Factors associated with asthma exacerbations during a long-term clinical trial of controller medications in children

Ronina A. Covar, MD,[a] Stanley J. Szefler, MD,[a] Robert S. Zeiger, MD, PhD,[b] Christine A. Sorkness, PharmD,[c] Mark Moss, MD,[c] David T. Mauger, PhD,[d] Susan J. Boehmer, PhD,[d] Robert C. Strunk, MD,[e] Fernando D. Martinez, MD,[f] and Lynn M. Taussig, MD,[a] for the Childhood Asthma Research and Education Network *Denver, Colo, San Diego, Calif, Madison, Wis, Tucson, Ariz, St Louis, Mo, and Hershey, Pa*

Background: Asthma exacerbations are a common cause of critical illness in children.
Objective: To determine factors associated with exacerbations in children with persistent asthma.
Methods: Regression modeling was used to identify historical, phenotypic, treatment, and time-dependent factors associated with the occurrence of exacerbations, defined by need for oral corticosteroids or emergency or hospital care in the 48-week Pediatric Asthma Controller Trial study. Children age 6 to 14 years with mild-to-moderate persistent asthma were randomized to receive either fluticasone propionate 100 μg twice daily (FP monotherapy), combination fluticasone 100 μg AM and salmeterol twice daily, or montelukast 5 mg once daily.
Results: Of the 285 participants randomized, 48% had 231 exacerbations. Using a multivariate analysis, which included numerous demographic, pulmonary, and inflammatory parameters, only a history of an asthma exacerbation requiring a systemic corticosteroid in the past year (odds ratio [OR], 2.10; $P < .001$) was associated with a subsequent exacerbation during the trial. During the trial, treatment with montelukast versus FP monotherapy (OR, 2.00; $P = .005$), season (spring, fall, or winter vs summer; $P \leq .001$), and average seasonal 5% reduction in AM peak expiratory flow (OR, 1.21; $P = .01$) were each associated with exacerbations. Changes in worsening of symptoms, β-agonist use, and low peak expiratory flow track together before an exacerbation, but have poor positive predictive value of exacerbation.
Conclusion: Children with mild-to-moderate persistent asthma with previous exacerbations are more likely to have a repeat exacerbation despite controller treatment. Inhaled corticosteroids are superior to montelukast at modifying the exacerbation risk. Available physiologic measures and biomarkers and diary card tracking are not reliable predictors of asthma exacerbations. (J Allergy Clin Immunol 2008;122:741-7.)

Key words: *Airway inflammation, asthma, bronchial hyperresponsiveness, childhood asthma, exacerbations*

The natural course of asthma includes episodic deterioration (exacerbations) that can result in missed school days, missed workdays by parents, urgent care or emergency department (ED) visit, hospitalizations, and mortality. In the context of a multicenter trial, children and adults with mild persistent asthma of recent onset were found to be at risk for a severe exacerbation at a 3-year cumulative prevalence of 6.5% and a yearly rate of systemic corticosteroid use of 0.21 per patient.[1] Exacerbations occur despite maintenance use of inhaled corticosteroids, as noted in the 4.3-year Childhood Asthma Management Program clinical trial, in which prednisone use occurred at a rate of 0.70 per patient/year even in a treatment group receiving inhaled corticosteroid, although the rate was 43% less than the placebo group.[2] Exacerbations represent a distinct component of patient-reported health status[3] and one of the major challenges to prevent. Therefore, it is essential to understand the factors that correlate with exacerbations.

The Childhood Asthma Research and Education Network's 1-year Pediatric Asthma Controller Trial (PACT), evaluated the efficacy and safety of 3 controlled treatment regimens in achieving the best asthma control in children with persistent asthma of mild-moderate severity.[4] During the run-in, participants enrolled in the study had minimal or no significant airflow limitation on the basis of FEV_1 percent predicted, moderate-to-severe bronchial

From [a]the Department of Pediatrics, National Jewish Medical and Research Center and University of Colorado Health Sciences Center, Denver; [b]the Department of Pediatrics, University of California San Diego, and the Department of Allergy, Kaiser Permanente, San Diego, [c]the Clinical Science Center, University of Wisconsin; the Department of Pediatrics, University of California-San Diego; [d]the Department of Public Health Sciences, Pennsylvania State University; [e]the Department of Pediatrics, Washington University, St Louis; and [f]the Arizona Respiratory Center, University of Arizona.

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Reprint requests: Ronina A. Covar, MD, National Jewish Medical and Research Center, 1400 Jackson Street, Denver, CO 80206. E-mail: covarr@njc.org.

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Abbreviations used
AROCC: Area under the receiver operating characteristic curve
ED: Emergency department
eNO: Exhaled nitric oxide
OR: Odds ratio
PACT: Pediatric Asthma Controller Trial
PEF: Peak expiratory flow
ROC: Receiver operating characteristic

responsiveness to methacholine, modest exhaled nitric oxide (eNO) concentrations, and relatively good asthma control on the basis of the Asthma Control Questionnaire score. PACT provided the opportunity to determine the physiologic, biologic, and temporal variables associated with asthma exacerbations in children with mild-to-moderate persistent asthma.

METHODS

Details of the PACT study and its procedures have been reported[4] and are briefly summarized. PACT was a multicenter 48-week randomized, double-blind, placebo-controlled, double-dummy, parallel-group study of 285 children 6 to 14 years of age with documented mild-moderate persistent asthma, screening FEV_1 $\geq$80% predicted, and methacholine reactivity. Treatments compared were fluticasone propionate 100 μg twice daily (FP monotherapy), FP 100 μg/salmeterol 50 μg in the morning and salmeterol 50 μg in the evening (PACT combination), and montelukast 5 mg in the evening. Spirometric lung function tests (including maximum bronchodilator reversibility), methacholine provocation challenge, and eNO and urinary leukotriene E_4 measurements were performed during each study visit at baseline and serially. Total serum IgE level, peripheral eosinophil count, and serum eosinophil cationic protein were obtained at baseline. Electronic peak expiratory flow (PEF) measurements (AM1; Jaeger-Toenies GmbH, Hoechburg, Germany), asthma symptom scores, and albuterol use were recorded manually in diaries twice daily. Adherence to inhaled medication was assessed as detailed elsewhere.[4]

The Institutional Review Board of the 5 Childhood Asthma Research and Education clinical centers and the Data Coordinating Center approved the study. Parents/guardians provided informed consent, with verbal assent given by children less than 7 years of age, and written assent from older children.

An asthma exacerbation was defined for this analysis as the development of acute asthma requiring systemic corticosteroids or emergency care (ED visit or hospitalization). This is a broader definition than was used for the primary analysis in which exacerbations did not include emergency care not associated with a prednisone course.[4] The resulting inclusion of 2 participants who went to the ED but did not receive prednisone did not affect the results found in this cohort with a low rate of emergency care use. Initiation of oral prednisone therapy was based on specific guidelines or on physician discretion.[4] The guidelines for initiating a prednisone course were use of >12 puffs albuterol in 24 hours (excluding preventive use before exercise) for diary card symptom code of 3 or PEF less than 70% of personal best before each albuterol use; diary symptom code of 3 (the most severe code) for $\geq$48 hours or longer; or PEF dropped to less than 50% of personal best despite albuterol treatment or physician discretion.[4]

Statistical analysis

Regression modeling was used to investigate associations between the occurrence of exacerbations and characteristics before randomization, treatment assignment, and time-dependent factors. A longitudinal data framework was constructed whereby the calendar year was divided into 4 seasons: June to August (summer), September to November (fall), December to February (winter), and March to May (spring). In this way, each participant contributed 4 data points to the analysis, 1 from each season. The response variable in the regression models was the presence or absence of an exacerbation during each season. The longitudinal independent variables in the regression models were defined as changes from baseline. Measurements that were obtained on a daily basis (eg, morning and evening PEF and PEF variability) were summarized for each participant as seasonal averages and defined as percentage decrease from baseline (2-week run-in period average) to standardize subjects relative to their pretreatment levels. For example, if a child's baseline PEF was 300 liters/min and his average PEF from June through August was 270 liters/min, then his summer PEF decrease from baseline would be 10%. The eNO measurements taken at clinic visits were also summarized as seasonal averages over the visits that occurred during that season.

Logistic regression analysis was then applied by using the generalized estimating equations approach to account for statistical dependence induced by the longitudinal nature of the data. A structured modeling building algorithm was used in this exploratory analysis. Univariate regression models including each of the baseline and seasonal measures were first used to narrow the list of covariates (statistically significant at $P < .05$) to be incorporated into the final multivariate model.

It is important to note that exacerbations could occur at any point during a given season. If an exacerbation occurred near the end of the season, then the data values for the independent variables were made up mainly of information collected before the exacerbation. However, if an exacerbation occurred near the beginning of the season, then the data values for the independent variables were made up mainly of information collected after the exacerbation. Thus, the longitudinal variables represent circumstances that were temporally near, but not necessarily preceding, exacerbations, and the results of the regression model should be interpreted as indications of associations with, rather than predictions of, exacerbations. Distinct exacerbations were defined as those occurring at least 6 days apart. There were 5 exacerbations that occurred within 2 weeks of the previous and 19 that occurred within 4 weeks of the previous. However, only 4 of those had any effect on the results because of the way our model is defined. As a result, the sensitivity analysis revealed that it did not make any difference to the results of our model. Twenty-five percent of second and third exacerbations occurred within 35 days of the previous and 50% within 67 days.

To explore the predictive value of daily diary data, an analysis focused on changes in symptoms, bronchodilator rescue use, and PEF immediately preceding exacerbations was also performed. Asthma symptoms, including cough and wheeze, use of albuterol for rescue, and PEF percent of personal best were examined alone and in combination. These variables were chosen because they were used to guide the subject's asthma action plan during the study. Four separate analyses were performed to assess predictive value for imminent exacerbations: 3 days before, 2 days before, the day before, and the day of initiation of corticosteroid or ED visit. All days more than 2 weeks before, or 2 weeks after, exacerbations were considered to be not associated with exacerbations and negative days. In each analysis, there was only 1 positive day for each exacerbation (ie, 3, 2, 1 or 0 days before to initiation). Separate receiver operating characteristic (ROC) curves of the various signals were plotted for each positive and area under the ROC curve (AROCC) calculated. AROCC can be interpreted as the probability that a randomly selected positive day will have a worse value (higher symptoms/rescue use or lower PEF) than a randomly selected negative day. The best possible AROCC, 1.0, indicates a perfect signal that is always present on a positive day and never present on a negative day. The worst possible AROCC, 0.5, corresponds to a coin-flip signal that is just as likely to be present on a positive day as on a negative day.

RESULTS

A total of 231 asthma exacerbations occurred in 48% of the participants during the course of the treatment phase. Twenty-two percent (n = 64) had 2 or more exacerbations (Fig 1). Of the exacerbations, 74 (53%), 35 (26%), and 29 (21%) were first, second, and third exacerbations, respectively. The mean ± SD (median) time to the first exacerbation was 127 ± 103 (99) days.

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