

7. Seung KB, Park D-W, Kim Y-H, et al. Stents versus coronary-artery bypass grafting for left main coronary artery disease. *N Engl J Med* 2008;358:1781-92.
8. Buszman PE, Kiesz SR, Bochenek A, et al. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. *J Am Coll Cardiol* 2008;51:538-45.
9. Sianos G, Morel M-A, Kappetein AP, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention* 2005;1:219-27.

10. Valgimigli M, Serruys PW, Tsuchida K, et al. Cyphering the complexity of coronary artery disease using the Syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. *Am J Cardiol* 2007;99:1072-81.

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Eosinophils in Asthma — Closing the Loop or Opening the Door?

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Although the origin of the concept that eosinophils are critical to asthma pathobiology remains controversial, there is consensus that Paul Ehrlich first identified a bilobed nucleated cell as an “eosin”-ophil in 1879 on the basis of the cell’s granular uptake of his newly discovered dye. These cells were soon found in airway tissues and “catarrh” (sputum) of patients with asthma. Over the years, eosinophils were identified as a prominent cell type in asthma, yet their role as either an “effector” or “innocent bystander” was not confirmed until the publication of articles by Nair et al.¹ and Haldar et al.² in this issue of the *Journal*.

In each of these studies, treatment with mepolizumab, a monoclonal antibody against interleukin-5 (a proeosinophilic cytokine), significantly reduced the number of lung and blood eosinophils in a small group of patients with severe corticosteroid-resistant asthma. Since both studies showed a significant reduction in asthma exacerbations in patients receiving mepolizumab, it would seem that the eosinophil does, in fact, play a central role in asthma and its outcomes. Or does it?

To address this question, it may be helpful to review the role of eosinophils in asthma. Soon after Ehrlich’s studies, asthma was considered to be an eosinophilic disease, with a general consensus that eosinophils were the sentinel inflammatory cell. This view prevailed until two clinical studies^{3,4} of a monoclonal antibody against interleukin-5 were completed about a decade ago. One of these studies used a laboratory model of human asthma on the basis of an inhaled-allergen challenge, and the other study analyzed traditional safety and efficacy measures in patients with mild-to-moderate asthma. The results of both these

studies were completely negative with respect to the role of eosinophils in the asthma outcomes that were measured. The combination of these studies hit the “eosinophil as center of the asthma universe” community by storm; soon many researchers were questioning the wisdom of focusing on eosinophils as the key effector cell in asthma.

With these findings in mind, an emerging appreciation of the heterogeneity of asthma led to the description of two asthma phenotypes on the basis of the presence or absence of tissue eosinophils.⁵ Patients with asthma who had eosinophilia had greater airway remodeling and more exacerbations, whereas those without eosinophilia had more airway obstruction. Subsequently, numerous studies supported the concept that although many patients with asthma do not have any eosinophilic inflammation, the presence of such inflammation identifies a more exacerbation-prone phenotype.⁶⁻⁹

The identification of this “eosinophilic” phenotype led to two clinical trials^{8,10} in which investigators modified the amount of corticosteroid (which has antieosinophilic effects) that the patients were receiving on the basis of the number of eosinophils in the sputum. The investigators, who were from the same groups as the authors of the two studies in this issue of the *Journal*, reported that the use of eosinophil numbers in sputum to determine the corticosteroid dose lowered the rate of asthma exacerbations. Furthermore, in the absence of eosinophils, a safe reduction in the corticosteroid dose was possible without triggering exacerbations. However, since corticosteroids have many effects on inflammatory processes beyond that on eosinophils, the causative role of eo-

sinophils in reducing exacerbations could not be confirmed. Corticosteroids were simply not a biologically informative intervention.

Thus, the studies by Nair et al. and Haldar et al. were built on three concepts: that the inhibition of interleukin-5 reduces eosinophilic inflammation, that not all asthma is eosinophilic, and that a reduction in eosinophils was associated with a decreased rate of exacerbations. Both groups of investigators used mepolizumab as an intervention and enrolled only patients with severe asthma who had persistent eosinophilic inflammation despite corticosteroid treatment. Although many treatment outcomes were measured, the only outcome that consistently improved was the exacerbation rate.

How do these new studies help move our understanding forward? Unlike previous studies of anti-interleukin-5 agents, the patients in these studies had a highly eosinophilic form of asthma. The persistent eosinophilic inflammation despite corticosteroid treatment appears to be more common in patients with adult-onset asthma than in those with childhood-onset asthma.^{6,7} In both studies, the average age at asthma onset was the mid-to-late 20s, and the percentage of patients with atopic disease was lower than expected.¹ Asthma that starts in adulthood is less likely to be typical "allergic asthma." Rather, late-onset eosinophilic asthma is associated with sensitivity to nonsteroidal antiinflammatory medications (aspirin) and with tissue eosinophilia.⁷ Although up to 40% of cases of severe asthma start later in life, the eosinophilic form of asthma probably represents less than 5% of the total number of cases of adult-onset asthma. Thus, the phenotype in these studies represents a small percentage of all patients with asthma and is perhaps more representative of a type of "hypereosinophilic" syndrome, which has previously been shown to respond to anti-interleukin-5 therapy, than actual asthma.^{11,12} The Canadian center where Nair et al. conducted their study screened hundreds of subjects to get the 20 that they studied. Even then, several subjects did not meet the reversibility or airway-hyperresponsiveness definition of "asthma."

In these two trials, the selective removal of eosinophils had no effect on other asthma outcomes, including the forced expiratory volume in 1 second, symptoms, and asthma control. Although

there was a differential effect of mepolizumab therapy on the patients' quality of life, the improvement was not clinically meaningful. This lack of effect becomes more obvious when comparing the patients' responses to systemic corticosteroid treatment. In contrast to the narrow range of effects related to eosinophils in patients receiving mepolizumab, the broader antiinflammatory effects of systemic corticosteroid significantly improved the outcomes independent of mepolizumab therapy. The results imply that eosinophils are not the only (or perhaps even the major) cell involved in disease pathogenesis, even in patients with severe asthma.

Finally, these two studies must be examined in light of the negative outcomes of anti-interleukin-5 therapy in patients with milder, more typical asthma.⁴ In patients with mild asthma (either before or after anti-interleukin-5 therapy), levels of eosinophilic inflammation did not have an effect on clinical outcomes in any way. This finding raises the question as to whether some eosinophil phenotypes respond differently to corticosteroid treatment and variably contribute to asthma outcomes.

These studies clearly confirm that in a subgroup of patients with eosinophilic asthma, eosinophils play a role in exacerbations. These particular eosinophils contribute to the pathobiology of asthma, and in this small subgroup, mepolizumab therapy had some clinical benefit. However, many patients with asthma do not have eosinophilia, and even in patients with eosinophilic asthma, mepolizumab had no effect on other physiological and clinical factors. These findings open the door, perhaps even further, to investigations of alternative cells and mediators in the broader world of asthma.

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1. Nair P, Pizzichini MMM, Kjarsgaard M, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009;360:985-93.
2. Haldar P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;360:973-84.
3. Leckie MJ, ten Brinke A, Khan J, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hy-

per-responsiveness, and the late asthmatic response. *Lancet* 2000;356:2144-8.

4. Flood-Page P, Swenson C, Faierman I, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med* 2007;176:1062-71.

5. Wenzel SE, Schwartz LB, Langmack EL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am J Respir Crit Care Med* 1999;160:1001-8.

6. Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218-24.

7. Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. *J Allergy Clin Immunol* 2004;113:101-8.

8. Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360:1715-21.

9. Simpson JL, Scott RJ, Boyle MJ, Gibson PG. Differential proteolytic enzyme activity in eosinophilic and neutrophilic asthma. *Am J Respir Crit Care Med* 2005;172:559-65.

10. Jayaram L, Pizzichini MM, Cook RJ, et al. Determining asthma treatment by monitoring sputum cell counts: effect on exacerbations. *Eur Respir J* 2006;27:483-94.

11. Plötz S-G, Simon H-U, Darsow U, et al. Use of an anti-interleukin-5 antibody in the hypereosinophilic syndrome with eosinophilic dermatitis. *N Engl J Med* 2003;349:2334-9.

12. Garrett JK, Jameson SC, Thomson B, et al. Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. *J Allergy Clin Immunol* 2004;113:115-9.

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