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Biomarkers in Severe Asthma

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INTRODUCTION

A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[1] Biomarkers useful in respiratory disease can be obtained using several different types of clinical samples (Box 1). In this review, we restrict our discussion to biomarkers that can be measured in blood, sputum, or exhaled gas and those that are cellular, biochemical, or molecular in nature. There are several potential applications of biomarkers in the study and management of severe asthma (Box 2). Of these potential applications, significant advances have been made in biomarkers of endotypes (ie, biologically related subtypes) of asthma and in those that are predictive of response to therapy. In particular, bio-markers of type 2 inflammation (defined as inflammation driven by the Th2-cytokines, interleukin [IL]-4, IL-5, and IL-13) have proven valuable for endotyping in asthma. Here we review the current state of knowledge with respect to biomarkers in severe asthma, stratifying them by those that relate to type 2 inflammation and those that do not.

Box 1

Sample types of biomarker measurement in respiratory disease

- Bronchoscopic samples
- Induced sputum
- Blood
- Urine
- Exhaled gases

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Box 2

Potential applications of biomarkers in severe asthma

- Understanding the biology
- Diagnosis and screening
- Assessment of severity, control, or prognosis
- Identification of endotypes (biologically related subtypes of disease)
- Application in clinical trials and safety monitoring
  - Pharmacodynamic biomarkers
  - Predictive of response

BIOMARKERS OF TYPE 2 INFLAMMATION

Sputum Eosinophils

Sputum eosinophils are obtained by sputum induction and are expressed as a percentage of inflammatory cells.[2] Upper limit of normal for sputum eosinophil differential is generally defined as approximately 1% to 2%,[2–4] with female gender and atopy associated with higher sputum eosinophil counts.[3] Sputum eosinophil count is increased in symptomatic individuals with asthma,[5] and elevated eosinophils can be found in 50% of corticosteroid-treated patients, and in 70% to 80% of corticosteroid-naive patients.[6] Sputum eosinophil count is elevated by allergen challenge and reduced by corticosteroids.[7,8] Studies of inhaled corticosteroid (ICS) reduction in patients with asthma show that an increase in sputum eosinophil count may be predictive of asthma exacerbation.[9–11]

Fractional Exhaled Nitric Oxide Concentration

Nitric oxide (NO) is synthesized by NO synthetases (NOSs).[12] Patients with asthma have high levels of NO in their exhaled breath, which is thought to be due to upregulation of inducible NOS (NOS2) in airway epithelial cells secondary to airway inflammation.[13] Chemiluminescence analyzers allow the measurement of NO concentration in gas phase.[14] A joint American Thoracic Society (ATS) and European Respiratory Society (ERS) guideline (last revised in 2005) recommends that fractional exhaled NO concentration (FeNO) in exhaled breath be expressed as parts per billion (ppb).[15] FeNO is elevated in asthma and decreased with inhaled steroids.[16] The distribution of FeNO value is skewed to the right with significant overlap between healthy controls and patients with asthma. Current smoking, atopy, and age influence the distribution of FeNO values.[17–22] The 2011 ATS clinical practice guideline on the interpretation of FeNO proposes cutoffs for clinical use of FeNO. It suggests that eosinophilic inflammation is unlikely in symptomatic patients with low FeNO (<25 ppb in adults and <20 ppb in children), whereas high FeNO (>50 ppb in adults and >35 ppb in children) suggests airway eosinophilia and steroid-responsive inflammation.[13]

Blood Eosinophils

There has been growing interest in less-invasive alternatives to sputum induction. Blood eosinophil counts are a potential surrogate biomarker for eosinophilic inflammation in asthma and are relatively easy to obtain. Although studies of blood eosinophil count as predictors of high sputum eosinophils in eosinophilic asthma have yielded somewhat mixed results,[23–25] blood eosinophil counts have been useful in selection of patients for eosinophil-targeting agents as described later in this article. The cutoff used in the clinical trials to define high blood eosinophil counts have ranged between 150 and 300 cells/μL.[23–27]

Periostin

Periostin is a matricellular protein that is secreted by bronchial epithelial cells and lung fibroblasts in response to Th2 cytokines, IL-13, and IL-4.[28,29] Whether and how periostin may contribute to asthma pathogenesis is still unclear. Although some results are conflicting, mouse models suggest a role of periostin in subepithelial fibrosis, eosinophil recruitment, and mucus production from goblet cells.[30–32] A study of sputum and blood eosinophils, periostin, FeNO, and immunoglobulin E (IgE) in patients with severe asthma found that periostin was the strongest biomarker predictor of sputum and tissue eosinophilia.[33] The cutoff range to define periostin-high or periostin-low groups for prognostication of treatment response have not been precisely defined, with some clinical studies using the median periostin level of the study population[34–36] and others using 50 ng/mL as the cutoff.[37]

OTHER BIOMARKERS OF TYPE 2 INFLAMMATION

Dipeptidyl peptidase-4 (DPP4) is highly expressed in lung epithelial cells, endothelial cells, and submucosal glands. In rat models, its enzymatic activity increases in bronchoalveolar lavage (BAL) fluid and parenchymal tissue after an allergen challenge.[38] Like periostin, the role of DPP4 in asthma is uncertain. DPP4 inhibition has effects on airway inflammation in animal models that depend on the route of administration (oral, aerosolized, topical).[39] Studies of DPP4 in human airway inflammation are limited. Other potential biomarkers of type 2 inflammation include urinary bromotyrosine (BrTyr),[40,41] monocyte chemoattractant protein-4 (MCP4), and eotaxin-2.[42,43]

BIOMARKERS UNRELATED TO TYPE 2 INFLAMMATION

Sputum Neutrophil

Using sputum induction and cytology, patients with asthma can be categorized as paucigranulocytic, eosinophilic, neutrophilic, and mixed. Airway neutrophilia is well documented in severe exacerbations of asthma[44]; however, the prevalence of neutrophilia in severe asthma between exacerbations remains somewhat uncertain.

In healthy subjects, neutrophils and macrophages predominate in the induced sputum (median neutrophil percentage 37% [10th and 90th percentile, 11%–64%]).[3] Cigarette smoking, infection, ozone, and endotoxin all increase sputum neutrophil counts.[3] In asthma studies, the cutoffs for elevated sputum neutrophil count have ranged between 40% and 76%.[25,45,46]

Sputum neutrophilia may represent a stable phenotype of severe asthma or, alternatively, could reflect response to therapy. In cluster analyses from the Severe Asthma Research Program (SARP), patients with the worst lung function despite maximal bronchodilator therapy had the highest sputum neutrophil count.[46] Conversely, other studies report that ICS use is associated with increased sputum neutrophils[47] and that, after tapering ICS, sputum neutrophilia was reduced. Combined increases in sputum eosinophils and neutrophils may identify patients with asthma with low lung function and increased symptoms.[45]

Interleukin-17

IL-17 can promote neutrophilic inflammation and plays a role in diseases such as psoriasis and ankylosing spondylitis.[48–51] Studies measuring IL-17 levels in induced sputum, BAL samples, and bronchial biopsies have found increased IL-17 levels in severe asthma.[52–55] Whether IL-17 plays a causative role in severe asthma is less certain, as a randomized trial of IL-17 blockade using Brodalumab, a humanized anti-IL17RA monoclonal antibody, in moderate to severe asthma was negative.[56] More recently, IL-17–producing cells and an IL-17–related gene expression signature were observed in severe asthma, and this IL-17 signature was orthogonal to type 2 inflammation.[57] One intriguing possibility raised by this data is the airway production of IL-17 may increase as type 2 inflammation is blocked in severe asthma. If so, a strategy that blocks both Th2 cytokines and IL-17 could be beneficial in severe asthma.

Other Non–Type 2 Inflammatory Biomarkers

Several other inflammatory biomarkers that are not associated with type 2 inflammation have been studied in severe asthma, including IL-6[58] and C-reactive protein.[59] Exhaled breath condensate pH may reflect underlying inflammatory process in the airway in asthma, as its levels may correlate with steroid treatment and asthma exacerbation.[60] More studies in these markers and others, including tumor necrosis factor α and biomarkers of oxidative stress are needed to better elucidate its role in asthma.

Special Considerations in Children

Periostin is a product of bone turnover and is elevated in children.[61] Thus, whether it will be useful as a biomarker of asthma in children is uncertain. Two recent studies show significantly higher periostin levels in children with asthma compared with healthy controls, suggesting that periostin may still have some value in this age group, although more studies are needed.[61,62] One study showed poor correlation between blood eosinophils and airway eosinophilia in children with severe asthma on high-dose ICS.[63] A BAL study of 69 children suggest that severe therapy-resistant asthma in children is characterized by eosinophilic, rather than neutrophilic predominant airways. However, there were no elevated cytokines in the BAL fluid suggestive of type 2 inflammation (IL-4, IL-5, IL-13) in these children compared with the control group.[64]

UTILITY IN SEVERE ASTHMA

Diagnosis

As asthma is heterogeneous with respect to type 2 inflammation, biomarkers such as FeNO are supportive rather than definitive for diagnosis of asthma.[13]

Prognosis

A study in SARP found no difference in FeNO level in severe as compared with non-severe asthma; however, when the groups were subdivided further, high FeNO levels in severe asthma identified those with greatest airflow limitation and reversibility, highest sputum eosinophils, and most emergency department visits and intensive care unit admissions, suggesting that FeNO may be used to risk stratify.[65] Elevated sputum neutrophils with or without concurrent sputum eosinophilia have been associated with a more severe asthma phenotype.[66] In a multivariable analysis of 224 patients with asthma on ICS, high baseline serum periostin level (≥95 ng/mL) was an independent risk factor for greater decline of lung function.[67] Furthermore, elevated levels of periostin have been found in aspirin-exacerbated respiratory disease and were again associated with more severe and eosinophilic asthma.[68]

Establishing a Baseline and Monitoring Control

How variable airway eosinophilia may be over time is uncertain. In one longitudinal study over 5 years, 70% of those with eosinophilic asthma (sputum eosinophils ≥2%) and 96% of those with noneosinophilic asthma retained their sputum phenotype.[69] However, one pro-con debate cited data from 40 patients with severe asthma, which showed that 60% of the patients changed their classification from eosinophilic (sputum eosinophils ≥2%) to noneosinophilic and vice versa.[70]

Endotyping

The observation that biomarkers of type 2 inflammation mark patients who have distinct immune cell infiltration, histological changes, and treatment response suggests that type 2 inflammation defines an endotype of asthma.[71] Formally, an endotype can be defined as patients who share a common underlying biology, and one review article suggested that investigation of a series of shared features could define an endotype (see Box 2).[72] Many of these proposed criteria for an endotype have been met for type 2 inflammation asthma, including association with treatment response. Those criteria that still require some investigation include studies of genetic predisposition and shared epidemiology.

Guiding Choice of Therapy in Severe Asthma

The concept of an endotype can inform precision medicine has been key in developing new therapies for severe asthma, especially because new therapies can be expensive and cumbersome and can have adverse effects.

The first example of using biomarkers to predict therapy in severe asthma comes from the development of mepolizumab, a humanized monoclonal antibody against IL-5. The first clinical trial of mepolizumab (in moderate asthma) did not use eosinophilia as inclusion criteria and failed to show benefit.[73] Subsequently, 2 studies in severe asthma that selected

patients based on persistent sputum eosinophilia showed a remarkable benefit in reduction of exacerbations with mepolizumab.[74,75] Subsequent larger trials confirmed these observations, informed the use of blood eosinophils as a surrogate for sputum eosinophils, and identified optimized threshold values for prediction of clinical response. In the DREAM study, mepolizumab, reduced exacerbations in patients with severe asthma who had sputum eosinophil count ≥3%, FeNO ≥50 ppb, or blood eosinophil count ≥300 cells/μl. Furthermore, baseline blood eosinophil count correlated with the reduction in exacerbations.[76] Post hoc analysis of the DREAM study showed that blood eosinophils ≥150 cells/μl predicted response to mepolizumab and that a single measurement was predictive of future elevated blood eosinophil levels.[27] Mepolizumab also reduced exacerbations, improved asthma symptoms, and had oral steroid-sparing effects in patients with eosinophilic inflammation (prerandomization blood eosinophil count ≥300 cells/μl, or 150 cells/μl during optimization phase) who required chronic oral steroids for their asthma.[77] In November 2015, the Food and Drug Administration approved mepolizumab for treatment of severe asthma in patients 12 years and older with an eosinophilic phenotype. Similarly, reslizumab, an anti-IL5 humanized monoclonal antibody, has also been demonstrated to improve lung function and quality of life in poorly controlled asthma with sputum eosinophilia ≥ 3% or blood eosinophil count ≥400/μL.[78,79]

An alternative approach to using biomarkers of type 2 inflammation to guide the use of biologics for severe asthma was the development of periostin as a predictive biomarker for response to lebrikizumab, an anti-IL-13 humanized monoclonal antibody. In a phase II study (MILLY study), lebrikizumab significantly improved lung function but not exacerbation rates when stratifying patients by elevated periostin levels.[35] Subsequently, 2 pooled phase IIb studies (LUTE and VERSE studies) demonstrated both improved lung function and reduced exacerbation in patients with periostin-high severe asthma.[37] The efficacy of lebrikizumab in mild asthma is less clear, as a study of patients with mild asthma not on ICS showed no significant clinical benefit with lebrikizumab.[36] Similarly, a phase IIb study of tralokinumab, a humanized anti-IL-13 monoclonal antibody, in severe asthma showed no decrease in asthma exacerbations, except in post hoc subgroup analysis, in which asthma exacerbations decreased in those with high periostin level and lung function improved in those with elevated DPP-4 level.[80]

Finally, post hoc analysis of a clinical trial of omalizumab, a widely used anti-IgE monoclonal antibody, identified potential biomarkers of response (reduction in exacerbations).[81] This is particularly interesting in that patients were already selected for those with a positive skin test or in vitro response to a relevant perennial aeroallergen. The investigators found that FeNO and blood eosinophils at baseline predicted response to omalizumab and that there was a trend for improved response in those with increased baseline levels of serum periostin.

Guide Dosing of Inhaled Corticosteroid

Randomized trials have demonstrated that the use of sputum eosinophil to guide ICS therapy can reduce asthma exacerbations without increasing the total amount of ICS used.[82,83] One meta-analysis showed that the use of sputum eosinophils to titrate asthma treatment reduced

exacerbations, whereas the use of FeNO reduced ICS dose in adults but failed to show significant improvement in asthma control.[84] In children with severe asthma, the use of sputum eosinophils to guide management was not shown to decrease asthma exacerbations or overall control compared with standard symptom-based management.[85] The use of FeNO to guide therapy in children resulted in somewhat higher ICS use without significant improvement in clinical outcomes.[84,86] The ATS/ERS guideline on severe asthma recommends that in adults, clinical criteria and sputum eosinophil counts, but not FeNO, be used for guiding therapy.[87]

Assess Adherence

According to collective experience of investigators in the ATS guideline, one of the most common causes of persistently elevated FeNO despite therapy is likely poor compliance.[13]

SUMMARY

Biomarkers have been critical for studies of disease pathogenesis and the development of new therapies in severe asthma. In particular, biomarkers of type 2 inflammation have proven valuable for endotyping and targeting new biological agents. Because of these successes in understanding and marking type 2 inflammation, lack of knowledge regarding non–type 2 inflammatory mechanisms in asthma will soon be the major obstacle to the development of new treatments and management strategies in severe asthma. Biomarkers can play a role in these investigations as well by providing insight into the underlying biology in human studies of patients with severe asthma.

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KEY POINTS

- Asthma biomarkers can be broadly categorized as those that relate to type 2 inflammation and those that relate to other biological processes.
- Biomarkers of type 2 inflammation include sputum and blood eosinophils, exhaled nitric oxide levels, and serum periostin.
- In severe asthma, biomarkers are particularly useful in defining endotypes (ie, biologically related subtypes) and in predicting response to therapy.