

# Bronchodilator Responsiveness: An Underappreciated Biomarker for Asthma Exacerbations



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Reversible airflow obstruction is a characteristic and often a diagnostic feature of asthma. In this issue of the *Journal of Allergy and Clinical Immunology. In Practice*,<sup>1</sup> Nicola Hanania and coauthors analyzed data from A Study of Omalizumab (Xolair) in Subjects with Moderate to Severe Persistent Asthma (EXTRA)<sup>2</sup> clinical trial to assess whether the degree of bronchodilator responsiveness (BDR) as well as spirometric indicators of fixed airflow obstruction (FAO) have value in predicting future exacerbations of asthma in patients with moderate-severe, poorly controlled disease.

The EXTRA trial<sup>2</sup> addressed the efficacy of omalizumab vs. placebo in patients with moderate to severe asthma who were receiving high-dose inhaled corticosteroids ( $\geq 500$   $\mu\text{g/d}$  of fluticasone twice daily) and long-acting beta agonists. Enrollment characteristics of recruited subjects included prebronchodilator forced expiratory volume in 1 second ( $\text{FEV}_1$ ) that ranged from 40% to 80% predicted. Although not a required entry criterion for EXTRA, BDR to inhaled albuterol was obtained in all subjects. These data now serve as a fortuitous opportunity to provide insight into the value and importance of this airway response to future exacerbations.

The 850 subjects enrolled in EXTRA had approximately 2 exacerbations in the preceding year, averaged 4 puffs of a rescue inhaler per day, were symptomatic at randomization, and had slightly elevated fractional exhaled nitric oxide (FeNO). Another question in the analyses by Hanania et al<sup>1</sup> was whether FAO, which they defined as an  $\text{FEV}_1/\text{FVC}$  (forced vital capacity) less

than 70% predicted, contributed to risks for exacerbations and whether this relationship was affected by the BDR.

To address these questions, Hanania et al<sup>1</sup> focused on the effects of omalizumab versus placebo treatment in relationship to pulmonary function characteristics: a comparison of fixed airflow obstruction (FAO+) versus no FAO (FAO-) as well as the presence ( $>12\%$  and 200 mL) or absence 12% or less (and  $<200$  mL) of BDR with albuterol to exacerbation risks and overall improvement in  $\text{FEV}_1$ .

Two major findings emerged based on their analyses of the EXTRA data.<sup>1</sup> First, omalizumab improved  $\text{FEV}_1$  values in the FAO- and high BDR populations; omalizumab did not improve  $\text{FEV}_1$  in the low BDR group, irrespective of FAO features. In addition, and of considerable interest to us, was their second observation, which identified the predictive value of BDR to asthma exacerbations. Four lung function provocation phenotypes were considered in their analyses: (1) FAO+/low BDR, (2) FAO+/high BDR, (3) FAO-/low BDR, and (4) FAO-/high BDR. The primary differentiating airway characteristic that identified risks for exacerbation was high BDR. In contrast, risks for exacerbations were not influenced by FAO, suggesting that a potentially valuable predictive phenotype characteristic for asthma exacerbations was BDR.

How do we put these data from Hanania et al<sup>1</sup> into perspective with current information about severe asthma and exacerbations? FAO is a marker of asthma severity and disease duration and is contributed to by multiple factors.<sup>3,4</sup> In the absence of high BDR, FAO did not predict risks for exacerbations, at least in the EXTRA population. Since the initial report of EXTRA, a *post hoc* analysis<sup>5</sup> identified the predictive benefit of type (T)2 inflammatory biomarkers, that is, peripheral blood eosinophils ( $>260$  cells/ $\mu\text{L}$ ) and FeNO ( $\geq 19.6$  ppb), to risk factors for exacerbations as well as increased treatment responsiveness to anti-immunoglobulin E. The current analyses by Hanania et al<sup>1</sup> adds an important clinical phenotypic characteristic based on measures of pulmonary physiology to identify risks for exacerbations and the probability of a beneficial response to omalizumab.

The Severe Asthma Research Program (SARP) has provided longitudinal observations on risks for exacerbations to further our understanding of this issue. Data from SARP indicate the complexity of identifying risks for exacerbations when this response is evaluated over longer-term follow-up. For example, Denlinger et al<sup>6</sup> described clinical, physiological, inflammatory, and comorbidity factors associated with exacerbation-prone asthma (EPA) in 709 SARP subjects. The 12-month rates of exacerbation were variable in this group and indicate that

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recurring exacerbations are not invariable in severe asthma: 41% had no exacerbations, 34% had infrequent (1 or 2) exacerbations, and 24% had 3 or more exacerbations and represent EPA. The SARP participants with EPA had lower lung function at baseline. In addition, and paralleling the findings of Hanania et al,<sup>1</sup> bronchodilator responsiveness was significantly associated with exacerbation rates ( $P = .002$ ).

How may we incorporate airflow reversibility into perspective biomarkers for exacerbation risks and responsiveness to treatment interventions and also possible mechanisms of action? First, airway reversibility has been previously recognized as a risk factor for exacerbations; thus, the current observations of Hanania et al<sup>1</sup> are not a total surprise, but confirm and further validate this association. Moreover, noting a significant benefit from omalizumab to reduce exacerbations in a BDR population raises the possibility that airflow reversibility, but not FAO alone, may be a biomarker to predict efficacy with omalizumab and, potentially, other biologics. Virtually every clinical trial that evaluated the efficacy of T2 biologics, that is, mepolizumab, benralizumab, reslizumab, and dupilumab, required BDR at enrollment.<sup>7</sup> Although BDR was generally included in these protocols as an entry requirement to ensure the existence of asthma, this pulmonary function trait may also be a highly informative biomarker for exacerbation risks as well as a potential indication for benefit from modulators of T2 inflammation.

What pulmonary functions are missing that could shed additional light on these observations. Hanania et al<sup>1</sup> did not assess changes in FVC or other physiological assessments of air trapping. In assessing airway closure as a distinguishing physiological characteristic of severe asthma, Sorkness et al<sup>8</sup> evaluated components of airflow limitation and air trapping in relation to alterations in FEV<sub>1</sub>. For their analysis, they included subjects from SARP with severe and nonsevere asthma. Air trapping was identified as a significant contributor to airflow obstruction in severe asthma, and reversibility of air trapping was associated with improvements in both FVC and FEV<sub>1</sub>. Air trapping is a risk factor for exacerbations<sup>9</sup>; therefore, reversal of air trapping improves airflow limitation and may reduce risks for exacerbations, and also be a pulmonary function measure to identify this risk.

Reversible airway obstruction also reflects instability of the bronchomotor tone, which can also enhance the susceptibility for airway obstruction.<sup>10</sup> This phenotypic attribute has been referred to as fragile asthma and is often found in patients most at risk for loss of asthma control. When patients with fragile airway control are exposed to provokers, such as a respiratory viruses or pollution, their unstable airways are at greater risk for airflow obstruction, which may progress to an exacerbation. It is also likely that ongoing airway inflammation contributes to labile bronchomotor tone. In this regard, although not part of the analysis by Hanania et al,<sup>1</sup> it would be informative to assess the relationship between BDR and traditional markers of inflammation, including the T2 biomarkers, eosinophils, and FeNO. Another relevant consideration is recognizing and appreciating that airway smooth muscle can also contribute to airway inflammation by generation of inflammatory mediators.<sup>11,12</sup>

Collectively, dysfunctional airway smooth muscle activity in asthma may be reflected in an increased bronchodilation response. This concept further underscores the clinical benefit that follows treatment to regulate bronchomotor tone.<sup>13</sup>

Because normalization of airway smooth muscle function is associated with an improvement in asthma control and overall airway health, it should continue to be considered that an essential goal of asthma treatment is to restore or maintain altered lung physiology. However, because treatments with bronchodilators alone are not sufficient to achieve and sustain asthma control, understanding the link between airflow obstruction reversibility and susceptibility for exacerbations represents a feasible and informative biomarker measure to identify patients at greater risks for loss of disease control. Improving airway function in asthma represents an achievable step forward to reduce burdens and risks of asthma. From our perspective, the data from Hanania et al<sup>1</sup> are a call to include measures of airflow reversibility as an important and informative phenotypic characteristic that helps to identify patients at risk for exacerbations and potentially as a marker for enhanced efficacy of biologics in severe asthma.

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