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The clinical role of fractional exhaled nitric oxide in asthma control

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ABSTRACT

Background: The potential role and characteristics of fractional exhaled nitric oxide (FeNO) remain unclear in the treatment of asthma.
Objective: To explore the clinical role of FeNO in asthmatic treatment.
Methods: We evaluated whether the mean or change of FeNO levels in the treatment period is associated with other conventional control parameters and predicted some clinical outcomes of asthma. We retrospectively analyzed the mean and percentage change of FeNO levels in the first 5 measurements at our hospital.
Results: The study found a significantly strong correlation between FeNO level at diagnosis and the largest changes of FeNO values from diagnosis. No significant correlations were observed between FeNO levels and other parameters (Asthma Control Test [ACT] score or forced expiratory volume in one second [FEV_1]) in mean and percentage change of values under treatment of asthma; however, significant positive correlations were found between ACT scores and FEV_1. The mean FeNO level revealed a significant negative correlation with an annual change in FEV_1 in individuals with asthma who were followed up for more than 2 years. Both the mean ACT score and percent predicted FEV_1 revealed a significant negative correlation with occasional use of systemic corticosteroids.
Conclusion: During conventional treatment of asthma, the largest changes of FeNO values from diagnosis were strongly correlated with FeNO levels at diagnosis. As for the unlikely conventional parameters, no significant associations were observed between FeNO levels and deterioration of asthma during the treatment periods. An elevated mean FeNO level may be a marker of decreased lung function in individuals with asthma.

Introduction

Fractional exhaled nitric oxide (FeNO) is a useful diagnostic tool for bronchial asthma.[1–3] FeNO is a noninvasive marker that reflects eosinophilic airway inflammation in individuals with asthma.[4,5] Control of eosinophilic airway inflammation by anti-inflammatory agents, such as inhaled corticosteroids, seems to improve the outcome of asthma. However, the universal use of FeNO in controls with asthma has not been advocated based on recent studies on tailoring asthma medications in accordance with FeNO levels that reflect airway eosinophilic level.[6] In most randomized clinical trials that compare adjustment of asthmatic medication based on FeNO level to control, the primary outcomes were exacerbations of asthma, such as those requiring systemic corticosteroids or hospitalization, and treatment failure.[7–10] It is necessary to explore clinical significances and features of FeNO in antecedent controls with asthma to definite clinical outcomes in clinical trials that compared adjustment of asthmatic medications with or without FeNO measurement.

The cutoff points of absolute value were adapted for interpretation of FeNO by conventional clinical guidelines[11] and clinical trials[6] when monitoring the eosinophilic airway inflammation. On the other hand, some reports have suggested that there is an association between change of eosinophilic airway inflammation and the clinical outcome of asthma. Sputum analyses of patients with severe asthma have revealed that a high variability of sputum eosinophils, rather than the amplitude at baseline or during a specified period, was associated with accelerated lung function decline.[12] In controls with asthma, variations of FeNO levels (diurnal or during 2 weeks) have been reported to be associated with exacerbations of asthma.[13] There is a possibility that variation

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of FeNO levels during the control period may predict the clinical outcome of asthma.

We retrospectively analyzed FeNO levels during the control period of asthma. To explore the clinical significances and features of FeNO measurement in controls with asthma, we evaluated whether the mean or changes of FeNO levels in the control period are associated with other conventional control parameters[14] and predict the clinical outcomes of asthma, particularly exacerbations and annual changes of lung function.

Methods

Study Participants and Design

This study was a retrospective, observational study. The individuals with asthma were recruited from the outpatient clinic at the Department of Pulmonary Medicine in Fukushima Medical University Hospital between September 2007 and October 2016. All participants were diagnosed according to the American Thoracic Society (ATS) criteria[15] and were regularly followed up at our outpatient clinic. Asthma was defined on a basis of recurrent episodes of at least one symptom (cough, wheeze, or dyspnea) associated with a demonstrated reversible airflow limitation (12% and 200-mL variability in forced expiratory volume in 1 second [FEV_1] spontaneously or with an inhaled short-acting β_2-agonist) and/or increased airway responsiveness. Severity of asthma was assessed according to the Global Initiative for Asthma 2012 guidelines and classified into 4 groups: mild intermittent, mild persistent, moderate persistent, and severe persistent. All participants provided written informed consent for analysis of their clinical data. The study was approved by the ethics committee of Fukushima Medical University.

We enrolled individuals with asthma who received standard asthmatic treatment by their attending physician and had undergone the Asthma Control Test (ACT),[16] spirometry, and FeNO measurement on the same day for clinical assessment on regular visits. These measurements were taken from individuals who had not had an asthma attack within the previous 4 weeks. In the present study, to analyze the variability and mean values of the control parameters, we enrolled individuals with asthma who had undergone the ACT, spirometry, and FeNO measurement on at least 5 occasions during the control period. The data of the first 5 measurements after beginning the asthmatic treatment in our outpatient clinic were applied to the analyses.

We defined follow-up visit as a regular visit in which individuals had undergone the ACT, spirometry, and FeNO measurement for clinical assessment after beginning the treatment of asthma. The period from the first to fifth follow-up visit was defined as the control period. For the initial assessment, the association between FeNO level at diagnosis and FeNO levels under treatment was studied. FeNO level measurement at diagnosis was performed before initiation of treatment of asthma. Patients who were already receiving treatment of asthma at the first visit were excluded from the initial analysis. Patients' highest, lowest, and mean FeNO levels in the first 5 measurements under treatment were compared with their FeNO levels at diagnosis. To analyze the largest amount of change in FeNO levels from diagnosis, we calculated the difference in FeNO between level at diagnosis and the lowest level in the first 5 measurements under treatment. A correlation of the largest amount of change in FeNO levels and FeNO level at diagnosis was studied. For secondary assessment, analyses of correlations between FeNO levels and conventional parameters (ACT scores and FEV_1) in the control period were performed. The mean levels and percentage change of each value in the control period were calculated, and the tripartite correlations were examined in 3 parameters (FeNO level, ACT score, and FEV_1). We defined percentage change of the parameters in the control periods as the ratio of the difference between largest value and lowest value to mean value in the first 5 measurements in the control period. Finally, the association between the 3 parameters in the control period and the clinical outcomes of asthma was studied. The clinical outcomes in the present study were asthma exacerbation and annual change in FEV_1 in the follow-up period. Asthma exacerbation was defined as worsening of asthmatic symptoms that required an occasional use of systemic corticosteroids, and the number of asthma exacerbations in the control period was calculated as rates per person year. Moreover, to analyze the correlation between FeNO and clinical outcomes in participants with controlled asthma, we defined the participants with controlled asthma as those with 20 or more in mean ACT score and 80% or more in mean predicted FEV_1.

FeNO Measurement

FeNO measurement was taken according to the ATS and European Respiratory Society recommendations[11] using a chemiluminescence analyzer (NA623N, Kimoto, Osaka, Japan). Measurement was performed, as described previously,[5] with the patient in a sitting position and without wearing a nose clip. From total lung capacity without holding their breath, the patient exhaled at a constant flow of 50 mL/s. FeNO was measured 3 times, with differences in measured values within 10%. The mean value of the 2 measurements was used as data for statistical analysis. FeNO value was expressed as parts per billion.

Blood Tests and Pulmonary Function Test

Blood tests included peripheral blood eosinophil count, serum nonspecific IgE, and antigen-specific IgE. A radioallergosorbent test for antigen-specific IgE was performed for weed, mites, house dust, cats, dogs, cedar, cypress, orchard grass, moths, *Aspergillus*, *Candida*, and *Alternalia*. Nonspecific IgE was measured by fluorescence enzyme immunoassay (UniCAP, Pharmacia & Upjohn, Uppsala, Sweden). Atopy was defined as either a nonspecific IgE concentration greater than or equal to 250 IU/mL or any positive antigen-specific IgE ($\geq$0.70 UA/mL). Pulmonary function testing was performed using rolling seal spirometers (Chestac-11 Cyber S-type, Chest MI Inc, Tokyo, Japan) to measure forced vital capacity and FEV_1. Tests were performed by experienced respiratory technicians according to ATS guidelines.[17] Forced vital capacity and FEV_1 were expressed as percent predicted values.

Statistical Analysis

All values are expressed as mean (SD) unless otherwise specified. The comparison between FeNO level at diagnosis and FeNO level during treatment was performed using a paired t test. The associations between FeNO levels at diagnosis and largest changes of FeNO in the control period, FeNO level and other parameters (ACT and FEV_1) in the control period, and 3 parameters (FeNO, ACT, and FEV_1) in the control period and clinical outcomes of asthma were determined using the Spearman rank correlation analysis. The annual change in FEV_1 was calculated from a linear regression analysis of FEV_1 in the control period. Individuals with asthma who had not undergone spirometry while receiving treatment of asthma for more than 2 years were excluded from this analysis. Finally, receiver operating characteristics (ROC) curves were constructed to discriminate individuals who were treated with occasional systemic corticosteroids once or more within a year and individuals with a decrease in FEV_1 of 40 mL or more per year using mean values of FeNO, ACT scores, and percent predicted FEV_1. $P < .05$ was considered statistically significant. Statistical analysis was performed with PASW Statistics Base for Windows, version 21 (IBM, Armonk, New York).