Biomarkers for severe eosinophilic asthma

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The last decade has seen the approval of several new biologics for the treatment of severe asthma-targeting specific endotypes and phenotypes. This review will examine how evidence generated from the mepolizumab clinical development program showed that blood eosinophil counts, rather than sputum or tissue eosinophil counts, evolved as a pharmacodynamic and predictive biomarker for the efficacy of treatment with mepolizumab in patients with severe eosinophilic asthma. Based on the available evidence and combined with clinical judgement, a baseline blood eosinophil threshold of 150 cells/μL or greater or a historical blood eosinophil threshold of 300 cells/μL or greater will allow selection of patients with severe eosinophilic asthma who are most likely to achieve clinically significant reductions in the rate of exacerbations with mepolizumab treatment. (J Allergy Clin Immunol 2017;140:1509-18.)

Key words: *Eosinophils, biomarkers, severe eosinophilic asthma*

Abbreviations used

DREAM: Dose Ranging Efficacy and safety With Mepolizumab in Severe Asthma
FENO: Fraction of exhaled nitric oxide
GINA: Global Initiative for Asthma
ICS: Inhaled corticosteroid
MENSA: Mepolizumab Adjunctive Therapy in Subjects with Severe Uncontrolled Refractory Asthma
OCS: Oral corticosteroid
RR: Rate ratio
SIRIUS: Steroid Reduction with Mepolizumab Study

Biological therapies, in addition to regular controller medication, for patients with severe asthma are becoming the new standard of care for patients who were previously without alternative treatment options.[1] Omalizumab, which neutralizes IgE, was the first biologic introduced for asthma in 2003 for patients who could not achieve asthma control with inhaled corticosteroids (ICSs), leukotriene inhibitors, and bronchodilators.[1-4] However, targeting treatment based on total or allergen-specific IgE levels was not completely effective in selecting patients likely to respond to therapy.[5,6] More recently, biologic therapies that disrupt IL-5 signaling and ultimately reduce eosinophil counts in blood and lung tissue (mepolizumab [GlaxoSmithKline, Research Triangle Park, NC] and reslizumab [Teva, Petach Tikva, Israel])[7-10] have been approved for treatment in patients with severe asthma and an eosinophilic phenotype (with baseline eosinophil counts at different threshold levels), a condition now termed severe eosinophilic asthma.[11-13] In addition, benralizumab (AstraZeneca, Cambridge, United Kingdom), which is currently in development, depletes eosinophil counts by antibody-dependent cell-mediated cytotoxicity through binding to the α chain of the IL-5 receptor on the eosinophil surface.[14-16] In clinical trials all 3 anti-targeted IL-5 pathway therapies (mepolizumab, reslizumab, and benralizumab) reduced rates of exacerbations in patients with severe eosinophilic asthma.[8,14,15,17-19] In addition, mepolizumab and benralizumab have been shown to reduce or eliminate the dependency for oral corticosteroids (OCSs) without a loss of asthma control.[20,21]

Some overlap in the asthma phenotypes, principally severe allergic asthma and severe eosinophilic asthma, can lead to an overlap in eligibility for the different biological therapies.[22] In circumstances in which the patient can be identified clearly as having a particular phenotype, the treatment options recommended in the Global Strategy for Asthma Management and Prevention (Global Initiative for Asthma [GINA]) guidelines are to prescribe anti-IgE and anti–IL-5 therapies, respectively.[1] Integral to the successful clinical development of these drugs has been identification and use of biomarkers to identify patients likely to respond to treatment.

A biomarker is any characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathologic processes, or responses associated with a therapeutic intervention.[23] There are several different types

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This article reports data from studies funded by GlaxoSmithKline.

Disclosure of potential conflict of interest: S. W. Yancey, O. N. Keene, F. C. Albers, H. Ortega, and S. Bates are employees of GlaxoSmithKline and hold stock/shares in GlaxoSmithKline. E. R. Bleecker has performed clinical trials administered by his previous employer, Wake Forest School of Medicine, for AstraZeneca, MedImmune, Boehringer Ingelheim, Pfizer, Cephalon/Teva, Forest, Genentech, GlaxoSmithKline, Johnson & Johnson (Jansen), Novartis, and Sanofi and has also served as a paid consultant for AstraZeneca, MedImmune, Boehringer Ingelheim, Pfizer, GlaxoSmithKline, Forest, Novartis, Regeneron, and Sanofi. I. Pavord has received honoraria for speaking at sponsored meetings from AstraZeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, and GlaxoSmithKline; received payment for organizing an educational event from AstraZeneca; received advisory board honoraria from Almirall, Genentech, Regeneron, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck, Schering-Plough, Novartis, Mylan Specialty (Dey Pharma), Napp Pharmaceuticals, and Respivert; and received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, and Napp Pharmaceuticals.

Received for publication August 9, 2017; revised October 13, 2017; accepted for publication October 17, 2017.

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0091-6749/$36.00

https://doi.org/10.1016/j.jaci.2017.10.005

of biomarkers that include pharmacodynamic, predictive, diagnostic, and prognostic biomarkers.

Pharmacodynamic biomarkers inform on the biological response to pharmacologic intervention. For example, the effect of anticoagulation treatments (eg, warfarin) for thromboembolic disease can be assessed by measuring prothrombin time as a pharmacodynamic biomarker.[24]

A predictive biomarker identifies patients likely to derive benefit from treatment or identify patients who are unlikely to respond, which thus influences clinical decisions. Although there are no predictive biomarkers for heart failure currently in routine use,[25] predictive biomarkers are used routinely in oncology. For example, for patients with invasive breast cancer, overexpression or gene amplification of human epidermal growth factor receptor 2 is predictive of response to drugs targeted at the human epidermal growth factor receptor 2, such as trastuzumab, pertuzumab, and lapatinib.[26] Conversely, in patients with rheumatoid arthritis, a characteristic interferon type I genetic signature was found to be predictive of nonresponse to rituximab.[27]

A diagnostic biomarker identifies patients with a specific condition or disease, whereas a prognostic biomarker categories the risk of disease progression in the absence of treatment. In the case of heart failure, the presence of increased concentrations of B-type natriuretic peptide, which is produced in response to myocardial stress, has both positive and negative diagnostic value.[28] B-type natriuretic peptide concentration on admission to the hospital also has a linear relationship with morbidity and mortality outcomes and is the gold standard prognostic biomarker for heart failure.[28]

In the case of asthma, early observations on the association between eosinophil overexpression and asthma severity were made in 1990 by Bousquet et al.[29] Multiple studies have since confirmed that blood, tissue, or sputum eosinophil counts can be used to characterize patients with severe asthma and eosinophilic inflammation.[30-37] Through the drug development process for mepolizumab, investigators identified blood eosinophils, rather than sputum eosinophils, as the treatment target for mepolizumab, providing an accessible and multipurpose biomarker for severe eosinophilic asthma.[18,19,38,39] This review will examine how evidence generated during the mepolizumab clinical development program showed that the blood eosinophil count can serve as a pharmacodynamic and predictive biomarker in patients with severe eosinophilic asthma.

PHARMACODYNAMIC BIOMARKERS FOR MEPOLIZUMAB TREATMENT RESPONSE

Mepolizumab binds with high specificity and affinity to human IL-5,[40] the key T2 cytokine responsible for regulation of blood and tissue eosinophils.[41] Mepolizumab prevents IL-5 from binding to the α chain of the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibits IL-5 signaling, blocking eosinophil survival and proliferation. Although the exact mechanism of action of IL-5 inhibitors is not fully elucidated, the desired physiologic goal is to neutralize the effect of activated eosinophils in blood and tissues, such as the lung.

During the development of mepolizumab, the pharmacodynamic response was assessed in blood, sputum, and tissue eosinophils.[18-20,42,43] Early studies showed that mepolizumab produced modest reductions in airway tissue and bone marrow eosinophil counts, suggesting limited pharmacodynamic effects in these compartments.[9] Haldar et al[43] then showed that treatment with 750 mg of intravenous mepolizumab in patients with severe asthma and sputum eosinophil counts of greater than 3% at least once in the previous 2 years reduced blood and sputum eosinophil counts during treatment, although sputum eosinophilia was present in 36% of exacerbations despite mepolizumab therapy.

After this, the Dose Ranging Efficacy and safety With Mepolizumab in Severe Asthma (DREAM) study (NCT01000506) was conducted, which was a phase 2b/3 clinical trial of mepolizumab in patients with severe asthma and eosinophilic inflammation and included assessments of the pharmacodynamic response of mepolizumab.[19] The inclusion criteria for the DREAM study are shown in Fig 1. Patients in the DREAM study received either placebo or 75, 250, or 750 mg of intravenous mepolizumab, representing a 10-fold dose range. At the 750-mg intravenous dose, there were comparable reductions of 88% in blood and sputum eosinophil counts; however, for the 250-mg intravenous dose, the reduction in blood eosinophil counts was 86% compared with 65% for sputum, and for the 75-mg intravenous dose, the reduction in blood eosinophil counts was 78% compared with 32% for sputum (Fig 2).[19] All doses of mepolizumab had similar beneficial effects on the primary outcome measure, the rate of clinical significant asthma exacerbations.

A second study[42] assessing a range of subcutaneous doses (12.5, 125, or 250 mg administered subcutaneously vs 75 mg administered intravenously) showed that this reduction in blood eosinophil count occurred 2 days after the first dose of mepolizumab, was dose dependent, and was not affected by administration route (intravenous vs subcutaneous) after adjusting for bioavailability.

Overall, results from the DREAM study and Pouliquen et al[42] suggest that blood eosinophil but not sputum or tissue eosinophil counts are the key pharmacodynamic biomarker response to mepolizumab treatment in patients with severe eosinophilic asthma. This is reflected by the reduction in exacerbation rates with mepolizumab versus placebo in these patients. Since then, studies of mepolizumab in patients with hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis, and eosinophilic esophagitis all show a consistent pharmacodynamic effect of mepolizumab on eosinophils that can be measured easily and reproducibly by using blood eosinophil counts.[18,19,42,44-47]

In addition to blood eosinophil counts, other potential pharmacodynamic biomarkers, such as fraction of exhaled nitric oxide (FENO), were assessed during the development of mepolizumab.[19,43] Nitric oxide is released by several pulmonary cells, including epithelial cells, eosinophils, and macrophages, and nitric oxide levels have been shown to be increased in patients with conditions associated with inflammation, such as asthma and viral infections. In the DREAM study across the 10-fold dose range of 75 to 750 mg administered intravenously, there was no pharmacodynamic response with FENO (Fig 2).[19] This lack of response to FENO was also shown in the earlier mepolizumab study by Haldar et al.[43] This suggests that FENO is not responsive to modulation through the IL-5 pathway and is potentially more relevant to different aspects of the T2 inflammatory response (eg, IL-13).

Because the clinical efficacy of mepolizumab was similar across all doses of mepolizumab (75, 250, and 750 mg), it was decided to progress the lowest dose (75 mg administered intravenously) of mepolizumab in further phase 3 studies. The