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A comparison of the efficacy of once-daily fluticasone furoate/vilanterole with twice-daily fluticasone propionate/salmeterol in asthma-COPD overlap syndrome

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ABSTRACT

Background: Asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS) is important because patients with ACOS have significantly worse outcomes compared with those with asthma or chronic obstructive pulmonary disease (COPD) alone. Inhaled corticosteroids (ICS), together with a long-acting β2 agonist (LABA), are recommended, but no therapeutic studies for ACOS have been conducted. Recently, fluticasone furoate/vilanterole (FF/VI) has been approved as the first once-daily ICS/LABA combination therapy for asthma and COPD.

Methods: A 12-week, randomized, open-label cross-over study was conducted in 16 patients with ACOS to compare the effectiveness of once-daily FF/VI 200/25 μg vs. twice-daily fluticasone propionate/salmeterol (FP/SAL) 500/50 μg. The study period included a 4-week run-in, the first 4-week treatment, and the second 4-week treatment. Respiratory functions, including forced expiratory volume in 1 s (FEV_1) and respiratory impedance using the forced oscillation technique (FOT), were measured, as was fractional exhaled nitric oxide (FeNO). A COPD assessment test (CAT) scores and asthma control test (ACT) scores were recorded 0, 4, and 8 weeks after randomization.

Results: The mean values for the FEV_1 were 1.33 (±0.29) L in the run-in period, 1.38 (±0.39) L after the FP/SAL treatment period, and 1.47 (±0.38) L after the FF/VI treatment period. The FEV_1 value after the FF/VI treatment was significantly greater than the value after the run-in period ($p < 0.01$). FOT parameters, FeNO levels, CAT scores, ACT scores, and other blood tests were not significantly different during the run-in period, the FP/SAL treatment period, and the FF/VI treatment period.

Conclusions: FF/VI, the first once-daily ICS/LABA, can provide substantial improvement in lung functions, indicating that FF/VI should be considered for the regular treatment of ACOS.

1. Introduction

Asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS) has been a focus of interest among clinicians [1–3], because patients with ACOS show a more rapid disease progression [4], a worse health-related quality of life, more frequent respiratory exacerbations [5], and increased co-morbidities and health care utilization than those with asthma or chronic obstructive pulmonary disease (COPD) alone [6,7]. ACOS is also relevant for many general internists, allergists, and pulmonologists, since it is frequently encountered clinically, with a 15 and 20% prevalence in populations with airway diseases [3,8]. The Spanish guidelines recommend inhaled corticosteroids (ICS) together with long-acting β2 agonist (LABA) as a first option to improve lung function and respiratory symptoms and to reduce respiratory exacerbations [9]. However, this treatment approach is based on extrapolation of data derived from studies in patients with asthma or COPD alone, since no therapeutic studies for ACOS have been conducted.

Fluticasone furoate/vilanterole (FF/VI) is a novel ICS/LABA combination being developed for once-daily administration for asthma

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and COPD. FF has greater anti-inflammatory activity and a longer duration of action than fluticasone propionate (FP) under conditions of oxidative stress, implying its efficacy in patients with COPD who experience high levels of oxidative stress [10]. VI is also a novel LABA with superior selectivity for the β2-receptor when compared with other LABAs, including salmeterol (SAL) [11]. Several studies have confirmed the efficacy and safety of FF/VI compared with an FP/SAL combination in patients with asthma or COPD alone [12–14], but the efficacy and safety in patients with ACOS remains obscure. Therefore, we conducted this study to obtain a head-to-head comparison of the efficacy and safety of FF/VI 200/25 μg once-daily versus FP/SM 500/50 μg twice-daily as a first clinical trial for ACOS.

2. Subjects and methods

This was a 12-week, randomized, open-label cross-over study to compare the effectiveness of FF/VI 200/25 μg, administered once-daily in the morning *via* the Ellipta™ dry powder inhaler (GlaxoSmithKline, Ware, UK), vs. FP/SAL 500/50 μg, administered twice-daily *via* the Diskus™ dry powder inhaler (GlaxoSmithKline, Evreux, France). Randomization was carried out by the sealed envelope method. This study (UMIN000014191) was conducted between April 2014 and Sep 2014 in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of our hospital. Written informed consent was obtained from each subject before participating in the study.

2.1. Subjects

A total of 16 patients with stable ACOS (16 males, no females) with a mean age of 74.2 ± 6.7 (±SD) (range 59–87) years participated in the study. All patients were ex-smokers with smoking history of 66.6 ± 38.5 (±SD) pack-years. Each patient was diagnosed with ACOS according to the past studies conducted by Gibson et al. and other study groups [1,2,15–17]. They had episodic respiratory symptoms, increased airflow variability [asthma; i.e., airway hyperresponsiveness (AHR) or bronchodilator response (BDR)] as well as incompletely reversible airway obstruction [COPD; post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) < 70% and post-bronchodilator FEV_1 <80% of predicted]. AHR was defined if a ≧20% FEV_1 fall from baseline occurred after inhalation of methacholine. BDR was also defined as an increase in post-bronchodilator FEV_1 ≧200 ml and 12% compared with pre-bronchodilator FEV_1.

All patients were allowed to take oral theophylline, leukotriene receptor antagonists, mucolytic agents, and/or inhaled tiotropium, as shown in Table 1. No patient had received oral steroid therapy for at least 8 weeks. This study was carried out when the patients' symptoms were mild and stable.

Table 1
Patient characteristics.

Age (years)	74.2 (6.7) range 59–87
Gender (male/female)	16/0
Body mass index (kg/m^2)	21.3 (2.5)
History of smoking (pack-years)	66.6 (38.5)
Treatment of theophylline (with/without)	13/3
Treatment of carbocysteine (with/without)	14/2
Treatment of tiotropium (with/without)	11/5
Treatment of LTRA (with/without)	13/3
DLCO as % predicted	68.3 (26.7)
DLCO/VA as % predicted	46.1 (18.8)

LTRA: leukotriene receptor antagonist, DLCO: lung carbon monoxide diffusing capacity, VA: alveolar volume.
Data are presented as mean (SD).

2.2. Study protocol

The test medication was stopped at 9.00 p.m. 2 days before the measurements to allow a washout time of 24 h or more before the measurement of respiratory functions at 10.00 a.m. on each test day. Each patient attended 4 times, separated by 4 weeks, at the same time each day. They received FP/SAL 500/50 μg twice-daily *via* the Diskus dry powder inhaler at least 4 weeks before randomization, as shown in Fig. 1. Subsequently, they were randomized into 2 groups and underwent treatment of FF/VI 200/25 μg once-daily in the morning *via* the Ellipta dry powder inhaler and FP/SAL 500/50 μg twice-daily *via* the Diskus dry powder inhaler, in a cross-over fashion. Respiratory functions, including vital capacity (VC), FEV_1, FVC, FEV_1/FVC, peak expiratory flow (PEF), forced expiratory flow at 25–75% (FEF25-75%), maximum expiratory flow rate at 75% forced vital capacity (MEF75), maximum expiratory flow rate at 50% forced vital capacity (MEF50), and respiratory impedance using forced oscillation technique (FOT), and fractional exhaled nitric oxide (FeNO), were measured, COPD assessment test (CAT) scores and asthma control test (ACT) scores were recorded, and electrocardiograms and blood examinations, including immunogloblin E (IgE), were performed at 0, 4, and 8 weeks after randomization.

2.3. Measurements

Respiratory functions were measured on a dry wedge spirometer (Chestac 8900™, Chest Co., Ltd., Tokyo, Japan) to assess the bronchoactive effect of the treatment regimens, using the same methods as previously reported [18,19]. FEF25-75% was measured as a small airway parameter. Respiratory impedance was measured by FOT using another device (MostGraph-01™, Chest Co., Ltd., Tokyo) according to the recommended techniques reported before [20,21].

FeNO level, a surrogate marker of eosinophilic airway inflammation, was measured using a commercially available device (NIOX MINO™, Aerocrine, Stockholm, Sweden) before any forced expiratory maneuvers [22].

The impact of COPD symptoms on patient health status were assessed and quantified by asking the patients to fill out the CAT, a simple questionnaire that is recognized as a reliable and valid tool to examine the impact of COPD symptoms over time [23]. It comprises 8 items scored 0–5 to give a total score of 40. The CAT scores of 1–10, 11–20, 21–30, and 31–40 represent categories of mild,

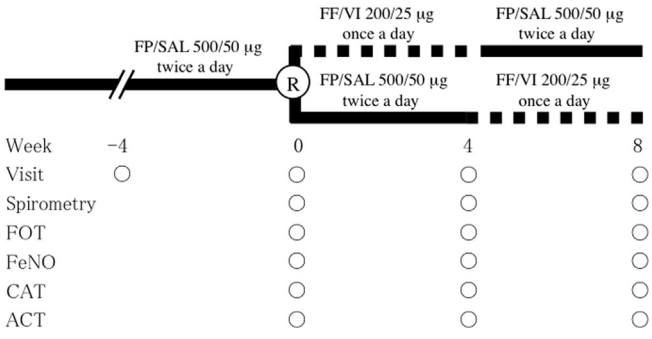

Fig. 1. Study design of a randomized, open-label cross-over manner. Solid line means treatment with fluticasone propionate/salmeterol (FP/SAL) and dotted line means treatment with fluticasone furoate/vilanterole (FF/VI). ACT, asthma control test; CAT, chronic obstructive pulmonary disease assessment test; FeNO, fractional exhaled nitric oxide; FOT, forced oscillation technique; R, randomization.