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Original article

Predicting future risk of exacerbations in Japanese patients with adult asthma: A prospective 1-year follow up study

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Abbreviations:
ACT, Asthma Control Test; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; JGL, Asthma Prevention and Management Guidelines; OCS, oral corticosteroids; NAEPP, National Asthma Education and Prevention Program; SD, standard deviation; TENOR, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens

ABSTRACT

Background: To avoid future risk is a definitive goal of long-term asthma management. Exacerbations are considered to be the most relevant future risk in real life asthma management. Few comparative studies have evaluated the risk factors associated with exacerbations in Japanese patients with asthma.
Methods: We performed the prospective 1-year follow up study in Japanese patients with adult asthma. A total of 189 patients with asthma were enrolled and followed up for 1 year. Finally, 181 patients completed the study protocol.
Results: Of 181 patients, 43 patients (23.8%) had exacerbations during the follow-up period. Among the 45 patients who had exacerbations during the preceding year, 32 patients (71.1%) had exacerbations. Prevalence of patients with previous exacerbations and those with previous admissions were significantly higher in patients with exacerbations than those with no exacerbation. Logistic regression analysis also identified a significant association between exacerbations during the follow-up period and exacerbations during the preceding year, admissions during the preceding 3 years, ACT score below 20, low % FVC (<80%), or low FEV_1 (<70%), respectively. Of the 55 patients with severe asthma, 29 patients (52.7%) had exacerbations. Among the 36 patients with severe asthma with previous exacerbations, 26 patients (72.2%) had exacerbations. The history of exacerbations during the preceding year was associated with a significantly increased risk of exacerbations both among the patients with severe asthma and those with non-severe asthma.
Conclusions: This study implicated that exacerbations during the preceding year reliably predict future risk of exacerbations in Japanese patients with asthma.

Introduction

Asthma is a chronic airway inflammatory disease and is clinically characterized by variable episodes of shortness of breath, chest tightness, wheezing and cough. With improvements in controller therapy, such as inhaled corticosteroids (ICS) and long-acting bronchodilators, it is now recognized that highly satisfactory levels of asthma control can be achieved and maintained for long periods.[1] However, certain triggers, such as virus infection and the changing of the season, cause exacerbations in patients with asthma. In addition, patients with severe asthma may require frequent bursts of oral corticosteroids (OCS) or even depend on daily OCS despite adequate treatments.[2,3]

The goals of asthma treatment in current guidelines, such as National Asthma Education and Prevention Program (NAEPP),[4] and Global Initiative for Asthma (GINA) guideline[5] have two points of view: one is to achieve current asthma control, and the other is to reduce asthma-associated future risk. Current asthma control was

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assessed by asthma symptoms, pulmonary function, and frequency of short-acting beta agonist use. Asthma-associated future risk involves exacerbations, admission, asthma death, fixed airflow limitation, and side-effects. During the past decade, admissions and death due to asthma have been dramatically decreased. Currently, exacerbations would be the most relevant future risk in long-term asthma management. Therefore, identification of risk factors associated with future exacerbations is of considerable importance to physicians, public health officials, and patients.

It is recognized that poor asthma control is a predictor of future instability in asthma control and asthma exacerbations.[6,7] Previous exacerbations,[8] low forced expiratory volume in 1 s (FEV_1) predicted,[9,10] a requirement for a short course of OCS,[11] hospitalization, or an emergency room visit[12] are also known to be major predictors for future exacerbations of asthma. Osborne *et al.* demonstrated that FEV_1 predicted <60% was the better predictor than histories of hospitalization, urgent care use or breathing problems in the past year.[13] Regarding Japanese patients with asthma, Sato *et al.* showed a combined analysis of patients-based questionnaire and FEV_1 could predict the risk for future asthma exacerbation.[14] However, the A comparison of risk factors associated with future exacerbations in Japanese patients with asthma has not been fully investigated. We therefore designed this prospective trial to assess the risk factors associated with future exacerbations in Japanese patients with adult asthma, following up for 1 year in clinical setting.

Methods

Study design

This study was prospectively carried out in the pulmonary and allergy units of the Showa University Hospital, Tokyo, Japan, between July 2012 and December 2013. Study protocol was reviewed and approved by the Showa University ethics committee and written informed consent was obtained.

Participants were followed up by the same physician for 1 year to determine whether they had exacerbations. Exacerbations were defined as an episode of worsening asthma requiring intravenous corticosteroid, 3 or more consecutive days of OCS use, an increase in systemic corticosteroids from an individual maintenance dose, or a visit to the emergency room. Treatments for asthma were adjusted in accordance with the Asthma Prevention and Management Guidelines, referred to the Japanese guideline (JGL),[15] during the study period. Briefly, if asthma was controlled for 3–6 months, step-down of the treatment was considered. If the patients were in poorly controlled or in uncontrolled, 1 step-up or 2 step-up of the treatment were considered, respectively. Asthma control was also assessed in accordance with JGL.[15] To identify potential factors associated with the development of exacerbations, the associations between the future risk of exacerbation and clinical parameters, including pulmonary function and fraction of exhaled nitric oxide (FeNO), were analyzed.

Study subjects

A hundred eighty-nine patients, regularly followed up at Showa University Hospital for at least 2 years and aged 20–80, were randomly enrolled. Patients who had exacerbations more than 6 times the preceding year, no exacerbation within the preceding 3 years, or a regular treatment with oral corticosteroid above 10 mg/day, were excluded. Patients with chronic obstructive pulmonary disease (COPD) or other lung disease, poor adherence to treatment (<80%), smoking history >20 pack-years, vocal cord dysfunction, or neurological disease were also excluded. The diagnostic criteria of asthma were mostly based on the GINA guideline. Briefly, asthma was diagnosed in patients who had a reversible airflow limitation that represented an increase of 12% and 200 ml in FEV_1 after the inhalation of salbutamol or the clinical treatment targeting asthma. Diagnoses of perennial allergic rhinitis and seasonal cedar pollinosis were based on clinical history and a positive serum allergen-specific IgE. The diagnosis of chronic rhinosinusitis was based on the standard criteria issued in the European Position Paper on Rhinosinusitis and Nasal Polyps guidelines.[16]

Assessments

Patients underwent extensive characterization and investigations, including medical history, severity, spirometry, fraction of exhaled nitric oxide (FeNO), blood tests for peripheral eosinophil count and IgE. Body mass index (BMI) was based on measured weight and height, and calculated as weight in kilograms divided by the square of the height in meters. Asthma control was assessed by using the validated Japanese version of the Asthma Control Test (ACT). Patients were subjectively evaluated for the degree of impairment caused by their asthma during the preceding 4 weeks by responding to five questions; activity limitation, shortness of breath, nighttime symptoms, use of rescue medication, and the patient's overall rating of asthma control. Treatment steps and asthma severity were classified according to the JGL.[15] Asthma severity was assessed on the basis of asthma control level and treatment step of JGL.[15] For descriptive purposes, mild intermittent, mild persistent, and moderate stage of severity were regarded as non-severe.

Spirometry was performed using a AS-302 spirometer (MINATO MEDICAL SCIENCE CO., LTD, Osaka, Japan) in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines[17,18] to determine FEV_1, forced vital capacity (FVC), FEV_1/FVC. The highest value from three technically satisfactory attempts was recorded. FEV_1 and FVC values are expressed as measured value, and predicted values of FEV_1 and FVC were obtained from the Japanese Respiratory Society guideline.[19]

FeNO was measured by a portable device (NIOX MINO; Aerocrine AB, Solna, Sweden) at an expiratory flow rate of 50 mL/s for 10 s. The sensor on the device was changed periodically, in line with the manufacturer's guidance. Measurements of FeNO were performed before spirometry.

Statistical analyses

To identify the factors associated with the development of exacerbations, variables were compared between the patients who had exacerbations and those who had no exacerbation during the 1-year follow-up period. The results are expressed as mean ± SD for continuous variables. All analyses were performed using JMP system version 12 (SAS Institute Inc., Cary, NC, USA). The differences in the continuous variables were analyzed using Mann–Whitney U test, and the differences in the categorical variables were analyzed using Pearson χ^2 tests. Values that were not normally distributed, such as IgE, were log-transformed to obtain normal distribution for regression analysis. In order to examine the association between exacerbations and each parameter, logistic regression analyses were performed using exacerbations as the outcome variable. These models were adjusted for age and sex. A value of $p < 0.05$ was considered significant for all statistical assessments.

Results

Baseline characteristics of the study subjects

One hundred eighty-nine patients were recruited and signed informed consents. Of these, 8 patients discontinued the study protocol (1 had pulmonary tuberculosis, 1 withdrew the consent