Predictors of Pulmonary Function Response to Treatment with Salmeterol/fluticasone in Patients with Chronic Obstructive Pulmonary Disease

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Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease and responses to therapies are highly variable. The aim of this study was to identify the predictors of pulmonary function response to 3 months of treatment with salmeterol/fluticasone in patients with COPD. A total of 127 patients with stable COPD from the Korean Obstructive Lung Disease (KOLD) Cohort, which were prospectively recruited from June 2005 to September 2009, were analyzed retrospectively. The prediction models for the FEV1, FVC and IC/TLC changes after 3 months of treatment with salmeterol/fluticasone were constructed by using multiple, stepwise, linear regression analysis. The prediction model for the FEV1 change after 3 months of treatment included wheezing history, pre-bronchodilator FEV1, post-bronchodilator FEV1 change and emphysema extent on CT (R = 0.578). The prediction models for the FVC change after 3 months of treatment included pre-bronchodilator FVC, post-bronchodilator FVC change (R = 0.533), and those of IC/TLC change after 3 months of treatment did pre-bronchodilator IC/TLC and post-bronchodilator FEV1 change (R = 0.401). Wheezing history, pre-bronchodilator pulmonary function, bronchodilator responsiveness, and emphysema extent may be used for predicting the pulmonary function response to 3 months of treatment with salmeterol/fluticasone in patients with COPD.

Key Words: Pulmonary Disease, Chronic Obstructive; Emphysema; Corticosteroids; Adrenergic beta-Agonists; Respiratory Function Tests
INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is usually progressive and is associated with an abnormal inflammatory response of the lung to noxious particles or gases (1). Previous studies have shown that regular treatment of COPD with an inhaled corticosteroid (ICS) improve pulmonary function and reduces the frequency of exacerbations, even though it does not modify the long-term decline of forced expiratory volume in 1 sec (FEV1) (2, 3). Combination therapy with an ICS and a long acting β2-agonist (LABA) is better in improving lung function and health status, and reducing daily symptoms and exacerbations than single therapy (4, 5).

COPD is a heterogeneous disease in terms of clinical, physiological, and pathological presentation. The chronic airflow limitation associated with COPD is caused by a variable contribution of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema). Thus, the therapeutic response to combination treatment with an ICS and a LABA is also variable. Previous COPD guidelines recommended the use of short-term (two weeks) oral corticosteroid therapy to identify COPD patients who might benefit from long-term treatment with an ICS (6). However, it was recently shown that the response to a short-term oral corticosteroid is a poor predictor of the long-term response to an ICS (7). Currently, there are no known good predictors of the responsiveness of COPD patients to treatment with an ICS and a LABA.

The aim of this study was to identify predictors of pulmonary function response to 3 months of treatment with salmeterol/fluticasone in patients with COPD.

MATERIALS AND METHODS

Patients

A total of 127 stable COPD patients who had been treated with salmeterol/fluticasone for 3 months were analyzed retrospectively. All patients were selected from the Korean Obstructive Lung Disease (KOLD) Cohort, which had 226 stable patients with obstructive lung disease (OLD) were prospectively recruited from the pulmonary clinics of 11 hospitals in Korea from June 2005 to September 2009 (Fig. 1). The inclusion criteria for the KOLD cohort have been described elsewhere (8). COPD was diagnosed based on smoking history (more than 10 pack-years) and the presence of airflow limitation that was not fully reversible (post-bronchodilator FEV1/forced vital capacity [FVC] < 70% and post-bronchodilator FEV1 < 80% predicted). We included COPD patients who had wheezing history or who showed partial reversibility of airflow limitation after inhalation of salbutamol.

Study protocol

Baseline clinical data were obtained after cessation of the following respiratory medications: an ICS for 2 weeks, an inhaled LABA for 2 days, an inhaled short-acting β2-agonist or inhaled short-acting anti-cholinergic for 12 hr. The baseline clinical data included demographic data, smoking history, chronic bronchitis history, wheezing history, pulmonary function tests, chest radiography and volumetric computed tomography (CT). Chronic bronchitis was defined as cough and sputum production on most days for a minimum of 3 months per year for at least 2 yr (9). Wheezing history was obtained through the following question: “Have you had wheezing or whistling in your chest at any time in the last year?” (10) Atopic status was assessed by a skin prick test to 11 common allergens, with a 10% histamine and saline control. Patients were considered to be atopic if they reacted with a wheal of larger than the histamine control for more than one of the allergens. After obtaining baseline data, patients were treated with a salmeterol/fluticasone propionate 50/500 µg dry powder inhaler twice per day for 3 months, and then spirometry and lung volume measurement were performed again after the morning medication. During the 3-month treatment period, only salbutamol was allowed as needed. Adherence to the treatment medication monitored and recorded by research coordinators.

Pulmonary function tests

Spirometry was performed using a Vmax 22 instrument (SensorMedics; Yorba Linda, CA, USA) or a PFDX machine (MedGraphics, St. Paul, MN, USA). To assess the post-bronchodilator change, spirometry was performed pre-bronchodilator and 15 min after

Fig. 1. Patients selection.
inhalation of salbutamol (400 µg) through a metered-dose inhaler (MDI) with a spacer. Lung volumes were measured by body plethysmography (V6200; SensorMedics, or PFDX). Diffusing capacity for carbon monoxide ($D_{\text{CO}}$) was measured by the single-breath method using a $V_{\text{max}}$229D (Sensor-Medics) or a Masterlab Body (Jaeger AB, Würzburg, Germany). The predicted values of FEV$_1$, forced vital capacity (FVC), FEV$_1$/FVC and $D_{\text{CO}}$ were calculated from Korean equations formulated using data from a healthy non-smoking population (11, 12). The predicted values of lung volumes were calculated from ECSC equations (13). All pulmonary function tests were performed as recommended by the American Thoracic Society/European Respiratory Society (ATS/ERS).

**Computed tomography**

Volumetric CT scans were performed using 16-slice multi-detector CT (MDCT) scanners, according to previous described scanning protocols (14). Image data were stored in the Digital Imaging and Communications in Medicine (DICOM) format. Using in-house software, images of the whole lung were extracted automatically and the attenuation coefficient of each pixel was measured and calculated. The cutoff level between normal lung density and a low-attenuation area (LAA) was defined as -950 HU (15). From the CT data, the volume fraction of the lung below -950 HU ($V_{\text{below-950}}$) was calculated automatically. The airway dimensions, wall area (WA), lumen area (LA) and wall area percentage (WA%, defined as $WA/[WA + LA] \times 100$), were measured near the origin of two segmental bronchi (right apical and left apico-posterior) selected by a consensus reading of two radiologists. The software automatically detects the airway lumen and the inner and outer boundaries of the airway wall by use of a full-width-half-maximum (FWHM) method (16). The mean value of each segmental bronchus was used for analysis.

**Statistical analysis**

To investigate factors associated with the initial maximal positive pulmonary function response to 3 months of treatment with salmeterol/fluticasone, changes in pre-bronchodilator FEV$_1$, FVC and inspiratory capacity (IC)/total lung capacity (TLC) before and after 3 months were used as the dependent variable in univariate and multivariate analyses. The FEV$_1$ and FVC changes were expressed as % of predicted normal values (% predicted) to avoid the potential problem that baseline FEV$_1$ and FVC appear to influence on FEV$_1$ and FVC changes if expressed as % of baseline (17). Selected independent variables were sex, age, body mass index (BMI), chronic bronchitis history, wheezing history, smoking status (current or ex-smokers, smoking pack-years), pulmonary function parameters and CT parameters. For data that had a normal distribution, we used Student’s t-test or a one-way analysis of variance (ANOVA) for categorical variables. For data that had a non-normal distribution, we used Mann-Whitney U test or the Kruskall-Wallis test for categorical variables. Relationships between two continuous variables were examined by Pearson’s correlation analysis. The prediction models for pulmonary function response to 3 months of treatment with salmeterol/fluticasone were constructed from multiple, stepwise, linear regression models. All statistical analyses were performed with the SPSS statistical package (version 12.0, SPSS Inc, Chicago, IL, USA), and $P$ values less than 0.05 were considered significant.

**Ethics statement**

This study was approved by the Asan Medical Center institutional review board (Approval No. 2005-0345) and institution review boards of other 10 hospitals. Written informed consent was obtained from all patients.

**RESULTS**

**Patient characteristics**

Table 1 lists the baseline characteristics of the 127 COPD patients. Of the enrolled patients, 123 (97%) were male. Mean age was 65.5 (SD: 7.6) yr, and mean smoking history was 46.3 (20.7) pack years. A total of 74 patients were classified as GOLD II (moderate COPD), 46 as GOLD III (severe COPD), and 7 as GOLD IV (very severe COPD). Ninety-one percent of subjects indicated that they had taken over 80% of the recommended medication dose.

| Parameters | Mean (SD) |
|------------|-----------|
| Age (yr) | 65.5 (7.6) |
| Male:female | 123:4 |
| Body mass index (kg/m$^2$) | 23.4 (3.3) |
| Current smoker:ex-smoker | 48:79 |
| Smoking history (pack-years) | 46.3 (20.7) |
| Atopic:non-atopic (missing = 15) | 8:104 |
| Pre-bronchodilator FEV$_1$ (L) | 1.49 (0.50) |
| Pre-bronchodilator FEV$_1$ (% predicted) | 47.9 (14.1) |
| Pre-bronchodilator FVC (L) | 3.22 (0.82) |
| Pre-bronchodilator FVC (% predicted) | 75.3 (16.5) |
| Pre-bronchodilator FEV$_1$/FVC (%) | 46.4 (10.3) |
| Post-bronchodilator FEV$_1$ change (L) | 0.170 (0.133) |
| Post-bronchodilator FVC change (L) | 0.278 (0.287) |
| TLC (% predicted) | 105.6 (18.9) |
| VC (% predicted) | 92.7 (20.0) |
| IC/TLC (%) | 32.2 (0.1) |
| FRC (% predicted) | 131.7 (33.3) |
| RV (% predicted) | 133.4 (62.5) |
| D$_{\text{co}}$ (% of predicted) | 74.6 (25.8) |
| Low attenuation area (%) | 20.2 (14.5) |
| Wall area (%) | 66.2 (5.0) |

FEV$_1$, forced expiratory volume in 1 sec; FVC, forced vital capacity; TLC, total lung capacity; VC, vital capacity; IC, inspiratory capacity; FRC, functional residual capacity; RV, residual volume; D$_{\text{co}}$, diffusing capacity for carbon monoxide; Low attenuation area, volume fraction of the lung below -950 HU at full inspiration computed tomography; Wall area, wall area/wall area + lumen area on computed tomography.
there were no significant differences in the mean FEV1, FVC and terol/fluticasone than patients with GOLD stage II. However, showed significantly larger TLC and functional residual capacity (FRC) reduction after the 3 months of treatment with salmeterol/fluticasone.

Data are expressed as means with standard deviations. FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity; TLC, total lung capacity; IC, inspiratory capacity; FRC, functional residual capacity; RV, residual volume.

Table 2. Pulmonary function response to short-acting bronchodilator and 3 months of treatment with salmeterol/fluticasone according to baseline GOLD severity stage

| Predictor                          | GOLD II (n = 74) | GOLD III, IV (n = 53) | P value |
|------------------------------------|------------------|-----------------------|---------|
| Post-bronchodilator FEV1 change (L) | 0.178 (0.129)    | 0.158 (0.139)         | 0.464   |
| Post-bronchodilator FVC change (L) | 0.239 (0.280)    | 0.333 (0.292)         | 0.496   |
| FEV1 change after 3 months of treatment (L) | 0.142 (0.227)    | 0.184 (0.217)         | 0.875   |
| FVC change after 3 months of treatment (L) | 0.145 (0.353)    | 0.282 (0.406)         | 0.160   |
| TLC change after 3 months of treatment (L) | -0.217 (0.625)   | -0.399 (1.123)        | 0.035   |
| IC change after 3 months of treatment (L) | 0.162 (0.413)    | 0.113 (0.361)         | 0.600   |
| IC/TLC change after 3 months of treatment (%) | 3.121 (5.470)    | 2.219 (6.840)         | 0.227   |
| FRC change after 3 months of treatment (L) | -0.245 (0.407)   | -0.406 (1.150)        | < 0.001 |
| RV change after 3 months of treatment (L) | 0.162 (0.413)    | 0.113 (0.361)         | 0.600   |

Univariate analysis of baseline clinical variables and pulmonary function response to 3 months of treatment with salmeterol/fluticasone

The FEV1, FVC and IC/TLC changes after 3 months of treatment were normally distributed without evidence of a separate responder group. The mean FEV1, FVC and IC/TLC changes after 3 months of the treatment were 0.160 (0.223) L, 5.1 (7.3)% predicted and 0.202 (0.380) L, 4.8 (9.0)% predicted, and 2.7 (6.1)%, respectively. There were no significant differences in the mean postbronchodilator FEV1 and FVC changes according to baseline GOLD severity stage. Patients with GOLD stage III or IV showed significantly larger TLC and functional residual capacity (FRC) reduction after the 3 months of treatment with salmeterol/fluticasone than patients with GOLD stage II. However, there were no significant differences in the mean FEV1, FVC and IC/TLC changes after 3 months of the treatment (Table 2).

Among categorical variables, COPD patients with wheezing history had significantly greater FEV1 and FVC changes after 3 months of treatment than those without wheezing history (7.8% vs 2.7% predicted for FEV1, P < 0.001; 7.3% vs 2.3% predicted for FVC, P = 0.002). Simple correlation analysis indicated that pre-bronchodilator FEV1 and FVC had a weak negative correlation with the FEV1 and FVC changes after 3 months of the treatment but that post-bronchodilator FEV1 and FVC had no significant correlation with FEV1 and FVC changes after 3 months of the treatment. The post-bronchodilator FEV1 and FVC changes had a positive correlation with the FEV1 and FVC changes after 3 months of the treatment. LAA had a weak negative correlation with the FEV1 change after 3 months of the treatment, but mean WA was not correlated with the FEV1, FVC and IC/TLC changes after 3 months of the treatment (Table 3).

Table 3. Correlation between baseline clinical variables and pulmonary function response to 3 months of treatment with salmeterol/fluticasone

| Predictor                          | R     | P value |
|------------------------------------|-------|---------|
| FEV1 change after 3-month treatment (% predicted) | R     | P value |
| Age (yr)                           | -0.028| 0.755   |
| Smoking pack-years                 | 0.020 | 0.820   |
| Body mass index (kg/m²)            | 0.146 | 0.101   |
| Pre-bronchodilator FEV1 (% predicted) | -0.267| 0.002   |
| Post-bronchodilator FEV1 (% predicted) | -0.141| 0.114   |
| Post-bronchodilator FEV1 change (% predicted) | 0.432 | < 0.001 |
| Pre-bronchodilator FVC (% predicted) | -0.326| < 0.001 |
| Post-bronchodilator FVC (% predicted) | -0.191| 0.032   |
| Post-bronchodilator FVC change (% predicted) | 0.338 | < 0.001 |
| TLC (% predicted)                  | 0.080 | 0.372   |
| IC/TLC (%)                         | -0.192| 0.030   |
| FRC (% predicted)                  | 0.153 | 0.087   |
| RV (% predicted)                   | 0.205 | 0.021   |
| DLco (% of predicted)              | 0.072 | 0.432   |
| Low attenuation area (%)           | -0.222| 0.015   |
| Wall area (%)                      | 0.039 | 0.675   |

Prediction models for pulmonary function response to 3 months of treatment with salmeterol/fluticasone

Multiple, stepwise, linear regression analysis showed that four variables, wheezing history, pre-bronchodilator FEV1, post-bron-
Table 4. Multiple linear regression models for pulmonary function response to 3 months of treatment with salmeterol/fluticasone

| Variables                                | β    | 95% CI       | R   |
|------------------------------------------|------|--------------|-----|
| FEV1 change (% predicted)                | 8.98 | 2.70-15.22   | 0.578 |
| Wheezing history                         | 3.54 | 1.18-5.90    |     |
| Pre-bronchodilator FEV1 (% predicted)    | -0.13| -0.22--0.04  |     |
| Post-bronchodilator FEV1 change (% predicted) | 0.55 | 0.26-0.84   |     |
| Low attenuation area (%)                 | -0.09| -0.18--0.01  |     |
| FVC change (% predicted)                 | 12.27| 5.34-19.20   | 0.533 |
| Pre-bronchodilator FVC (% predicted)     | -0.15| -0.23--0.06  |     |
| Post-bronchodilator FVC change (% predicted) | 0.55 | 0.34-0.76 |     |
| IC/TLC (%)                               | 8.42 | 4.04-12.80   | 0.401 |
| Pre-bronchodilator IC/TLC (%)            | -0.23| -0.36--0.11  |     |
| Post-bronchodilator FEV1 change (% predicted) | 0.34 | 0.10-0.58 |     |

FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity; IC/TLC, inspiratory capacity/total lung capacity; Low attenuation area, volume fraction of the lung below -950 HU at full inspiration computed tomography; β, unconditioned coefficient; CI, confidence interval.

Wheezing is the most common symptom reported by asthmatic patients, but is also commonly reported by COPD patients (20). Marini et al. (21) reported that wheezing patients with chronic airflow obstruction differed from non-wheezing patients with chronic airflow obstruction by their bronchodilator response. Our results showed the COPD patients with a wheezing history had a significantly higher mean FEV1 and FVC changes after bronchodilator and 3 months of treatment than those without such a history. Our study also showed a positive correlation between bronchodilator responsiveness (post-bronchodilator FEV1 and FVC changes) and the FEV1 and FVC changes after 3 months of treatment. Previous studies showed that corticosteroid reversibility in COPD patients was related to features of asthma (22). Recently, Kitaguchi et al. (23) also reported that wheezing and bronchodilator responsiveness were significant determinant for the reversibility in response to an ICS.

This study also showed that COPD patients with lower pre-bronchodilator FEV1 and FVC have better responses to our combination treatment. On the contrary, there was no significant effect of post-bronchodilator FEV1 on the response to combination treatment. A post-hoc analysis in the TORCH study showed similar results in that the severity of COPD which was assessed by post-bronchodilator FEV1, was not related to the FEV1, improvements after a combination treatment (19). This result might be explained as follows. The lack of a relation between COPD severity and treatment responsiveness may be caused by the fact that pre-bronchodilator FEV1 and post-bronchodilator FEV1 change relate to treatment responsiveness. The post-bronchodilator FEV1 and FVC (which is unrelated to responsiveness) are the sum of the value of pre-bronchodilator FEV1 and FVC and the grade of bronchial wall thickening were significant determinants for bronchodilator responsiveness and for the responsiveness to the treatment with an ICS. However, other two studies found no significant differences in bronchodilator responsiveness among groups classified according to severity of emphysema (25, 26). Previously,
our study group has shown that emphysema dominant COPD patients (LAA ≥ 20% and pre-bronchodilator FEV₁ ≥ 45% predicted) responded poorly to the 3 months of combination treatment (27). In this study, LAA had a weak negative correlation with the FEV₁ change after 3 months of the treatment. This result might be explained as follows. For COPD patients, the major determinants of FEV₁ are small airway disease and emphysema. If a COPD patient has a more significant emphysema component than that of small airway disease, he or she would be expected to have a poorer response to pharmacologic treatments that predominantly target small airway disease. In this study, mean WA was not correlated with the FEV₁ and FVC change after 3 months of the treatment. A previous report showed that large airway dimension serve as a useful surrogate for small airway remodeling (28). Nonetheless, it is possible that the lack of a significant relationship between WA and treatment response may be due to the relatively imprecise and indirect estimate of small airway wall area. There are two factors that could have potentially confounded our volumetric CT result. First, we used three different MDCT scanners, and different scanners may have graded the emphysema index differently. A method that corrects for differences between different CT scanners has not yet been established. Second, we used only two large airways to evaluate airway dimension.

In this study, 19.7% of included patients had overlapping diagnoses of COPD and asthma (overlap syndrome). Those patients with overlap syndrome could affect our study results. However, subgroup analysis after excluding patients with overlap syndrome showed the similar results. Our study has two limitations. First, we did not consider airway inflammatory markers. Previous studies showed an increased number of eosinophils in bronchoalveolar lavage fluid in a subset of patients with COPD who responded to short-term administration of oral corticosteroids (29) and sputum eosinophil counts were significantly correlated with reversibility in response to ICS treatment (23). If we had included airway inflammatory markers, we might have been able to develop more powerful prediction models. Second, 97% of our patients were male. Gender may have a substantial influence on treatment response in COPD patients (30), so we cannot generalize our results to females.

In conclusion, wheezing history, baseline pulmonary function, bronchodilator responsiveness, and emphysema extent in COPD patients may be used for predicting the pulmonary function response to 3 months of treatment with salmeterol/fluticasone.

Conflict of Interest Statement
J. S. Lee, S.W. Ra, E. J. Chae, J-H Lee, E-K Kim, Y. K. Lee, T-H Kim, J. W. Huh, W. J. Kim, J. H. Lee, S-M Lee, S. Y. Lee, S. Y. Lim, T. R. Shin, H. I. Yoon and S. S. Sheen have no conflicts of interest to disclose. J. B. Seo has been an investigator in a government-sponsored study (2006-2008 Korea Science and Engineering Foundation).

Y-M. Oh has been an investigator in university-sponsored studies (Asan Institute for Life Science, University of Ulsan College of Medicine) and an industry-sponsored study (MSD Korea, and AstraZeneca Korea), and has participated as a speaker at scientific meetings organized and financed by various pharmaceutical companies (Handok, GlaxoSmithKline, AstraZeneca Korea, MSD Korea, and Boehringer Ingelheim) and a magazine company (Korea Doctors’ Weekly). S-D. Lee serves as a consultant to GlaxoSmithKline, and has participated as a speaker at scientific meetings organized and financed by various pharmaceutical companies (GlaxoSmithKline, AstraZeneca Korea, and Boehringer Ingelheim).

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Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease and their responses to combination therapy (inhaled corticosteroid [ICS] + long acting β-agonist [LABA]) are variable. Currently, reliable predictors for the responsiveness of COPD patients to the combination therapy are lacking. Here we investigated the parameters of pulmonary function test and radiological findings in the COPD patients treated for 3 months with salmeterol and fluticasone. The results show that wheezing history, pre-bronchodilator pulmonary function, bronchodilator responsiveness, and emphysema extent may be used for predicting the pulmonary function response to 3 months of treatment with the combination therapy.