiac complications. Imatinib dramatically improves the clinical situation of these patients within 1 month, and it is hoped

that it also will improve their long-term survival. The cytokine-driven forms of HES are considered to have a better prognosis, and the availability of mepolizumab might reduce corticosteroid-mediated adverse effects; however, it is unlikely that mepolizumab is able to delete T-cell clones, which have been identified as IL-5-producing cells in some patients. Because such clonal T cells may transform into a T-cell lymphoma, the current therapeutic options for these patients are not satisfying. Moreover, it is unclear whether mepolizumab is useful to reduce HES-associated symptoms and prevent end-organ damage. There are some concerns in this respect, because the antibody seems to deplete eosinophils from affected organs only partially.

Besides the progress in HES therapy, there is some progress regarding measurement of treatment responses. For instance, the presence or absence of the abnormal fusion protein in PDGFRA-associated HES [19] or immunophenotypically abnormal T-cell clones [4,5] allows monitoring of therapeutic effects. In other cases, however, eosinophil numbers and clinical presentations remain the only parameters that are used. No other marker, including eosinophil-derived basic proteins, has been validated. Moreover, no marker is available that predicts eosinophil-mediated tissue damage.

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