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Lung function and symptom improvement with fluticasone propionate/salmeterol and ipratropium bromide/albuterol in COPD: Response by beta-agonist reversibility ☆

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ABSTRACT

This retrospective analysis of data from two multi-center, randomized, double-blind, parallel group studies compared the efficacy of fluticasone propionate/salmeterol (FSC) 250/50 mcg twice daily with ipratropium bromide/albuterol (IB/ALB) 36/206 mcg four times daily in albuterol-reversible ($n = 320$ [44%]) and non-reversible ($n = 399$ [56%]) patients with COPD. In reversible and non-reversible patients, both treatments significantly increased FEV_1AUC_{0-6h} from baseline and the magnitude of improvement was larger in reversible patients. FSC increased FEV_1AUC_{0-6h} by 1.46 ± 0.08 and 1.98 ± 0.13 l-h at Day 1 and Week 8, respectively, in reversible patients, compared with 0.71 ± 0.06 and 0.94 ± 0.10 l-h in non-reversible patients ($p < 0.001$). With IB/ALB, increases were 1.46 ± 0.08 and 1.19 ± 0.11 l-h at Day 1 in reversible patients and Week 8, respectively, and 0.89 ± 0.06 and 0.74 ± 0.09 l-h ($p \leqslant 0.041$) in non-reversible patients. After 8 weeks, in both the reversible and non-reversible populations, the FEV_1 AUC_{0-6h} significantly increased with FSC treatment ($p \leqslant 0.002$) and significantly decreased with IB/ALB ($p \leqslant 0.010$). In both reversibility groups, improvement in Transition Dyspnea Index (TDI) scores, overall daytime diary symptom scores and nocturnal symptom measures were significantly greater with FSC treatment compared with IB/ALB ($p \leqslant 0.044$). Reversibility status was not predictive of the magnitude of reduction in symptom scores. We conclude that both reversible and non-reversible patients receive greater clinical benefit with FSC compared with IB/ALB and acute bronchodilator reversibility is not useful for differentiating patients based on symptomatic responses to FSC compared with IB/ALB.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is an increasing worldwide public health burden. In the United States, COPD is the fourth leading cause of mortality exceeded only by cardiovascular disease, cancer, and cerebrovascular disease [1]. The primary characteristic of COPD is progressive airflow limitation that is not fully reversible [2,3]. Spirometric determination of a post-bronchodilator $FEV_1/FVC \leqslant 0.7$ is used to demonstrate airway obstruction found in COPD and confirm its diagnosis [2,3]. However, differential diagnosis by spirometry alone is complicated by the development of fixed or non-reversible airway obstruction characteristic of COPD in patients with chronic persistent asthma [4,5]. Although airway obstruction in COPD is not fully reversible, bronchodilator responsiveness is common in COPD and bronchodilator medications are recommended for symptomatic disease management by national and international treatment guidelines [2,3]. Bronchodilator reversibility can be defined as a post-bronchodilator increase in FEV_1 of $\geqslant 12\%$ and $\geqslant 200$ mL from baseline [2,3,6].

In an attempt to not include patients with a primary diagnosis of asthma, bronchodilator reversibility has been an exclusion criteria in many COPD clinical trials [7,8] and has been used by regulatory agencies for the diagnosis of COPD in registration trials in some countries. In addition, bronchodilator responses over time have been used as primary efficacy parameters to register therapies for this disease [9–13]. Exclusion based on reversibility is becoming less common with the understanding that bronchodilator responsiveness at a single-time point in COPD may not predict the clinical efficacy of bronchodilator medications [10,14–17]. However, acute bronchodilator reversibility may predict inflammatory characteristics and long-term prognosis [18–22]. Thus, it is important to investigate whether acute bronchodilator reversibility predicts responses to different therapeutic regimens in COPD.

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In two previously published clinical studies, we compared the short-term efficacy of fluticasone propionate/salmeterol 250/50 (FSC) twice daily and ipratropium bromide/albuterol 36/206 μg (IB/ALB) four times daily in patients with COPD [23,24]. In these studies, acute bronchodilator reversibility to albuterol status was obtained to characterize the patient population and permitted stratification of the treatment groups by initial bronchodilator reversibility. For the total patient population, treatment with FSC resulted in greater improvement in lung function and symptom measures compared with IB/ALB. To further characterize the relative treatment response of these different combination therapies, we performed a retrospective analysis of the previously published data to evaluate the clinical response to FSC and IB/ALB by baseline albuterol reversibility status.

2. Materials and methods

2.1. Patients

Male and female patients at least 40 years of age, with a diagnosis of COPD and no previous history of asthma, including childhood asthma, were eligible for the studies. In addition, patients were required to have a pre-albuterol FEV_1/FVC ratio of $\leqslant 0.7$ and a FEV_1 >0.70 L and $\leqslant 70\%$ of predicted normal or a pre-albuterol FEV_1 $\leqslant 0.70$ L and $\geqslant 40\%$ of predicted normal, a $\geqslant 10$ pack-year history of cigarette smoking, and use of an inhaled prescription short-acting bronchodilator for the symptomatic management of COPD for at least 30 days prior to enrollment. Concurrent use of inhaled or oral corticosteroids, long-term oxygen therapy, long-acting bronchodilators, theophylline, ipratropium bromide, ipratropium bromide/albuterol, and leukotriene antagonists was not allowed.

2.2. Study design

Two identical, randomized, double-blind, double-dummy, parallel-group studies were performed at a total of 87 clinical research centers in the United States (study numbers SCO40011 and 40012). Institutional Review Board approval and patient written informed consent were obtained prior to the conduct of study procedures. Study visits were conducted at screening, randomization (Day 1) and after 4 and 8 weeks of treatment. Following screening, patients completed an 8–14 day run-in period to obtain baseline symptom data and evaluate disease stability.

Reversibility was determined at screening with post-dose spirometry performed 30 min after subjects self-administered 180 μg of albuterol via metered-dose inhaler (MDI). Spacers were not used. Non-reversibility was defined as an absolute volume increase in FEV_1 of <200 mL from pre-albuterol baseline or an absolute volume increase $\geqslant 200$ mL but $<12\%$ of baseline FEV_1; reversible was defined as an absolute volume increase of $\geqslant 200$ mL and $\geqslant 12\%$ from baseline.

Eligible patients were randomized (1:1) to FSC 250/50 twice daily (ADVAIR DISKUS® 250/50) or IB/ALB 36/206 μg four times daily (Combivent®) via MDI for 8 weeks. To ensure blinding, each patient received a double-blind DISKUS and MDI. Patients were instructed to take one inhalation from the DISKUS in the morning and one in the evening, approximately 12 h apart, and to take two inhalations from their MDI four times daily, approximately 4–6 h apart.

At randomization and Week 8, serial spirometry was performed immediately pre-dose and 0.5, 1, 2, 4, and 6 h after one inhalation from the DISKUS device and two inhalations from the study MDI. Dyspnea was evaluated using the Baseline Dyspnea Index (BDI) and the Transitional Dyspnea Index® (TDI) [25]. A clinically meaningful difference between treatments for the TDI has been defined as 1.0 unit [26]. Throughout the study, subjects recorded daily severity ratings for daytime symptoms of shortness of breath, tiredness, activity limitations, frustration with symptoms, and nighttime sleep symptoms on diary cards. Each symptom was rated using a 0–100 visual analog scale (VAS) where zero indicated 'none/not-at-all' and 100 indicated 'worst it has ever been/as bad as it can be'. For overall assessment of daytime symptoms, a combined score was obtained by adding VAS scores for symptoms of shortness of breath, tiredness, activity limitation, and frustration with symptoms (maximum combined daytime symptom score: 400). Patients were required to be symptomatic as demonstrated by a combined daytime symptom score of 120 on at least 4 out of the 7 days prior to randomization. Additional diary card evaluations included morning peak expiratory flow (AM PEF), nighttime awakenings due to respiratory symptoms and the percent of COPD symptom-free nights.

2.3. Statistical analysis

Data analysis was performed on the intent-to-treat population, consisting of all patients who were randomized to blinded study medication. For the individual studies, a sample size of approximately 350 patients provided $>90\%$ power to detect a difference in pre-dose FEV_1 change from baseline of 100 mL. The treatment groups were stratified based on albuterol reversibility and the purpose of this stratification was to ensure similar distribution of reversible and non-reversible patients within the treatment groups. Subgroup analyses by albuterol responsiveness were indicated a priori in the protocol if each stratum met sufficient enrollment. Two-sided statistical tests were used for all analyses and p-values $\leqslant 0.05$ were considered statistically significant. p-Values were based on the least-squares means from analysis of covariance models calculated after adjustment for treatment, investigator, and baseline value. Analysis of percent symptom-free nights, sleep symptoms, and nighttime awakenings were performed on the a priori defined population of patients reporting at least one nighttime awakening during the 7 days immediately prior to randomization.

3. Results

3.1. Patient characteristics

A total of 726 patients were enrolled with 362 and 364 patients randomly assigned to the FSC and IB/ALB groups, respectively. Patient withdrawals consisted of 95 (13%) total patients with a similar number of patients who withdrew from the FSC (46 [13%]) and IB/ALB (49 [13%]) groups. Demographic and baseline characteristics at screening for the reversible and non-reversible groups by treatment group are shown in Table 1. The groups had similar demographic and baseline characteristics with the exception of albuterol response. Both groups had moderate to severe COPD with mean FEV_1 values of 42% and 44% of predicted normal in the reversible and non-reversible groups, respectively. Mean BDI scores were consistent with a moderate respiratory impairment due to dyspnea. Mean post-albuterol percent and volume increases in FEV_1 from baseline were 29% and 348 mL, respectively, in the reversible group and 8% and 94 mL for the non-reversible group.

The number of reversible and non-reversible patients by severity of post-bronchodilator FEV_1 at baseline is shown in