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Research Article

The Change in Pulmonary Function among Well-Controlled Mild Asthmatics after Initiation of Inhaled Corticosteroids

Yasuaki Masaki[1,2], Hirokazu Taniguchi[*2], Tomomi Ichikawa[2], Kazuki Shimokawa[2], Takeshi Tsuda[2], Hideaki Furuse[2], Kensuke Suzuki[2], Ryuji Hayashi[1], Kazuyuki Tobe[1]

[1]*First Department of Internal Medicine, Faculty of Medicine, University of Toyama, Japan*

[2]*Division of Respirology, Department of Internal Medicine, Toyama Prefectural Central Hospital, Japan*

**Corresponding author: Dr. Hirokazu Taniguchi, Division of Respirology, Department of Internal Medicine, Toyama Prefectural Central Hospital, 2-2-78 Nishinagae, Toyama 930-8550, Japan, Tel: +81-76- 424-1531; Email: tan-tym@umin.ac.jp*

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Abstract

Background

An accelerated decline of pulmonary function over time can occur in asthmatics. We investigated pulmonary function in treatment-naïve mild asthmatics after the start of inhaled corticosteroids and explored the risk factors for rapid loss of FEV_1.

Methods

We retrospectively assessed fifty patients with treatment-naive mild asthma who were well controlled after receiving inhaled corticosteroid over two years. The change in FEV_1 over time was assessed through the linear regression of FEV_1 by year through the best FEV_1 obtained during the six months after the start of inhaled corticosteroid. Asthmatics were assigned to three groups (group A, group B and group C) according to changes in FEV_1.

Results

The change in FEV_1 was -0.039 ± 0.12 L/year in all asthmatics, -0.164 ± 0.096 L/year in group A (n=16), -0.042 ± 0.022 L/year in group B (n=17) and 0.079 ± 0.082 L/year in group C (n=17). The lung function loss in most individuals was not related to asthma exacerbation. The best FEV_1 % predicted during the first six months in group A was higher than that in group B (p=0.054) and group C (p=0.006). The early improvement of pulmonary function in group A was greater than in group B (p=0.013) and group C (p=0.078).

Conclusions

The change in pulmonary function in treatment-naïve patients with mild asthma was variable after the initiation of inhaled corticosteroids. Airway reversibility during the early treatment period had some relation to loss of lung function.

Keywords: Bronchial Asthma; Pulmonary Function Test; Inhaled Corticosteroid; Chronic Airflow Obstruction

Abbreviations

ANOVA: Analysis of Variance;

FEV_1: Forced Expiratory Volume in One Second;

SD: Standard Deviation

Introduction

Asthma is characterized by variable airway narrowing, which is the cause of symptoms and physiological changes [1]. Several studies have shown that asthma can lead to permanent airway obstruction and that asthmatics experience a more accelerated decline of forced expiratory volume in one second (FEV_1) than normal subjects [2-9]. Airway remodeling may be associated with an increased rate of decline in lung function among patients with asthma [10-15]. However, an accelerated decline of pulmonary function does not occur in all asthmatics [16]. The prevalence of and factors associated with the accelerated decline of pulmonary function in patients with asthma are not fully elucidated.

Recently, many guidelines for the treatment of bronchial asthma have been published [1,17,18]. Treatment steps determined by asthma symptoms represent treatment options in these guidelines. Inhaled corticosteroids are the most effective controller medications currently available for adult asthmatics [1], and they reduce bronchial hypersensitivity and asthma attacks, improving the quality of life of asthmatics. Several studies have reported that inhaled corticosteroids can partially restore the longitudinal decline of the pulmonary function of asthmatics [19,20].

We conducted a retrospective observational study on treatment-naïve patients of bronchial asthma with well-controlled symptoms during treated with only inhaled fluticasone propionate without other asthmatic controller drugs. The objective of this study was to investigate the change in pulmonary function among these asthmatic patients and elucidate the risk factors associated with the accelerated decline of pulmonary function.

Materials and Methods

Study Design and Subjects

We retrospectively examined the medical records of patients who visited the division of respirology in Toyama Prefectural Central Hospital because of mild asthma symptoms, such as cough, wheezing, episodic breathlessness and chest tightness, between 2001 and 2005. The eligible patients had not been diagnosed as having asthma before the first presentation, were diagnosed with asthma, were with well or fairly controlled symptoms during treated with 400 micrograms per day of inhaled fluticasone propionate without other asthmatic controller drugs and had a respiratory function test every two months or more frequently throughout the observational period. A well or fairly controlled patient was defined as a patient who did not experience exacerbation or a patient who experienced an exacerbation requiring systemic corticosteroid therapy during the observational period. The diagnosis of asthma was based on the history of characteristic symptom patterns and evidence of variable airflow limitation parallel with the definition of the Global Initiative for Asthma (GINA). We excluded patients who had other respiratory disease or had two or more frequent exacerbations. We enrolled fifty consecutive asthmatic patients who met the criteria for two years after the first visit. Data were collected for two years after the first visit based on medical records at Toyama Prefectural Central Hospital.

We selected ten consecutive patients as a control group to analyze FEV_1. Patients with non-asthmatic eosinophilic bronchitis [21] (atopic cough [22]) or cough variant asthma [23] were enrolled as controls in this study. They were treated with H_1 antihistamines and/or inhaled corticosteroids for two years, and their pulmonary function was measured more frequently than every two months.

The study protocol was approved by the institutional review boards at Toyama Prefectural Central Hospital.

Pulmonary Function Test

Spirometric tests were performed using a computerized SUPER SPIRO D-21 (CHEST, Japan) between 9 a.m. and 11 a.m. pulmonary function was measured when the patient did not have exacerbation. Forced expiratory volume in one second (FEV_1) and forced expiratory volume in one second as a percentage of predicted (FEV_1 % predicted) were examined based on medical records. Predicted FEV_1 was calculated using the formula provided by the Japanese Respiratory Society [24].

It was previously reported that pulmonary function in treatment-naïve asthmatics improved after the administration of inhaled corticosteroids and declined again after six months [20]. Therefore, we defined the "first" data of pulmonary function tests as the result of the first examination (Figure 1). We defined the "initial" data of pulmonary function tests as the best result during six months after the initiation of treatment with inhaled corticosteroids [2]. Thus, we assessed first FEV_1, first FEV_1 % predicted, initial FEV_1 and initial FEV_1 % predicted for each patient. In previous studies, the change in pulmonary function was calculated on the basis of two measured FEV_1 values obtained during consecutive tests. However, because of the fluctuation in pulmonary function due to circadian changes and diurnal variability in asthmatic patients, it is difficult to assess the exact rate of decline of pulmonary function using only two observational results. In this study, therefore, we calculated the linear regression of FEV_1 plotted by time (year), and we

analyzed the FEV_1 coefficient as the change in FEV_1 per year [2]. The predicted decline of FEV_1 per year in each patient was also calculated using the formula provided by the Japanese Respiratory Society [24].

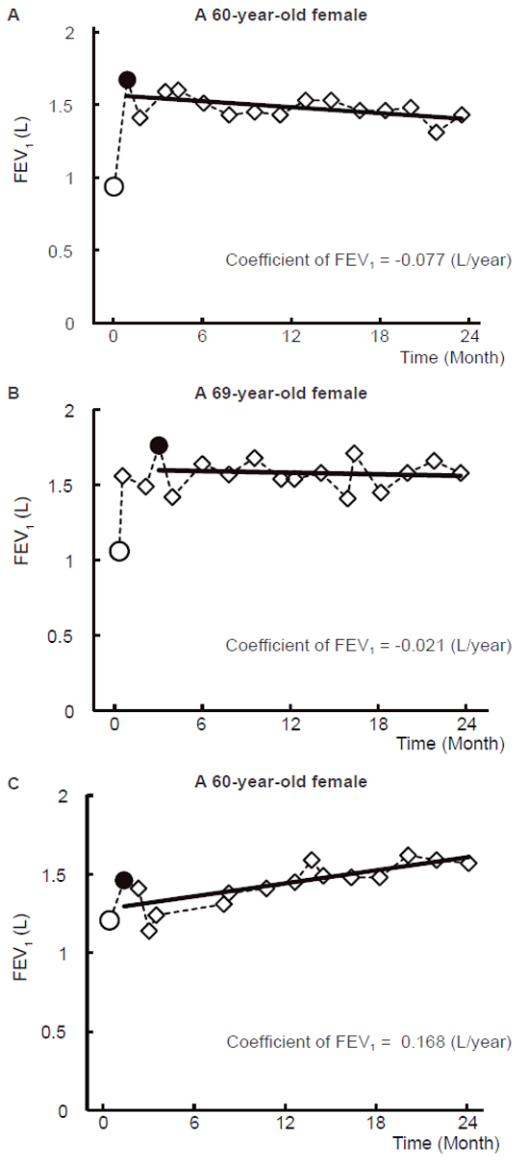

Figure 1. FEV_1 charts of three representative treatment-naïve patients with mild asthma over a two-year period before and after the start of inhaled corticosteroid treatment. The first FEV_1 level, which is the FEV_1 level before the start of inhaled corticosteroid, is shown with an open circle (○). With treatment, the FEV_1 level changed. The initial FEV_1 level, which is the best result during the period of six months after the start of treatment, is shown with a closed circle (●). The linear regression lines of FEV_1 after initial FEV_1 are also shown. (A) A 60-year-old female experienced a rapid decrease of her pulmonary function. Her change in FEV_1 was estimated to be -0.077 (L/year) using the coefficient of FEV_1. She was stratified to group A. (B) A 69-year-old female with mild decline of her pulmonary function was stratified to group B. Her change in FEV_1 was calculated to be -0.021 (L/year). (C) The FEV_1 of a 60-year-old female was slowly improved with treatment. Her change in FEV_1 was estimated to be +0.168 (L/year). She was assigned to group C.

Analysis

To identify high-risk patient groups that exhibited an accelerated decline of FEV_1, each patient was assigned (in a 1:1:1 ratio) to one of three groups (group A, group B and group C) according to changes in FEV_1. Patients with the lower one third of FEV_1 change were assigned to group A. We considered group A to be the high-risk group that exhibited accelerated FEV_1 decline. We compared the characteristics of the three groups. We also calculated the ratio of the difference between the initial FEV_1 % predicted and the first FEV_1 % predicted to the initial FEV_1 % predicted {*i.e., (initial FEV_1 % predicted – first FEV_1 % predicted) /initial FEV_1 % predicted*} and considered it to represent the early improvement of pulmonary function after treatment initiation.

Statistics

The data are expressed as the mean ± SD. The between-group differences were determined using an analysis of variance (ANOVA) or chi-square test. We performed an unpaired t-test to compare each group and a paired t-test to compare repeated-measure data within the group. Linear regression analysis was used when appropriate, and statistical correlation was evaluated using Pearson's test. A $p < 0.05$ was adopted as significant throughout the study. All of the p values were two sided.

Results

Patient Characteristics

Among fifty patients, nineteen were women, and thirty-one were men (Table 1). Thirty patients had atopic asthma, and twenty patients had non-atopic asthma. The patients were aged twenty-four to seventy years old at the first visit. Ten patients were ex-smokers, three patients were smokers, and thirty-seven patients were non-smokers. We selected ten additional patients as a control group. Four patients in the control group had non-asthmatic eosinophilic bronchitis (atopic cough), and six patients had cough variant asthma (Table 1). The compliances of drug administration of all patients were good.

Evaluation of the change in FEV_1 in patients with asthma and patients with cough variant asthma or non-asthmatic eosinophilic bronchitis.

The change in FEV_1 was -0.039 ± 0.12 L/year in asthmatics (range from -0.469 to 0.2624 L/year; Figure 2 and Figure 3)

and -0.040 ± 0.063 in patients with cough variant asthma or non-asthmatic eosinophilic bronchitis (range from -0.156 to 0.080; Figure 3). The predicted change in FEV_1 in asthmatics was -0.028 ± 0.001 L/year (range from -0.032 to -0.026 L/year; Figure 3). The difference between the observed and predicted change in FEV_1 in asthmatics was not significant (p = 0.543; Figure 3). The change in FEV_1 was not significantly different between patients with asthma and patients with cough variant asthma or non-asthmatic eosinophilic bronchitis (p = 0.976; Figure 3). In asthmatics, a history of smoking and atopic or non-atopic asthma did not affect the change in FEV_1 per year (p = 0.901 and p = 0.962, respectively; Table 1).

Table 1. Baseline characteristics of asthmatic patients and patients with cough variant asthma or non-asthmatic eosinophilic bronchitis.

Variable	Asthmatic patients (n=50)	Patients with cough variant asthma (n=6) or non-asthmatic eosinophilic bronchitis (n=4)
Patient age (year)	49.0 ± 14.4	55.1 ± 15.0
Male/female, n/n	19/31	6/4
Smoker/nonsmoker, n/n	13/37	3/7
Atopic/nonatopic, n/n	30/20	8/2
Change level of FEV1 (L/year)	-0.040 ± 0.123	-0.040 ± 0.063
Frequency of asthma exacerbation (/person/year)	0.02	0
First FEV1 % predicted (%)	78.3 ± 18.9	105.6 ± 9.56
Initial FEV1 % predicted (%)	96.8 ± 17.2	114.3 ± 9.39

Values are presented as mean ± SD. FEV1, forced expiratory volume in one second. FEV1 % predicted, forced expiratory volume in one second as a percentage of predicted.

Table 2. Baseline characteristics of asthmatic patient groups.

	group A (n=16)	group B (n=17)	group C (n=17)
Patient age (year)	47.5 ± 17.0	51.7 ± 12.6	47.7 ± 14.1
Male/female, n/n	4/12	8/9	7/10
Smoker/non-smoker, n/n	3/13	4/13	6/11
Atopic/nonatopic, n/n	9/7	9/8	10/7
Pet owner/non-owner, n/n	0/16	1/16	1/16
With allergic sinusitis, without sinusitis, n/n	0/16	0/17	0/17
Change level of FEV1 (L/year)	-0.164 ± 0.096	-0.041 ± 0.022	0.079 ± 0.082
Frequency of asthma exacerbation (/year/person)	0.0313	0.0294	0
First FEV1 % predicted (%)	77.3 ± 24.2	84.0 ± 17.4	73.7 ± 13.5
Initial FEV1 % predicted (%)	106.3 ± 16.8	95.2 ± 15.1	89.5 ± 16.3

Values are presented as mean ± SD. FEV1, forced expiratory volume in one second. FEV1 % predicted, forced expiratory volume in one second as a percentage of predicted.

The change in FEV_1 per year in asthmatics was not correlated with age (p = 0.594, r = -0.077) or first FEV_1 % predicted (p = 0.9894, r < 0.001). However, the change in FEV_1 was weakly correlated with initial FEV_1 % predicted (p = 0.0324, r = -0.303).

Stratification into three groups according the order of the change in FEV_1 and their background.

The patients were stratified according to the order of the calculated longitudinal change in FEV_1 (Figure 2). The change in FEV_1 was -0.164 ± 0.096 L/year in Group A, -0.042 ± 0.022 L/year in Group B and 0.079 ± 0.082 L/year in Group C (Table 2). The longitudinal change in FEV_1 in each group was significantly dif-

ferent ($p < 0.001$). The age, gender, number of smokers, atopic status, complication of allergic sinusitis, pet ownership and frequency of asthma exacerbation were not significantly different between the three groups (Table 2). Asthma exacerbation was observed in only two individuals, and the lung function loss in most individuals was not related to asthma exacerbation.

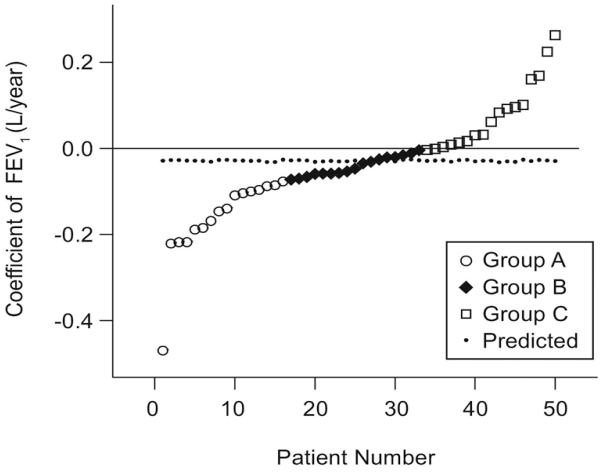

Figure 2. The FEV_1 coefficient and stratification of patients with mild asthma to the three groups. The longitudinal change in FEV_1 over a two-year period was assessed with the FEV_1 coefficient with the best FEV1 during the first six months after the start of inhaled corticosteroid. The FEV_1 coefficient of each patient is shown in ascending order of his or her coefficient. More than half of the patients exhibited a loss of pulmonary function. Nearly one third of patients experienced improvement in their pulmonary function. Patients with the lower one third of the FEV_1 coefficient were stratified to group A and are shown with an open circle (○, n = 16). Patients with the middle one third were group B and shown with a rectangle (◆, n = 17). Patients with the upper one third were assigned to group C and shown with an open square (□, n = 17). Small closed circles (•) are the predicted change in FEV1 in each individual.

The first FEV_1 % predicted and initial FEV_1 % predicted between groups.

The first FEV_1 % predicted in the three groups was not significantly different ($p = 0.275$; Table 2). However, the initial FEV_1 % predicted in the three groups was significantly different ($p = 0.014$; Table 2 and Figure 4). The initial FEV_1 % predicted was significantly higher in group A than in group C ($p = 0.006$). There was no significant difference in initial FEV_1 % predicted between group A and group B or between group B and group C ($p = 0.054$ and $p = 0.300$, respectively).

The rate of pulmonary function improvement after the initiation of inhaled corticosteroids was different between the groups.

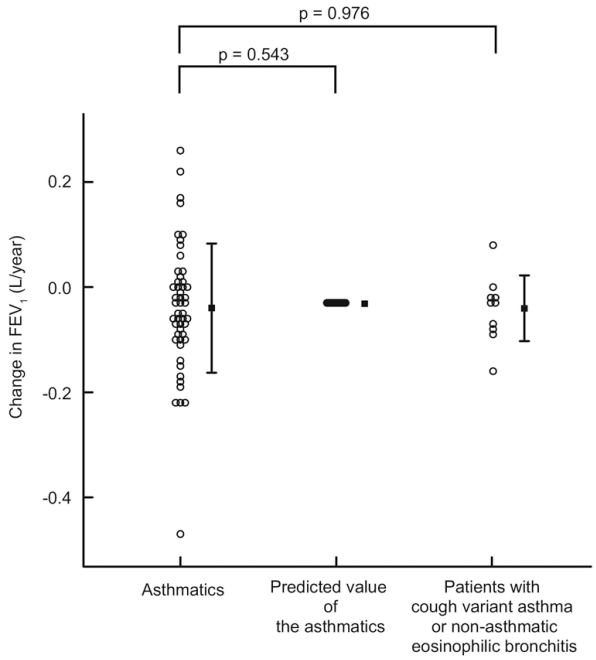

Figure 3. The change in FEV_1 in asthmatics and patients with cough variant asthma (n = 6) or non-asthmatic eosinophilic bronchitis (n = 4). In asthmatics (n = 50), observational and predicted [24] change levels are shown. The open circles (○) are the observational or predicted value of each patient. The square and error bar represent the mean and the SD of each group. The change in FEV_1 in asthmatics was widely distributed compared with patients with cough variant asthma or non-asthmatic eosinophilic bronchitis. In the asthmatics, observational and predicted changes in FEV_1 were not significantly different ($p = 0.543$ using paired t-test). The mean change in FEV_1 in the asthmatics was equivalent to patients with cough variant asthma or non-asthmatic eosinophilic bronchitis ($p = 0.976$ using unpaired t-test).

The difference between initial FEV_1 % predicted and the first FEV_1 % predicted in individuals was significant in all asthmatic individuals ($p < 0.001$; Table 1). The difference between initial FEV_1 and the first FEV_1 in individuals was also significantly different within stratified groups ($p < 0.001$ in group A, $p = 0.012$ in group B, $p < 0.001$ in group C; Table 2 and Figure 5).

The early improvement in pulmonary function after the initiation of inhaled corticosteroid was assessed by the ratio of the difference between the initial FEV_1 % predicted and the first FEV_1 % predicted to the initial FEV_1 % predicted. The early improvement levels were significantly different between the groups ($p = 0.020$). The early improvement in group A was greater than in group B ($p = 0.013$; Figure 6). The mean early improvement was not significantly different between group A and group C ($p = 0.078$) or between group B and group C ($p = 0.276$).

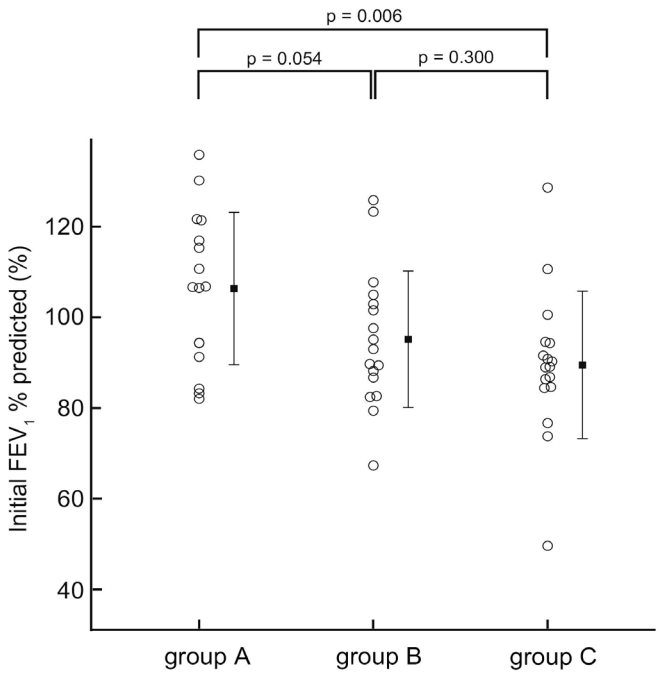

Figure 4. The initial FEV_1 % predicted in the asthmatic patient group stratified according to the longitudinal change in FEV_1. The square and error bar represent the mean and the SD in each group. ANOVA indicates that the initial FEV_1 % predicted was different in each group (p = 0.014). The initial FEV_1 % predicted in group A was significantly higher than that in group C (p = 0.006). The difference in the initial FEV_1 % predicted between group A and group B (p = 0.054) or between group B and group C (p = 0.300) was not significant.

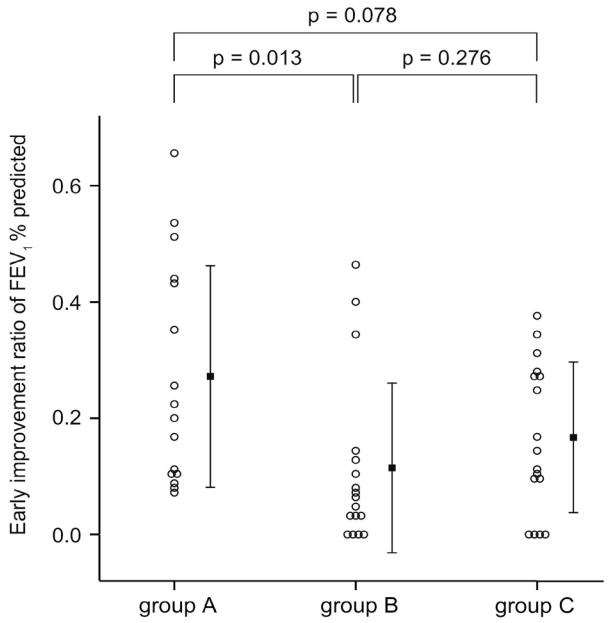

Figure 6. The early improvement ratio of FEV_1 % predicted in the groups. The best improvement level after the start of inhaled corticosteroid in a six-month period was calculated using the difference between initial FEV_1 % predicted and first FEV_1 % predicted divided by initial FEV_1 % predicted, where the first FEV_1 was the FEV_1 before the start of inhaled corticosteroids, and the initial FEV_1 was the best FEV_1 in a six-month period after the start of inhaled steroid. The square and error bar represent the mean and the SD in each group. ANOVA indicates that the early improvement ratios of FEV_1 % predicted in each group were different (p = 0.020). The early improvement ratios of FEV_1 % predicted in group A was significantly higher than that in group B (p = 0.013). No significant differences were found between group A and group C (p = 0.078) or group B and group C (p = 0.276).

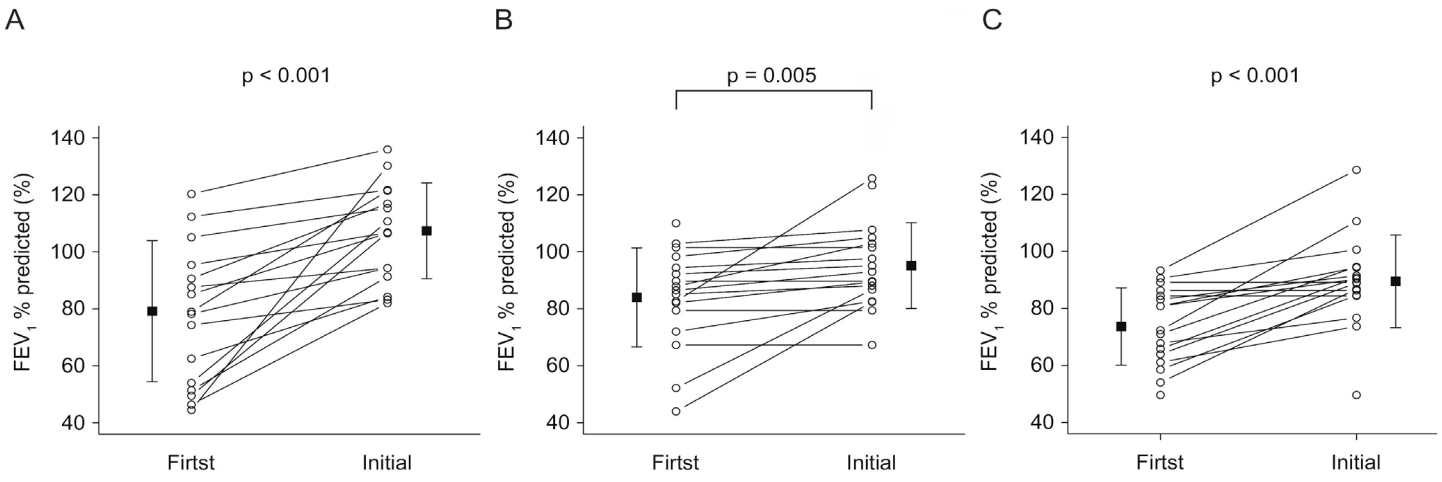

Figure 5. The first FEV_1 and initial FEV_1 of each patient in the groups. The first FEV_1, which was the FEV_1 before the start of inhaled corticosteroid, and the initial FEV_1, which was the best FEV_1 in a six-month period after the start of inhaled steroids, in group A (A), group B (B) and group C (C) are presented. The square and error bar represent the mean and the SD in each group. The initial FEV_1 was significantly higher than the first FEV_1 in in all groups (p < 0.001 in group A and group C, p = 0.012 in group B).

Discussion

In this study, we assessed the treatment effect of inhaled corticosteroids on the change in pulmonary function over two years among treatment-naïve patients with mild asthma. Evaluating the longitudinal change of pulmonary function in patients with asthma is sometimes ambiguous because of its variability. Because this study is limited by its retrospective design, there seems to be several bias in this study. Estimating the longitudinal decline of pulmonary function using the difference in measured FEV_1 at two examinations may be inappropriate because measurements could be influenced by variability. In this study, the change in FEV_1 over time was estimated as the FEV_1 coefficient, which was calculated using the linear regression of frequently measured FEV_1 by time after initial FEV_1, as we previously reported [2]. Using the coefficient of frequently measured FEV_1, we can minimize the effect of variability because frequent measurements offset variability in a patient.

We previously reported that a decline in pulmonary function over time was observed in all forty-nine patients with moderate or severe asthma [2]. However, in this study, the longitudinal change in FEV_1 in treatment-naïve patients with mild asthma was variable after the initiation of inhaled corticosteroids. Some individuals exhibited an accelerated loss of pulmonary function (Figure 1A and Figure 2). In agreement, a decline of pulmonary function over time reportedly did not occur in all asthmatics in a previous study [16]. Interestingly, FEV_1 improvement over two years was also observed in nearly one third of patients.

We stratified patients based on the longitudinal change in FEV_1 to assess the risk factors associated with a rapid loss of pulmonary function. Most patients who rapidly lost their pulmonary function were assigned to group A (Figure 2). The patients in group B experienced a relatively mild decline of pulmonary function, which was not different from that of normal subjects in another report [24]. Many asthmatics in group C exhibited improvement in their pulmonary function over time.

Asthma exacerbations are reportedly associated with a more rapid loss of lung function [25-29]. In this study, two participants experienced an asthma exacerbation. The lung function loss in other individuals was not related to asthma exacerbation. The smoking history was also not different between the groups.

The initial FEV_1 was significantly higher in group A than in group C. Consistent with this, we previously reported that initial FEV_1 % predicted was related to the decline in pulmonary function per year among moderate or severe asthmatics [2]. This relation can be explained by physiological pulmonary functional change to some degree because an absolute value of decline in pulmonary function could be proportional to basal pulmonary function.

In this study, the early change in pulmonary function after the initiation of inhaled corticosteroids had some relation to a rapid loss of pulmonary function (Figure 6). The degree of airway reversibility reportedly correlates with airway inflammation [30]. The early change in pulmonary function may reflect the severity of airway inflammation and predict changes in pulmonary function over time. Patients who had the greatest degree of reversibility were at the greatest risk of developing fixed airflow obstruction and had the greatest loss of lung function [31]. We speculate that clinical symptom of bronchial asthma is not always close relations with pulmonary function tests, and each patient of bronchial asthma has their own stability of bronchus disrelated with symptoms. We suspect that stability of bronchus reflects the change of pulmonary function. Unstable bronchus lead airway reversibility with bronchodilator and chronic airflow obstruction, and stable bronchus lead non-reversibility and chronic airflow non-obstruction. More studies on the early treatment effect and longitudinal outcome in treatment-naïve patients with mild asthma are needed.

Treatment with inhaled corticosteroids could be associated with an attenuation of the decline in pulmonary function [19, 20]. The FEV_1 coefficient of patients in group C was 0.079±0.082 L/year, which indicates that their pulmonary function slowly improved over time. Inhaled corticosteroids might ameliorate pulmonary function in this group. In contrast, patients in group A experienced a rapid reduction in lung function despite receiving the same dose of inhaled corticosteroid. Pulmonary function might improve in some patients in group A and more rapidly in some patients in group C if they received more intensive or appropriate treatment. Airflow limitation in asthmatics may reflect many conditions, such as the reversible airway edema with chronic bronchial inflammation, airway smooth muscle contraction, bronchial hypersecretion [1], decreased elastic recoil [32] and airway remodeling [10-13]. Some of these changes are related to the reversibility of asthma. Some may also result in an irreversible narrowing of the airways. More precise research on the mechanisms and effective treatments of asthmatic patients with an accelerated decline in lung function is warranted.

Conclusion

The change in pulmonary function after initial FEV_1 in treatment-naïve patients with mild asthma was variable after the initiation of inhaled corticosteroid. Airway reversibility in the early treatment period might have some relation to loss of lung function. Further investigation is needed to characterize asthmatic individuals who have the greatest loss of lung function. The development of treatment to slow a rapid loss of lung function in this population is also needed.

Conflicts of Interest

The authors have reported no significant conflicts of interest regarding any companies/organizations whose products or services may be discussed in this article.

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