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Characterization of asthma endotypes: implications for therapy

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ABSTRACT

Objective: To describe the concept of precision medicine in treating severe asthma and the utility of relevant biomarkers.

Data Sources: PubMed was searched for published articles on human clinical trials using biologics for T-helper type 2 cell (T_H2)-low and T_H2-high asthma.

Study Selections: Studies were selected if they were double-masked, randomized, placebo-controlled trials published in peer-reviewed journals and relevant to the topic.

Results: Multiple immune response modifiers have been evaluated in T_H2-high asthma geared at blocking interleukin (IL)-5, IL-13, immunoglobulin E, prostaglandin D_2, and other pathways. Currently, 3 immune response modifiers approved by the Food and Drug Administration are available for treating severe T_H2-high asthma (1 anti-immunoglobulin E and 2 anti–IL-5 monoclonal antibodies) and other T_H2-high therapies are in various stages of clinical development. Thus far, many of the T_H2-high therapies have shown better efficacy when certain biomarkers are elevated, especially blood eosinophils. The T_H2-low endotype does not have any readily available point-of-care biomarkers, so T_H2-low asthma is often diagnosed based on a lack of T_H2-high biomarkers. These patients tend to have greater resistance to steroids and the development of therapies has lagged behind that for T_H2-high asthma.

Conclusion: Two major endotypes for asthma have been described, T_H2-high, manifested by increased eosinophils in the sputum and airways of patients, and T_H2-low, with increased neutrophils or a pauci-granulocytic profile. Using these classifications and specific biomarkers has led to promising new therapeutics, especially for T_H2-high asthma.

Introduction

This review covers key pathologic pathways in asthma and the therapeutic potential of immune response modifiers relevant to these pathways. We discuss strategies to optimize treatment with immune response modifiers, including the role of precision medicine. The focus is on understanding the biology of severe asthma and the utility of biomarkers to predict responsiveness to these novel therapies. Precision medicine is important several reasons. First, and foremost, the use of immune response modifiers is extremely expensive and could be fraught with potential adverse events. Therefore, understanding phenotypes and endotypes of disease to aid in the appropriate use of these therapies is critical. This not only will promote better therapeutic responses but also might prevent possible adverse consequences.

Traditional phenotyping classifies patients with asthma based on triggers (allergens, exercise, infections, or aspirin), clinical presentation, or inflammatory markers (eosinophils or neutrophils).[1] Endotyping refines these groups based on their pathophysiologic mechanisms. For asthma, 2 major endotype categories of disease have been put forth: T-helper type 2 cell (T_H2)-high (T2-high) and T_H2-low (T2-low).[2] The former is manifested by increased eosinophils in the sputum and airways of patients. The latter is manifested by increased neutrophils or a pauci-granulocytic profile with normal levels of eosinophils and neutrophils in the sputum and airways. Each type would be expected to respond uniquely to therapies (Fig 1).

T2-Low Asthma

For T2-low asthma, different inflammatory cells and structural cells that release cytokines and mediators are believed to be important. Specific mediators implicated in the pathogenesis of neutrophilic inflammation include interleukin (IL), IL-8, IL-23, IL-17, and IL-23.[2] These patients tend not to respond to corticosteroids as well as

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patients with T2-high asthma. There have been attempts to block these key mediators to decrease neutrophilic inflammation. A specific example includes the use of an IL-8 antagonist, CXC chemokine receptor 2 blocker, in severe asthma with sputum neutrophils.[3] A preliminary study with 12 patients indicated that blood and sputum neutrophils were significantly decreased after 4 weeks of therapy and there were no significant adverse consequences. There were fewer mild exacerbations with CXC chemokine receptor 2 blocker treatment but no statistically significant changes were noted with pulmonary function or symptom scores. For pauci-granulocytic inflammation, it is believed that these patients might benefit from intensive bronchodilator therapy such as long-acting muscarinic antagonists and/or long-acting β-agonists. These patients, similar to those with neutrophilic predominant inflammation, tend to have greater resistance to steroids. They also could be appropriate candidates for bronchial thermoplasty.[2]

T2-High Asthma

The majority of new drug development has targeted Type 2-high asthma manifested different important inflammatory cells, including mast cells, T_H2 cells, natural killer T cells, and type 2 innate lymphoid cells.[2] In addition, the airway epithelium stimulated by T_H2 cytokines could release mediators such as thymic stromal lymphopoietin that could promote further inflammation. Targeting cytokines and mediators produced by these inflammatory cells has been rewarding in initial clinical trials in appropriately selected patients. Indeed, antagonists of IL-5 and IL-13, thymic stromal lymphopoietin, and chemoattractant receptor homologous molecule expressed on T_H2 lymphocytes (CRTH2) have shown clinical benefits in selected patient populations. The remainder of the discussion focuses on choosing the correct biomarker that facilitates better therapeutic responses.

Different biomarkers have been identified, but for point-of-care decision making, biomarkers that can be measured simply and inexpensively would be optimal. In this regard, blood eosinophils have been shown to be an important biomarker for predicting clinical responses with anti–IL-5, anti-IgE, anti–IL-4/IL-13, corticosteroids, and CRTH2 antagonists. Allergen-specific IgE has proved somewhat useful in predicting responses to anti-IgE. Two unique molecules, periostin and dipeptidyl peptidase-4 (DPP-4), appear to better predict responses to antagonists of IL-13. Although biomarkers in induced sputum and exhaled breath also have shown some clinical utility, they are predominantly research tools and not specifically useful at this time for the point-of-care decision-making processes needed.

Specific Therapies Targeting T2-High Pathways

IL-5–Based Therapy

Interleukin-5 is important for the growth and differentiation of eosinophils and their migration into key inflammatory sites such as the airways. There have been 2 major strategies aimed at blocking the effects of IL-5. The first strategy includes the 2 monoclonal antibodies that bind to IL-5. These 2 monoclonal antibodies, mepolizumab and reslizumab, were recently approved by the US Food and Drug Administration for the therapy of severe asthma of the eosinophilic phenotype. The second strategy involves a monoclonal antibody, benralizumab, that binds to the IL-5 receptor. This results in enhanced antibody-dependent cell-mediated cytotoxicity resulting in apoptosis of eosinophils and basophils.[4]

Mepolizumab

An early study in 2007 evaluated 362 patients with uncontrolled moderate to severe symptomatic asthma despite inhaled corticosteroid (ICS) treatment with 250 or 750 mg of mepolizumb intravenously monthly for 3 months in a randomized, double-blinded, placebo-controlled fashion.[5] Lung function, β-agonist use, symptoms, exacerbation rates, and quality of life were unaffected by either dose of mepolizumab compared with placebo. However, mepolizumab treatment did decrease blood and sputum eosinophils. Subsequent studies targeted patients with eosinophilic asthma at least 12 years old on high-dose ICSs with a second controller with or without long-term oral corticosteroids.

In 61 patients with refractory eosinophilic asthma and a history of recurrent severe exacerbations, 750 mg of mepolizumab intravenously once a month for 50 weeks decreased exacerbations to a mean of 2.0 vs an average of 3.4 exacerbations per subject in patients on placebo.[6] Blood and sputum eosinophils were decreased. Symptoms were improved, although lung function was not altered with treatment.

In a large study of 616 patients with eosinophilic asthma from 81 centers and 13 countries, patients with a history of recurrent severe exacerbations were treated with 3 different intravenous doses of mepolizumab (placebo, 75 mg, 250 mg, and 750 mg).[7] Patients were treated every 4 weeks for 13 total infusions. All 3 doses decreased exacerbation events, ranging from 39 to 52%, and time to first exacerbation, emergency department visits, exacerbation-induced hospitalizations, and eosinophil counts in blood and sputum. In this study, the efficacy of mepolizumab was related to baseline blood eosinophil counts and the number of exacerbations the preceding year.

In a 2013 meta-analysis of 7 randomized placebo-controlled trials with 1,131 subjects, mepolizumab treatment of patients with eosinophilic asthma decreased the risk of exacerbations and improved quality of life.[8] In this analysis, no significant differences were noted in lung function testing in mepolizumab- vs placebo-treated patients.

A more recent study in 2014 evaluated patients with a history of asthma exacerbations the prior year and blood eosinophil counts higher than 150 cells/μL at screening or higher than 300 cells/μL in

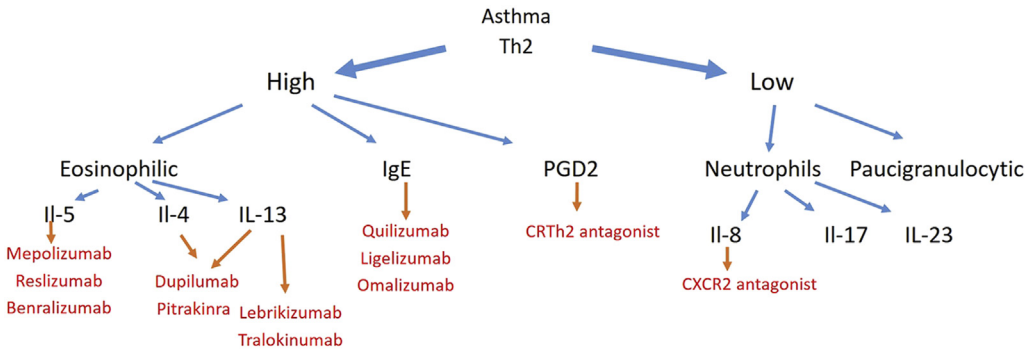

Figure 1. Therapeutic targets for asthma based on endotypes. IgE, immunoglobulin E; IL, interleukin; PGD2, prostaglandin D_2; Th2, T-helper type 2 cell.