Original Article

Asthma Exacerbation Rates in Adults Are Unchanged Over a 5-Year Period Despite High-Intensity Therapy

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What is already known about this topic? Prior asthma exacerbations increase the short-term risk of subsequent asthma exacerbations.

What does this article add to our knowledge? For patients on high-intensity pharmacologic treatment, the risk of exacerbations does not change over time, and prior exacerbations increase the risk of subsequent asthma exacerbations over a several-year period, in spite of therapy.

How does this study impact current management guidelines? New therapeutic options are needed for patients who experience asthma exacerbations in spite of high-intensity pharmacologic treatment.

BACKGROUND: Few data exist regarding the natural history of asthma exacerbations over time.
OBJECTIVE: To evaluate the frequency and risk factors of asthma exacerbation occurrence over a 5-year period in a large cohort of adult patients with persistent asthma.
METHODS: Health insurance claims from the Truven Health MarketScan database were analyzed for 2543 patients who had full medical and drug claims for years 2006 to 2011, did not have co-occurring chronic obstructive pulmonary disease in the index year (2006), and were treated with high-dose inhaled corticosteroids and long-acting β2-agonists for at least 120 days ("high intensity" therapy) in the index year. A retrospective analysis was conducted to assess the pattern of severe exacerbations (encounter with health care system and steroid burst) over time and their associations with the other measures of health status.
RESULTS: Despite the use of high-intensity asthma therapy, there was only a small decrease in total asthma exacerbations over time, but no significant time trend for asthma hospitalizations. An exacerbation in the prior year increased the risk for exacerbations almost 8-fold, (odds ratio 7.8 [95% CI, 7.1-8.6]). A 50% increase in exacerbation risk (odds ratio 1.5 [95% CI, 1.4-1.6]) was associated with continued high-intensity treatment for the duration of the study. Patients with encounters of chronic obstructive pulmonary disease after the index year were at 60% increased risk of an exacerbation.
CONCLUSIONS: This study showed that exacerbation rates for patients with asthma in a real-world setting remained relatively constant over time, and continuous high treatment intensity was not associated with a substantially lower risk of exacerbations. **(J Allergy Clin Immunol Pract 2014;2:570-4)**

Key words: *Asthma; Exacerbations; Natural history; Inhaled corticosteroids; Long-acting β-agonists*

Asthma affects 18.8 million people in the United States[1] and imposes a substantial humanistic and economic burden on patients and society. Asthma exacerbations have particularly important adverse effects on the quality of life of people with asthma, and exacerbations account for the largest proportion of the nondrug direct costs of asthma care.[2] Risk factors for asthma exacerbations, such as prior exacerbations[3,4] and asthma severity,[4] have been defined but generally over no more than a 1-year period of follow-up. Few data exist regarding the year-to-year occurrence of asthma exacerbations and risk factors for their occurrence over longer time periods. The purpose of this study was to evaluate the natural history and risk factors of asthma exacerbation that occur over a 5-year period in a large cohort of patients with persistent asthma on high-intensity (HI) asthma treatment. Asthma severity in this study was based on treatment intensity, as suggested by current national asthma guidelines for patients on controller therapy.[5]

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Abbreviations used
COPD- Chronic obstructive pulmonary disease
ED- Emergency department
HI- High-intensity asthma treatment
CD-9- International Classification of Diseases, Ninth Revision
ICS- Inhaled corticosteroid
LABA- Long-acting β-agonist
OR- Odds ratio

METHODS

Data source

This study used the Truven Health MarketScan Commercial Claims and Encounters research database (Ann Arbor, Mich), composed of health insurance claims from more than 200 large employers and more than 100 health plans across the United States that provide private health care coverage. The database covers more than 78 million patients from the working population, age 65 years old and younger, and their dependents. This database reflects the real world of treatment patterns by using patient encounters with the health care system from all providers of care, including inpatient, outpatient, emergency department (ED), office visit, and pharmacies at the patient level. This database is fully Health Insurance Portability and Accountability Act compliant.

Study design and population

This study was a retrospective cohort analysis. Study subjects were identified by a claim for a primary asthma diagnosis (International Classification of Diseases, Ninth Revision [ICD-9] 493.x) during the index year (2006). To be included in this study, at index, patients needed to be at least 18 years of age, have at least 120 days filled of high-dose inhaled corticosteroid (ICS) and long-acting β-agonist (LABA) medication (defined as HI asthma treatment), not have a diagnosis of chronic obstructive pulmonary disease (COPD), and be continuously enrolled with both medical and drug coverage for the entire study period from 2006 to 2011 or to death. Drug usage (ie, filling at least 1 prescription for any medication, not necessarily asthma related) during each calendar year (2006-2011 or death) also was required to confirm the use of the patient's drug coverage. As defined in the Healthcare Effectiveness Data and Information Set (HEDIS) measures,[6] COPD was defined by using the following ICD-9 diagnosis codes: 491.2x, 492.x, 493.2x, 496, 506.4, 518.1, and 518.2. High-dose ICS thresholds were defined by using the National Institutes of Health Severe Asthma Research Program[7] definitions (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). The daily dose calculation was based on the method by Lafeuille et al.[8] Due to the nature of claims databases, drug information is based on prescriptions filled, not prescriptions used or prescribed.

Exacerbations

Exacerbations were defined as an oral corticosteroid prescription within 7 days of a hospitalization, emergency department (ED) visit, outpatient encounter or physician office visit with a diagnosis of asthma (primary ICD-9 code of 493 or secondary ICD-9 code of 493 with other respiratory primary diagnosis). The proportion of patients and the rate (exacerbations/subject per year) of total exacerbations as well as those exacerbations that led to a hospitalization, were calculated for years 2007 to 2011.

Analysis

Regression models were used to assess whether there was a time trend for exacerbations. The regressions also were used to assess the association between exacerbations over time and previous exacerbations, HI asthma treatment over the entire follow-up period (in addition to the index year), COPD status, age, and sex over the 5-year period of the study (2007-2011). Previous exacerbations were modeled as a time-varying covariate; all other covariates were modeled as constant over time: HI asthma treatment (at least 120 days filled of high-dose ICS and LABA medication per year) was assessed over the entire 5-year period, age was set at index, and patients were considered positive for COPD if they had a diagnosis code at any time during the study because the onset of COPD may be several years before diagnosis. Some potential exacerbation risk factors were not available in the data set, such as lung function, smoking status, race, and socioeconomic status. In all the models, 2 different outcomes were assessed: any exacerbation and asthma hospitalization. Regression analysis was conducted by using generalized estimating equations to account for clustering within patients over time. An autoregressive correlation matrix with robust errors using a binomial logit-link structure was used for all generalized estimating equation models, except for analyses of exacerbation rates, which used a Poisson log-link structure. To assess whether these relationships were the same for patients who were continuously treated with HI asthma treatment, all analyses were repeated after restricting the population to those who were treated with HI asthma treatment for at least 120 days per year in all 5 years.

An analysis also was conducted to assess the impact over time of frequent exacerbator status in year 1. Frequent exacerbator status was modeled as 0, 1, and 2 or more exacerbations, either any exacerbation or exacerbations that required a hospitalization or an ED visit. Frequent exacerbator status was evaluated alone and, when adjusting for time, HI asthma treatment, age, and sex. The generalized estimating equation regressions for the frequent exacerbator analyses used the same framework as the other regressions, except that these regressions analyzed the years 2008 to 2011 because 2007 was used to assess exacerbator status. Regression analyses were conducted with Stata IC version 12.1 (2011) (College Station, Texas), and data management was conducted by using SAS version 9.1.3 (SAS Institute Inc, Cary NC).

RESULTS

Baseline characteristics and medications received

Baseline demographics and patient characteristics are displayed in Table I. This study identified 2543 patients with asthma who received HI asthma treatment without a diagnosis of COPD during the index year. The average age of the patients was 48 years, and 63% were women. At index, 97% of the patients were on ICS plus LABA combination therapy, and the remaining 3% were on separate ICS and LABA products. During the index year of 2006, 41% of patients had an asthma exacerbation, with 2% of patients having an asthma exacerbation that resulted in a hospitalization. Between 2007 and 2011, there was a marked reduction in the percentage of patients who received each type of most asthma maintenance medications, including ICS, LABA, leukotriene modifiers, and theophylline (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). However, 725 patients (28.5%) received HI treatment for the entire study period.