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An empirical trial of one-week treatment with inhaled corticosteroids for distinguishing asthmatic syndrome from asthma mimics

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Abstract

Asthma is a complex clinical disease characterized by airway hyperresponsiveness and airway inflammation. It is commonly diagnosed and treated on the basis of the clinical impression of the physician, although national guidelines recommend documenting reversible airflow obstruction. Asthma-like symptoms are shown in asthma mimics, including mitral valve disorder, allergic rhinitis and Sjögren's syndrome. This study examined whether a response to 1 week of inhaled corticosteroids (ICS) was useful for distinguishing asthma mimics from asthmatic syndrome, including definitive asthma and eosinophilic bronchitis. This study included 126 subjects who had episodes of wheezing at night and/or in the early morning. Airway hyperresponsiveness (AHR), bronchodilator reversibility (BR), and eosinophilia in sputum (Eo) were measured. Asthma was diagnosed by a classical definition for asthma determination proposed by the Ciba symposium, and clinical observation for 2 years. The clinical response to the treatment was assessed based on the symptom score on a visual-analogue scale and the clinical peak-expiratory flow rate (PEFR) within the first week after treatment with ICS. In total, 110 of the 126 subjects (87%) were diagnosed with asthmatic syndrome, as either definitive asthma (72%) or eosinophilic bronchitis (15%), whereas the remaining 16 participants were considered to have asthma mimics due to an alternative diagnosis. Patients with definitive asthma and eosinophilic bronchitis, but not those with asthma mimics, showed improved symptom scores and their clinical PEFR was improved within the first week of ICS treatment. In this study, we demonstrated that diagnosis using the patient response to ICS was an effective alternative tool for distinguishing asthmatic syndrome from asthma mimics.

Key words: asthmatic syndrome, diagnosis, inhaled corticosteroids

Introduction

Asthma is a chronic inflammatory disorder of the airways, associated with increased airway responsiveness (AHR), and usually widespread but variable airway obstruction that is often reversible, either spontaneously or with treatment. The definition of asthma has not been widely accepted, because asthma is a clinical syndrome characterized by episodes of wheezing at night and/or in the early morning. About one-third of patients with physician-diagnosed asthma did not have asthma[1-4] when objectively assessed by the American Thoracic Society

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(ATS) criteria.[5] It has therefore been recommended that physicians should perform spirometry more frequently to establish the diagnosis of asthma, as recommended by the national asthma guidelines, in addition to relying on patients' symptoms.[6]

AHR, sputum eosinophilia (Eo), and bronchodilator reversibility (BR) are widely used to support a diagnosis of asthma. AHR is a characteristic feature of asthma, which is often associated with airway inflammation, however, not only some patients with allergic rhinitis,[7,8] but also some patients with Sjögren's syndrome[9–11] or mitral stenosis,[12–15] exhibit AHR. The presence of Eo is another factor supporting a diagnosis of asthma. A relatively large population of adult asthma cases is characterized by neutrophilic airway inflammation,[16–20] in particular those with a severe form of the disease.[21–24] On the other hand, while eosinophilic airway inflammation is the hallmark of asthma, it has also been reported in other conditions, such as allergic rhinitis and eosinophilic bronchitis.[25]

The GINA guideline states that asthma is defined as chronic eosinophilic bronchitis, reversible airflow limitation and airway hyperresponsiveness, however, no specific approach for diagnosing asthma has been completely evaluated at the primary care level. Some asthmatic patients meet these three criteria, but a gold standard of measurement for the diagnosis of asthma does not currently exist.[26] General physician can mistakenly receive an asthma diagnosis using only a typical symptom, such as wheezing at night and/or in the early morning, because the symptom often mimics those other conditions, named as asthma mimic, including sinusitis, congestive heart failure, pulmonary embolism, chronic obstructive pulmonary disease, and so on. In this situation, it was reported that the most specific test is the BR test for the diagnosis of asthma.[27]

A classical definition for asthma was proposed by the Ciba symposium that specified "a widespread narrowing of the bronchial airways, which changes in severity over short periods of time either spontaneously or under-treatment".[28,29] A week-long trial of an oral corticosteroid has been demonstrated to be a diagnostic tool for asthma. Inhaled corticosteroids (ICS) have been shown to improve airway obstruction within 1 week.[30] In this study, we demonstrated that 1-week treatment with ICS may be useful for diagnosing asthmatic syndrome, including asthma and eosinophilic bronchitis.

Materials and Methods

Subjects

Male and female patients who had episodes of wheezing at night and/or in the early morning, and were steroid-naïve, were enrolled in the study. Patients were eligible for enrollment if they had a forced expiratory volume in one second (FEV_1) at baseline of 60% and over of the predicted value at the first visit (visit 1) to our hospital. Patients were excluded who had symptoms of chest pain or hemosputum and who had abnormal findings on chest Xp. In addition, current smokers and former smokers with a Brinkman Index of more than 400 were excluded in order to rule out chronic obstructive pulmonary disease. The study was approved by the local ethics committee, and all subjects gave their informed consent.

Lung function and airway responsiveness

At visit 1, spirometry was conducted between 9 : 00 and 11 : 00 AM at the clinic using a standard spirometer (Minato, Tokyo) in accordance with the reproducibility and acceptability criteria of the American Thoracic Society[31] and a standard quality control system.[32] Positive BR was defined as $>12\%$ and a 200 mL increase of FEV_1 after β_2 inhalation. One week after the patients' first visit, the patients came for a second visit (visit 2), and the airway response was measured directly by examining the dose-response curve of respiratory resistance (Rrs) drawn by the Astograph (Chest, Tokyo) during continuous inhalation of methacholine according to our previous report.[33] An assessment of airway responsiveness was derived from the minimum dose of methacholine (Dmin) needed to increase the Rrs and the dose of methacholine needed to reduce respiratory conductance by 35% (PD_{35}-Grs). Positive airway AHR was defined as <10 units of Dmin.

Sputum collection and processing

Spontaneous sputum was collected at visit 1. The subjects were instructed to spit after a deep cough into a wide-mouthed jar, which was then sent without delay to the cytology laboratory. If no spontaneous sputum was coughed up, then sputum was induced using 0.9% NaCl inhalation for 5 min. In the laboratory, the sputum was transferred to a Petri dish placed against a black

or dark background. This method allows for easier identification of saliva or plugs from the lower respiratory tract. Small aliquots of sputum were finely distributed over two microscope slides using metal spatulas. The smears were air-dried and stained with the Leishman method[34] using a commercial kit (Eosinostain®; Daiichi, Tokyo) or with the May-Grünwald-Giemsa method. Eo was defined as ≥4% eosinophils on two occasions or >10% eosinophils on one occasion.

Definition of asthma and other diseases

The inclusion criteria required for a definitive diagnosis of asthma are as follows:

1) Determination proposed by Ciba symposium[29]

and

2) Clinical observation for 2 years to exclude any diseases mimicking asthma.

At visit 1, all subjects required treatment with ICS (equivalent to 400 μg per day of fulticasone propionate) and oral theophylline at 200 mg per day. All patients were asked to visit one week later for visit 2 and to record their degree of wheezing as the wheezing score, scored on a 0 to 10 scale, as a visual analogue at each point on the third day, fifth day and one week after visit 1. If the wheezing score and/or clinical PEFR had not improved by visit 2, then the treatment was replaced with other options, such as diuretics for heart failure or local steroids for allergic rhinitis. If the wheezing score and/or clinical PEFR had improved, clinic assessments were performed one week after visit 1, and every month thereafter. In addition, we assessed objective airflow limitations using the clinical PEFR at every visit using a rescue dose of short-acting β_2 inhalation.

Eosinophilic bronchitis was diagnosed in patients who were Eo positive without AHR and BR. All patients were clinically observed for 2 years in order to exclude asthma mimics. Mitral valve disorder was diagnosed by a cardiologist using echocardiography. Allergic rhinitis and Sjögren syndrome were diagnosed by specialists.

Statistical analysis

The statistical studies were performed using the statistical software program SPSS ver. 16 for Windows (SPSS Inc., Chicago, IL, USA). Subsequently, the levels of sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) in the diagnosis of asthma were calculated manually. The difference in the wheezing score and clinical PEFR during the time-course between three groups (definitive asthma, eosinophilic bronchitis, and asthma-mimic) was analyzed by ANOVA and post-hoc analysis.

Results

Characteristics of patients

Among the 166 outpatients, all of whom visited our hospital due to episodes of wheezing at night and/or in the early morning, 126 patients were eligible for our study. Forty subjects were excluded; 17 for severe airway obstruction with FEV_1 <60%, 20 who were unable to collect spontaneous and/or induced sputum, two with an abnormal chest Xp, and one with chest pain. Of the 126 patients, 110 were diagnosed with asthmatic syndrome, including 91 with definitive asthma and 19 with eosinophilic bronchitis, whereas the 16 remaining participants were diagnosed as having a disease mimicking asthma, and included 7 patients with allergic rhinitis, 4 with Sjögren's syndrome, 2 with mitral valve disorders, and 3 who were unclassified (Table 1). Twelve of the 91 patients with definitive asthma had sinusitis, and five of those had gastro-esophageal regression disease (GERD) as a complication.

Sensitivity and specificity of diagnostic tools

Figure 1 shows the distribution of subjects who were positive for AHR, BR, and Eo. There was a greater overlap of the three tests in the patients with definitive asthma. All of the patients with definitive asthma demonstrated airway hyperresponsiveness, whereas 87% had sputum eosinophilia, and 60% of those with bronchial reactivity (BR) had AHR.

The induced sputum of 10% of the enrolled patients was used for inflammatory analysis. Induced sputum separated from saliva is similar to lower respiratory secretions expectorated spontaneously.[35] Definitive asthma was accompanied by a significant increase in sputum eosinophil percentages [9.6% (±4.3) versus 3.4 (±2.1), $p<0.05$], an increase in FEV_1 after β_2 inhalation [12.7% (±2.1) versus 5.4 (±4.9), $P<0.01$], and Dmin [1.4 units (±7.1) versus 4.7 units (±2.9), $P<0.05$], in comparison to the levels in asthma mimic cases (Table 1). Patients with eosinophilic bronchitis demonstrated higher numbers of sputum Eo than those with asthma-mimics [7.1% (±2.6) versus 3.4% (±2.1),

Table 1 Characteristics of the subjects

	Definitive asthma	Eosinophilic bronchitis	Asthma-mimics			Unclassified
			Sjögren's syndrome	Mitral valve disorder	Allergic rhinitis	
n.	91	19	4	2	7	3
Female/male	49/42	11/8	4/0	1/1	3/4	1/2
				8/5		
Age	41±19	38±17	34±5	71±4	35±14	45±21
				47±18		
Dmin, unit	1.4±0.7†	12.4±2.1	4.6±1.5	6.2±2.3	3.1±2.4	14.6±3.4
				4.7±2.9		
%pred. FEV_1	73.6±10.4†	86.9±8.3	91.4±6.3	75.6±12.1	91.6±7.4	89.3±8.1
				86.2±6.7		
Increase of FEV_1 after β_2-inhalation, %	12.7±2.1†	5.4±6.1	4.7±5.3	12.6±0.4	5.6±4.2	4.3±3.6
				5.4±4.9		
% sputum eosinophils	9.6±4.3†	7.1±2.6†	2.4±1.3	2.6±1.1	5.7±2.3	1.8±0.9
				3.4±2.1		
Positive rate of AHR (%)*	91 (100%)	0 (0%)	4 (100%)	2 (100%)	7 (100%)	0 (0%)
Positive rate of BR (%)*	55 (60.4%)	0 (0%)	0 (0%)	2 (100%)	0 (0%)	0 (0%)
Positive rate of Eo (%)*	79 (86.8%)	19 (100%)	0 (0%)	0 (0%)	3 (46%)	0 (0%)

*The definitions of positive tests were: <10 units of the minimum dose of methacholine (Dmin) needed to increase the respiratory resistance for airway hyperresponsiveness (AHR), ≥12% and 200 mL increase of forced expiratory volume in one second (FEV_1) for bronchodilator response (BR), and ≥4% eosinophils on two occasions or >10% eosinophils once for sputum eosinophils (Eo).
†; $P<0.05$, in comparison to patients with asthma-mimics.

$P<0.05$] (Table 1).

The sensitivity, specificity, positive predictive value and negative predictive value for the diagnosis of definitive asthma were calculated independently for the three parameters: AHR, BR and Eo, and the sensitivity and specificity were compared (Table 2). In definitive asthmatic patients, the diagnostic results of AHR were as follows: sensitivity, 91 (100%) of 91; specificity, 22 (62.9%) of 35; positive predictive value, 91 (87.5%) of 104. The diagnostic results of BR were as follows: sensitivity, 55 (60.5%) of 91; specificity, 33 (94.3%) of 35; positive predictive value, 55 (96.5%) of 57. The diagnostic results of Eo were as follows: sensitivity, 79 (86.9%) of 91 patients; specificity, 13 (37.2%) of 35 patients; positive predictive value, 79 (78.3%) of 101 patients. Among the 91 patients with definitive asthma, 51 subjects (56%) had positive results for all three tests. Using AHR as the only objective marker of asthma identified 9% of the participants with definitive asthma, whereas the combination of BR and AHR or that of Eo and AHR identified 4% and 30%, respectively (Figure 1). None of the subjects with isolated positive AHR or positive Eo had definitive asthma. Of the 126 patients, 104 (83%) who had episodes of wheezing at night and/or in the early morning tested positive for AHR. Of the 126 patients, 101 (81%) who had episodes of wheezing at night and/or in

the early morning tested positive for Eo.

Response to inhaled corticosteroids

There were no differences in the rescue dose of short-acting β_2-inhalation among the three groups. The degree of wheezing was scored and recorded on a visual analogue scale from 0 to 10 at each time after ICS. At visit 2, the clinical response to inhaled corticosteroids was assessed on the basis of the symptom score on a visual analogue scale and the clinical PEFR. Patients with definitive asthma and eosinophilic bronchitis, but not those with asthma mimics, showed improvements in both the symptom score and the clinical PEFR within one week. At one week, ICS caused a greater reduction in the wheezing score (2.3±3.5 points vs. 7.1±2.4 points, $P=$

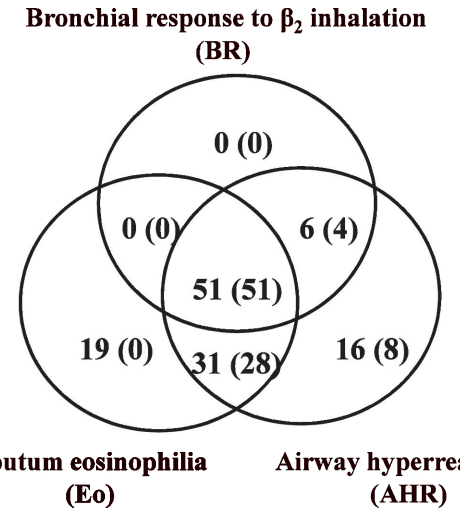

Fig. 1 Concordance of airway hyperresponsiveness (AHR), the bronchodilator response to β_2-inhalation (BR), and sputum eosinophilia (Eo) (Venn diagram). Parentheses indicate the number of patients with definitive asthma. Of 126 total patients, 110 patients were diagnosed with asthmatic syndrome, including 91 with definitive asthma and 19 with eosinophilic bronchitis, whereas the 13 remaining participants were diagnosed with asthma-mimics due to diagnosis of another cause and 3 were unclassified. Thirteen patients had asthma-mimics, 7 had allergic rhinitis, 4 had Sjögren's syndrome, and 2 had mitral valve disorders.

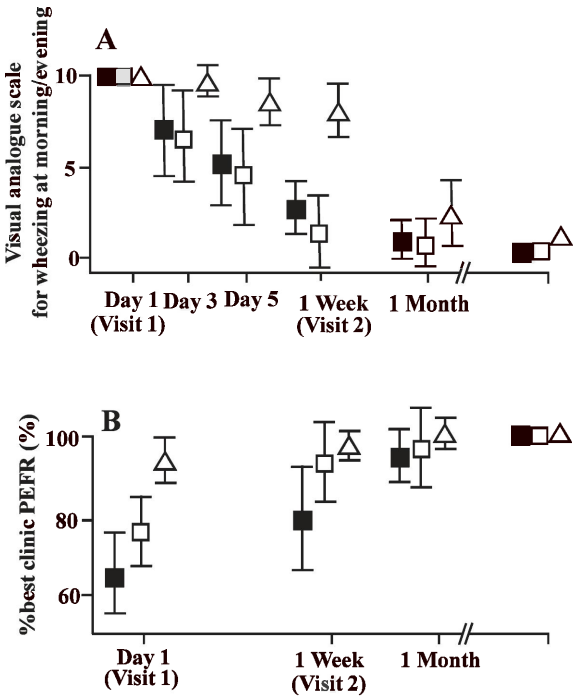

Fig. 2 The effects of inhaled corticosteroids (ICS) and low-dose theophylline on the degree of wheezing at night and/or in the early morning, shown as a visual analogue scale (A) and the percent of the best clinical peak expiratory flow rate (cPEFR) (B) in 91 patients with definitive asthma (■), 19 patients with eosinophilic bronchitis (□), and 16 patients with diseases mimicking asthma (△). In the definitive asthmatic patients and eosinophilic bronchitis patients, ICS resulted in a significant reduction in the wheezing score (Panel A) and an increase in the cPEFR (Panel B) within one week, in comparison to the asthma mimic patients. *P* values represent the time-treatment interaction over the period of the entire trial (corresponding values for efforts at one week appear in the Results section). Each character represents the means, and the bars represent the 95% confidence intervals.

Table 2 The sensitivity, specificity, and positive predictive value for the diagnosis of definitive asthma

	Sensitivity	Specificity	Likelihood rate	Positive predictive value
BR	60.5%	94.3%	21.1	96.5%
AHR	100%	62.9%	21.2	87.5%
Eo	86.9%	37.2%	1.2	78.3%
BR+AHR	100%	62.9%	4.4	87.5%
BR+Eo	91.2%	31.5%	1.1	77.6%
AHR+Eo	100%	8.6%	1.1	74.0%
BR+AHR+Eo	56%	100%	1.1	100%

Abbreviations: AHR, airway hyperresponsiveness; BR, bronchodilator response; Eo, sputum eosinophils.

0.03) (Figure 2A) and a greater increase in PEFR (52±14% vs. 8±5%, $P=0.02$) (Figure 2B) in asthmatic patients that in those with diseases mimicking asthma.

Discussion

Asthma is characterized by three components, airway hyperresponsiveness (AHR), bronchodilator reversibility (BR), and sputum eosinophilia (Eo), however, when asthma is diagnosed in general practice, it is still both an under- or over-diagnosed disease.[1–4,6] One of the reasons is that asthma is a clinical syndrome characterized by symptoms such as wheezing at night and/or in the early morning. Asthma-like symptoms are present not only in patients with asthma, but also in those with diseases that mimic asthma, including mitral valve disorders, allergic rhinitis, and Sjögren's syndrome with AHR. Another reason is that objective measurements of spirometry, the AHR test, and sputum analysis for the diagnosis of asthma are not commonly used in general practice.

In this study, we first assessed which objective measurements were more effective in definitively diagnosing asthma. Our results were consistent with a report by Yurdakul and colleagues,[27] which demonstrated that the AHR test is the most valuable for making a definitive diagnosis of asthma. In this study, only 55% of the definitive asthma cases demonstrated positivity for all three components (AHR, BR, and Eo). The highest specificity of airway response to β_2 inhalation for the diagnosis of definitive asthma implied that if a patient tested BR positive, then there was a low possibility that the patient had a disease other than definitive asthma. We also demonstrated that 83% of the patients who had episodes of wheezing at night and/or in the early morning tested positive for AHR.

Since there is no gold standard method for making an accurate diagnosis of asthma, and since asthma is often misdiagnosed, a standard for diagnosis is needed.[36] International guidelines regarding the management of asthma support the early introduction of corticosteroids to control symptoms and to improve lung function by reducing airway inflammation. ICS alone has been reported to improve airway obstruction within one week.[36] Since ICS is a suitable treatment for moderate asthma,[37–39] we used a moderate dose of ICS as an empirical trial for diagnosing asthmatic syndrome. Eo was the best predictor of both a short- and long-term response to corticosteroids.[40] ICS are effective in suppressing a chronic cough without asthma associated with sputum eosinophilia.[41] We demonstrated that a short course of ICS for the treatment of definitive asthma and eosinophilic bronchitis, but not asthma-mimics, was determined to improve both the symptoms and cPEFR within the first week of treatment. Most patients with asthma have eosinophilic airway inflammation, including those with definitive asthma and eosinophilic bronchitis, and therefore have a good response to treatment with ICS.[42]

Eosinophilic bronchitis differs from asthma in that there is no variable airflow obstruction or airway hyperresponsiveness,[42,43] however, asthma and eosinophilic bronchitis are characterized by similar inflammatory infiltrates of eosinophils in the submucosa of the lower airway. Asthma, chronic obstructive pulmonary disease (COPD), and eosinophilic bronchitis often have an overlapping clinical picture, which in some instances makes an accurate clinical diagnosis difficult.[44] We would like to emphasize that patients with eosinophilic airway disorders who had episodes of wheezing at night and/or in the early morning, may be treated with ICS and low-dose theophylline before examination.

In this study, we excluded smokers with wheezing, because cigarette smoking has been reported to impair the therapeutic responses to corticosteroids in asthmatic patients,[45] however, our data included some bias. First, all of the patients had mild-to-moderate, but not severe, flow limitation, because severe patients cannot be assessed for AHR. Some reports have demonstrated that therapy-resistant asthma may likely consist of several clinical subgroups characterized by exacerbating factors such as gastro-esophageal reflux and sinusitis.[18,47] In this paper, the low prevalence of complications of sinusitis or GERD in definitive asthma may have contributed to the high response to ICS. In addition, our patients, who demonstrated mild-to-moderate severity, might have been more likely to respond to ICS. Second, almost all of the patients (86.8%) with definitive asthma showed positive eosinophilia in their sputum. In this study, we distinguished eosinophilic asthma from non-eosinophilic asthma, but we did not assess neutrophilia in the sputum, which may be present in patients with non-eosinophilic persistent

asthma as a form of heterogeneity of airway inflammation.[47]

The symptom of wheezing at night and/or in the early morning was linked with Eo as well as airway hyperreactivity. Based on the present findings, an empirical 1-week trial using ICS is recommended as an objective marker for distinguishing asthmatic syndrome from asthma-mimics. For the minority of patients for whom this diagnostic approach is unsuccessful in general practice, consultation with a pulmonary specialist is appropriate for sequential diagnostic testing, including chest radiographs, the purified protein derivative test for tuberculosis, computed tomography of the sinuses, or the methacholine challenge test.

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