Biologics and biomarkers for asthma, urticaria, and nasal polyposis

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

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Activity Objectives:

1. To understand the immunopathologic mechanisms underlying different phenotypes of allergic disorders.
2. To describe the mechanism of action of the biologic agents available for treatment of the allergic diseases of asthma, nasal polyposis, and urticaria.
3. To distinguish the biologic agent associated with clinical improvement in different allergic phenotypes with distinct underlying mechanisms.

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Many patients with allergic disorders continue to have uncontrolled symptoms despite new and better pharmacologic options. Novel biologic agents that target specific and critical pathophysiologic pathways have been developed to better manage these patients. The utility of biologic agents for the management of allergic diseases has been facilitated by recent advances in better characterizing patients, including identification of relevant biomarkers that predict clinical responsiveness. This has led to the ability to phenotype and endotype patients, allowing for a more rational approach to picking a specific biologic agent for a specific patient. In this review I focus on point-of-care biomarkers that enhance the usefulness of biologics to manage uncontrolled asthma, urticaria, and nasal polyposis. I discuss biologic agents already approved for the management of allergic and respiratory disorders and biologics currently in development or recently abandoned because of a lack of efficacy or intolerable side effects. The successes and failures of biologics in clinical trials have facilitated our ability to better understand which molecules and pathways are most important in the pathogenesis of allergic diseases and in the development of symptoms and impairment in individual patients. (J Allergy Clin Immunol 2017;139:1411-21.)

Key words: *Biologics, asthma, urticaria, nasal polyps, mAbs, cytokines, IgE*

Despite recent advances in the pharmacologic management of allergic and respiratory disorders, many patients continue to have uncontrolled symptoms. Advances in the understanding of key pathophysiologic mechanisms involved in allergic and respiratory disorders have led to the possibility of more targeted therapy or "precision medicine."[1] Precision medicine recognizes that even in patients with similar clinical presentations of a disease, the underlying pathophysiologic mechanisms can be diverse, leading to a spectrum of responses to a specific therapeutic agent

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Abbreviations used
CAPS: Cryopyrin-associated periodic syndrome
DPP-4: Dipeptidyl peptidase 4
FDA: US Food and Drug Administration
FENO: Fraction of exhaled nitric oxide
IVIG: Intravenous immunoglobulin
LS: Least square
TSLP: Thymic stromal lymphopoietin

in patients with the same disease. For example, although corticosteroids have been remarkably effective in the management of a number of allergic disorders, including asthma, not all patients respond to them. There is a bell-shaped curve for all pharmacotherapies, indicating that distinct mechanisms of disease are likely present in nonresponders versus responders.

Researchers have relied on the development of biologic agents that target specific and critical pathways important in the pathogenesis of allergic and respiratory disorders to address the lack of responsiveness to a number of pharmacologic agents. A biologic agent refers to an antibody, vaccine, or interleukin used to treat disease, and in this article I will focus on the utility of mAbs as biologics for the management of allergic and respiratory diseases. However, as with traditional pharmacotherapies, not all patients respond to these biologic agents.[1,2] Specific phenotypes and endotypes resulting from variations in genetic, biologic, and immunologic mechanisms coupled with distinct environmental exposures results in the heterogeneity noted in responsiveness to biologic and pharmacologic agents.

Finding which pathogenic factors are important in individual patients is a challenge in treating allergic and respiratory diseases. Broad-spectrum biologic agents that affect multiple immune pathways are problematic because of potential adverse consequences. Because of the potential for significant adverse events and the high cost of biologics, attempts at identifying biomarkers to help predict clinical responsiveness and adverse event profiles in individual patients have been critical in determining the potential utility of specific biologics for individual patients.[1-5]

The characteristics of an ideal biomarker include not only the ability to identify either a clinical or treatment response but also the ease with which the biomarker can be collected and measured at the point of care. For example, although sputum eosinophils predict responsiveness to inhaled corticosteroids and many of the biologics in patients with asthma, this is a difficult-to-obtain biomarker and is not readily available to clinicians.[1-6] In this review, I will focus on biologics for the management of allergic and respiratory disorders and putative biomarkers that are easy to obtain at the point of care.

The advent of biologics for the management of allergic and respiratory diseases began many years ago but came to the forefront with the approval by the US Food and Drug Administration (FDA) of omalizumab for the treatment of chronic, persistent, moderate-to-severe perennial allergic asthma in 2003. Since then, omalizumab has been approved for the management of chronic spontaneous urticaria. In addition, many other biologics have been examined for allergic and respiratory disorders, especially asthma. The recent approval of 2 anti–IL-5 mAbs for severe asthma and the imminent approval of several other agents for asthma and other allergic disorders have provided allergists/immunologists with unique opportunities to better manage their patients. As experts in the understanding of how these biologics work, we also have the opportunity to assess and manage adverse events associated with these agents.

In this review I will focus on the utility of biologics for several allergic and respiratory disorders, especially asthma, urticaria, and nasal polyps. Biologics in the management of atopic dermatitis will be covered elsewhere. I will review the clinical effectiveness of these agents and provide some insights into how to pick patients who might best respond therapeutically. In addition, I will review differences between similar agents in regard to dosing and secondary end point results in clinical trials that might influence individual patient preferences.

ASTHMA

Of the diseases likely to be treated with biologics by allergists and immunologists, asthma is the most prominent. There are 3 biologics currently approved by the FDA for asthma, omalizumab, mepolizumab, and reslizumab, and a number of others are in clinical development (Table I).[7-35]

There are 2 major inflammatory phenotypes defined for asthma: type 2–high and type 2–low asthma.[1-5] The former is typically characterized by eosinophilic inflammation and the latter by either a neutrophilic or paucigranulocytic inflammatory pattern. Most of the biologic agents developed for asthma therapy have focused on the type 2–high pattern of inflammation, probably because there are more readily available biomarkers that one can measure to identify these patients (eg, blood eosinophils). Patients with type 2–low asthma are more difficult to characterize and identify. Thus far, neutrophilic inflammation has not been detectable based on readily available point-of-care biomarkers. A recent study by Maes et al[36] has suggested that certain micro-RNAs in sputum might be able to accurately identify neutrophilic inflammation in the airways of patients with asthma, but most clinicians are unable to obtain satisfactory sputum samples from these patients. Paucigranulocytic inflammation is characterized by the absence of either an eosinophilic or neutrophilic inflammatory pattern. These patients likely respond best to intensive bronchodilator therapy with no specific biologics on the horizon to treat them.[2] Neither patients with neutrophilic nor those with paucigranulocytic asthma respond well to corticosteroids.[1,2]

Type 2–low asthma

Biologics expected to work best in patients with the neutrophilic phenotype include agents that block key cytokines important for neutrophil chemotaxis, growth, and differentiation, including IL-8, IL-17, and IL-23.[1,2] The neutrophil chemotactic agent IL-8 acts through the chemokine receptor CXCR2. In a small cohort of patients with severe asthma and sputum neutrophilia, a CXCR2 antagonist (SCH527123) given for 4 weeks reduced sputum neutrophil counts and mild asthma exacerbations but did not lead to significant improvements in lung functions or symptom scores.[37]

O'Byrne et al[38] investigated the safety and efficacy of AZD5069, a CXCR2 antagonist, as an add-on therapy in 640 patients with uncontrolled severe asthma. Treatment with this selective CXCR2 antagonist did not reduce the frequency of severe