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Original Research

ASTHMA

Association Between Neutrophilic Airway Inflammation and Airflow Limitation in Adults With Asthma*

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Background: **There is debate about the mechanisms of persistent airflow limitation in patients with asthma. Chronic inflammation is assumed to be important, although there is limited and contradictory information about the relationship between airway inflammation and postbronchodilator FEV_1.**

Methods: **We have assessed the cross-sectional relationship between prebronchodilator and postbronchodilator FEV_1 and measures of airway inflammation after allowing for the effects of potential confounding factors. Multivariate analysis was performed on data collected from 1,197 consecutive patients with asthma seen at the respiratory outpatient clinic at Glenfield Hospital between 1997 and 2004. Relationships between induced sputum total neutrophil and differential eosinophil cell counts, and prebronchodilator and postbronchodilator lung function were examined.**

Results: **Sputum total neutrophil but not differential eosinophil count was associated with lower postbronchodilator FEV_1. Both differential eosinophil and total neutrophil count were associated with lower prebronchodilator FEV_1. These effects were independent after adjustment for age, smoking, ethnicity, asthma duration, and inhaled corticosteroid use. A 10-fold increase in neutrophil count was associated with a 92 mL reduction (95% confidence interval, 29 to 158; p = 0.007) in postbronchodilator FEV_1.**

Conclusions: **In this large heterogeneous population of adults with asthma, we have shown that prebronchodilator FEV_1 is associated with neutrophilic and eosinophilic airway inflammation, whereas sputum total neutrophil counts alone are associated with postbronchodilator FEV_1. This supports the hypothesis that neutrophilic airway inflammation has a role in the progression of persistent airflow limitation in asthma and raises the possibility that this progression and the development of COPD share a common mechanism.** ***(CHEST 2007; 132:1871–1875)***

Key words: asthma; eosinophil; induced sputum; lung function; neutrophil

Abbreviations: CI = confidence interval; ICS = inhaled corticosteroid; PC_{20} = provocative concentration of methacholine causing a 20% fall in FEV_1

Asthma has been associated with an increased rate of decline in lung function: in a 15-year follow-up study by Lange et al,[1] adults with asthma showed a greater decline in lung function than those without the disease, with an unadjusted loss of 38 mL/yr occurring in patients with asthma, compared to a loss of 22 mL/yr in control subjects. One goal of asthma management is to stop long-term respiratory disability by preventing this loss of lung function, so a clearer understanding of the mechanisms involved in the development of fixed airflow obstruction is important. Factors that have been associated with an increased rate of decline include smoking,[2] duration of asthma,[2] and absence of atopy.[3] Chronic airway inflammation is widely assumed to be important in the genesis of fixed airflow obstruction, although previous studies[4–7] examining the relationship between airway inflammation and postbronchodilator FEV_1 have produced conflicting results.

ten Brinke et al[7] showed that the only independent factor associated with persistent airflow limita-

tion was a differential sputum eosinophilia, whereas Woodruff et al[8] demonstrated that raised differential sputum eosinophil and neutrophil counts were both associated with a lower prebronchodilator FEV_1. One difficulty of studies of this kind is that definition of best FEV_1 is imprecise in a condition that is associated with variable airflow obstruction, although increasing study numbers might allow important relationships to become apparent. We set out to investigate the relationship between prebronchodilator and postbronchodilator FEV_1 and measurements of eosinophilic and neutrophilic airway inflammation in a large, well-characterized population of adults with asthma.

Materials and Methods

Subjects

A total of 1,197 consecutive patients seen in the respiratory outpatient clinic at Glenfield Hospital between November 1997 and March 2004 were included in the study. Glenfield Hospital is a secondary care facility covering a population of 1 million people of mixed ethnicity and social class. The main indications for referral for assessment of airway disease were diagnostic uncertainty and poor symptom control. Informed consent for the assessment of airway inflammation was obtained for all patients as part of the clinical assessment of airway disease, and the ethics committee from the University Hospitals of Leicester gave ethical approval for the study. All subjects had symptoms of asthma and objective evidence of airway hyperresponsiveness and/or variable airflow obstruction as demonstrated by one or more of the following: a provocative concentration of methacholine causing a $> 20\%$ fall in FEV_1 (PC_{20}) < 8 mg/mL; an increase in $FEV_1 \geq 15\%$ 20 min after inhalation of 200 μg of albuterol; or peak expiratory flow variability $> 20\%$ of mean based on peak expiratory flow recorded twice daily over a 2-week period. Methacholine challenge was not performed if FEV_1 was $< 70\%$ of predicted. In this situation, patients were included if they had a $> 15\%$ improvement in FEV_1 20 min after bronchodilator. Atopy was defined as a wheal 2 mm greater than control on skin-prick testing or specific IgE (Pharma CAP; ALK-Abelló; Madrid, Spain) to one or more of dust mite, grass, tree, cat, dog, or Aspergillus allergens. Smoking history was recorded as pack-years and was validated against other hospital or primary care records or exhaled carbon monoxide monitoring if there was doubt about its veracity.

Measurements

Spirometry was performed using a spirometer (Vitalograph; Vitalograph Ltd; Maids Moreton, UK) as the best of three consecutive readings within 100 mL, and skin-prick tests were performed using standard techniques.[9] Prebronchodilator and postbronchodilator measurements were recorded 20 min after the inhalation of 200 μg of albuterol via spacer. Induced sputum was obtained and processed as previously described.[10] Methacholine challenge was performed using a Wright nebulizer (Aerosol Medical Ltd; Colchester, UK) and the Juniper tidal breathing method.[11]

Protocol

At the first visit, patients underwent spirometry, methacholine challenge testing, sputum induction, skin-prick testing, and measurement of specific IgE to common aeroallergens; history of cigarette smoking and duration of symptoms were recorded. At the next visit, prebronchodilator and postbronchodilator FEV_1 values were recorded.

Analysis

Eosinophil counts were expressed as a percentage of nonsquamous cells because eosinophil differential counts are log-normally distributed.[10,12,13] Neutrophil counts were expressed as the total number of neutrophils per gram of sputum. Neutrophil counts were expressed in this way because sputum differential neutrophil counts increase with age,[14] have a biphasic distribution in our population, and because increases in neutrophilic airway inflammation are better reflected by the total neutrophil count rather than the differential.[15] Multiple independent regressions were used to identify predictors of postbronchodilator and prebronchodilator FEV_1. We also performed backward stepwise linear regression to further identify independent associations. Age, height, gender, and ethnic origin are known to be associated with these outcomes and were therefore included in the model. Total neutrophil counts and percentage eosinophil counts were log-transformed prior to analysis to fulfil the model assumption of normal distribution. Atopy and inhaled corticosteroid (ICS) use were considered potential confounders and were entered into the models as binary variables. Duration of asthma symptoms was also considered a possible cofactor and was entered as a continuous variable. All analysis was performed using statistical software (SPSS 10 for Windows; SPSS; Chicago, IL).

Results

Patient demographics are given in Table 1.

Postbronchodilator FEV_1

Postbronchodilator FEV_1 was significantly predicted by this model (Table 2) [$R^2 = 0.43$, $p < 0.001$]. ICS use was associated with a lower postbronchodilator FEV_1 by 223 mL on average (95% confidence

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