Original Article

Asthma Exacerbations Associated with Lung Function Decline in Patients with Severe Eosinophilic Asthma

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What is already known about this topic? While there are some reports investigating the decline in lung function associated with asthma exacerbations, limited data exist in patients with severe eosinophilic asthma.

What does this article add to our knowledge? This study provides further evidence of the impact of frequent asthma exacerbations and related decline in lung function in patients with severe eosinophilic asthma.

How does this study impact current management guidelines? Preventing exacerbations should be one of the most important treatment goals and therefore disease management approaches, including step-down of controller therapy, should be carefully considered in patients with severe disease who are prone to exacerbations.

BACKGROUND: Limited data describe the association between the frequency of asthma exacerbations and the decline in lung function in severe asthma.
OBJECTIVE: To determine whether asthma exacerbations are associated with enhanced decline in lung function.
METHODS: Changes in lung function were analyzed retrospectively using data from the DREAM and MENSA studies of mepolizumab intervention in patients with severe asthma. Patients were either nonsmokers or former smokers. A linear regression model was used to analyze the relationship between the number of exacerbations and decline in FEV_1 across treatment groups.
RESULTS: In a combined post hoc analysis, 57% (n = 572) of patients had no exacerbations and experienced an improvement in postbronchodilator FEV_1 of 143 mL. In contrast, in patients who experienced 3 or more exacerbations, there was a decrease in postbronchodilator FEV_1 of 77 mL in the combined analysis. The linear modeling analysis estimated that for each exacerbation seen during the observational period, there was a decrease of 50 mL in FEV_1 ($P < .001$).
CONCLUSIONS: A direct relationship between the number of exacerbations in patients with severe eosinophilic asthma and decline in lung function was observed. Repeated exacerbations may be associated with accelerated loss of lung function. **(J Allergy Clin Immunol Pract 2018;■:■-■)**

Key words: *Severe asthma; Exacerbations; Decline in lung function; FEV_1*

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Conflicts of interest: The authors are employees of GlaxoSmithKline (GSK) and hold stocks/share options in GSK.

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INTRODUCTION

Asthma is characterized by the presence of reversible airflow obstruction[1]; however, as disease severity increases, structural changes in the airways can contribute to irreversible airflow obstruction. Accelerated loss of lung function over time has been reported in longitudinal prospective and retrospective studies in patients with asthma.[2-5] However, accelerated decline in lung function does not occur in all patients.[6] Risk factors associated with an accelerated loss of lung function include age, male sex, smoking, longer duration of disease, black race, airway eosinophils, and asthma exacerbations.[5-10] The frequency of acute severe exacerbations has also been associated with a more rapid decline in FEV_1 in patients with chronic obstructive pulmonary disease (COPD).[11,12]

The prevention of structural airway wall remodeling is highly desirable in the management of asthma, as these changes lead to

Abbreviations used
COPD- Chronic obstructive pulmonary disease
FVC- Forced vital capacity
OCS- Oral corticosteroid

irreversible airflow obstruction despite prolonged steroid therapy.[10] Recurrent asthma exacerbations are a significant problem in patients with asthma, particularly in patients with severe eosinophilic asthma.[8,13-16] We hypothesized that the enhanced tendency for disease exacerbation in uncontrolled eosinophilic airway inflammation leads to progressive airway remodeling with consequent loss of lung function. Pulmonary function testing, which has been used in clinical settings and epidemiological studies, can link changes in mechanical properties of airways with airway remodeling.[17] The Dose Ranging Efficacy and Safety with Mepolizumab (DREAM) and Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) studies were multicenter, randomized, double-blind, placebo-controlled trials designed to assess the effect of mepolizumab on exacerbation frequency over 12 and 8 months, respectively.[14,15] These studies provide an opportunity to retrospectively assess in each study individually as well as combined whether exacerbations are associated with a loss of lung function.

METHODS

Study population

DREAM was a placebo-controlled randomized study using intravenous mepolizumab (75 mg, 250 mg, and 750 mg every 4 weeks) for 52 weeks. MENSA was a placebo-controlled double-dummy randomized study with subcutaneous (100 mg every 4 weeks) and intravenous mepolizumab (75 mg intravenous every 4 weeks) administration for 32 weeks (protocol 207348). The patients with severe asthma who participated in these studies were required to have evidence of 2 or more exacerbations requiring treatment with systemic corticosteroids in the previous 12 months despite current therapy and had direct or indirect evidence of eosinophilic inflammation. All patients had treatment requirements of at least 880 μg of inhaled fluticasone propionate equivalent per day with or without maintenance oral corticosteroids (OCSs) and required additional controller medication. Additional details are available in previous publications.[14,15] Participants provided written informed consent. The study protocols (DREAM: NCT01000506; MENSA: NCT01691521) were approved by local ethics committees.

Clinically significant exacerbations

Exacerbations were defined as worsening of asthma requiring use of systemic corticosteroids for 3 or more days and/or hospitalization and/or emergency department visit. In those on maintenance oral steroids, an exacerbation was defined as a doubling of oral steroid dose for at least 3 days and/or hospitalization and/or emergency department visit. Exacerbations were confirmed by objective changes that patients recorded daily in an electronic diary.

Lung function testing

Spirometry testing met the American Thoracic Society standards. The spirometer was calibrated in accordance with the manufacturer's instructions. FEV_1 and forced vital capacity (FVC) were measured at each corresponding visit. Spirometry was performed within 1 hour of the baseline visit. Patients were asked to withhold short-acting beta-2-agonists for 6 or more hours and long-acting beta-agonists for 12 or more hours before clinic visit. Predicted values were calculated using the Third National Health and Nutrition Examination Survey values with adjustments for ethnicity and race.[18] The maximum postbronchodilator procedure was used to conduct reversibility (up to 600 μg inhaled salbutamol).

Statistical analysis

The last pulmonary function measure that occurred at least 28 days after the most recent exacerbation was used in the analysis. This approach aimed to reduce the confounding effect of an acute exacerbation on lung function. The corresponding number of exacerbations before this last measurement of lung function was used in the analysis. A linear regression model was used to analyze the relationship between the number of exacerbations and decline in FEV_1 and FVC over the observational periods. The model for calculating the adjusted mean and linear trend in each study adjusted for covariates of exacerbation category (0, 1, 2, $\geq$3 exacerbations), treatment, baseline lung function, region, exacerbations in the year before the study (2, 3, $\geq$4) as an ordinal variable, baseline maintenance OCS (OCS vs no OCS), sex, age (as continuous variable), and log of baseline eosinophil count. Combined estimates were calculated using inverse variance weighted fixed-effects meta-analysis. The analysis allows for differences in lung function across treatment groups but assumed a common decline in lung function with each exacerbation. We also performed analysis for each treatment group separately instead of combined across treatment groups. A sensitivity analysis was conducted using the last pulmonary function measure that occurred at least 14 days after the most recent exacerbation (see this article's Online Repository at www.jaci-inpractice.org). All analyses were post hoc and were performed using SAS version 9 (SAS Institute, Cary, NC).

RESULTS

Population

A total of 1192 patients with severe asthma participated in these studies. The mean age of this patient population was 49 years, and they were predominantly women (60%). A total of 24% were former smokers (<10 pack-year history) and the rest of the patients never smoked. The mean duration of asthma was 20 years and 28% were on maintenance OCS for disease management. The mean rate of exacerbations in the previous year was 3.6. The prebronchodilator FEV_1 percent predicted was 60% and the mean FEV_1 reversibility was 26% (Table I).

The statistical analysis included a total of 1004 patients; 188 patients were excluded from analysis because of missing postbronchodilator lung function data or because of absence of any lung function measure occurring at least 28 days after an exacerbation. We also conducted a sensitivity analysis evaluating events occurring at least 14 days after an exacerbation. The results showed a similar effect as seen in events occurring at least 28 days after an exacerbation (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Table II describes the baseline characteristics on the basis of the number of exacerbations that occurred during the observational period for the population analyzed. Patients who experienced more than 1 exacerbation during the observation period had at baseline numerically lower FEV_1, higher use of maintenance OCS, and a higher level of uncontrolled disease as measured by the Asthma Control Questionnaire, compared with those with no exacerbations. Those who experienced more exacerbations during the studies had a greater exacerbation rate in the previous year. Blood