EDITORIALS

Anti–Interleukin-5 Monoclonal Antibody to Treat Severe Eosinophilic Asthma

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Despite the availability of treatments such as glucocorticoids, leukotriene antagonists, long-acting bronchodilators, and a monoclonal antibody directed against IgE, a substantial proportion of patients with asthma continue to have uncontrolled disease.[1] Exacerbations requiring hospitalization and ongoing treatment with a regular maintenance dose of systemic glucocorticoids cause substantial morbidity and impair the quality of life of these patients.

Recognition of the components of the airway disease that contribute to the severity (airway hyperresponsiveness and inflammation and airflow limitation) and the underlying mechanisms of those abnormalities is a logical starting point on the path toward the development of strategies to target and mitigate these factors.[2] For example, airway hyperresponsiveness is considered to be the direct target of bronchial thermoplasty to treat severe asthma.[3] Another approach that is aimed at the inflammatory component of asthma is the use of monoclonal antibodies against specific type 2 helper T-cell cytokines (e.g., interleukin-4, interleukin-13, and interleukin-5), since these proteins are thought to be major drivers of the inflammatory component of asthma.[4]

The use of antibodies against interleukin-5 did not work in studies in which patients were identified only on the basis of clinical criteria.[5,6] Thus, the challenge has been to find clinically applicable biomarkers to identify patients who will have a response to specific monoclonal antibody–based therapies. For example, it made sense to attempt to identify an "eosinophilic phenotype" as a useful method of characterizing patients who are likely to have a response to anti–interleukin-5 treatments.[6,7] This approach worked, and monoclonal antibodies against interleukin-5, when administered intravenously, were effective in decreasing both the rate of asthma exacerbations[8-10] and the maintenance dose of systemic glucocorticoids used to control asthma[11] in patients with sputum eosinophilia of more than 3%.

Two studies[12,13] now published in the *Journal* report the efficacy of mepolizumab, the same anti–interleukin-5 monoclonal antibody that was evaluated in three of the above-mentioned studies,[9-11] which was administered monthly in patients with severe asthma. The drug was safe and had an acceptable side-effect profile, at least in the short term, in the majority of patients; the drug triggered the production of neutralizing antibodies in the blood of only a few patients. The studies illustrate two new clinical observations that have important practical applications. First, the subcutaneous administration of a lower dose of the drug (100 mg) than was previously reported was shown to be efficacious. Second, characterization of the eosinophilic phenotype on the basis of a blood eosinophil count of more than 300 cells per microliter despite concurrent treatment with high doses of glucocorticoids was sufficient to select patients who were likely to have a response to this therapy. Both these observations make it potentially simple and easy for practitioners to identify patients who are likely to benefit and administer the drug to them.

However, these studies do not suggest that all patients with uncontrolled asthma who have peripheral blood eosinophilia will require an ex-

pensive anti–interleukin-5 therapy for clinical benefit. The patients who were selected for the study by Ortega et al.[12] had high baseline rates of exacerbation (mean, 3.6 per year), which suggests that their doses of inhaled glucocorticoids and long-acting bronchodilators had perhaps not been optimized. The exacerbation rate decreased to 1.75 exacerbations per year with placebo treatment, 0.93 per year with the 75-mg intravenous dose of mepolizumab, and 0.81 per year with the 100-mg subcutaneous dose of mepolizumab. Although the magnitudes of the reductions in exacerbations with the two routes of administration (mean effects of 47% and 53%, respectively) were similar and greater than the reduction achieved with placebo, it is remarkable that the patients receiving placebo had a 50% reduction, as compared with their baseline rate. It is well recognized that even in the most well-characterized patients with severe asthma, the lack of adherence to the prescribed therapy is the most common cause of poor asthma control.[14] Furthermore, the judicious use of currently available therapies guided by sputum cell counts has been shown to lead to substantial reductions in exacerbations, decreases that are clinically equivalent to those reported for biologic therapies and are likely to be more cost-effective.[15] This finding would suggest that most patients in this clinical trial might have had improvement in symptoms without mepolizumab simply by the institution of good clinical practice, as recommended by current international guidelines.

In contrast, the treatment effects reported in the study by Bel et al.[13] involving patients with oral glucocorticoid-dependent asthma are more impressive. There is a desperate need for effective therapies for patients who are truly dependent on systemic glucocorticoids for their asthma control. However, in the study by Bel et al., among patients receiving mepolizumab, the mean percentage reduction in the dose of glucocorticoids (50%) and the proportion of patients who had this reduction (54%) were lower than reductions that have been reported for higher doses of the drug (750 mg) administered intravenously in patients with sputum eosinophilia (87% dose reduction and 100% of patients, respectively[11]). Anti–interleukin-5 therapies are the only treatments that have so far been shown in well-conducted, randomized clinical trials to be effective in lowering the dose of oral glucocorticoids in patients in whom the minimum maintenance dose has been carefully established. Although the reduction of eosinophils in blood and sputum may be associated with decreases in the dose of glucocorticoids used to achieve an overall improvement in asthma control, it may be associated with only modest improvement in airway hyperresponsiveness, which confirms the hypothesis that eosinophils only partially contribute to the physiological abnormalities that characterize asthma.

Anti–interleukin-5 therapy offers an important advance in our ability to care for patients with severe eosinophilic asthma, particularly as a method of decreasing exacerbations in patients who are dependent on daily use of oral glucocorticoids (provided they do not have any parasitic infestations). Although persistent blood eosinophilia may be sufficient to identify patients who are likely to have a response to this treatment, whether this biomarker is sufficient or is as effective as airway eosinophilia in monitoring the response to treatment remains to be seen. Among such patients, sputum eosinophil levels are much more sensitive to change than are blood eosinophil levels or measurements of the forced expiratory volume in 1 second. When doses of glucocorticoids are reduced, sputum eosinophil levels may increase as early as 3 months before an exacerbation.[16]

Since airway eosinophils were not monitored in the studies by Ortega et al. and Bel et al., it is not possible to know whether better outcomes could have been achieved by adjusting the mepolizumab dose to suppress these levels. In addition, further evaluation is required to determine the most effective dose and the most effective route and frequency of administration of the drug in these patients, particularly in those who require daily oral glucocorticoids. Given that multiple cytokines and pathways contribute to eosinophil recruitment to the airway, the simultaneous administration of more than one monoclonal antibody might have additive clinical efficacy. In the meantime, it is reasonable to consider anti–interleukin-5 therapy for patients with severe asthma who are receiving high doses of systemic glucocorticoids and who continue to have an elevated eosinophil count in sputum or blood regardless of their atopic status.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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This article was published on September 8, 2014, at NEJM.org.

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DOI: 10.1056/NEJMe1408614

FFR-Guided PCI — FAME May Not Be So Fleeting after All

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Treatment strategies for patients with stable coronary artery disease are driven by the principles of reducing symptoms of coronary insufficiency, preventing myocardial infarction, and prolonging survival. Although percutaneous coronary intervention (PCI) plays a primary role in treating acute coronary syndromes, current guidelines relegate it largely to a secondary role in treating stable coronary disease.[1,2] These recommendations are derived from studies, most notably the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, which showed that angiography-guided PCI plus medical therapy, though effective at reducing symptoms, was no better at preventing death or myocardial infarction than medical therapy alone.[3]

Entry into the COURAGE trial required evidence of ischemia on stress testing and an angiographic stenosis of at least 70% that was amenable to PCI. Visual estimation of coronary stenoses is imprecise, and the correlation with ischemia is poor for moderate (50 to 80%) stenoses.[4] Stress testing, even when combined with imaging, may not accurately identify culprit lesions in the presence of multivessel disease. Cardiovascular interventionists have long speculated that with more accurate identification and revascularization of ischemia-producing lesions, PCI might improve not only symptoms but also "hard" clinical outcomes, such as prevention of myocardial infarction or death.

Fractional flow reserve (FFR), a physiological index of blood-flow reduction caused by a coronary stenosis, is readily calculated in the catheterization laboratory by measuring the pressure gradient across that stenosis during reactive hyperemia. Values of 0.75 or less reliably correlate with objective ischemia, whereas values of more than 0.80 rarely do, regardless of the angiographic appearance.[5] The superiority of FFR over angiography in identifying ischemia-producing stenoses provided the rationale for the Fractional Flow Reserve versus Angiography for