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Bronchodilator responsiveness and onset of effect with budesonide/formoterol pMDI in COPD

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KEYWORDS
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Summary
Background: Chronic obstructive pulmonary disease (COPD) patients are thought to have limited bronchodilator response, determined by changes in forced expiratory volume in 1 s (FEV_1). In this study, we assessed bronchodilator response in patients with COPD using not only FEV_1 but also changes in lung volume expressed as forced vital capacity (FVC) and inspiratory capacity (IC). We also evaluated the speed of onset of bronchodilation.
Methods: Data were from 2 randomized, double-blind, placebo-controlled studies (6-months [NCT00206154]; 12-months [NCT00206167]) in patients with moderate to very severe COPD. Treatments: twice daily budesonide/formoterol pressurized metered-dose inhaler (pMDI) 320/9 μg, budesonide/formoterol pMDI 160/9 μg, formoterol dry powder inhaler (DPI) 9 μg, placebo.
Results: The percentage of patients with FEV_1 improvement (≥12% and ≥200 mL; American Thoracic Society [ATS] criterion) was 34–39% post-albuterol (screening). On day of randomization (DOR), a larger proportion receiving formoterol-containing treatment exhibited reversibility within 60 min: FEV_1 (57–59%). Similar results were seen for IC (50–61%) and FVC (57–67%) using the same improvement criteria. The time to ≥15% FEV_1 improvement on DOR was 5.0, 4.8, and 7.3 min for budesonide/formoterol 320/9, budesonide/formoterol 160/9, and formoterol, respectively. Time to ≥15% FEV_1 improvement was better maintained with budesonide/formoterol than formoterol at treatment end (6 and 12 months).

Abbreviations: ATS, American Thoracic Society; BUD, budesonide; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 s; FM, formoterol; FVC, forced vital capacity; IC, inspiratory capacity; ICS, inhaled corticosteroid; LABA, long-acting β_2-adrenergic agonist; PBO, placebo; pMDI, pressurized metered-dose inhaler; TLC, total lung capacity; TORCH, Towards a Revolution in COPD Health; UPLIFT, Understanding Potential Long-Term Impacts on Function with Tiotropium trial.

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Conclusions: Most patients with moderate to very severe COPD exhibit ATS-defined bronchodilator reversibility based on flow and lung volume measures after budesonide/formoterol pMDI or formoterol treatment. Budesonide/formoterol pMDI also has a rapid (within 5 min) onset of bronchodilation that is maintained over time compared with formoterol alone.

Introduction

Chronic obstructive pulmonary disease (COPD) is a treatable and preventable disease with airflow obstruction that is not fully reversible.[1,2] Characterization of bronchodilator responsiveness is complex in patients with COPD since several factors may influence the results of reversibility testing, including daily variation in initial airway caliber and forced expiratory volume in 1 second (FEV_1).[1,3] In addition, poor short-term bronchodilator response does not preclude a long-term response to maintenance bronchodilator therapy.[4,5] Thus, current COPD guidelines recommend against using reversibility testing to predict a patient's clinical response to long-term bronchodilator therapy.[1,3]

Patients with COPD are thought to have a limited response to bronchodilators. However, Tashkin et al. reported that over half of the patients with moderate to very severe COPD in the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial demonstrated reversibility to 2 short-acting bronchodilators combined (ipratropium bromide 80 $\mu g \times 4$ inhalations followed by albuterol 400 $\mu g \times 4$ inhalations) based on a $\geq$12% and $\geq$200 mL improvement in FEV_1.[6] In that study, a smaller proportion of patients with more severe obstruction (Global initiative for chronic Obstructive Lung Disease [GOLD] stages III and IV) manifested a significant FEV_1 response compared with patients with milder obstruction (GOLD stage II).[6] Although not sufficiently emphasized in the article, a review of the data from that study showed that a large proportion of the GOLD stage III–IV patients had a response in terms of lung volume as measure by forced vital capacity (FVC).[6] In addition, inspiratory capacity (IC) was not reported in that study.[6] Clinical benefits of maintenance therapy with a long-acting β_2-adrenergic agonist (LABA) administered alone or in combination with an inhaled corticosteroid (ICS) also have been demonstrated in patients with COPD across COPD severity categories.[7–11]

Treatment with the combination of the ICS budesonide and the LABA formoterol administered in one dry powder inhaler (DPI; Symbicort™ Turbuhaler™, AstraZeneca, Lund, Sweden) has been shown to improve pulmonary function, health-related quality of life, and symptoms in patients with COPD and to reduce the rate of exacerbations compared with placebo.[8,10] Two small studies ($n = 20$ randomized[12] and $n = 90$ randomized[13]) showed that patients with COPD treated with budesonide/formoterol experienced a greater bronchodilator response compared with formoterol alone[12] and a faster onset of effect compared with formoterol alone[12] or fluticasone propionate/salmeterol.[13]

We hypothesized that compared with albuterol or formoterol, the combination of budesonide/formoterol would provide a larger bronchodilator response, measured not only by FEV_1 but also in terms of lung volumes. In addition, we tested whether the speed of bronchodilator response is faster for the combination of budesonide/formoterol compared with either monocomponent. To test these hypotheses, we used pooled data from 2 active- and placebo-controlled phase III clinical studies (6 months and 12 months, respectively) of more than 3500 patients with moderate to very severe COPD.[14,15] From these 2 studies, we evaluated the magnitude and onset of bronchodilation in the subset ($n = 1109$) of patients for whom sequential lung function studies were performed.

Methods

Patients

Details of the studies have been reported previously.[14,15] In brief, the populations consisted of patients $\geq$40 years of age with moderate to very severe COPD, representative of those patients with COPD likely to be treated with an ICS/LABA combination.

Study design and treatments

Both studies were randomized, double-blind, double-dummy, parallel-group, multicenter trials (NCT00206167 and NCT00206154). Clinic visits occurred at screening, randomization, and months 1, 2, 4, and 6 in the 6-month study and at the same time points and months 9 and 12 in the 12-month study. Patients previously receiving ICS or ICS/LABA therapy before study enrollment received ICS monotherapy, and patients previously receiving anticholinergic therapy received ipratropium bromide at a stable dose during a 2-week run-in period. ICS therapy was discontinued at randomization; ipratropium therapy was allowed to continue during the randomized treatment period. Albuterol rescue medication was permitted throughout the study. After the run-in period, patients who met the eligibility criteria were randomized in each trial to one of the treatments shown in Fig. 1. The study protocols were approved by the human studies review board committee at each site, and written informed consent was obtained from patients. The studies conformed with the Declaration of Helsinki.

Outcome variables

Spirometry was performed according to American Thoracic Society (ATS) recommendations.[16] In the subset of patients who were willing and able to undergo serial spirometry, FEV_1 was measured predose and 5, 15, 30, 60, 120, 180, 240, 360, 480, 600, and 720 min after study medication on the day of randomization and at the end of months 2 and 6 in the 6-month study and on the day of randomization and at the end of months 6 and 12 in the 12-month study. On