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Predictors of asthma exacerbation among patients with poorly controlled asthma despite inhaled corticosteroid treatment

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ABSTRACT

Background: Asthma exacerbations are associated with decreased quality of life and increased health care usage. Identification of characteristics that predict increased risk of future exacerbations in patients with suboptimal control of asthma could guide treatment decisions.
Objective: To examine patient characteristics associated with risk of asthma exacerbations in patients with uncontrolled persistent asthma.
Methods: A retrospective analysis of adults and children with inadequately controlled asthma despite asthma controller therapy and enrolled in 2 randomized trials was conducted. Baseline characteristics of subjects who experienced an asthma exacerbation during the treatment period were compared with those of subjects who did not experience an exacerbation.
Results: Of 718 subjects (402 adults and 295 children), 108 adults (27%) and 110 children (37%) experienced an asthma exacerbation during the study period. Unscheduled health care visits for asthma or use of oral corticosteroids in the previous year were significantly associated with asthma exacerbation during the study period ($P < .01$). Adult subjects who experienced an exacerbation had significantly lower forced expiratory volume in 1 second compared with those who did not (2.3 vs 2.5 L, respectively, $P = .02$). Children who experienced an exacerbation had lower baseline pre- and post-bronchodilator ratios of forced expiratory volume in 1 second to forced vital capacity (77% vs 81%, $P < .01$; 82% vs 86%, $P < .001$, respectively). Symptom scores on validated questionnaires were significantly worse in adults but not in children who developed an exacerbation.
Conclusion: Spirometric measurements can help identify adults and children at increased risk for asthma exacerbation. Symptom scores could be helpful in identifying adults who are at high risk for exacerbations but could be less helpful in children.

Introduction

Asthma currently affects 18.7 million adults (8%) and 6.8 million children (9.3%) in the United States and as many as 300 million people worldwide.[1] Most patients being treated for asthma have poor asthma control.[2–4] In most patients with uncontrolled asthma, intensification of treatment is successful in achieving control.[5] However, poor adherence to prescribed medications and unwillingness of patients to increase controller therapy because of fears about adverse effects are major contributors to poor asthma control.[6] In 2011, more than half of patients with asthma had an asthma attack.[1] Asthma exacerbations are potentially life-threatening events and are associated with decreased quality of life and increased health care usage. Health care costs for asthma are largely related to care for asthma exacerbations.[7–9] Risk factors for asthma exacerbations in patients

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with well-controlled asthma have been identified and include previous asthma exacerbation, use of bronchodilator therapy, decreased pulmonary function measurements, and need for larger amounts of controller therapy.[10–14] Relatively few studies have identified risk factors in patients with poorly controlled asthma.[10,15] Sputum eosinophil count has been found to be predictive of asthma exacerbations, but measurements are not practical in the clinic setting.[16] Identification of characteristics that predict increased risk of future exacerbations in patients with suboptimal control of asthma could be helpful to patients and providers in making asthma treatment decisions requiring step-up of asthma treatment.

The present retrospective analysis used data previously collected from a large group of well-characterized children and adults during 2 randomized, placebo-controlled studies of proton pump inhibition in the treatment of asthma[17,18] conducted by the multicenter Asthma Clinical Research Centers. Those trials showed that the addition of a proton pump inhibitor (PPI) did not affect asthma outcomes. The goal of the present study was to determine prevalence and risk factors for asthma exacerbations in adults and children with uncontrolled asthma despite use of inhaled corticosteroids (ICSs) at baseline.

Methods

Study Population

The Study of Acid Reflux in Children with Asthma (SARCA) and the Study of Acid Reflux in Adults with Asthma (SARA) were multicenter, randomized, double-blinded, placebo-controlled trials of the effectiveness of lansoprazole (SARCA) and esomeprazole (SARA) in the treatment of children and adults, respectively, with inadequately controlled asthma despite therapy with moderate or high doses of ICSs with or without long-acting β-agonists (LABAs). SARCA was conducted from 2007 through 2011 and SARA was conducted from 2004 through 2008 at 19 American Lung Association Asthma Clinical Research Centers. Details of the study design of SARA and SARCA are described elsewhere.[17,18] All subjects or guardians provided written informed consent that was approved by the local institutional review board. The 2 studies were registered at clinicaltrials.gov (NCT00069823 and NCT00442013). Patients were eligible if they were 6 to 17 years of age (SARCA) or at least 18 years old (SARA), had physician-diagnosed asthma with the diagnosis supported by an increase of at least 12% in post-bronchodilator forced expiratory volume in 1 second (FEV_1) or a positive methacholine challenge test reaction, were being treated with inhaled glucocorticoids ($\geq$176 μg/d of fluticasone or equivalent for children and $\geq$400 μg of fluticasone or equivalent for adults), and had no change in controller therapy for at least 8 weeks before enrollment. Eligible subjects also demonstrated poor asthma control defined as more than 1 acute episode of asthma requiring unscheduled medical care in the previous year or a score of at least 1.25 for children and 1.5 for adults on the Juniper Asthma Control Questionnaire (ACQ) at the screening visit. Children were excluded if their FEV_1 was lower than 60% predicted; adults with FEV_1 lower than 50% predicted were excluded. Participants were excluded if they smoked cigarettes within the previous 6 months or had a history of at least 10 pack-years of smoking. Subjects were randomized to treatment with a PPI or matching placebo for a 24-week treatment period during which they continued their previous asthma controller therapy. Daily morning peak flow was measured and recorded, as were asthma symptoms and health care usage. Baseline asthma control was measured using the Asthma Control Test[19] in children and the ACQ in children and adults.[20] The Asthma Symptom Utility Index (ASUI)[21] and the Juniper Mini-Asthma Quality of Life Questionnaire (AQLQ)[22] also were collected at baseline. Participants returned to the study center for assessments of outcome measurements every 4 weeks, at which time information related to asthma exacerbations was collected.

Definition of Asthma Exacerbation

In the 2 studies, an asthma exacerbation was defined as a requirement for oral corticosteroids or an urgent health care visit for asthma symptoms.

Statistical Analyses

Child participants (SARCA) and adult participants (SARA) were analyzed separately. Each population was divided into the following 2 groups: participants with exacerbation (at least once) and participants without exacerbation, regardless of treatment group. Descriptive statistics (mean, 95% confident interval, count, and proportion) were used to summarize baseline demographics. Continuous measurements (eg, FEV_1, ACQ scores) were compared between participants with and without an exacerbation using the Wilcoxon rank-sum test because not all measurements were normally distributed. The χ^2 tests were used for categorical variables to test for statistically significant differences. For categorical variables, Fisher tests were performed. P values less than .05 (2-sided) were considered to indicate statistical significance. The statistical package SAS 9.3 (SAS Institute, Cary, North Carolina) was used to perform all analyses.

Results

Study Population

Three hundred six children were enrolled in SARCA and 412 adults were enrolled in SARA. Data from 295 children and 402 adults who had information related to asthma exacerbations were included in the analyses. For children enrolled in SARCA, mean age was 11 years, age at asthma onset was 3 to 4 years, 50% were black, and mean pre-bronchodilator FEV_1 was 92% of predicted. Sixty-seven percent of participants reported use of oral corticosteroids in the previous year.[17] Fifty-nine percent of children were being treated with combination inhaled glucocorticoids and LABA, with the remaining children being treated with ICS alone. For adults enrolled in the SARA study, mean age was 42 years, age at asthma onset was 17 years, approximately 50% had a body mass index of at least 30 kg/m^2, and mean pre-bronchodilator FEV_1 was approximately 77% predicted.[18] Approximately half the adult patients reported use of oral corticosteroids in the previous year. Eighty-one percent of adults were being treated with ICS and LABA, and 19% were being treated with ICS alone. Because use of PPIs was not shown to lead to a difference in incidence of asthma exacerbations in either age group, the placebo and active treatment groups were combined for analysis.

Baseline Characteristics Associated with Exacerbation

Children

One hundred ten of 295 children (37%) enrolled in SARCA experienced an asthma exacerbation during the 24-week treatment period (Table 1). Asthma exacerbation in children was significantly associated with younger age ($P = .04$) but not with sex, race, or body mass index. Unscheduled health care visits for asthma or use of oral corticosteroids in the previous year were significantly associated with asthma exacerbation during the subsequent study period. Eighty-three percent of children who developed an exacerbation had an unscheduled visit for asthma in the previous year compared with 69% of children without an exacerbation ($P < .01$). Eighty percent of children who developed an exacerbation during the treatment period had been treated with oral corticosteroids in the previous year compared with 61% of children who did not develop an exacerbation ($P < .001$). Of