



Advances in the diagnosis and treatment of eosinophilia

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Purpose of review

Eosinophils play an important role in the pathogenesis of allergic, infectious and malignant diseases. Over the last decade, new diagnostic tools and treatment modalities have led to the re-evaluation of the existing definition of eosinophilic disorders. This review discusses a recent proposal for new terminology and classification of hypereosinophilia. The results of targeted therapy for hypereosinophilia-related disorders are also summarized.

Recent findings

A panel of multidisciplinary experts agreed on unifying definitions and criteria of eosinophilia-associated disorders and created a new classification of hypereosinophilia-related conditions based on clinical, haematological and laboratory findings as well as the underlying cause of hypereosinophilia. Recent results of the treatment of idiopathic hypereosinophilic syndrome (HES) with the anti-interleukin 5 monoclonal antibody mepolizumab showed its efficacy and manageable safety profile. The treatment of platelet-derived growth factor alpha (PDGFRA)-positive HES with imatinib demonstrated long-lasting efficacy and low likelihood of drug resistance.

Summary

The unifying terminology and definitions should aid physicians caring for patients with hypereosinophilia. Despite much progress, serum biomarkers correlate with disease severity and predict responses to treatment that are needed. There is also a great need for understanding and specific therapy for PDGFRA-negative HES.

Keywords

classification, eosinophilia, hypereosinophilic syndrome, treatment

INTRODUCTION

Eosinophils play a pivotal role in inflammatory processes, tissue injury, remodeling and fibrosis. Eosinophil development and differentiation in the bone marrow is mediated by specific transcription factors. Maturation and exit from the marrow is promoted by eosinophilopoietic cytokines, mainly interleukin (IL)-5, but also granulocyte-macrophage colony-stimulating factor and IL-3. Activated T cells remain the primary source of IL-5; IL-5 is regarded as playing an essential role in the promotion of reactive eosinophilia in blood and marrow in allergic and parasitic diseases, as well as in Churg–Strauss syndrome (CSS) and some variants of hypereosinophilic syndrome (HES). Exposure to IL-5 is known to prolong the survival of eosinophils and promote the secretion of eosinophil granule contents [1].

The central role of IL-5 in the development and functioning of eosinophils has prompted the development and studies of anti-IL-5 monoclonal antibodies as steroid-sparing agents for several

eosinophilia-associated disorders. Studies have demonstrated the effectiveness of this treatment strategy [2–4].

PATHOPHYSIOLOGY OF EOSINOPHILIA

In response to a variety of stimuli, eosinophils are activated and invade most organ systems, thereby causing organ dysfunction and disease. Typically, eosinophils in peripheral blood represent less than 5% of total leukocytes. Eosinophilia is defined as absolute blood eosinophil count (AEC) exceeding

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KEY POINTS

- A panel of international experts have agreed on unifying terminology and criteria of eosinophilic-related disorders.
- A new term 'hypereosinophilia of undetermined significance' describing patients with idiopathic, benign hypereosinophilia with no underlying cause was introduced.
- Mepolizumab, an anti-IL-5 antibody, has shown long-lasting efficacy with a manageable safety profile for PDGFRA-negative HES.
- Tyrosine kinase inhibitor-imatinib represents the first-line treatment for PDGFRA-mutated HES with an excellent response rate and long-term effectiveness at low doses.

$0.5 \times 10^9/l$. Hypereosinophilia refers to AEC greater than $1.5 \times 10^9/l$ [5]. It should be mentioned that tissue eosinophilia may be accompanied or not accompanied by blood eosinophilia and vice versa. Whereas a modest number of eosinophils are found in normal tissues, for example, the gastrointestinal tract, their excessive infiltration may result in organ damage and lead to local or systemic disease. Hypereosinophilia is associated with inflammation, tissue fibrosis and has a tendency to cause thrombosis presumably because of tissue infiltration by eosinophils and release of their granule contents. This may impair the function of critical organs, for example, heart, lungs or central nervous system. The candidate mechanisms by which eosinophils cause tissue damage have been proposed and this was presented in detail elsewhere [6]. This current review will focus on the recent clinical advances in the field of eosinophilia.

DEFINITIONS AND CLASSIFICATION OF EOSINOPHILIA

The introduction of new diagnostic tools and treatment modalities has prompted modification of the existing criteria of HES established nearly 40 years ago [7]. Some key questions are as follows:

- (1) Should a HES patient remain untreated for 6 months despite features of organ dysfunction?
- (2) How should the clinician manage a patient with blood hypereosinophilia without signs of tissue infiltration?
- (3) What is the proper classification for a patient with eosinophilia-associated organ damage and AEC less than $1.5 \times 10^9/l$?
- (4) How should a patient, originally diagnosed as idiopathic hypereosinophilia, be classified after

the identification of a fusion gene involving platelet-derived growth factor receptor α (PDGFRA) [8]?

To deal with these important questions, experts first recommended that the original Chusid criteria for HES should be loosened, with the requirements for the duration of hypereosinophilia as well as the degree of eosinophilia modified when there is documented organ damage [9]. Then a panel of multidisciplinary experts agreed on new terminology, criteria and classification of eosinophilic disorders [10¹¹]. The most important new findings can be outlined as follows:

- (1) The term hypereosinophilia should be used when the AEC is greater than $1.5 \times 10^9/l$ on two occasions with a minimum of a 1-month interval. The exception is when the AEC is greater than $1.5 \times 10^9/l$ and there is life-threatening organ dysfunction and/or tissue eosinophilia is documented. For the diagnosis, the following criteria should be met: eosinophils should constitute more than 20% of all nucleated cells in the bone marrow section; massive tissue infiltration by eosinophils should be found in tissue biopsies by pathologic study; and specific staining should reveal local deposition of eosinophil-derived contents.

The proposed classification of hypereosinophilia includes four variants that are as follows:

- (1) familial clustering with unknown pathogenesis;
- (2) asymptomatic eosinophilia of undetermined significance with no known underlying cause (HE^{us});
- (3) neoplastic eosinophilia with the evidence of myeloid/eosinophilic clonality;
- (4) reactive eosinophilia mostly cytokine-driven with known underlying nonclonal cause.

According to a new proposal, the patients with an aberrant T-cell population in blood and hypereosinophilia-associated organ damage are now regarded as a variant of reactive HES.

TREATMENT CONSIDERATIONS

HES patients generally require treatment, but the management of patients with severe blood hypereosinophilia without organ involvement is challenging. The expert panel proposed the term HE^{us} for patients with benign, idiopathic hypereosinophilia; but there was no consensus regarding the therapeutic management for HE^{us} patients. Treat or not to treat? – this question remains open.

In my opinion, this new diagnostic terminology accurately reflects this patient population. It also clearly indicates the need for long-term follow-up information on these patients, similar to the need for more information about patients with monoclonal gammopathy of undetermined significance [11]. In my practice, I follow patients with eosinophilia at 3–6 month intervals. In my observation, patients may remain asymptomatic for months or even years despite the long-lasting elevation of blood levels. When AEC is greater than $5.0 \times 10^9/\text{l}$, I usually start treatment with corticosteroids in order to avoid end-organ damage, but this management is not supported by literature data. Others prefer to implement the treatment with higher counts, for example, AEC exceeds $30 \times 10^9/\text{l}$, but this is, again, not endorsed by the evidence [12].

The identification of organ damage in a patient with HE^{us} is synonymous with the HES diagnosis and, when present, the initiation of treatment is inevitable. A major challenge regarding the HE^{us} patients is to define the risk factors that may predict the transformation to HES, but such data has yet to be published. The definition of eosinophilia-attributable organ involvement is another problem. As was mentioned previously, histological evidence of tissue eosinophilia is absolutely necessary for the diagnosis of HES. However, it is extremely difficult to implement this criterion in clinical practice because the involved organs are often inaccessible for biopsy or the biopsy procedures are associated with high risk of severe complications. Imaging studies are often inconclusive. From a practical point of view, the diagnosis of hypereosinophilia-related organ dysfunction is often made by the exclusion of other causes, as in a recent report of a large series of HES patients [13].

The expert panel proposed clinical and laboratory parameters to be performed on patients with hypereosinophilia [5], but the list of recommended investigations was long and expensive. For example, immunophenotyping of T cells by flow cytometry as well as molecular assays by PCR are not widely available and can be performed only in specialized laboratories. Although samples may be shipped for some of these tests, there is a clear need for simplified diagnostic methods and specific biomarkers that accurately predict prognosis for these patients.

NEW TESTS AND TREATMENTS

Eosinophils exhibit a variety of characteristic alterations when activated [5]. Sialic acid immunoglobulin-like lectins (Siglecs) are cell surface proteins found predominantly on leukocytes. Siglec-8 is

uniquely expressed on eosinophils and mast cells and weakly on basophils [14]. This protein is engaged in apoptosis of human eosinophils, and IL-5 priming increases Siglec-8-mediated apoptosis, a finding that may have a potential clinical implication [15]. In fact, studies in IL-5 transgenic mice with hypereosinophilia have shown that administration of an antibody directed against Siglec-8 resulted in a prompt and significant reduction of blood eosinophilia [16]. Thus, Siglec-8 may be a promising target for monoclonal antibodies in eosinophilia-related conditions [17]. Recently, a novel assay for the measurement of serum Siglec-8 was developed, but its utility needs to be validated [18].

NEW DEVELOPMENTS IN DIAGNOSIS

A variety of serum cytokines and chemokines have been used as markers of different eosinophilia-related disorders. Some of them were found to be elevated in patients with active CSS and also in HES patients. Therefore, they may not serve as biomarkers distinguishing between these disorders [19,20]. These findings have been confirmed in a large retrospective study including CSS and HES patients. Despite the fact that some serum markers were elevated in CSS/HES when compared with healthy controls, there were similarities between eosinophilia-related conditions [21]. Recently, Wilson *et al.* [22] reported on serum IL-5 receptor α (IL-5R α) levels in patients with blood eosinophilia including patients with idiopathic HES and PDGFRA-positive HES. It was demonstrated that serum soluble IL-5R α levels correlated positively with blood AEC and that an elevation of the serum IL-5R α levels was associated with increased serum IL-5 and IL-13 levels and other markers of eosinophil activation. An inverse correlation was found between surface expression of IL-5R α on blood eosinophils and AEC. These results may have clinical implications with respect to novel agents targeting IL-5R α [23].

RESULTS OF CURRENT CLINICAL TRIALS

The therapeutic approach to eosinophilic disorders has changed during the past several years. The identification of specific targets may influence the prognosis and improve the quality of life. Benralizumab is a humanized monoclonal antibody targeting IL-5R α , and this compound has been tested in a phase I study of patients with asthma. This treatment resulted in marked decrease of AEC as well as serum eosinophil cationic protein levels [23]. Taking into account these promising results, the further

studies of individuals with CSS/HES are expected to be initiated. Another IL-5 targeting agent, mepolizumab, has been investigated for the treatment of many eosinophilic disorders including HES. A randomized, placebo-controlled study of 85 HES patients receiving prednisone at 20–60 mg daily (q.d.) was designed in order to evaluate the efficacy of mepolizumab as a steroid-sparing agent. The primary end point of a reduction of the prednisone dose to 10 mg daily or less for eight or more consecutive weeks was achieved in 84% of patients on mepolizumab if compared with 43% in the placebo group [2]. Recently, the results of mepolizumab treatment for PDGFRA-negative HES were reported, confirming its high efficacy and manageable safety profile as a steroid-sparing agent in long-term observation [24[¶]]. Alemtuzumab, an anti-CD52 antibody, has been reported to be effective for refractory HES patients [25]. Twelve patients were included in this retrospective analysis; 10 (83%) achieved complete hematologic response and the remaining two individuals met partial response criteria. It was found that alemtuzumab maintenance for patients in remission resulted in a significantly longer progression-free survival if compared with the patients who did not continue the antibody treatment [25]. Alemtuzumab may be an alternative therapeutic option for HES patients who failed prior therapy and are not candidates for allogeneic stem cell transplantation, but it appears to be a relatively expensive and poorly tolerated treatment. Targeted therapies for eosinophilic disorders that are currently available or in clinical trials were presented in a recently published review by Wechsler *et al.* [26[¶]].

COMMENTS ON PRINCIPLES AND UNCERTAINTIES IN MANAGEMENT

Despite the progress that has been made in the development of targeted agents, the glucocorticosteroids and hydroxyurea remain the cornerstone of therapy for PDGFRA-negative HES [13]. Our group reported on the results of steroid treatment for 33 patients with HE^{us} and idiopathic HES. The median starting dose of steroids was 30 mg daily and 64% of treated individuals achieved complete remission. In our study, therapy was well tolerated with only a single case of severe gastric complications. In another report, imatinib mesylate was found to be effective in three out of seven steroid-resistant or intolerant patients [27].

The updated results of imatinib mesylate treatment for PDGFRA-positive HES were published last year from the Mayo Clinic. Twenty-two patients with mutated *FIP1L1-PDGFR*A (F/P) were identified

and, of these, 18 were treated with imatinib mesylate. Most patients (77%) received imatinib mesylate at 100 mg daily. One individual was found to be intolerant to imatinib mesylate, the remaining 17 patients achieved complete remission. Median follow up of the imatinib mesylate-treated population was 6 years. These results confirmed the impressive response to low doses of imatinib mesylate with the low probability of developing secondary resistance. However, the authors' conclusion is that the therapy with imatinib mesylate should be continued indefinitely [28].

Our results are in line with those of the Mayo study. Twenty-five patients with mutated F/P received imatinib mesylate at a starting dose of 100 mg daily. All responded promptly and after a median follow up of almost 6 years remained in remission. Imatinib mesylate at 100 mg weekly was found to be sufficient for response maintenance. However, in contrast to the final statement of the Mayo Group, we discontinued imatinib mesylate therapy in two patients who had negative PCR in consecutive assays for 5 years and they are still disease-free with more than 1 year being off therapy [29]. The presence of PDGFRA mutation in eosinophilia-associated acute leukemia or lymphoma was also associated with very impressive and sustained responses to imatinib mesylate despite the failure of prior therapy with conventional chemotherapy [30]. Most F/P-positive patients are adult male and only single case reports included children. Only four F/P-mutated children have been described in the literature so far. Three children received imatinib mesylate with excellent responses [31].

In contrast to the previously mentioned population with PDGFRA mutations, there is a lack of long-term survival data for individuals with PDGFRA-negative HES. Podjasek *et al.* [32[¶]] presented the 19-year experience of HES-related mortality at Mayo Clinic, probably the largest report published. The study included 247 HES patients, of whom 23 died (10%), but the cause of death was identified in only 15 patients. Most individuals died of presumably eosinophilia-attributable cardiac damage and unrelated infections and malignancies. Only two patients developed thrombotic phenomena likely to be secondary to HES. Unfortunately, there are no data on histologic studies of affected organs. Moreover, blood eosinophilia before death was only available for a small minority of these patients.

CONCLUSION

In summary, in 2013 important changes were introduced to better define and classify patients with

hypereosinophilia. With the exception of PDGFRA-mutated HES cases, the molecular mechanisms remain unknown for the vast majority of these patients, and therefore targeted therapy is not possible. On the other hand, we are witnessing rapid development of monoclonal antibodies targeting IL-5/IL-5R α , but thus far these agents are not available beyond clinical trials. Steroids and hydroxyurea remain the first-line therapeutic options for the HES population, but their long-term administration may be associated with severe side-effects. IL-5/IL5R α are promising targets currently being investigated. Treatment of PDGFRA-positive HES with imatinib mesylate results in an excellent response rate, long-term efficacy and a low likelihood of drug resistance. The question remains open whether these patients will be cured following imatinib mesylate discontinuation. Future studies should focus on a better understanding of the pathogenesis of HE^{us}. The other challenge is to identify the serum biomarkers that may predict disease severity and responsiveness to therapy. Better diagnostic tools are also required for the evaluation of eosinophilia-related end-organ damage.

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Conflicts of interest

There are no conflicts of interest.

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