Biomarkers in asthmatic patients: Has their time come to direct treatment?

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Asthma is a heterogeneous disease with multiple phenotypes that have variable risk factors and responses to therapeutics. Mild-to-moderate asthma often responds to traditional medications, whereas severe disease can be refractory to inhaled corticosteroids, long-acting β-agonists, and leukotriene receptor antagonists. There is robust research into the variable phenotypes of asthma. Biomarkers help define the specific pathophysiology of different asthma phenotypes and identify potential therapeutic targets. The following review will discuss the current use of biomarkers for the diagnosis of asthma, triaging the severity of a patient's disease, and the potential efficacy of treatments. This information can be used to define certain patient populations that are more likely to respond to inhaled corticosteroids or biologics. As knowledge of patient phenotypes and endotypes and biological agents to target specific classes of asthma emerge, the ability to provide personalized care to asthmatic patients will follow. (J Allergy Clin Immunol 2016;137:1317-24.)

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Abbreviations used
FENO: Fraction of exhaled nitric oxide
ICS: Inhaled corticosteroid

Biomarkers, or biological markers, are traceable substances used to examine organ function or other aspects of health.[1] Medical biomarkers can also provide information about the pathophysiology of an underlying disease, the course of an illness, and/or the response to treatment.[2] At their best, biomarkers could inform us whether a disease is present or absent, define its severity, provide information about its progression, serve to select the most effective treatment, and/or serve as guidance about the affected subject's survival (Fig 1). With precision medicine on the forefront of patient care and the desire to select the most effective treatments, biomarkers are needed to provide and play an important, expanding, and directive role by allowing physicians to predict the susceptibility, or responsiveness, of a given disease to a specific treatment. Asthma is at the forefront of this concept and for good reasons, but do we have the right biomarkers to meet this need at this time?

Biomarkers have long been an important and informative aspect of medicine, beginning with the simple measurement of body temperature to detect a fever and its significance to underlying health. The presence of a fever, for example, tells us about a change in a patient's health and possibly the underlying cause, an infection. The regression of a fever can also be informative as to the effectiveness of an intervention and indication that a patient is on the road to recovery. Blood pressure is another example of a longstanding and informative biomarker; it detects an underlying condition, hypertension, as well as risks for cardiac, renal, or neurologic disease, and is an obvious target guide for treatment. Although pulmonary function measurements tell us about the consequence of asthma and its severity and are a reflection of responsiveness to treatment, they do not always inform us about the underlying cause of disease or necessarily the factors contributing to these processes.

Biomarkers have been arbitrarily classified into 3 types.[2] Type 0 refers to a marker related to the natural history of the disease. At present, type 0 biomarkers in asthmatic patients are not available, but the Asthma Predictive Index is a helpful indicator of risk for disease in the unaffected child.[3] Type 1 biomarkers reflect drug activity or act as markers of responsiveness and are taking on a greater importance as precision medicine comes into play with more biologics available for the treatment of asthma. Finally, type 2 biomarkers refer to surrogate markers, such as cholesterol, which might act as an indicator (or risk) of cardiovascular disease.

Physicians already use biomarkers to more effectively track disease progression,[4] such as hemoglobin A1c, which not only measures the average blood sugar over time but also provides insight into the effectiveness of glycemic control agents. Moreover, hemoglobin A1c is a surrogate for the prognosis of disease and the likelihood of end-organ damage from diabetes.[5] Similarly, physicians use a virologic biomarker, the $CD4^+$ T-cell count, or the peripheral circulating viral load in the diagnosis, treatment, and prognosis of HIV.[4] In particular, the viral load relates to disease etiology, severity, responsiveness to treatment, and survival. $CD4^+$ T-cell counts can also serve to

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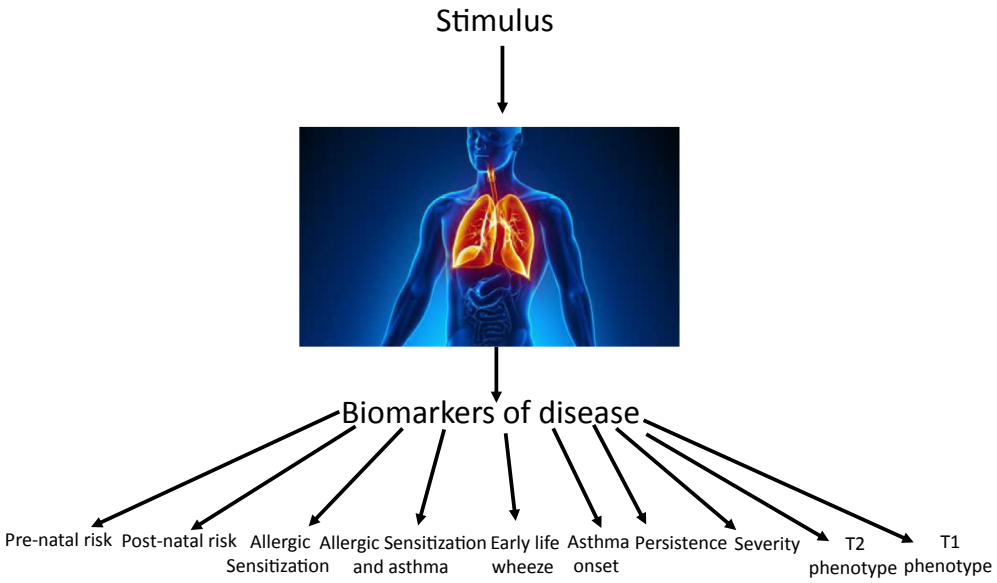

FIG 1. Potential biomarkers in relationship to asthma, beginning with prenatal risk for disease and extending to markers associated with treatment selection.

reflect the prognosis and guide responses to antiretroviral treatment in patients with AIDS.[6,7] These biomarkers have clear clinical and practical relevance and have directed patient care toward improved outcomes.

Biomarkers in asthmatic patients have yet to reach the level of precision found with HbA1c levels or $CD4^+$ counts. However, a number of biomarkers have been identified that help define asthma phenotypes and predict patient characteristics most likely to reflect responsiveness to specific therapies.

We will review the current but limited menu of biomarkers in asthmatic patients and how they might help define phenotypes and endotypes, predict disease severity, and select patient groups who will be most responsive to biologic therapies. To be most useful, biomarkers in asthmatic patients must first be vetted in large cohorts of patients, be readily accessible by measurements using standard methods to ensure widespread and accurate use, and display robust sensitivity, specificity, accuracy, and reproducibility.

WHAT HAS BEEN LEARNED AND WHAT INSIGHT HAS BEEN GAINED FROM BIOMARKERS IN ASTHMATIC PATIENTS?

Asthma is a heterogeneous disease, and for some patients, particularly those with severe disease, existing therapies have limited efficacy.[8] This is not surprising because a wide variety of cells and inflammatory molecules act in concert in a complex manner to drive the development, severity, and pattern of inflammation in asthmatic patients and, theoretically, to eventually determine various clinical phenotypes of disease. From these efforts, it has been possible to identify biomarkers in asthmatic subpopulations and from this information gain greater insight into what treatments might be most effective.[9] From these efforts, a small number of relevant biomarkers have emerged: eosinophil counts, fraction of exhaled nitric oxide (FENO) values, and periostin and IgE levels. However, as will be discussed, these 4 biomarkers have limitations because they are primarily important and related to patients with a T_H2-high, now referred to as T2 to include both T_H2 cells and non-T_H2 cells as a source of cytokines, component to their asthma. Although they are helpful in this situation, a significant proportion of asthmatic patients do not express a T2 pattern and instead have, for example, neutrophils or no specific cell type involved in their airway dysfunction. Therefore the T2 markers, although highly meaningful, do not convey the full story.

EOSINOPHILS

Eosinophils are a longstanding feature or characteristic of asthma and, as a consequence, are considered fundamental to the pathophysiology of this disease, its severity, and possibly its etiology, at least in some patients.[10] The histology of the lung in asthmatic patients is associated with and often characterized by eosinophilic infiltration of the airway. Based on the inflammatory capacity of the eosinophil, its presence has been believed to reflect airway injury, to contribute to airway hyperresponsiveness and remodeling, and to be a direct causative link to asthma pathophysiology.[11] Moreover, early studies that measured peripheral blood eosinophil counts found significant correlations between this cell's presence and disease severity, as well as a marker reflecting clinical improvement as their numbers decreased in response to treatment.[12,13]

This cell's positioning as a relevant biomarker is supported by animal models for asthma, in which ablation of eosinophils after administration of mAbs directed toward IL-5 reduces airway inflammation and bronchial hyperresponsiveness after an allergen provocation.[14] Based on these associative findings, the eosinophil was considered the causative cell of asthma, and its presence was considered an ultimate biomarker for asthma because it marked the presence of disease, its severity, and its responsiveness to treatment.

However, initial studies in broad-based asthmatic populations with anti–IL-5 mAb treatment found no effect on lung function, symptoms, or exacerbations despite a nearly total ablation of circulating eosinophils.[15] These findings led to a reassessment of the significance of eosinophils to asthma, what their presence meant, and under what conditions this cell had a relationship