## Grand Rounds Review

# Biologics in Asthma—The Next Step Toward Personalized Treatment

**Jared Darveaux, MD, and William W. Busse, MD** *Madison, Wis*

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**Overall Purpose/Goal:** To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

**Target Audience:** Physicians and researchers within the field of allergic disease.

**Accreditation/Provider Statements and Credit Designation:** The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates these educational activities for a maximum of 1 AMA PRA Category 1 Credit. Physicians should only claim credit commensurate with the extent of their participation in the activity.

**List of Design Committee Members:** Jared Darveaux, MD, and William W. Busse, MD

**Activity Objectives**

1. To identify future and current treatment options for patients with asthma who are suboptimally controlled.

2. To describe how specific patient endotypes can direct selection of biological agents.

3. To describe the mechanisms of many of the monoclonal antibodies being developed for the treatment of asthma.

**Recognition of Commercial Support:** This CME has not received external commercial support.

**Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations:** J. Darveaux declares that he has no relevant conflicts. W.W. Busse has received consultancy fees from Novartis, GlaxoSmithKline, and Roche; has received consultancy fees from Genentech for the Consultant and Data Monitoring Board; has received consultancy fees from Boston Scientific for the Data Monitoring Board and consultancy fees from ICON for the Study Oversight Committee; has received research support from the NIH/NIAID and NIH/NHLBI; and receives royalties from Elsevier.

**Asthma is a multifaceted disease and is associated with significant impairment and risk, and a therapeutic response that is highly variable. Although current treatments are usually effective for patients with mild-to-moderate disease, patients with more severe asthma are often unresponsive to current efforts, and there remains a need for agents with properties that may achieve control in these individuals. There is ongoing research to identify bioactive molecules that contribute to the pathophysiology of asthma, and many of these have been identified as potential therapeutic targets to improve control of this disease. As a consequence of these efforts, monoclonal antibodies have been developed and tested as to their effectiveness in the treatment of asthma. The assessment of these new treatments has identified particular pathways that, in selected patients, have shown benefit. The following review will discuss the current and future use of biological agents for the treatment of asthma, their efficacy, and how certain patient phenotypes and endotypes may be associated with biomarkers that may be used to select treatments to achieve greatest effectiveness of their use. As knowledge of the effects of these biological agents in asthma emerges, as well as the patients in whom they are most beneficial, the movement toward personalized treatment will follow.** © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:152-60)

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Department of Medicine, Section of Allergy Pulmonary and Critical Care Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wis

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Corresponding author: William W. Busse, MD, Department of Medicine, Section of Allergy Pulmonary and Critical Care Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wis. E-mail: wwb@medicine.wisc.edu.

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*Abbreviations used*
*AQLQs- Asthma quality of life questionnaires*
*EPR3- Expert Panel Report 3*
*$FEV_1$- Forced expiratory volume in 1 second*
*$F_ENO$- Fractional exhaled nitric oxide*
*GM-CSF- Granulocyte–macrophage colony-stimulating factor*
*ICS- Inhaled corticosteroids*
*IFN-β- Interferon beta*
*IFN-γ- Interferon gamma*
*IL- Interleukin*
*LABA- Long acting beta agonist*
*SNPs- Single nucleotide polymorphisms*
*Th1- T helper 1*
*Th2- T helper 2*
*TNF-α- Tumor necrosis factor alpha*
*TSLP- Thymic stromal lymphopoietin*

Guidelines for the diagnosis and management of asthma were established to provide an evidence-based approach for the treatment of this disease.[1] In the Expert Panel Report 3 (EPR-3), 6 treatment steps were identified and based on patients' disease severity, as reflected by symptoms, lung function, frequency of exacerbations, and response to treatment.[1] For the majority of patients with asthma, disease control is achieved within the first 3 treatment steps that include the use of inhaled corticosteroids (ICS) either alone or in combination with long-acting beta-agonists (LABA) or leukotriene receptor antagonist. This approach has provided a safe and effective mode of treatment.

When patients do not respond completely to these initial treatment choices, the approaches over the next 3 escalating steps is not always straightforward—a situation aptly captured in a recent editorial by Drs. Erika von Mutius and Jeffrey Drazen[2] where they said:

> Asthma is both easy and hard to treat. It is easy to treat because the vast majority of patients with asthma require little medication for a lot of benefit. In a patient with asthma previously untreated with a controller (i.e., a medication whose primary mechanism of action is not acute bronchodilation), initiating therapy with a controller often results in an improvement in asthma symptoms and lung function and a reduced number of asthma exacerbations. In the language of current asthma thinking, this approach addresses both the impairment and risk domains of asthma treatment. Asthma becomes hard to treat when asthma control is not obtained with the health care provider's first choice of a controller; this usually means that treatment needs to be stepped up and leads to the question, "My patient needs more treatment, but what will offer the greatest likelihood of improvement?"[2]

For patients who fall into this therapeutic dilemma, the next choices are limited and have begun to extend into the use of biologics. Although the use of biologics in asthma is a relatively new effort, significant advances have been made, and with these advances has come the promise for a more personalized and, hopefully, effective treatment for selected patients, particularly those with more severe disease. The results of trials with biological treatments in asthma, and what direction they will provide for future treatment, are the basis of the following discussion.

## WHAT ARE THE TREATMENT OPTIONS FOR THE "UNRESPONSIVE" PATIENT WITH ASTHMA?

Airway inflammation in asthma is complex, interactive, and redundant, as well as variable from patient to patient, and within individual patients (Figure 1). A wide variety of cells, inflammatory molecules, and resident airway tissues participate in the development, persistence, severity, and pattern of inflammation in asthma, and likely are critical determinants to the translation of various clinical phenotypes. Although these multiple pathways contribute to airway inflammation, injury, and repair, along with bronchial smooth muscle dysfunction, some of these inflammatory products are likely to have a more dominant role than others and may serve to contribute to the pathophysiology in selected patients. IgE production, eosinophils, mast cells, and subpopulations of lymphocytes (ie, Th2 [T-helper 2]), with an ever-expanding list of key cytokines, ie, interleukin (IL)-4, -5, -9, -13, and -33, have emerged as major contributors to the pathogenesis of asthma. Immune cells, such as Th2 lymphocytes, produce IL-5 to further promote eosinophil development, as well as IL-3, IL-4, IL-6, IL-9, IL-13, and granulocyte–macrophage colony-stimulating factor (GM-CSF), to enhance the inflammatory response.[3,4] Also likely contributing are the recently discovered type 2 innate lymphoid cells. These nonspecific innate immune effector cells on stimulation with thymic stromal lymphopoietin (TSLP) and IL-33, produce Th2-associated cytokines such as IL-5, IL-13, and Il-4.[5] It is postulated that these type 2 innate lymphoid cells, contribute to an allergen-independent eosinophilic asthma phenotype. IL-33 is a cytokine released by epithelial cells in response to damage and, in turn, stimulates production of IL-4 and IL-13 to promote IgE production, airway hyperresponsiveness, inflammation, Th2 lymphocyte development, and eosinophil migration.[3,6,7] Based on this schema, a number of cytokines have been identified as intriguing potential therapeutic targets in asthma treatment, particularly for patients who are not responsive to usual medications.

A first step to try to modify the effects of these inflammatory pathway mediators has been the development of monoclonal antibodies that can "knock out" or perhaps, more appropriately, "knock down" these amplification steps and, hence, block inflammatory pathways that lead to ongoing disease and resulting symptoms. The experiences gained with these biological interventions have not only shed light on the contribution of various molecules to clinical asthma but also begun to provide the new avenues of treatment. Moreover, these experiences have begun to identify characteristics of patients most likely to benefit from more selective interventions. Consequently, the use of biologics in asthma is providing a road map to personalized treatment, which may, in turn, have greater specificity for mechanisms germane to an individual patient's disease expression.

### IgE as a treatment target in asthma

Allergic sensitization is present in the majority of patients with asthma.[3,8] Based on this close association with asthma, its likely mechanisms to disease, and a reasoned target of treatment, anti-IgE was an initial biological agent developed, and the only one currently approved in asthma. Omalizumab (Genetech, San Francisco, Calif/Novartis, East Hanover, NJ) is an injectable humanized monoclonal antibody directed against the Cε3 domain of IgE and prevents an interaction with its high-affinity receptor (FcεRI) on mast cells, basophils, eosinophils, Langerhans cells, and dendritic cells.[9] Omalizumab is currently recommended for the treatment of patients (>12 years in the United States) with