Characteristics of Asthma Resistant to Moderate Dose Inhaled Corticosteroid Treatment on Bronchial Hyperresponsiveness

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Abstract

Object This study was performed to determine the clinical characteristics of asthmatics with bronchial hyperresponsiveness (BHR) that could not be normalized by 6 months of treatment with a moderate dose of an inhaled corticosteroid (ICS).

Methods Thirty-four symptomatic patients with mild to moderate asthma, who had never received any ICS, were treated with 200 µg of inhaled fluticasone propionate twice a day for 6 months. Spirometry, BHR to methacholine, exhaled nitric oxide (NO) and eosinophils in induced sputum were examined before and 2 and 6 months after beginning treatment.

Results FEV₁ was increased and bronchial responsiveness, exhaled NO and sputum eosinophilia were significantly decreased 2 and 6 months after starting ICS treatment. Bronchial responsiveness was further decreased at 6 months together with a further increase in FEV₁. In 13 patients, BHR was not normalized despite the 6 months of treatment. This group showed a higher prevalence of males, those with a smoking history and airflow limitation, a higher eosinophil count in the sputum following 6 months of treatment and a longer history of asthma. Multiple, stepwise, linear regression analysis showed that sputum eosinophilia and lower FEV₁/FVC following 6 months of treatment and a longer history of asthma were significant independent determinants for BHR after 6 months of ICS treatment.

Conclusions These findings suggest that the resistance to a moderate dose of ICS for BHR in asthmatics may be significantly associated with remained airflow limitation, eosinophilic airway inflammation resistive to moderate dose of ICS, and delayed introduction of ICS therapy.

Key words: asthma, inhaled corticosteroid (ICS), exhaled nitric oxide, eosinophilic airway inflammation, bronchial hyperresponsiveness (BHR)

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Introduction

Chronic allergic airway inflammation is the major cause of the symptoms and bronchial hyperresponsiveness (BHR) in asthma, even in mild cases (1). Such inflammation may lead to changes in airway structure, causing irreversible airflow limitation and persistent symptoms (2, 3). Inhaled corticosteroids (ICS) decrease the airway inflammation, im-

prove lung function, lessen symptoms and BHR and reduce mortality (4-6). Therefore, ICS is considered the first line of treatment in asthma.

In 1994, Haahtela et al (7) reported that early intervention with ICS in newly diagnosed asthmatic adults improves the prognosis of asthma. They compared two groups of newly diagnosed asthma patients treated with 1,200 µg/day of inhaled budesonide for two years followed by 400 µg/day of inhaled budesonide at the beginning of a three-year study or

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with terbutaline for two years followed by 1,200 µg/day of inhaled budesonide. The degrees of improvement in lung function and bronchial responsiveness to histamine and asthma control were less in patients with delayed budesonide treatment as compared with those treated with budesonide at the beginning of the three-year study. Early treatment with inhaled budesonide resulted in long-lasting control of mild asthma. In a recent a 3-year study in patients with recent onset mild persistent asthma, early once-daily treatment with low-dose budesonide (400 µg/day) also reduced the risk of severe asthma exacerbation by almost half, and resulted in more symptom-free days and a reduced need for courses of systemic corticosteroids and additional treatment for asthma (8). This report provided evidence on which to base recommendations for treatment regarding the use of ICS in mild persistent asthma (9).

The present study was performed to examine whether early intervention with 200 µg of inhaled fluticasone propionate (FP) twice a day for 6 months can improve BHR to methacholine together with improvement of allergic airway inflammation in adult patients with mild to moderate asthma that had not ever been treated with any ICS from the onset of asthma. We also examined the characteristics of asthmatic patients whose BHR did not improve despite 6 months of treatment with a moderate dose of inhaled FP. As an index of allergic airway inflammation, we examined eosinophilia in induced sputum and measured the concentration of exhaled nitric oxide (NO). Exhaled NO has been proposed as a non-invasive marker of airway inflammation in asthma (10), and it has been demonstrated that there are relationships between exhaled NO and markers of mucosal eosinophilic inflammation in asthma (11). Jones et al (12) reported that exhaled NO measurements were as useful as induced sputum analysis and BHR in assessing airway inflammation and predicting loss of control in asthma following steroid withdrawal. Exhaled NO may be a useful indicator in the longitudinal assessment of asthma control.

Materials and Methods

Subjects

Forty-two symptomatic patients with mild to moderate bronchial asthma, who had never received treatment with any ICS from the onset of asthma, were recruited from our outpatient clinic. Asthma was defined as a clinical history of intermittent wheeze, cough, chest tightness, or dyspnea, documented reversible airflow limitation either spontaneously or with treatment with an inhaled β_2 -agonist and BHR to methacholine. Among the 42 patients initially enrolled, 34 completed the study. The remaining 8 patients dropped out during the study because of the administration of systemic corticosteroids and/or with an add-on leukotriene receptor A antagonist (LTRA) and/or a long-acting β_2 -agonist (LABA) due to exacerbation (5 patients) and no admission to hospital or no adequate sputum sample obtained (3 patients). Ta-

Table 1. Characteristics of the 34 Patients with Asthma

Age, yr	48.4±2.9
Sex (males/females)	20/14
Smoking history, n	16
Severity (step 1/2/3), n	4/13/17
Duration of illness, months	42.7±9.7
VC, % of pred.	106.1±2.5
FEV ₁ , % of pred.	85.5±2.8
FEV ₁ /FVC, %	76.2±2.3
DLco, % of pred.	100.0±3.0
Induced sputum	
Total cells, x10 ⁵ /g	158.9±64.8
Macrophage, %	18.1±2.9
Lymphocyte, %	5.6±0.8
Neutrophil, %	56.1±4.8
Eosinophil, %	20.5±3.9
Exhaled nitric oxide, ppb	166.6±22.2
Dmin, U	2.1±0.4

Values are means±SEM.

ble 1 shows the characteristics of the 34 patients. The patients ranged in age from 15 to 74 years, with a mean of 48.4±2.9 years. Five patients were current smokers, and 11 were former smokers. In accordance with the Global Initiative for Asthma (GINA) guidelines (9), the patients were classified as follows: intermittent mild asthma, 4 patients; persistent mild asthma, 13 patients; and moderate persistent asthma, 17 patients. The durations of asthma histories were from 2 to 228 months, with a mean of 42.7±9.7 months. All asthmatic patients were taking an inhaled β_2 -agonist when needed. The patients with intermittent mild asthma were treated only with an inhaled β_2 -agonist when needed. Of patients with persistent mild asthma, 7 were taking no treatment and 6 were treated with oral theophylline and/or a long-acting inhaled β_2 agonist (LABA). All patients with moderate persistent asthma were taking oral theophylline and/or LABA and/or LTRA. All patients were free from airway infections for 1 month prior to the study. All subjects gave informed consent to participation in the study, which had the approval of the hospital's ethical committee.

Study design

Symptomatic adult patients with mild to moderate asthma from our outpatient clinic, who had not been treated with any ICS from the onset of asthma, were enrolled in the study. At initial consultation, each patient underwent a standard clinical assessment, which consisted of a history and physical examination and completion of a medical questionnaire, laboratory tests, including the measurement of serum total IgE and IgE radioallergosorbent test (RAST) to 26 common allergens, chest radiography and pulmonary function tests (Chestac-55V; Chest Co., Ltd., Tokyo, Japan). At the second visit, the concentration of exhaled NO was measured, and then the bronchial responsiveness to methacholine

was examined. The following day, sputum was collected following induction with hypertonic saline. After completion of baseline measurements, all patients were treated with 200 µg of inhaled fluticasone propionate (FP) twice a day in addition to their previous treatment regimen. Exhaled NO, spirometry and bronchial responsiveness were again measured in all patients, and their induced-sputum was obtained at 2 and 6 months after the start of ICS.

Bronchial responsiveness to methacholine

Bronchial responsiveness was estimated using the continuous methacholine inhalation method combined with simultaneous measurement of respiratory resistance (*Rrs*; cmH₂O/L/s) using the device developed by Takishima et al (13) (Asthograph; Chest, Tokyo, Japan). Briefly, methacholine chloride (Daiichi Kagaku Yakuhin Co., Tokyo, Japan) diluted with physiological saline was inhaled during tidal breathing from a nebuliser in 10 steps at concentrations that doubled at every step (from 49 µg/ml to 25 mg/ml). After recording the baseline *Rrs* during inhalation of physiological saline for 1 min, inhalation of methacholine chloride was performed at 1-min intervals until the *Rrs* reached approximately twice the baseline value, or until the maximum concentration had been administered. The cumulative dose of inhaled methacholine at the inflection point where *Rrs* began to increase (*Dmin*) was adopted as the marker for bronchial responsiveness. This parameter was measured in terms of a unit defined as 1-min inhalation of 1 mg/ml methacholine. The total cumulative dose of methacholine at inhalation of the maximum dose (25 mg/ml) was 50 units. AHR was defined as *Dmin* ≤ 12.5 U (13, 14).

Sputum collection and analysis

We collected sputum induced by inhalation of hypertonic saline as described previously (15). The method of sputum induction was as follows: prior to the induction of sputum, all subjects inhaled a β₂-agonist, and 3.5% hypertonic saline was nebulized with an ultrasonic nebulizer (NE-V10B; Omron, Tokyo, Japan) for a period of 10 min. If the appropriate sputum could not be obtained, 4.5% hypertonic saline was nebulized for periods of 5 min. Nebulization was discontinued if the FEV₁ decreased by more than 20% or if problematic symptoms occurred. The nebulization was continued for at least 10 minutes and stopped after 15 minutes or if a good quality sputum sample of ≥ 2 ml was obtained. For collection of induced sputum, the subjects were asked to rinse their mouths and throats and then to try to cough up sputum into a sterile plastic dish. The sputum was then separated from contaminating saliva by macroscopic examination, and the mucus plug was removed from the dish onto a sterile plastic container, after which the volume of the sample was determined. The sample was overlaid with an equal volume of Hank's balanced salt solution (HBSS) containing 1 mM dithiothreitol (Sigma Chemicals, Poole, UK) and incubated at 37°C for 15 minutes. The incubated suspension was then washed twice with HBSS. After the resid-

ual mucous was removed by filtering the suspension with gauze, the eluent was used for total and differential cell counts. The total cell count, except that of squamous cells, was determined with a standard hemocytometer, normalized for weight and expressed as number of cells × 10⁵ /g wet weight of sputum. Cell smears were prepared by centrifugation (Autosmear; Sakura, Tokyo, Japan) and stained with May-Grünwald-Giemsa stain for differential cell counting, which was carried out in a blinded fashion. The slides were coded and 500 cells were counted for differential leukocyte counting. The results of the differential leukocyte counts were expressed as percentages of nucleated cells except for squamous and epithelial cells.

Measurement of exhaled nitric oxide

Fractional exhaled NO concentration was measured using a chemiluminescence analyzer (CLM-500; Shimadzu, Kyoto, Japan) calibrated with a certified NO calibration gas mixture as described previously (16, 17). The analyzer was sensitive to NO levels as low as 2 parts per billion (ppb), with a response time of less than 200 ms, and was adapted for online recording of NO concentrations. The analyzer sample flow rate was kept constant at 600 ml/min. Each subject was seated comfortably and NO was sampled *via* a mouthpiece without the use of a nose clip. Following deep breathing by mouth, each of the subjects inhaled NO-free gas, also *via* the mouth, to their total achievable lung capacity followed by slow exhalation. The online single exhalation technique with an exhalation rate of 2 L/min and positive expiratory mouth pressure of 8–10 cmH₂O was applied, according to the recommendations of ATS (17). The mean exhaled NO concentration of three acceptable end-expiratory plateau measurements was calculated.

Data analysis

The values shown in the text, figures and tables are means ± SEM. Comparison of variables at baseline, 2 months and 6 months were performed by two-way analysis of variance. Comparative tests between the variables at each time point were conducted with paired *t*-tests. Comparison of variables between the two groups (normalized BHR group and remaining BHR group) was performed by one-way analysis of variance, followed by comparisons with unpaired *t*-tests. Multiple, stepwise, linear regression analysis was performed to identify which variables were significant determinants for the resistance to inhaled corticosteroid treatment on BHR. The *p* < 0.15 was used first to identify candidate variables, and then variables were removed from the regression model if the *p* value was more than 0.1. All statistical analyses were performed with the use of a Windows-compatible software program (Stat Flex ver. 5.0, Artech Ltd., Osaka, Japan). A *p* value of less than 0.05 was considered significant for the results of all statistical analyses.

Figure 1. Changes in FEV₁ following treatment with 200 μ g of inhaled fluticasone propionate twice a day for 6 months. * P <0.05 and ** P <0.01 vs. pre-treatment FEV₁. † P <0.05 vs. FEV₁ at 2 months.

Figure 3. Changes in the concentrations of exhaled nitric oxide (NO) following treatment with 200 μ g of inhaled fluticasone propionate twice a day for 6 months. ** P <0.01 vs. pre-treatment exhaled NO.

Figure 2. Changes in Dmin following treatment with 200 μ g of inhaled fluticasone propionate twice a day for 6 months. Airway responsiveness was estimated by the continuous methacholine inhalation method with simultaneous measurement of respiratory resistance (R_{rs}) using an Astograph. Dmin; cumulative inhaled methacholine dose (1 Unit=1min of inhalation of 1mg/ml methacholine) when R_{rs} began to increase. ** P <0.01 vs. pre-treatment Dmin. † P <0.05 vs. Dmin at 2 months.

Figure 4. Changes in eosinophil counts in induced sputum following treatment with 200 μ g of inhaled fluticasone propionate twice a day for 6 months. ** P <0.01 vs. pre-treatment eosinophil counts.

Results

Pulmonary function tests and bronchial responsiveness

At baseline measurements (Table 1), 11 patients showed decreases in FEV₁/FVC of less than 70%, and all patients showed BHR to methacholine. DLco was within the normal range in all patients. Following treatment with 400 μ g/day of inhaled FP, FEV₁ was increased significantly at 2 months (2.75 ± 0.18 L) from baseline (2.53 ± 0.15 L), and showed a further significant increase at 6 months (2.85 ± 0.16 L)

(Fig. 1). Following the 6 months of treatment, 8 patients still showed FEV₁/FVC <70%. Dmin was increased significantly at 2 months (17.5 ± 3.5 U) from baseline (2.1 ± 0.4 U), and showed a further significant increase at 6 months of treatment with inhaled FP (24.1 ± 3.6 U) (Fig. 2). Dmin values reached within the normal range of more than 12.5 U in 13 and 8 patients at 2 and 6 months, respectively, and these subjects showed improved BHR. However, Dmin remained less than 12.5 U in 13 patients despite 6 months of treatment with inhaled FP.

Exhaled NO and sputum eosinophilia

The mean concentration of exhaled NO, 166.6 ± 22.2 ppb, in patients with asthma before treatment with inhaled FP was increased significantly above the normal range in our laboratory (mean $\pm$ SD; 37.4 ± 8.6 ppb). The amount of exhaled NO was decreased significantly at 2 months (76.4 ± 7.1 ppb) and 6 months (70.4 ± 9.3 ppb) as compared with baseline values. However, the decrease at 6 months was not sig-

Table 2. Differences in Normalized AHR and Remaining AHR Groups Following 6 Months of Treatment with 200µg FPbd

	Normalised AHR	Remaining AHR
Number	21	13
Male/Female	9/12	11*/2
Age, yr	47±4	50.8±3.8
Smoking history, n (%)	7 (33.3)	9 (69.2)*
d-FEV ₁ , L	0.30±0.08	0.35±0.14
Baseline		
FEV ₁ , % of pred.	91.5±2.7	75.3±4.7 **
FEV ₁ , %	77.9±2.0	70.6±3.1
Sputum eosinophils, %	18.5±4.7	23.7±7.0
eNO, ppb	135.0±19.6	217.6±46.4
Dmin, U	2.96±0.65	0.79±0.19
At 6 months following ICS-treatment		
FEV ₁ , % of pred.	102.2±3.0	83.4±5.2 **
FEV ₁ , %	82.4±1.7	68.6±3.6 **
Sputum eosinophils, %	1.3±0.4	10.5±5.4 *
eNO, ppb	65.4±12.5	78.3±14.0
Dmin, U	36.6±3.6	4.0±1.2 *
Duration of illness, months	23.7±9.4	73.3±17.8 *

Values are means±SEM. FP, fluticasone propionate; d-FEV₁, difference from baseline FEV₁ at 6 months; eNO, exhaled nitric oxide. *p<0.05, **p<0.01 vs. normalized AHR group.

nificantly different from the value at 2 months (Fig. 3). Cell analysis of induced sputum obtained before treatment with inhaled FP showed increased relative eosinophil counts. The eosinophil counts were decreased significantly at 2 months (6.9±2.5%) and showed a tendency toward a further decrease at 6 months (4.8±2.2%) from the baseline (20.5±3.9%) (Fig. 4).

Characteristics of asthma patients whose bronchial responsiveness was still increased despite 6 months of treatment with inhaled FP

The values of Dmin in 13 patients with asthma were not increased over 12.5 U despite 6 months of treatment with inhaled FP at 400 µg, and they still showed increased bronchial responsiveness to methacholine (remaining BHR group), and were resistant to a moderate dose of ICS treatment for BHR. In the remaining BHR group, 6 patients still sometimes complained of wheezing in the morning and/or at night or showed variability of peak expiratory flow rate (PEFR). The remaining BHR group showed a significantly greater prevalence of males and subjects with a smoking history, while the values of FEV₁ (% of predicted values) before and 6 months after ICS-treatment and FEV₁/FVC at 6 months after commencement of treatment were significantly lower as compared with the 21 patients who showed improvement in BHR by 6 months of treatment (normalised BHR group) (Table 2). In six patients in the remaining BHR group, FEV₁/FVC was still <70% and 4 still had a few symptoms or variability of PEFR, whereas only 2 patients in the normalized BHR group showed FEV₁/FVC <70%. Furthermore, the numbers of eosinophils in induced sputum from the patients in the remaining BHR group at 6 months after commencement of ICS treatment were significantly higher than those in the normalized BHR group, whereas there was no significant difference in eosinophils at baseline and in the concentration of exhaled NO both at baseline and at 6 months after commencement of treatment. There was

no significant difference in the values of Dmin at baseline between the two groups. The duration of asthma history until the first treatment with ICS in the remaining BHR group was significantly longer than that in the normalized BHR group. Multiple, stepwise, linear regression analysis was performed on Dmin following 6 months of ICS treatment among variables including smoking history, Dmin at baseline, duration of asthma history, spirometry, sputum cell analysis, eNO both at baseline and 6 months after commencement of the treatment. The regression model for lower values of Dmin following 6 months of ICS treatment was significant ($r=0.63$, $p=0.002$) and comprised the following determinants; eosinophil counts in induced sputum (partial $R^2=0.07$, $p=0.10$) and lower FEV₁/FVC (partial $R^2=0.27$, $p=0.017$) following 6 months of ICS treatment and a longer history of asthma until the first treatment with ICS (partial $R^2=0.16$, $p=0.049$). This model accounted for 33.9% of Dmin following 6 months of ICS treatment.

Discussion

In this study, treatment with 200 µg of inhaled fluticasone propionate twice a day for 6 months resulted in a significant increase in FEV₁, improvement of BHR and a decrease in exhaled NO and eosinophils in induced sputum in 34 symptomatic patients with mild to moderate asthma who had never received any ICS from the onset of asthma. However, BHR failed to normalize in 13 patients treated with ICS added to previous treatments for 6 months. These patients showed a higher prevalence of males associated with a smoking history and persistent airflow limitation, higher eosinophil counts in sputum following ICS treatment for 6 months, and a longer duration of asthma history. Multiple, stepwise, linear regression analysis revealed that sputum eosinophilia and lower FEV₁/FVC following 6 months of treatment and a longer history of asthma were significant independent determinants for BHR 6 months after ICS treat-

ment. These findings suggest that the resistance to a moderate dose of ICS for BHR in these asthmatics may be significantly associated with persistent airflow limitation, eosinophilic airway inflammation resistant to a moderate dose of ICS, and the delayed introduction of ICS therapy.

The eosinophil counts in sputum following 6 months of treatment were significantly higher in the remaining BHR group compared with those in the normalized BHR group. BHR to methacholine is closely related to airway inflammation (18, 19), and the improvement in BHR may be closely associated with the reduction of airway allergic inflammation, which is reflected by the reduction in eosinophil count with ICS treatment. Therefore, in asthmatics of the remaining BHR group, the 6 months of inhaled FP treatment at the moderate dose of 400 µg/day could not induce a sufficient improvement in the eosinophilic airway inflammation, which might be considered to result in poor improvement in BHR. Exhaled NO has been shown to be a marker of airway eosinophilia (10, 11), and to decrease following treatment with ICS (20). In the present study, exhaled NO fell rapidly following 2 months of treatment with FP without further improvement at 6 months. However, there was no significant difference in the level of exhaled NO following 6 months of treatment between the normalized BHR group and the remaining BHR group, and the reduction of exhaled NO was not consistent with the improvement in BHR following ICS treatment. Recent studies have demonstrated that exhaled NO levels may not accurately reflect airway inflammation in ICS-treated patients (21, 22). The levels of exhaled NO in steroid-naïve asthmatic subjects fall rapidly following ICS intervention, even with low-dose therapy, and prospective studies have not consistently correlated reductions in exhaled NO levels with changes in eosinophil numbers or improvements in BHR.

Overbeek et al (23) demonstrated that a delayed introduction of ICS of 2.5 years in asthmatics leads to less improvement in PC₂₀ although similar improvements were observed in FEV₁. In the START trial (24), mild to moderate symptomatic asthma patients who had never been treated with ICS were given ICS for 2 years. A significant negative correlation was found between the duration of symptoms and maximum increases in peak expiratory flow rate or FEV₁, and a 2-year delay in treatment with ICS significantly reduced the expected improvement in airway function. It has been suggested that the greatest benefits are achieved if treatment with ICS is started within 2 years of symptom onset (7, 25). In the present study, 13 patients in whom BHR did not normalize despite treatment with 400 µg/day of ICS for 6 months had a longer duration of asthma history until introduction of ICS (>2 years in 10 of 13 patients). The delayed introduction of ICS therapy from onset of asthma was an important factor for poor improvement in BHR by the treatment with a moderate dose of ICS in mild to moderate asthma. In addition, FEV₁/FVC remained lower than 70% following ICS treatment in 6 of these 13 patients, and the inhalation of a β₂-agonist also could not increase their FEV₁/

FVC over 70% (data not shown), suggesting the possibility of the presence of fixed airflow limitation. Eosinophilic airway inflammation also remained to a greater extent as compared with that in the normalized BHR group. Airway remodeling is a possible mechanism for the development of fixed airflow limitation that is observed in chronic asthma patients (26). Ward et al (27, 28) have demonstrated that airway inflammation, airway remodeling, and BHR in asthma are inter-related and 40% of variation in BHR was predicted from the thickness of the reticular basement membrane (RBM), one of histological change in airway remodeling, and airway inflammation. Not only airway inflammation and BHR but also the thickness of RBM will be able to be improved by a long-standing ICS therapy. However, hypertrophy of the airway smooth muscle and fibrosis changes of RBM, which cause fixed airflow limitation, are irreversible structural changes even with a long-standing ICS therapy, which has been suggested to be caused by poor control of asthma for a long time and insufficient anti-inflammatory therapy, ICS, for asthma (29). In this study, multiple regression analysis showed that 33.9% of variation in BHR evaluated by Dmin was explained by a significant regression model comprised of persistent sputum eosinophilia and airflow limitation following 6 months of ICS treatment and the duration of asthma history up to the first treatment with ICS. Because some patients in the remaining BHR group still showed some symptoms or variability of PEFR, the dose of 400 µg/day of fluticasone may be insufficient to improve their BHR and airway inflammation. However, delayed introduction of ICS therapy may also lead to the development of airway remodeling, resulting in remaining airflow limitation, which is one contributing factor for poor improvement in BHR, together with the remaining eosinophilic airway inflammation. Therefore, early intervention with sufficient ICS therapy is very important to improve not only symptoms and pulmonary function but also BHR in its earlier stage and to prevent the development of airway remodeling.

In the present study, the prevalence of a smoking history was significantly greater in remaining BHR group as compared with the normalized BHR group. It was demonstrated that neither lung functions nor eosinophil markers changed in smokers with asthma even following treatment with high-dose budesonide (1,600 µg/day) (30), and that current smokers have more asthma symptoms, more frequent asthma attacks and higher asthma severity scores as compared to those who have never smoked and ex-smokers (31). Most of the subjects having a smoking history were ex-smokers and only 3 asthmatics in the normalized BHR group and 2 asthmatics in the remaining BHR group were current smokers. We could not completely exclude the complication of chronic obstructive pulmonary disease (COPD), however, no low attenuation area on chest high-resolution computed tomography (HRCT) could be found. Although multiple regression analysis did not show the smoking history to be a significant predicted factor, smoking history may contribute

to the poor improvement in eosinophilic inflammation and BHR in response to ICS therapy.

In conclusion, poor improvements in BHR, airflow limitation and eosinophilic airway inflammation in response to

treatment with a moderate dose of ICS may be associated with delayed introduction of ICS therapy in asthma. Early intervention with a sufficient dose of ICS in asthma is important to obtain good asthma control.

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