Bronchodilation and bronchoconstriction: Predictors of future lung function in childhood asthma

Kelan G. Tantisira, MD, MPH,[a,b,c] Anne L. Fuhlbrigge, MD, MS,[a,b] James Tonascia, PhD,[d] Mark Van Natta, MHS,[d] Robert S. Zeiger, MD, PhD,[e,f] Robert C. Strunk, MD,[g] Stanley J. Szefler, MD,[h] and Scott T. Weiss, MD, MS,[a] for the Childhood Asthma Management Program Research Group* *Boston, Mass, Baltimore, Md, San Diego and La Jolla, Calif, St Louis, Mo, and Denver, Colo*

Background: Persistently low levels of lung function are associated with subsequent symptoms in patients with asthma as children.

Objectives: We hypothesized that objective measures of baseline pulmonary function would be independently associated with future lung function in the Childhood Asthma Management Program and that these associations might vary with treatment.

Methods: We evaluated the association of FEV_1, airway responsiveness, and bronchodilator response at randomization as predictors of longitudinal growth in FEV_1 at the 48-month follow-up visit in the 1041 Childhood Asthma Management Program participants.

Results: Baseline levels of airway responsiveness and bronchodilator response were significantly associated with baseline level of lung function. In multivariate models, higher bronchodilator response ($\beta = 0.22$; $P < .0001$), log PC_{20} ($\beta = 1.82$; $P < .0001$), and FEV_1 ($\beta = 0.58$; $P < .0001$) at randomization were each associated with higher levels of prebronchodilator FEV_1, as a percent of predicted, after 4 years. Similar associations were noted for prebronchodilator forced vital capacity and FEV_1/forced vital capacity ratio. Baseline bronchodilator response was a particularly powerful predictor of lung function improvements while on inhaled corticosteroids, whereas airway responsiveness was a better predictor in subjects not randomized to any controller medications.

Conclusion: We conclude that baseline bronchodilator response, airway responsiveness, and level of FEV_1 are independent predictors of subsequent level of FEV_1 in childhood asthma and may have treatment-specific prognostic significance for persistence of symptoms into early adulthood.

Clinical implications: In asthma, bronchodilator and bronchoconstrictor responses are independent predictors of future lung function and should not be used interchangeably; bronchodilator response may indicate good response to inhaled corticosteroids. (J Allergy Clin Immunol 2006;117: 1264-71.)

Key words: *FEV_1, PC_{20}, methacholine, bronchodilator, corticosteroid, asthma, natural history*

Asthma is a leading cause of pediatric hospitalizations and school absences.[1] However, the natural history of childhood asthma and the factors that modify this history have yet to be defined fully. Although an estimated 30% to 70% of children improve or outgrow their asthma,[2-4] a

From [a]the Channing Laboratory and [b]the Pulmonary Division, Brigham and Women's Hospital and Harvard Medical School, Boston; [c]the Pediatric Pulmonary Unit, Massachusetts General Hospital, Boston; [d]the CAMP Coordinating Center, Bloomberg School of Public Health, Johns Hopkins University, Baltimore; [e]the Department of Allergy-Immunology, Kaiser Permanente Medical Center, San Diego; [f]the Department of Pediatrics, University of California San Diego, La Jolla; [g]the Department of Pediatrics, Washington University School of Medicine, St Louis; and [h]the Department of Pediatrics, National Jewish Medical and Research Center, Denver.

*Members of the CAMP Research Group are detailed in the Online Repository for this article at www.jacionline.org.

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Reprint requests: Kelan Tantisira, MD, MPH, Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, 181 Longwood Avenue, Boston, MA 02115. E-mail: kelan.tantisira@channing.harvard.edu.

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Abbreviations used
BD: Bronchodilator response at randomization
CAMP: Childhood Asthma Management Program
FVC: Forced vital capacity
$lnPC_{20}$: Natural log–transformed PC_{20}

significant proportion of patients with asthma as children remain symptomatic into adulthood. Low spirometric flow, as measured by FEV_1 persisting from childhood into early adulthood has consistently been associated with continued asthma symptoms as adults.[4-6] Low FEV_1 also predicts subsequent asthma attacks in children and adults and relapse of asthma symptoms on withdrawal of therapy.[7-9] FEV_1 is endorsed by the National Asthma Education and Prevention Program as an important means for grading asthma severity.[10] Therefore, determination of factors influencing longitudinal measures of lung function, including FEV_1, in childhood asthma has clinical and prognostic significance.

In identifying factors influencing FEV_1 over time, several objective measures of pulmonary function, including baseline level of lung function, airway responsiveness, and bronchodilation, have been independently evaluated.[11] In general, levels of FEV_1 tend to track over time with lower basal levels of FEV_1 predicting lower FEV_1 at subsequent time points.[4,12-15] Greater airway hyperresponsiveness, measured by PC_{20} or similar measure, has also been consistently associated with subsequent decrements in FEV_1.[4,16-18] Studies of the relationship of basal bronchodilator response to subsequent measurements of FEV_1 have produced conflicting results, however, with some studies associating high bronchodilator response with relative improvement[19,20] and others with subsequent decrements in FEV_1.[21] Of concern, because bronchodilator response and airway responsiveness are tightly linked to baseline FEV_1, associations noted with these measures of airway tone may actually be a proxy for associations with FEV_1. To date, no longitudinal study of childhood asthma has focused on the simultaneous evaluation of all 3 of these correlated objective measures as predictors of future lung function.

We hypothesized that baseline bronchodilator response, airway responsiveness, and level of lung function would each independently predict improved lung function over time in patients with asthma as children. We tested this hypothesis in the subjects participating in the Childhood Asthma Management Program (CAMP). Incorporating all 3 predictors into the same analytic model allows assessment of the association of each predictor over and above the other 2, addressing the concern about the correlation of measures of airway tone with basal level of lung function. Because there is a paucity of information regarding its association with subsequent lung function in children, we focused on bronchodilator response as a predictor of primary interest. In addition, because biological interactions between β-agonist (which mediate bronchodilator responsiveness) and glucocorticoid pathways exist,[22,23] we hypothesized that the association of bronchodilator response with subsequent lung growth would be enhanced in children taking inhaled corticosteroids.

METHODS

Study population

The CAMP was a multicenter, randomized, double-blind clinical trial testing the safety and efficacy of inhaled budesonide or nedocromil each versus placebo over a period of a mean 4.3 years. Trial design, methodology, and primary clinical outcome results have been published.[24,25] Each patient's parent or guardian signed a consent statement, with each child providing assent. Institutional Review Board approval was obtained for all participating CAMP centers and the data coordinating center. Entry criteria included asthma symptoms and/or medication use for ≥6 months in the previous year and airway responsiveness with a $PC_{20} \leq 12.5$ mg/mL to methacholine. A 6-week screening period that included therapy with only as-needed albuterol preceded randomization. The children had mild-to-moderate asthma, as defined by the presence of symptoms or use of an inhaled bronchodilator as least twice weekly or by the use of daily medication for asthma.[25] Visits with spirometry occurred at randomization, 2 and 4 months after randomization, and every 4 months thereafter. Methacholine studies were performed during the screening period, at 8 months, then yearly. Bronchodilator response to albuterol was assessed at randomization and all subsequent visits in which methacholine was not administered. Adherence to therapy was measured biweekly via use of diary cards.[24,25]

Pulmonary function testing

Spirometry and methacholine testing were performed at least 4 hours after use of short-acting bronchodilators and 24 hours after use of long-acting bronchodilators.[24] At least 3 maneuvers meeting American Thoracic Society standards were required, with at least 2 reproducible (FEV_1 and forced vital capacity [FVC] within 5% of best) maneuvers required for each test. Equations used to predict average values of lung function measures for age, sex, and height were race-corrected.[26,27] Postbronchodilator values were obtained at least 15 minutes after administration of 2 puffs of albuterol (90 μg/puff). Airway responsiveness was performed by standardized procedures.[24]

Measures

The primary outcome was prebronchodilator FEV_1 as a percent predicted (FEV_1%). Other outcomes included prebronchodilator FVC as a percent of predicted and FEV_1/FVC ratio. In contrast with the primary clinical trial,[25] we focused on prebronchodilator measurements, because these measurements have been the standard for other natural history[4,12-15] and clinical trial[28,29] studies of asthma in children. Each was measured as an absolute value at the 4-year follow-up visit (primary analytic outcome) and as a percent change from baseline.

Our predictors included bronchodilator response (BD) and prebronchodilator FEV_1% at randomization, as well as PC_{20} values obtained during screening. BD was calculated by using raw values of FEV_1 via the following equation:

$$BD = 100 * (\text{postbronchodilator } FEV_1 - \text{prebronchodilator } FEV_1) / \text{prebronchodilator } FEV_1$$

PC_{20} values were natural log–transformed ($lnPC_{20}$). The specific baseline lung function measure used (ie, FEV_1, FVC, or FEV_1/FVC) in a given analysis corresponded to the comparable 4-year outcomes.