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Comparison of airway dimensions with once daily tiotropium plus indacaterol versus twice daily Advair® in chronic obstructive pulmonary disease

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ABSTRACT

Background: Current guidelines recommend combining long-acting bronchodilators with different modes of action in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD). We evaluated the effects of airway dimensions and pulmonary function with tiotropium plus indacaterol versus Advair®.

Methods: Subjects ($n = 46$) were randomized to receive tiotropium (18 μg once daily) plus indacaterol (150 μg once daily) or Advair® (50/250 μg twice daily) for 16 weeks. Airway geometry was determined by quantitative computed tomography (luminal area, Ai; total area of the airway, Ao; wall area, WA; and percentage wall area, WA/Ao and wall thickness, *T*). Spirometry (forced expiratory volume in 1 s, FEV_1; forced vital capacity, FVC and inspiratory capacity, IC) and St. George's Respiratory Questionnaire (SGRQ) were evaluated.

Results: Tiotropium plus indacaterol significantly increased CT-indices including Ai corrected for body surface area (Ai/BSA), and decreased WA/BSA, WA/Ao and $T/\sqrt{BSA}$ compared with Advair® ($p < 0.05$, respectively). In physiological parameters, mean difference in IC was significantly higher under treatment with tiotropium plus indacaterol than Advair® ($p < 0.05$). The changes in Ai/BSA, WA/BSA, WA/Ao and $T/\sqrt{BSA}$ were significantly correlated with changes in IC ($r = 0.535$, $p = 0.011$; $r = -0.688$, $p < 0.001$; $r = -0.555$, $p = 0.002$ and $r = -0.542$, $p = 0.007$; respectively). There were more significant improvements in SGRQ scores after treatment with tiotropium plus indacaterol than Advair®.

Conclusions: These findings suggest that dual bronchodilation with tiotropium plus indacaterol is superior in airway geometry and lung function compared with Advair® in COPD.

1. Introduction

Current guidelines recommend treatment with long-acting inhaled bronchodilators for patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) [1]. Treatment with a combination of bronchodilators from different pharmacological classes have been shown to provide additional benefits compared with a single inhaler [2–6]. Concurrent use of the long-acting muscarinic receptor antagonist (LAMA)-tiotropium, and the long-acting β_2-adrenergic receptor agonist (LABA)-indacaterol, had been shown to provide superior bronchodilation and improvements in air trapping compared with monotherapy [7].

In addition, combining a LABA with an inhaled corticosteroid (ICS) decreases exacerbation rate, and improves dyspnea and quality of life [8–11], and attenuates forced expiratory volume in 1 s (FEV_1) decline in COPD [12]. However based on current treatment recommendation [1], the use of ICS is reserved for high risk patients with severe or severe airflow limitation and who are having two or more exacerbations per year requiring treatment.

Quantitative computed tomography (CT) has been widely used to evaluate structural changes in the airways [13,14] and lung parenchyma in COPD patients [15,16]. Cross-sectional studies have

Abbreviations: LAMA, long-acting muscarinic receptor antagonist; LABA, long-acting β_2-adrenergic receptor agonist; ICS, inhaled corticosteroid; FVC, forced vital capacity; Ai, luminal area; Ao, total area of the airway; WA, wall area; WA/Ao, percentage wall area; *T*, wall thickness; BSA, body surface area; IC, inspiratory capacity; SGRQ, St. George's Respiratory Questionnaire.

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shown that CT indices that quantify airway wall thickening and the presence and severity of emphysema are correlated with pulmonary function measurements [13–15,17]. Recently, we have shown that triple inhalation therapy of tiotropium and Advair® reduces airway wall thickness and pulmonary hyperinflation than monotherapy [18].

We hypothesized that dual bronchodilators (LAMA and LABA) may provide morphological and physiological benefits compared with using a combined LABA and ICS. Thus, in this study we compared the effect of once daily dual therapy of LAMA-tiotropium and LABA-indacaterol versus twice daily Advair® on airway geometry and pulmonary function, in subjects with moderate-to-severe COPD.

2. Material and methods

2.1. Subjects

The subjects were all ex-smoker patients >40 years of age with a diagnosis of COPD; a cigarette smoking history >10 pack-years; a post-bronchodilator FEV_1 between 30% and 80% of predicted value, and FEV_1/FVC (ratio of FEV_1 to forced vital capacity <0.70). Exclusion criteria included a current diagnosis of asthma; clinically significant medical disorder other than COPD; supplemental use of oxygen for exertion; or exacerbation needing treatment with antibiotics, systemic glucocorticosteroids. All subjects gave their written, informed consent, and the study protocol was approved by our hospital's ethics committee and institutional review boards.

2.2. Study design

This was a randomized, open-label, parallel-group, 16-week treatment study (Fig. 1). After a pre-screening wash-out period (up to 7 days) and a 14-day run-in period, patients were randomly allocated to receive treatment with tiotropium 18 μg once daily by Handihaler (Boehringer Ingelheim Pharma, Ingelheim, Germany) plus indacaterol 150 μg by Breezhaler (Novartis, London, UK) or Advair® (50 μg salmeterol/250 μg fluticasone propionate) twice daily (Glaxo Smith Kline, London, UK). Rescue inhaler short-acting β_2-adrenergic receptor agonist-salbutamol 200 μg by Ventolin (Glaxo Smith Kline, London, UK) was permitted when necessary to relieve symptoms throughout the study. Subjects were not permitted to use long-acting bronchodilators (LAMAs, LABAs, theophylline) or ICSs before the screening period. The treatment duration was 16 weeks, with clinical visits in weeks 4, 8, 12 and 16. Pulmonary function, CT and assessment of quality of life (QoL) were carried out at screening and in week 16. At the final visit, it was confirmed that the participants had last inhaled either bronchodilators about 2 h previously and repeated lung function tests and CT. Adverse events were recorded at each visit, notably the vital signs and blood chemistry, and the ECG assessment was performed at the final visit.

2.3. Outcomes and measurements

The primary objective was to demonstrate superiority of tiotropium plus indacaterol compared with Advair® for the effect on airway dimensions. The important secondary objectives were also compared the effect of tiotropium plus indacaterol versus Advair® on bronchodilator effect and health status during the treatment period.

2.4. CT measurement

All subjects were scanned with a 64-detector CT (Aquilion-64, Toshiba Medical, Tokyo, Japan) at full inspiration. Scans were obtained at 120 kV, 200 mA, with a slice thickness of 1 mm. Images were reconstructed with both soft-tissue and bone algorithm at a slice thickness of 1 mm and an interval of 0.5 mm. The following airway dimensions of the apical segmental bronchus of the right upper lobe (RB1) were measured using the full-width at half maximum principle [13]: luminal area (Ai), total area of the airway (Ao), wall area (WA = Ao − Ai), percentage wall area (WA/Ao% = WA/Ao × 100), and absolute wall thickness (*T*). Because airway size may be affected by body size, Ai, WA, and *T* were normalized to body surface area (BSA). To assess changes in lung volume, the cross-sectional area of the lung was measured before and after treatment by tracing the outer perimeter of the lung parenchyma on the same slice that was used for measurement of airway dimensions [19]. Airway dimensions were measured by a single observer (J.O.) in a blind fashion. Intraobserver error was tested with an observer measuring Ai and WA/Ao% twice in 10 randomly selected subjects. Reproducibility was assessed with Bland-Altman analysis. Details about data reproducibility are described elsewhere [20].

2.5. Pulmonary function

After inhaling a short-acting bronchodilator, pulmonary function tests were performed with a Fudak-77 (Fukuda Elect, Tokyo, Japan). FVC, FEV_1, FEV_1%, and inspiratory capacity (IC) were measured. Residual volume (RV) was measured using the helium dilution method, and functional residual capacity (FRC), total lung capacity (TLC), alveolar volume (V_A), and carbon monoxide transfer factor (D_LCO/V_A) were measured by the single-breath method. Data were expressed as percentages of predicted values according to the prediction equations of the Japanese Respiratory Society [21].

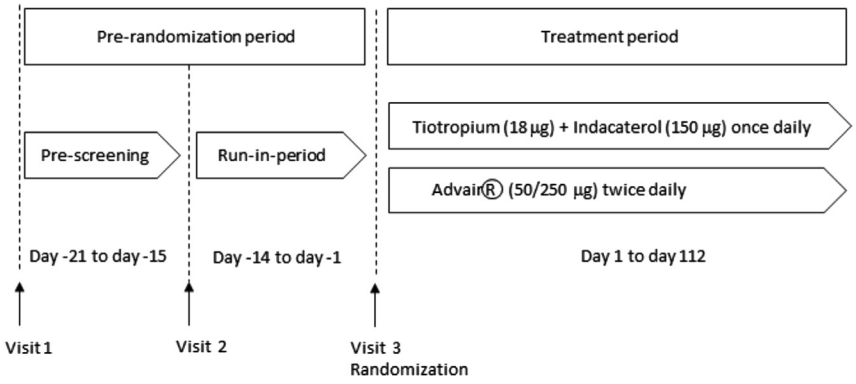

Fig. 1. Study design.