Clinical reviews in allergy and immunology

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Asthma phenotypes and the use of biologic medications in asthma and allergic disease: The next steps toward personalized care

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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 molecular phenotypes of asthma and how these can be used to predict response to therapy.
2. To understand which interventional trials have most shaped the paradigm of phenotype-directed, targeted asthma therapies

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Traditionally, asthma and allergic diseases have been defined by broad definitions and treated with nonspecific medications, including corticosteroids and bronchodilators. There is an increasing appreciation of heterogeneity within asthma and allergic diseases based primarily on recent cluster analyses, molecular phenotyping, biomarkers, and differential responses to targeted and nontargeted therapies. These pioneering studies have led to successful therapeutic trials of molecularly targeted therapies in defined phenotypes. This review analyzed randomized double-blind, placebo-controlled trials of molecularly targeted therapies in defined allergic disease and asthma phenotypes. IgE was the first successful biological target used in patients with allergic disease and asthma. This review shows that therapies targeting the canonical type 2 cytokines IL-4, IL-5, and IL-13 have shown consistent efficacy, especially in asthmatic patients with evidence of T_H2/type 2 inflammation ("type 2 high"). As of yet, there are no successful trials of targeted therapies in asthmatic patients without evidence for type 2 inflammation. We conclude that further refinement of type 2 therapies to specific type 2 phenotypes and novel approaches for patients without type 2 inflammation are needed for asthma and allergic disease treatment. (J Allergy Clin Immunol 2015;135:299-310.)

Key words: *Asthma phenotypes, biologic therapies, eosinophils, IgE, IL-4, IL-5, IL-13, T_H2/type 2 inflammation*

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Asthma and allergies are common yet heterogeneous chronic diseases. The definition of asthma, reversible airflow limitation or bronchial hyperresponsiveness with appropriate clinical symptoms, is relatively broad and nonspecific, such that multiple clinical phenotypes meet this simple definition.[1] Asthma

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Abbreviations used
ACQ: Asthma Control Questionnaire
DBPC: Double-blind, placebo-controlled
FDA: US Food and Drug Administration
FENO: Fraction of exhaled nitric oxide
ICS: Inhaled corticosteroid
IL-4Rα: IL-4 receptor α
IL-5Rα: IL-5 receptor α
LABA: Long-acting β-agonist
OCS: Oral corticosteroid
TSLP: Thymic stromal lymphopoietin

treatments are predominantly nonspecific anti-inflammatory drugs (corticosteroids) and bronchodilators (β_2-agonists), which work in most patients. However, even responses to these treatments vary. Although multiple factors can contribute to poor responses, underlying pathobiological differences are increasingly recognized to play a role.

In contrast to asthma, allergy is defined as "the result of immune reactions to antigens known as allergens" in which the body is predisposed to produce specific IgE antibodies after exposure to these allergens.[2] Type I immediate hypersensitivity allergic reactions include allergic rhinitis, allergic asthma, and food allergy.[2] Although there is some heterogeneity in patients with allergic disease as well, less phenotypic characterization has been reported.

A phenotype involves the complex interaction of many genetic and environmental factors in conjunction with observable characteristics, such as lung function (for asthma) or specific IgE responsiveness to particular allergens.[2] Asthma phenotyping has involved biased and unbiased approaches to grouping clinical, physiologic, and hereditary characteristics.[3-11] Studies have supported the importance of age of onset, eosinophils, and lung function, but definitive clustering of these characteristics or their relation to pathobiology remains uncertain.[4,5,11,12]

IDENTIFYING TYPE 2 CHARACTERISTICS FOR TARGETED THERAPY

Identification of T_H1 and T_H2 immunity in the early 1990s and widespread efficacy of inhaled corticosteroids (ICSs) led to the hypothesis that asthma/allergies were primarily driven by T_H2 immunity involving the cytokines IL-4, IL-5, and IL-13.[13-16] Despite this, pathobiologic studies suggested differences in inflammatory/immune processes across asthmatic patients,[17] and early studies of T_H2-targeted therapies were not efficacious.[18,19]

Although it had been reported for years that corticosteroid responses were dependent on lung eosinophils, asthma phenotype was rarely considered when planning therapy.[5,11,17] Phenotype-directed therapy began to evolve when an mAb to IL-5 (mepolizumab) was specifically developed for eosinophilic asthma. In contrast to previous studies in nonselected asthmatic patients, antieosinophilic therapy reduced exacerbations and systemic corticosteroid requirements in patients with eosinophilic asthma.[20,21] By using a different approach, epithelial biomarkers for type 2/IL-13 inflammation were first identified *in vitro* and then identified *ex vivo* in a subset of patients.[22,23] Three genes (chloride channel, calcium activated, family member-1 *[CLCA1]*; periostin *[POSTN]*; and *SERPINB2*) upregulated in response to IL-13 *in vitro* were identified in fresh human airway epithelial cells from approximately 50% of corticosteroid-naive patients with mild asthma. The remaining asthmatic patients and healthy (nonatopic) control subjects had low expression of these "T_H2/type 2" genes. Those in the type 2–high cluster were more atopic, had higher tissue eosinophil counts, and had more bronchial hyperresponsiveness. Importantly, the T_H2/type 2–high cluster improved with inhaled fluticasone, whereas those without the type 2 signature did not.[23] These studies were some of the first to demonstrate improved efficacy of targeted and untargeted therapies when directed to patients whose characteristics suggest they should be more responsive to those therapies. Identifying molecular pathways that contribute to clinically meaningful outcomes (through targeted therapy) could ultimately lead to identification of disease endotypes, none of which have yet been fully described in asthmatic patients.[24,25]

TYPE 2–RELATED THERAPIES

The evolution of asthma treatment holds the promise of development of precision medicine, biologic therapies specifically targeted to the right patients to improve efficacy and decrease risk. Pathobiologic studies combined with therapeutic trials of type 2–targeted therapies have confirmed the existence of a type 2 asthma phenotype. These findings spurred further studies of type 2–targeted therapy in patients with biomarker evidence for type 2 inflammation.

Overview: Type 2 immune-related targets

For more information, see Fig 1, Table I,[18-21,26-56] and Table E1 in this article's Online Repository at www.jacionline.org.

Type 2–targeted biologic therapies either approved or in clinical trials include those targeted to IgE, IL-5, IL-13, IL-4 receptor α (IL-4Rα), and thymic stromal lymphopoietin (TSLP). IL-4 and IL-13 are central to type 2 inflammation, with GATA3 being their master transcription factor. IL-4Rα is the common receptor subchain for both IL-4 and IL-13, which is present in both the type 1 (dimerized with γc) and type 2 (dimerized with IL-13 receptor α1) receptors. IL-4 activates both type 1 and type 2 receptors, whereas IL-13 only activates type 2 receptors. Thus IL-13 cannot activate T cells, but both IL-4 and IL-13 can promote IgE isotype switching in B cells.[15,16,57] IgE binds to the high-affinity IgE receptor, which activates mast cells/basophils associated with type I hypersensitivity when cross-linked by allergen. IL-5 is critical to eosinophil development and survival and, interestingly, is generated in high amounts (as is IL-13) by the newly identified type 2 innate lymphoid cells.[58] Although IL-4 is required for T_H2 priming and maturation, T_H2 differentiation is enhanced by cytokines, such as TSLP.[59] Thus numerous components of type 2–related immune processes are now therapeutic targets for asthma/allergies.

Biomarkers: Type 2 molecular phenotypes

Biomarkers are needed to target type 2 therapies to the correct patients. Type 2 biomarkers identified to date include periostin, fraction of exhaled nitric oxide (FENO), and sputum/blood eosinophils. Early on, sputum eosinophil counts were determined