Biologic and New Therapies in Asthma

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KEYWORDS

• Biologics • Asthma • Anti-IL-5 • Anti-IL-13 • Anti-IL-4 • Th2 • CRTH2 • Anti-IgE

KEY POINTS

- T2-high asthma patients are identified by elevated sputum or blood eosinophils, fractional exhaled nitric oxide (FeNO), and antigen-specific immunoglobulin E (IgE).
- T2-low asthma patients are identified by increased neutrophils or paucigranulocytic findings in the sputum.
- T2-low asthma patients respond poorly to corticosteroids and new biologics approved for asthma.
- T2 targeted therapies discussed in this review include antagonists of interleukin-5 (IL-5), IL-13, IL-4, chemoattractant receptor homologous molecule on T2 cells, and IgE.

INTRODUCTION

Asthma is a complicated chronic disease that affects people from childhood to the elderly. In the United States, approximately 17.7 million adults and 6.3 million children have asthma. In 2011, 1.8 million emergency room (ER) visits carried a primary diagnosis of asthma. The average length of hospitalization for patients with asthma was 3.6 days. In 2013, the average number of lost school days was 13.8 million, and the average number of lost work days was 10.1 million. From 2006 to 2010, approximately 38% of children and 50% of adults with asthma had uncontrolled symptoms. An estimated cost of US$19.7 billion annually makes asthma 1 of the top 10 prevalent conditions impacting health care system costs.[1] The question remains, why with current therapeutic regimens are patients still uncontrolled? Phenotypic heterogeneity among asthma patients contributes to the variable severity and control of the disease.

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Traditional classification of patients with asthma reflected associated triggers, including exercise, viruses, cigarette smoke, allergens, and aspirin. The National Institutes of Health–sponsored Severe Asthma Research Program (SARP) used cluster analysis to provide unbiased methods to define various asthma phenotypes. The SARP data, as well as other studies, indicated that early-onset disease is consistently associated with more atopy and allergic conditions over a range of severities, whereas adult-onset disease is often associated with obesity and was more common in women. A cluster of adult-onset patients with mild airflow obstruction has fewer exacerbations, but another cluster with moderate airflow obstruction is more exacerbation prone.

In categorizing patients by the observable clinical characteristics, researchers are attempting to link these to underlying molecular mechanisms of their disease, in other words, the endotype (**Fig. 1**). To date, primarily 2 endotypes of asthma are described, Th2-high (T2 high) and Th2-low (T2 low).[2–4] Patients with Th2-high asthma have increased eosinophils in their sputum and airways, whereas T2-low asthma patients have either an increase in neutrophils or a paucigranulocytic (minimal inflammatory cells) profile in their sputum and airways. In this review, the focus is on defining what is currently known about the pathophysiology of underlying inflammation intrinsic to these endotypes, including key pathways and cytokines, to better target therapy. Furthermore, the utility of point-of-care biomarkers to guide optimal treatments with controllers and especially biologics is discussed. This step is the first step in precision medicine where medications are targeted toward patients with the anticipation of optimal therapeutic effect.

PATHOPHYSIOLOGY

T2-Low Asthma or Non-T2 Asthma

Studies of patients with severe asthma unresponsive to typical therapeutic regimens in the 1990s illustrated that some of these individuals had neutrophilic inflammation.[5] Only about 50% of patients with severe asthma exhibit increased eosinophils along with heightened expression of transforming growth factor -β and increased synthesis of collagen beneath the bronchial subepithelial basement membrane.[5] The subset of patients with neutrophil predominance does not exhibit typical T2 cytokines. Neutrophil-predominant patients typically have an onset of disease in adulthood and are generally less corticosteroid responsive. Key cytokines involved in the pathogenesis of these patients include those produced by T helper 1 (Th1) and Th17 cells. The role of Th17 cells and IL-17 in asthma is not defined; however, in experimental asthma models, IL-17A contributes to airway remodeling by stimulating fibroblast proliferation.[6,7] IL-17 is also increased in sputum of patients with severe asthma and can induce the production of IL-8, a potent neutrophil chemoattractant. In a clinical trial targeting IL-17A, IL-17F, and IL-25 via inhibition of the IL-17 receptor α, there was little benefit in patients with mild to moderate asthma.[8] It is important to note that patients with sputum neutrophilia were not enriched for in this study, and this could have resulted in the overall lack of efficacy. Other targets evaluated for this endotype include antagonists of tumor necrosis factor (TNF)-α and IL-1. These proinflammatory cytokines are upregulated in asthmatics with neutrophilic inflammation.[9] Blocking TNF-α in severe asthma has had variable success, but a relatively high risk of adverse effects has resulted in a lack of further clinical development for asthma.[10]

Interleukin-8 (IL-8) is a potent mediator of neutrophil chemotaxis through the chemokine receptor CXCR2. A CXCR2 antagonist has been studied for potentially treating neutrophilic airway inflammation. In preliminary study of 12 patients with increased