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Fractional exhaled nitric oxide levels as a predictor of long-term prognoses in patients with mild asthma

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ABSTRACT

Background: There is a growing belief that patients with bronchial asthma (BA) should be provided an individualized and optimized treatment plan. We aimed to clarify the predictors of long-term prognoses in patients with mild BA.

Methods: We conducted a retrospective study of consecutive patients who were newly diagnosed with mild BA at Iwate Medical University from 2011 to 2013, focusing on achievement of full asthma control based on the Asthma Control Test as an indicator of prognosis. Predictors were identified on the basis of a chart review.

Results: Among 71 patients with mild BA, 37 patients completed regular clinic visits for 1 year. Nineteen (51.4%) of these patients achieved full asthma control. Current smoking and the fractional exhaled nitric oxide (FeNO) level at the first patient visit were identified by multivariate logistic regression as possible predictors of the discontinuation of clinic visits and achievement of full asthma control, respectively. Low FeNO levels at the first clinic visit yielded a receiver operating characteristic-area under the curve of 0.860 (95% confidence interval [CI]=0.774–0.975) for the achievement of full asthma control. Using an FeNO cut-off level of 34 parts per billion yielded a sensitivity of 76.5% (95% CI=59.5–88.2%) and specificity of 73.7% (95% CI=58.5–84.2%).

Conclusion: Our preliminary results suggested that patients with newly diagnosed mild BA who display higher FeNO levels at their first clinic visits should be appropriately educated during early visits to receive optimal treatment and complete regular clinic visits.

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1. Introduction

Over the last decade, mild asthma has constituted the majority of asthma cases [1,2]. Mild asthma generally has a satisfactory long-term prognosis [3]. Monotherapy, using an inhaled corticosteroid (ICS), or an ICS in combination with a long-acting beta-agonist is also effective for the treatment of mild asthma, as well as moderate-to-severe asthma [4]. Once asthma is adequately controlled, step-down of the ICS dosage is recommended to avoid adverse effects, followed by withdrawal, if possible [5–10]. Individualization of asthma care is essential for ensuring optimal asthma treatment in each patient, as responsiveness to ICS therapy varies among patients [11]. It has been reported that approximately 20% of patients with mild asthma, which includes cough variant asthma (CVA), achieved successful withdrawal from ICS therapy [12,13]. In contrast, mild asthma tends to be underdiagnosed, undertreated, and inadequately controlled, as many patients with mild asthma do not seek treatment, even though this can occasionally result in a severe asthma attack [1,2]. In clinical practice, clinic visits of patients with mild asthma are often self-discontinued. Among such patients, however, the characteristics of patients whose asthma therapy should normally be continued, given their asthmatic symptoms, remain to be elucidated. The predictors of long-term prognoses in patients with mild asthma would allow clinicians to provide early appropriate education to those who should continually receive asthma therapy, in order to prevent their discontinuation of clinic visits.

An increasing body of evidence suggests the clinical relevance of the fractional exhaled nitric oxide (FeNO) level in patients with asthma. The level of FeNO increases in proportion to the severity of bronchial wall inflammation or induced-sputum eosinophilia [14–17]. The FeNO level of patients at the first clinic visit has diagnostic value for asthmatic conditions [18]. In addition, increases in FeNO levels are associated with deterioration in asthma control, whereas FeNO levels can be reduced in a dose-dependent manner with anti-inflammatory treatment. However, the benefit of FeNO measurements to the reduction of maintenance treatment in asthma patients has not yet been fully established [19–21]. Furthermore, FeNO levels can be influenced by various factors, including smoking [22,23]. As FeNO is a simple, safe, and reproducible biomarker, additional applications of this biomarker in the clinical treatment of asthma are expected.

Limited information is available regarding the predictors of long-term prognoses in patients with mild asthma. In this study, we first aimed to identify a predictor of the self-discontinuation of regular clinic visits among patients with newly diagnosed mild asthma. Each patient was provided with an action plan, including an explanation of asthma cure and the subsequent stepping down or stepping up of treatment. Second, we sought to identify an early predictor of favorable and unfavorable prognoses in patients with mild asthma, based on the Asthma Control Test (ACT), and identified lower FeNO levels at the time of initial diagnosis of asthma as a possible predictor of full asthma control [24]. Our results may be useful for clinicians in creating individualized treatment plans for patients with mild asthma during their early visits.

2. Patients and methods

2.1. Subjects

This retrospective study consisted of 71 consecutive patients who visited the general outpatient clinic in the Department of Pulmonary Medicine, Iwate Medical University Hospital, between January 2011 and January 2013. Patients were selected if they were newly diagnosed with mild asthma and if they had never received an ICS or had not taken anti-allergic medications within 3 months of their first visit to our clinic. Bronchial asthma (BA) was diagnosed as follows: (1) wheeze or cough for longer than a minimum of 3 months, (2) clinical efficacy of an ICS, and (3) any of a number of the criteria [25]. These were: [A] a positive indication of airway reversibility after inhalation of a short-acting β2 agonist, [B] response to a provocative concentration of methacholine, or [C] sputum eosinophil counts >3% or FeNO levels >22 parts per billion (ppb). Mild asthma was defined as a forced expiratory volume within 1 s ($FEV_{1.0}$ predicted) of >80% at the first diagnosis of asthma. The patients had no abnormalities on chest radiographs or CT scans, and had no prior history of treatment for pulmonary disease. Patients with CVA were also included in the present study, whereas those with atopic cough were excluded. A treatment action plan for mild asthma, including asthma cure and the step-up and step-down strategy, was given to each patient at treatment commencement. According to the global initiative for asthma guidelines, once asthma is controlled for 3 months, a gradual reduction in maintenance therapy is attempted, in order to identify the minimum dose required to control asthma, in principle [3]. When the ACT score was 25, asthma was assumed as be fully controlled [26]. In patients who satisfied the criteria for full asthma control in 3 consecutive clinic visits shortly after the initiation of ICS, step-down was started earlier than 3 months after the initiation of ICS therapy [24]. Asthma exacerbation was defined as the continuation of symptoms for more than 2 consecutive days, including wheezing and expiratory dyspnea during the day, or nighttime awakenings attributable to asthma, or a decline in $FEV_{1.0}$ of more than 20% [27]. The ICS dosage was stepped up in patients who experienced asthma exacerbation. Patients were required to continue regular clinic visits for at least 1 year to confirm the absence of subjective and objective exacerbations of asthma, even if asthma therapy was withdrawn. Patients who achieved withdrawal from ICS therapy were additionally requested to continue intermittent visits for at least 1 year after the cessation of therapy. No patient required oral corticosteroids during the period of asthma treatment. The study was approved by the Ethics Committee of Iwate Medical University (H26-112, 06/11/2014).

2.2. Blood tests

Blood tests included peripheral blood eosinophil counts and evaluations of non-specific IgE and antigen-specific IgE levels