Original Article

Progression of Irreversible Airflow Limitation in Asthma: Correlation with Severe Exacerbations

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What is already known about this topic? Severe exacerbations of asthma have been proposed to induce airway structural changes leading to an accelerated decline in lung function. A reduced bronchodilator response has been used as a surrogate marker for airway remodeling in asthma.

What does this article add to our knowledge? The occurrence of severe asthma exacerbations is correlated with the progression of airflow limitation and reduction in airway reversibility that occurred over time.

How does this study impact current management guidelines? This study suggests that the prevention of asthma exacerbations could have a pivotal role in the attenuation of the long-term adverse consequences of structural and functional changes in the airways.

BACKGROUND: Severe exacerbations of asthma are periods of excess functional and pathological changes in the airways that have been proposed to induce airway remodeling.
OBJECTIVE: The objective of this study was to explore whether severe exacerbations are correlated with the decline in post-bronchodilator forced expiratory volume in 1 second (FEV_1) and loss of bronchodilator reversibility (BDR).
METHODS: We examined the changes in FEV_1 and BDR in 140 nonsmoking patients with well-controlled asthma at baseline and correlated these changes with the frequency of severe asthma exacerbations.
RESULTS: A 3-year follow-up assessment was completed in 128 patients. A total of 28 (21.9%) patients experienced at least 1 severe exacerbation with a mean rate of 0.16 $year^{-1}$. The exacerbation rate was significantly correlated with an annual rate of decline in FEV_1 ($\rho = 0.49$, $P < .0001$). Both patients with 1 exacerbation and those with 2 or more exacerbations had greater declines in FEV_1 than patients with no exacerbations (no exacerbation, 13.6 mL/year; 1 exacerbation, 41.3 mL/year; 2 or more exacerbations, 58.3 mL/year; $P < .01$ and $P < .0001$, respectively). The changes in BDR from baseline to the end of the study in patients who did or did not experience an exacerbation were −1.2% and 0.1%, respectively ($P < .0005$). The changes in BDR were significantly correlated with the annual rates of change in FEV_1 ($r = 0.40$, $P < .0001$).
CONCLUSION: The occurrence of severe exacerbations of asthma is correlated with the progression of irreversible airflow limitation over time. This suggests that asthma exacerbations could have the long-term adverse consequences of structural and functional changes in the airways. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;■:■-■)

Key words: *Airway inflammation; Airway remodeling; Airway reversibility; Bronchodilator; Lung function*

A subset of patients with asthma is known to have rapid loss of lung function despite steroid therapy.[1-4] There is a great need to define targets for attenuation of the progression of airway obstruction. Persistent airflow limitation is believed to be a consequence of structural and functional changes in the airways, possibly due to abnormal injury and repair responses of the airway tissues.[5,6] Severe exacerbations of asthma are periods of excess pathological and functional changes in the airways that have been proposed to induce airway remodeling.[7,8] Also, excessive bronchoconstriction often occurs during the exacerbations, and this mechanical stress may have the potential to induce structural changes in the airways.[9]

Structural and functional changes seen in asthmatic patients can include thickening of the basement membrane of the airway wall, formation of an elastic fiber network, angiogenesis, an

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Abbreviations used
ACT- Asthma Control Test
BDR- Bronchodilator reversibility
FeNO- Exhaled nitric oxide fraction
FEV_1- Forced expiratory volume in 1 second
FVC- Forced vital capacity
GINA- Global Initiative for Asthma
ICS- Inhaled corticosteroids

increase in airway smooth muscle (ASM) mass, and ASM dysfunction.[1] A reduced bronchodilator response (BDR) has been used as a surrogate marker for airway remodeling in asthma.[2,10-12] However, no prospective study has examined whether severe exacerbations are correlated with the decline in post-bronchodilator forced expiratory volume in 1 second (FEV_1) and reduction in airway reversibility in asthma.

The FLOAT (Factors affecting the Long-term Asthma Therapy) study is a 3-year, prospective, cohort investigation of patients with well-controlled asthma, which was undertaken to examine the factors associated with changes in asthma control and lung function. Asthma control, severe exacerbations, pre- and post-bronchodilator forced vital capacity (FVC), FEV_1, and exhaled nitric oxide fraction (FeNO) were surveyed during the study. The main results of the FLOAT trial have been reported previously.[13] The rate of change in FEV_1 among patients with controlled asthma was highly variable and the rapid decline in FEV_1 was associated with a loss of asthma control. We also found that the rapid decliners were more likely to be older, to have higher levels of FeNO, and to have had severe exacerbations.[13] The FLOAT trial also provided a unique opportunity to examine the associations between the frequency of severe asthma exacerbations and the decline in post-bronchodilator FEV_1 and loss of airway reversibility in a longitudinal, prospective study.

METHODS

Study patients

The characteristics of the present cohort have been published previously.[14] A total of 250 patients with asthma following inhaled corticosteroids (ICS) therapy for more than 4 years were recruited from the Wakayama Medical University Hospital. All patients had a history of episodic dyspnea, wheezing, and documented significant airway reversibility and/or airway hyperresponsiveness. Current smokers and patients with >10-pack-year smoking history were not included in this analysis. Also, patients with poor adherence to asthma treatment (defined as <80% adherence calculated by dividing the number of days supplied for a medication by the number of days between the visits) or with other pulmonary diseases such as chronic obstructive pulmonary disease were excluded.[14] In this prospective study, 140 patients with well-controlled asthma were selected based on the Global Initiative for Asthma (GINA) guidelines (twice or less/week daytime symptoms, no nocturnal symptoms, no limitation of daily activities, twice or less/week need for reliever, normal lung function [≥70% FEV_1/FVC ratio and ≥80% FEV_1 % of predicted], no exacerbation in the previous 1 year).[1] A total of 78 patients with partly controlled asthma (1-2 of these features) and 26 patients with uncontrolled asthma (≥3 of these features) were not included. Also, 6 patients under the age of 25 years at recruitment were excluded because lung function normally increases to a maximal value in early adulthood and then declines.[15] The flow diagram of the present study is shown in Figure 1. Informed written consent was obtained from each participant.

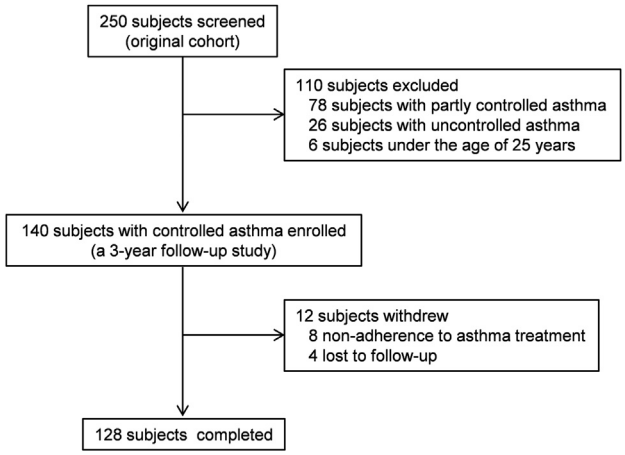

FIGURE 1. Disposition of the study patient population.

Study design

The study subjects were followed with Asthma Control Test (ACT), spirometry, and FeNO every 3 months over a 3-year period. Medical records including medication use and adherence to asthma treatment were also obtained. Blood eosinophil numbers and serum specific immunoglobulin E (IgE) for common inhaled allergens (house dust mite, cedar, ragweed, cocksfoot, dog, and cat) were examined. Positive specific IgE to at least 1 allergen was assumed to confirm the presence of atopy. ICS doses and use of other controllers were not fixed during the follow-up period because this was a purely observational study. The study was approved by the ethics committee of Wakayama Medical University (IRB #526) and registered with the University Hospital Medical Information Network (UMIN 000012105).

Study assessments

The FVC and FEV_1 values were measured using a dry rolling seal spirometer. The use of asthma controllers within 24 hours before an examination was prohibited for all study visits. Reversibility of FEV_1 was measured after administration of 400 μg of salbutamol. The post-bronchodilator FEV_1 was selected to reflect loss of lung function as in other studies following lung function in patients with asthma over time.[3,8] The annual changes in FEV_1 and BDR were estimated by fitting a least-squares regression line. In total, 3288 FEV_1 measurements were analyzed excluding lung function data during periods of worsening asthma (4 weeks before and 4 weeks after the start of a severe exacerbation). On the basis of the magnitude of change in FEV_1 over a 3-year period, we labeled those of less than the 25th percentile as rapid decliners, and greater than the 25th percentile as nonrapid decliners. All rapid decliners had an estimated rate of decline in FEV_1 of more than 40 mL/year. The FeNO was measured by an online NO analyzer (NIOX MINO; Aerocrine, Solna, Sweden) as previously described.[16] The ACT is a questionnaire that assesses the asthma condition. A validated Japanese translation has been used in some earlier studies in Japan.[13,14]

Severe asthma exacerbations

A recent American Thoracic Society/European Respiratory Society task force report was used to define exacerbations as events outside the patient's usual range of day-to-day asthma variation, requiring a