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Measurement of fractional exhaled nitric oxide in real-world clinical practice alters asthma treatment decisions

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ABSTRACT

Background: Assessment of asthma using clinical measures alone often fails to detect underlying airway inflammation. Fractional exhaled nitric oxide (FeNO) is a recognized biomarker of type 2 airway inflammation in asthma. Measurement of FeNO is instrumental in the assessment and management of patients with corticosteroid-sensitive asthma.
Objective: To determine the impact of measuring FeNO on asthma management in real-world clinical practices.
Methods: Clinicians from 337 US practices performed a clinical assessment and recorded treatment plans before and after measuring FeNO in 7,901 patients with asthma. Airway inflammation was classified as low, intermediate, or high according to the clinician's usual procedures, including clinical examination, spirometry, and symptoms. Clinicians recorded asthma medication plans, indicating medications to be initiated, continued, or stopped. FeNO measurement was performed, followed by documentation of any change(s) in the treatment plans based on the FeNO value (eg, initiating new medications or changing the dose of or discontinuing existing medications).
Results: Clinical assessment was concordant with FeNO measurement in only 56% of cases, matching FeNO more frequently in patients with low inflammation (64%) vs high inflammation (34%). After FeNO measurement, clinicians modified their treatment plan in 31% and altered prescriptions for inhaled corticosteroids in 90% of cases. Inhaled corticosteroids were initiated or their dose increased in 66% of patients with high inflammation but discontinued or their dose decreased in only 9% of patients with low inflammation.
Conclusion: Measurement of FeNO enabled clinicians to assess underlying airway inflammation, leading to a significant revision of their treatment plans compared with real-world clinical assessment of asthma alone.

Introduction

Asthma is a chronic inflammatory disease of the airways, and recognition and treatment of underlying airway inflammation is central to effective asthma management. Evidence-based guidelines emphasize the importance of ongoing assessment of asthma control, periodic adjustments to therapy, and monitoring the patient's treatment adherence.[1,2] In the outpatient setting, asthma control is primarily assessed by clinical signs and symptoms and the use of validated questionnaires. Spirometry also is used for measuring airflow to evaluate the severity of airway obstruction and response to therapy.

Unfortunately, although these assessments are important, they do not directly reflect on the extent of underlying airway inflammation,[3] which is driven in part by the activation of antigen-specific T-helper type 2 cells, leading to the production of different inflammatory cytokines. Of these cytokines, interleukin-4 and interleukin-13 have been shown to induce gene transcription for the inducible nitric oxide (NO) synthase enzyme in epithelial cells of the airway, leading to the release of NO in expired breath.[4,5] Measurement of fractional exhaled NO (FeNO) is recommended as a useful technique for assessing steroid-responsive type 2 inflammation in the airway.[6–10] FeNO has high sensitivity and specificity in the diagnosis of asthma, and it correlates well with the results of induced sputum and bronchial challenge testing.[8,10,11] However, unlike induced sputum and bronchial challenge testing, FeNO

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measurement is rapid and noninvasive and can be assessed at the point of care.

In addition to its complementary role in asthma diagnosis, the use of FeNO for patient assessment and ongoing monitoring is supported by substantial evidence. Measurement of FeNO can identify patients who have poor asthma control,[12] those at greater risk for exacerbations,[13–18] and those at risk of progressive loss of lung function.[19] Furthermore, FeNO levels predict steroid responsiveness[20–23] and can help to identify patients with asthma who are likely to benefit from biologic therapies targeting type 2 inflammation.[14,24,25] Ongoing patient assessment using FeNO is beneficial for guiding corticosteroid dosing[20,26,27] and monitoring patient adherence to corticosteroid therapy.[28–30] International respiratory societies have endorsed the use of FeNO to aid in the diagnosis and management of asthma in adults and children.[2,21] In particular, the American Thoracic Society (ATS) has recommended cut points for interpreting FeNO measurements: values less than 25 ppb in adults (<20 ppb in children) are considered low inflammation; intermediate values are 25–50 ppb in adults (20–35 ppb in children); and values greater than 50 ppb in adults (>35 ppb in children) are considered high inflammation.[21] Most recently, the National Institute for Health and Care Excellence published an updated guideline for asthma, which recommends measuring FeNO together with spirometry for the diagnosis of asthma and in the management of patients who remain symptomatic on inhaled corticosteroids (ICSs).[2] Likewise, other national and international societies and professional organizations have recognized newer evidence that supports the value of FeNO in asthma management and have included it in recent versions of their guidelines (eg, Agency for Healthcare Research and Quality in 2017, Global Initiative for Asthma in 2018, American Academy of Pediatrics in 2017, and country-specific documents from Germany, Spain, Czech Republic, China, and Japan).[31–38]

Despite acknowledgment of the benefits of FeNO for measuring type 2 inflammation in asthma, its impact on treatment decisions made by clinicians is rarely reported.[3] The objective of this investigation was to explore the real-world impact of FeNO monitoring on subsequent treatment decisions by clinicians managing patients with asthma.

Methods

Design

The methodology for this analysis was based on a pilot study by LaForce et al.[3] A brief survey consisting of 4 questions (Experience NIOX Form; eFigure 1) was conducted in a large sample of US asthma specialist practices, which included allergists and pulmonologists, but not primary care physicians. Invited clinicians had not previously used FeNO in their practices, ensuring that the survey provided an unbiased impact assessment of the value of adding FeNO to clinical practice. No other selection criteria were specified, and data on the number of clinicians who elected not to participate were not collected. Patients with asthma were not stratified by asthma severity, control, or medication use, mirroring real-world clinical practice. Clinicians were encouraged to test all new patients with asthma presenting to their clinic, and any further inclusion criteria were not specified, reflecting the real-world nature of the analysis.

Health care providers were asked to assess their patients' level of airway inflammation as low, intermediate, or high using clinical measures that they would normally use in their day-to-day practice (including pulmonary function testing, asthma symptoms and control, quality-of-life questionnaires, and physical examination). Responses were captured in their answer to question 1. Respondents also indicated on the form (question 2) any asthma medications that would be prescribed or continued (for patients who were already using asthma medications) as a result of their clinical assessment.

After recording their clinical assessment and actions to be taken, clinicians measured the FeNO levels of their patients and recorded this information on the evaluation form. Based on the FeNO level, clinicians indicated whether their treatment approach would change (question 3) and, if so, how it would change (question 4).

The effects of FeNO measurement on changes to corticosteroids were analyzed for each subgroup of airway inflammation by treatment with ICSs, ICSs plus long-acting β-agonists, and oral corticosteroids. Clinicians indicated whether medications were started or the dose was increased (stepped up), discontinued, or decreased (stepped down).

Assessments

Fractional exhaled NO was measured using the Food and Drug Administration–cleared NIOX devices (Circassia Pharmaceuticals, Inc, Morrisville, North Carolina). These devices are designed to register a FeNO value only if the test is performed correctly and an adequate sample is supplied, thus eliminating the need for repeated measurements. In addition, inhalation through the device handle and mouth piece passes the inspired air over a scrubber to remove contamination from ambient NO levels before expiration and measurement of FeNO, ensuring that all NO measurements reported reflect only NO originating from the airway epithelium. The FeNO value was reviewed by the clinicians only after they had completed their clinical assessment and indicated their treatment plan for the patient. Completed forms were tabulated and results were summarized descriptively, as reported.

Results

Clinical Assessment and Treatment Plans

The analysis included data from 337 US practices involving 7,901 adult patients (≥12 years old) with asthma. Clinicians assessed airway inflammation as being low in 4,247 (53.8%), intermediate in 2,749 (34.8%), and high in 905 (11.5%) patients. Based on clinical assessment alone, clinicians indicated that they would prescribe or continue the following asthma medications: short-acting β-agonists in 4,312 (54.6%), ICSs in 2,265 (28.7%), ICSs plus long-acting β-agonists in 2,704 (34.2%), leukotriene receptor antagonist in 1,365 (17.3%), oral corticosteroids in 471 (6.0%), and "other" in 584 (7.4%) patients. Most respondents selecting other medications used this category to indicate that the patient was not currently prescribed an asthma medication. Less common medications specified included long-acting muscarinic antagonists, biologic therapies, and antihistamines.

FeNO Measurement and Concordance with Clinical Assessment

The FeNO measurements were categorized according to the ATS cutoff points for low (<25 ppb), intermediate (25–50 ppb), and high (>50 ppb). FeNO values were low in 5,083 (64.3%), intermediate in 1,802 (22.8%), and high in 1,016 (12.8%) patients. Clinical assessments for the 3 levels of airway inflammation were compared with equivalent categories defined by the FeNO measurement for each patient (Table 1). Across the full analysis set, clinical assessment matched FeNO classification in slightly more than half the patients (4,457 of 7,901, 56.4%).

Subgroup analysis was conducted based on the objectively defined FeNO categories. Within the low inflammation subgroup (FeNO <25 ppb), clinical assessments matched FeNO in nearly two thirds the patients (3,271 of 5,083, 64.4%). Conversely, within the high inflammation subgroup (FeNO >50 ppb), clinician assessment