The role of eosinophils in common diseases — such as asthma, parasitic disease, or allergic reactions — remains speculative. Even more puzzling is the eclectic group of rare disorders that constitute the hypereosinophilic syndromes. These syndromes are characterized by persistently high levels of blood eosinophils and their toxic mediators (e.g., eosinophil cationic protein and eosinophil-derived neurotoxin), accompanied by severe multiorgan damage. The hypereosinophilic syndromes exclude secondary causes of eosinophilia such as infection while including myeloproliferative and lymphoproliferative variants, associated eosinophilic conditions that fulfill specific diagnostic criteria (e.g., the Churg–Strauss syndrome and mastocytosis), and the complex, undefined conditions affecting a large group of patients that do not meet any specific criteria yet are characterized by clinically significant symptoms and end-organ dysfunction. Due to the significant overlap in clinical presentation of these entities, establishing a definitive diagnosis can be challenging.

Regardless of the specific variant of the hypereosinophilic syndrome affecting a given patient, achieving disease control without long-term sequelae has been difficult. This may reflect the varied pathogenesis of the hypereosinophilic syndromes, including defects in the regulation of eosinophilopoiesis in the bone marrow, perturbed eosinophil recruitment and survival in tissue, and differential activation and release of toxic mediators from eosinophils. The clinical care of these patients has historically involved nonspecific suppression or eradication of eosinophils without a patient-specific, mechanism-based approach. Systemic corticosteroids, hydroxyurea, and interferon alfa have been the mainstay of therapy but are not effective, or are associated with considerable adverse effects, in many patients. Advances in molecular diagnostic techniques have resulted in the identification of several etiologic subtypes of the hypereosinophilic syndrome that may respond to new, targeted therapies, as shown by the response to the tyrosine kinase inhibitor imatinib mesylate in FIP1L1-PDGFRα positive patients. However, a majority of cases of the hypereosinophilic syndromes remain unclassified and are difficult to treat, and innovative, minimally toxic therapeutic agents are desperately needed.

In this issue of the Journal, Rothenberg et al. report on a clinical advance for a large proportion of patients with this orphan disease. In their large, double-blind, placebo-controlled trial of patients with the hypereosinophilic syndrome, patients treated with mepolizumab, a monoclonal antibody against interleukin-5 — a key cytokine involved in eosinophil maturation, proliferation, and survival — had not only a sustained reduction in eosinophil levels but also a significant corticosteroid-sparing effect, as compared with patients receiving placebo, without any increase in clinical activity of the hypereosinophilic syndrome. The daily prednisone dose was reduced by 79% between baseline and week 36 among patients treated with the anti–interleukin-5 therapy and could be tapered to 10 mg or less daily in twice the number of patients in the anti–interleukin-5 group as in the placebo group. Almost 50% of patients receiving anti–interleukin-5 antibody could be completely weaned from corticosteroids during the treatment period and remained corticosteroid-free until study completion. Over the 9-month treatment period, the rates of adverse events other
than those due to the hypereosinophilic syndrome were similar in the active-treatment group and the placebo group.

Although treatment with this anti–interleukin-5 antibody appears to represent an advance for patients with the hypereosinophilic syndromes, several questions remain unanswered, and there are several caveats. How long do the effects of this biologic agent last, and will rebound eosinophilia recur when treatment is stopped? What is the ideal dose to achieve a sustained response? Because not all patients with the hypereosinophilic syndrome had a response to therapy and many were unable to have corticosteroids withheld for an extended period of time (possibly due to underlying adrenal suppression), can we identify a priori responders and nonresponders? Since the eosinophil is central to the pathogenesis of these syndromes, what is different about the biology of nonresponders that makes them less likely to have a response? In the absence of specific biomarkers that are able to predict responsiveness, who are ideal candidates for this effective but probably expensive and potentially risky therapy? Since disease control was achieved with a daily prednisone dose of 10 mg or less in as many as 38% of patients receiving placebo by the end of the study, it seems that aggressive attempts to reduce corticosteroid dosing should be attempted first in all patients, until we can identify specific biomarkers. Lastly, although this study focused on patients with the hypereosinophilic syndrome who were already being treated with corticosteroids, is there a role for anti–interleukin-5 antibody as first-line therapy in lieu of corticosteroids?

Another important question is whether eosinophil-targeted therapy can be used in patients with other eosinophilic disorders. Although anti–interleukin-5 antibody has shown some efficacy in treating eosinophilic esophagitis, there has been considerable disappointment in the effect of this type of antibody in patients with asthma. Studies of experimentally induced asthma by Leckie et al. and Flood-Page et al. have shown that an anti–interleukin-5 antibody effectively reduced eosinophil counts in both blood and sputum but did not result in significant improvement in other clinical end points, such as lung function. Although there is hope that this therapy will have some benefit in subgroups of patients with asthma with more of an eosinophil-predominant phenotype, or that higher doses may better eradicate the extent of tissue infiltration, supportive studies have been lacking to date and the role of the eosinophil in the pathogenesis of asthma has remained murky. Perhaps this therapy has greater potential in other eosinophil-mediated diseases such as eosinophilic pneumonia or the Churg–Strauss syndrome.

Nonetheless, with its ability to combat eosinophilia and prevent infiltration of and damage to organ tissue by eosinophils, anti–interleukin-5 treatment certainly brings new hope to many patients with the hypereosinophilic syndromes whose disease is currently refractory to conventional therapies or who have side effects from them. It is important to recognize that this therapy's greatest contribution may be to teach us about the biologic characteristics of eosinophils. Advances in molecular biology lead to treatments that can be good for patients and even better for understanding the pathogenesis of their mysterious conditions. In a virtuous cycle, better understanding should lead to the identification of biomarkers that will help clinicians decide who will benefit most from exciting new therapies such as anti–interleukin-5 antibodies.

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