CHEST Original Research

COPD

Comparison of a Combination of Tiotropium Plus Formoterol to Salmeterol Plus Fluticasone in Moderate COPD*

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Background: **A 6-week, multicenter, randomized, double-blind, parallel-group study was conducted in patients with COPD to compare lung function improvements of tiotropium, 18 μg qd, plus formoterol, 12 μg bid, to salmeterol, 50 μg bid, plus fluticasone, 500 μg bid.**

Methods: **Following a screening visit, subjects entered a run-in period in which they received regular ipratropium. At randomization, patients were assigned to either tiotropium plus formoterol or salmeterol plus fluticasone. After 6 weeks of treatment, a 12-h lung function profile was obtained. The coprimary end points were FEV_1 area under the curve for the time period 0 to 12 h (AUC_{0-12}) and peak FEV_1.**

Results: **A total of 729 patients were screened, and 605 patients were randomized and treated. A total of 592 patients (baseline FEV_1, 1.32 ± 0.43 L/min [±SD]) were included in the analysis. After 6 weeks, the 12-h lung function profiles in the group receiving tiotropium plus formoterol were superior to those in the group receiving salmeterol plus fluticasone (mean difference in FEV_1 AUC_{0-12}, 78 mL [$p = 0.0006$]; mean difference in FVC AUC_{0-12}, 173 mL, $p < 0.0001$). Also, peak responses were in favor of tiotropium plus formoterol (difference in peak FEV_1, 103 mL [$p < 0.0001$]; difference in peak FVC, 214 mL [$p < 0.0001$]), as were FEV_1 and FVC at each individual time point after dose ($p < 0.05$). Predose FVC was significantly higher with the bronchodilator combination, while predose FEV_1 and rescue medication use did not differ significantly between groups. Both treatments were well tolerated.**

Conclusions: **Tiotropium plus formoterol was superior in lung function over the day compared to salmeterol plus fluticasone in patients with moderate COPD. Long-term studies in patients with severe COPD are warranted to assess the relative efficacy of different treatment combinations.**

Trial registration: **Clinicaltrials.gov Identifier: NCT00239421.**

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Key words: combination treatment; COPD; fluticasone; formoterol; lung function; salmeterol; tiotropium

Abbreviations: AUC_{0-12} = area under the curve for the time period 0 to 12 h; CI = confidence interval; FAS = full analysis set; PEFR = peak expiratory flow rate

International guidelines[1,2] for the treatment of COPD recommend pharmacologic therapy with one or more bronchodilators in patients with moderate disease, and addition of an inhaled corticosteroid in patients with severe or very severe COPD. Long-acting bronchodilators such as tiotropium, salmeterol, or formoterol are preferred over short-acting agents,[1] and have been demonstrated to ameliorate the symptoms of patients in numerous clinical trials.[3–12] Also, the additive effects of combinations of different classes of bronchodilators have been shown.[13–15] While long-acting bronchodilators have the potential to reduce exacerbations of COPD,[16–19] the increasing risk for exacerbations in more severe COPD provides the

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rationale for add-on treatment with an inhaled corticosteroid.[18–21] However, beyond the reduction of exacer-

bations, the combination of a long-acting β-agonist with an inhaled corticosteroid offered additional bronchodilator efficacy over the bronchodilator alone in several studies.[18,21–23]

We wondered whether maximal bronchodilatation can be achieved by a frequently prescribed combination of two long-acting bronchodilator drugs from different classes, or alternatively by a popular mixed combination including an inhaled corticosteroid. Hence, the present study compared the bronchodilator response of the combination of tiotropium, 18 μg qd, plus formoterol, 12 μg bid, to the combination of salmeterol, 50 μg bid, plus fluticasone, 500 μg bid. Serial spirometric measurements were conducted over 12 h after morning inhalation, when COPD patients are active and in most need of bronchodilation.

Materials and Methods

Study Objectives and Overall Design Description

This was a 6-week, multicenter, randomized, double-blind, quadruple-dummy, parallel-group study in COPD patients conducted in eight countries between January 2004 and September 2004 (study code 205.287). The objective of the study was to compare the spirometric efficacy between treatment with tiotropium inhalation capsules, 18 μg qd, plus formoterol inhalation capsules, 12 μg bid, and salmeterol, 50 μg bid via aerosol inhalation, plus fluticasone, 500 μg bid, via aerosol inhalation.

Subjects entered a 2- to 4-week run-in period. At screening, pulmonary function tests were performed prior to and 60 min after inhalation of 80 μg of ipratropium and 400 μg of salbutamol. At the second clinical visit (baseline), predose lung function was assessed, and patients were randomized to blinded treatment. After 3 weeks of treatment, predose FEV_1 and FVC were quantified and patient compliance was checked. After 6 weeks of treatment, serial pulmonary function tests were scheduled over 12 h after dosing.

The study was conducted according to the revised Declaration of Helsinki, the requirements of good clinical practice, and other international and local regulations. The study was sponsored by Boehringer Ingelheim and Pfizer.

Recruitment of Subjects

Key inclusion criteria were age ≥ 40 years, a smoking history > 10 pack-years, a diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease,[1] and a relatively stable airway obstruction with a postbronchodilator FEV_1 < 80% of predicted normal[24] and FEV_1/FVC < 70% at visit 1, and predose FEV_1 ≤ 65% of predicted at visit 2.

Key exclusion criteria were a history of asthma or significant diseases other than COPD, and treatment with inhaled steroids within 2 months prior to screening or during the run-in period in order to avoid any bias potentially caused by residual effects, or by withdrawal of inhaled corticosteroids. Oral steroids were not allowed for a period of 6 weeks prior to the screening visit. Tiotropium was not allowed during the run-in period. Patients who had been receiving tiotropium before the study underwent a 4-week run-in period (patients not receiving tiotropium, 2 weeks) to ensure an adequate washout prior to the baseline lung function test.

Study Medication and Medication Restrictions

During the run-in period, all patients received ipratropium, 40 μg qd, on a regular basis. On days 1 to 41, the study medication was administered according to a quadruple-dummy design as follows: the patients inhaled one capsule (tiotropium or matching placebo) using the HandiHaler device (Boehringer-Ingelheim; Ingelheim, Germany) once daily in the morning, one capsule (formoterol or matching placebo) using the Foradil Aerolizer (Novartis Pharmaceuticals; East Hanover, NJ) device twice daily, and two inhalations from each metered-dose inhaler (salmeterol or matching placebo, fluticasone or matching placebo) twice daily in the morning and in the evening, with a dosing interval of about 12 h. On day 42 (visit 4), a predose pulmonary function testing was performed prior to the last morning inhalation and the subsequent 12-h spirometry.

At all clinical visits, the investigator monitored the inhalation procedure and reinforced correct inhalation technique. During the entire study period, patients recorded daily rescue salbutamol use and peak flow rates on their diary cards. The following medications were prohibited during the study: inhaled steroids other than the study medication, oral steroids (except for the control of acute exacerbations as deemed medically necessary), β-agonists and anticholinergics other than the supplied rescue medication and study medication, and once-a-day theophylline preparations.

Spirometry

Pulmonary function was assessed at each of the four visits using calibrated spirometers with the patient in a seated position having abstained from salbutamol for at least 8 h. The highest FEV_1 and the highest FVC each obtained on any of three tests meeting American Thoracic Society criteria[25] were recorded and normalized according to established standards.[24]

Time points were "predose" in the morning, and 60 min after bronchodilation with 400 μg of salbutamol and 80 μg of ipratro-

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