Small Airway Targeted Therapy in Pediatric Asthma: Are We There Yet?

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Asthma is characterized by inflammation of proximal and distal airways. As new formulations of extrafine aerosol particles have become available, targeting small airways for the management of asthma has been investigated. As new studies attempt to explore the correlation between small airway dysfunction and clinical outcomes in asthma, well-designed clinical trials are needed to compare targeted and standard therapy for asthma management especially in pediatric patients.

TARGETING SMALL AIRWAYS (<2 mm in diameter) in the management of asthma has received more attention recently. Many conditions have been associated with small airway obstruction.¹ Studies have shown small airway plugging and obstruction with fatal asthma indicating the role of small airways in severe asthma.^{1–3} Furthermore, small airway dysfunction has been associated with exercise-induced asthma, nocturnal asthma, increased risk of exacerbations, and bronchial hyperresponsiveness.⁴

Increased resistance of small airways may be assessed noninvasively by spirometry, nitrogen wash out, body plethysmography, impulse oscillometry (IOS), and using imaging (high resolution computed tomography or conventional chest X-ray).³ Inflammation of the small airways has been assessed with a fraction of expired nitric oxide utilizing mathematical modeling to isolate alveolar nitric oxide concentrations (CaNO).⁵ From a pragmatic point of view, the question is how these measurements correlate with standard lung functions, spirometry, and symptoms of asthma. It has been suggested that forced expiratory flow at 25%–75% (FEF_{25–75%}) of forced vital capacity (FVC) and FEF_{50%} would measure airflow at the end of expiration, hence the assessment of small airway obstruction.³ However, these measurements are highly variable, effort dependent, and can only be interpreted when FVC is normal and there are no reported normal values. Studies in pediatrics are particularly important; specifically, young children and infants 1–6 years of age, as by definition they have smaller airway diameters than adults.⁶ Data from longitudinal childhood studies have shown a decrease in FEF_{25–75%} in asthmatic children with history of wheezing.⁷ Recently, Rao and colleagues investigated correlation between FEF_{25–75%} and asthma severity

and morbidity in a retrospective study of 744 children 10–18 years of age.⁸ A chart review of asthma outcomes and assessment was done for 1 year prior and after the date of the spirometry. Spirometry data were divided into 3 groups: normal spirometry (defined as normal FEV₁, FEV₁/FVC, and FEF_{25–75%}), abnormal FEV₁/FVC, and abnormal FEF_{25–75%} and FEV₁/FVC. Normal spirometry values for FEV₁, FEV₁/FVC were defined per the latest National Asthma Education and Prevention Program's (NAEPP) Expert Panel Report 3 (EPR3) guideline⁹ and normal FEF_{25–75%} was defined as one standard deviation from the mean for all data points. The authors concluded that patients with lower FEF_{25–75%} and normal FEV₁ showed an increase in asthma exacerbations, use of systemic steroids, and severity of asthma compared with those with normal spirometry.

Shi et al. assessed asthma severity and control in 101 asthmatic patients, 6–17 years of age in a cross-sectional study.¹⁰ The assessment of control was defined by the NAEPP guidelines.⁹ IOS was measured to investigate the correlation between asthma control and severity with small airway dysfunction. Fifty-seven patients had controlled asthma compared with 44 with uncontrolled asthma. In the uncontrolled group, 95% of the patients had normal FEV₁ and 36% had normal FEF_{25–75%}. The IOS measurement in this study was used to determine the cut points that differentiate between controlled and uncontrolled asthma.

To assess the use of IOS to predict loss of asthma control, patients with controlled asthma were followed for an additional 8–12 weeks when asthma control was reevaluated.¹¹ The power analysis was based on the previous study and a change in peripheral airway IOS. Thirty-eight patients remained controlled and 16 patients became uncontrolled

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based on the assessment at the follow-up visit. The uncontrolled group had a significantly lower FEV1/FVC ratio compared with the group who maintained control at baseline and a significantly lower FEV1/FVC and FEF_{25–75%} at the follow-up visit compared with those who stayed controlled. Based on both studies,^{10,11} the authors suggested a cut point of 7 and 9.5 cm H₂O L^{−1} for low-frequency reactance area (AX) to predict risk of losing asthma control. As the study was powered based on IOS values, it is not clear if it offers any additional value over spirometry. As investigations to find a standard way to measure small airway dysfunction in the pediatric population continues, the proposed measurements have not yet translated to the spirometry or asthma symptoms.

The use of metered-dose inhaler (MDI) products with extrafine particles of inhaled corticosteroids have been suggested for targeted therapy of small airways.^{6,12} In theory, small particles (<2 μm) should have a greater chance of reaching small airways, but at the same time increased overall lung deposition from ultrafine particle MDIs may increase systemic availability decreasing the therapeutic index.¹³ Studies comparing ultrafine to coarse particle inhaled corticosteroids to improve small airway inflammation are inconclusive. Goldin et al. investigated ultrafine hydrofluoroalkane-propelled beclomethasone dipropionate (HFA-BDP, 200 mcg daily) compared with chlorofluorocarbon-propelled beclomethasone dipropionate (CFC-BDP, 200 mcg daily) on small airways as measured by high resolution computed tomography in adult patients with asthma.¹⁴ In this double-blind, parallel group trial, for 4 weeks the HFA-BDP had greater efficacy in the peripheral airways as measured by computed tomography techniques. However, lung deposition of radiolabeled HFA-BDP and CFC-BDP studies has shown a 53% deposition of HFA-BDP in the lungs compared with 4% deposition of CFC-BDP given at the same dose,¹⁵ so that the effect on small airways in this study could simply be contributed to a significantly higher total lung dose of BDP. When equipotent doses of HFA-BDP (400 mcg/day) and fluticasone propionate dry powder inhaler (FP-DPI, 500 mcg/day) were compared over 3 months in adult patients with uncontrolled asthma, air trapping as measured by high resolution computed tomography decreased with both inhaled corticosteroids with no difference between treatments.¹⁶

Studies in pediatrics have been inconclusive. Robroeks and colleagues compared the effect of HFA-BDP (200 mcg daily) and FP-DPI (200 mcg daily) on small airways in 33 children, 6–12 years old with moderate persistent asthma in a 6-month crossover study.¹⁷ No difference was reported in small airways as measured by CaNO and bronchial NO flux. A review of studies in infants suggested greater lung delivery from ultrafine particle inhaled corticosteroids, but currently, there is no evidence of improved efficacy.⁶ It is also not known if HFA-BDP produces significant growth suppression in children at the relatively low dose of 80 mcg/day.¹⁸

As the body of literature increases, it provides more insight and understanding of small airway dysfunction and what is considered a clinically significant dysfunction and its clinical effect. Clinicians need to be aware of small airway inflammation especially in patients with severe or nocturnal asthma. Furthermore, studies that are designed to target clinical consequence of small airway dysfunction,

such as nocturnal asthma or bronchial hyperresponsiveness, would provide more conclusive data for targeted therapy. Well-designed clinical trials are warranted to compare targeted versus standard therapies and to evaluate the safety and efficacy of recommended agents. The pathophysiology and assessment of small airway dysfunction in the pediatric population remain to be elucidated. Large pediatric clinical trials are warranted to understand the impact of targeting the small airways on lung function and other clinical outcomes in patients with different asthma severity.

Author Disclosure Statement

Drs. Raissy and Blake have no conflicts of interest or financial ties to report.

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