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Effects of tiotropium on lung function in severe asthmatics with or without emphysematous changes

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ABSTRACT

The effects of tiotropium, an inhaled long-acting anti-cholinergic agent, on lung function were investigated in obstructed severe asthmatics with and without emphysematous changes despite maximal recommended treatments with high-dose of inhaled glucocorticoids and inhaled long-acting β_2-agonists.

We conducted a double-blind, placebo-controlled study of an inhaled single-dose of tiotropium in 18 asthmatics with emphysema and 18 without emphysema in a crossover manner. The primary efficacy outcome was the relative change in forced expiratory volume in 1 s (FEV_1) from baseline to 60 min, and the secondary outcome was a relative change in FEV_1 from baseline to 12 h. Subsequently, the patients were treated with tiotropium inhaled once daily for 12 weeks in an open label manner, and lung function and symptoms were evaluated.

At baseline, patients with or without emphysema had a mean FEV_1 of 55.9% before tiotropium and 56.8% before placebo, or 77.4% before tiotropium and 77.6% before placebo of the predicted value and were taking a mean dose of inhaled glucocorticoids of 1444 or 1422 μg/day. Among patients with emphysema, the increase from baseline FEV_1 was 12.6 percentage points higher at 60 min after tiotropium than after placebo. Among patients without emphysema, the increase from baseline FEV_1 was 5.4 percentage points higher at 60 min after tiotropium than after placebo.

Tiotropium resulted in improved lung function and symptoms in asthmatics with and without emphysema. These findings suggest that tiotropium will provide a new strategy for the treatment of bronchial asthma and of overlapping asthma and COPD.

1. Introduction

Bronchial asthma is emerging as a heterogeneous disease, and there is significant variability in response to treatment [1,2]. Despite treatment with an inhaled corticosteroid (ICS) plus a long-acting β_2-agonist (LABA), many patients have uncontrolled asthma that requires more intensive therapies.

Previous studies have shown that anti-cholinergic agents provide equal to or greater bronchodilatation than β_2-adrenoreceptor agonists in chronic obstructive pulmonary disease (COPD), while short-acting anti-cholinergic agents result in less bronchodilation than β_2-agonists in asthmatic patients [3]. Tiotropium bromide is an anti-cholinergic agent with long-lasting action which is led by a slow-dissociation rate of this antagonist from acetylcholine M_1 and M_3 receptors [4,5]. There is accumulating evidence showing effects of tiotropium on COPD in both symptoms and lung function, which suggests a very important role in controlling COPD [6]. On the other hand, studies reporting the clinical efficacy of tiotropium on asthmatics have been limited.

Recently, it was demonstrated that the addition of tiotropium improved symptoms and lung function in patients with mild-to-moderate asthma uncontrolled with only low-dose ICS, and its effects were found to be noninferior to those of salmeterol [7]. Furthermore, tiotropium was reported to be noninferior to

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salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma [8], and the addition of tiotropium to high-dose ICS plus LABA improved lung function in patients with uncontrolled severe asthma [9]. Therefore, in addition to the effects on COPD, long-acting anti-cholinergic agents are also considered to be useful to control asthma.

Asthma and COPD occur commonly, and, in clinical practice, there are patients who have the clinical features of both diseases. Such disease state is recently getting recognized as an "overlap syndrome" between bronchial asthma and COPD. It is possible that asthmatic patients with COPD may respond favorably to anti-cholinergic agents. However, patient with overlap syndrome were typically excluded from most of clinical trials. Here, we studied the effect of a single-dose of tiotropium on lung function in obstructed severe asthmatics with and without emphysematous changes despite maximal recommended treatments with high-dose of ICSs and inhaled LABAs, in a randomized double-blind placebo-controlled crossover design. Subsequently, the effects of open-labeled uncontrolled treatment with once-daily treatment with tiotropium for 12 weeks were evaluated.

2. Methods

2.1. Study subjects

The study was conducted in the outpatient clinic of the Department of Pulmonary Medicine of Kyushu University Hospital and National Fukuoka-Higashi Medical Center. Patients with severe asthma, who did not suffer from other disorders, for example, liver, kidney, or metabolic diseases, were recruited. The diagnosis of asthma was based on a history consistent with asthma, diffuse expiratory wheezes heard on auscultation of the chest, eosinophils over 3% of total cells in sputum, and the demonstration of an increase of 12% or more and 200 ml or more in their forced expiratory volume in 1 s (FEV_1) following the inhalation of 2 puffs of albuterol. Despite treatment with a high-dose ICS and an inhaled LABA, all of the participants had had poorly controlled symptomatic asthma: cough, wheeze, or breathlessness in the daytime or at night. Patients with any of the following were also excluded from the study: a supplemental oxygen therapy, an upper respiratory tract infection within 6 weeks prior to screening, a known hypersensitivity to anti-cholinergic drugs, known symptomatic prostatic hypertrophy, and narrow-angle glaucoma (Table 1).

Among these asthmatics, those who met the following criteria were placed in the group of asthma with emphysematous changes. The criteria of emphysema were based on the following definition [10]: to be aged > 40, to have a smoking history of >10 pack-years, and to have a stable airway obstruction with an $FEV_1 \leq 80\%$ of predicted normal values and an $FEV_1 \leq 70\%$ of forced vital capacity (FVC). In addition to these criteria, an applied visual score of emphysema on the chest HRCT over 10 [11] and decreased D_{LCO} ($\leq 80\%$ of predicted normal values) were also included in diagnostic criteria (Table 1). The qualitative analysis of emphysema was carried out according to a visual score introduced based on the assessment of severity and extent [12]. Briefly, severity was graded on a 4-point scale: 0, no emphysema; 1, low attenuation areas <5 mm in diameter; 2, circumscribed low attenuation areas >5 mm in diameter with intervening normal lung; 3, diffuse low attenuation areas without intervening normal lung. The extent of emphysema was on a 4-point scale: 1, $<25\%$ of the lung parenchyma involved; 2, 25–50% lung involvement; 3, 50–75% lung involvement; 4, $>75\%$ lung involvement. For each hemislice, the severity score was multiplied by that of extent. The scores from the six hemislices were then summed to yield a cumulative emphysema score that ranged from 0 to 72. Eighteen patients were diagnosed with emphysema in addition to asthma.

Table 1
Inclusion and exclusion criteria of the present study.

Common inclusion criteria for all subjects
History consistent with asthma
Diffuse expiratory wheezes heard on auscultation of the chest
Eosinophils over 3% of total cells in sputum
β_2-agonists reversibility to 2 puffs albuterol of an increase of 12% or more and 200 ml or more in their forced expiratory volume in 1 s (FEV_1)
Poorly controlled symptomatic asthma despite treatment with a high-dose ICS (dose of 800 μg/day, equiv. BDP or more) and an inhaled LABA
Inclusion criteria for subjects with emphysematous change
Age over 40 years
Smoking history of >10 pack-years
Stable airway obstruction with an $FEV_1 \leq 80\%$ of predicted normal value
$FEV_1 \leq 70\%$ of forced vital capacity (FVC)
Visual score of emphysema on the chest HRCT over 10
Decreased $D_{LCO} \leq 80\%$ of predicted normal values
Exclusion criteria for subjects without emphysematous change
Current smoker or smoking history of >10 pack-years
Presence of low attenuation area on the chest HRCT
Decreased $D_{LCO} \leq 80\%$ of predicted normal values
Common exclusion criteria for all subjects
Supplemental oxygen therapy
Upper respiratory tract infection within 6 weeks prior to screening
Known hypersensitivity to anti-cholinergic drugs
Known symptomatic prostatic hypertrophy
Narrow-angle glaucoma

In the other asthmatic group, diagnosed with "pure" bronchial asthma, the exclusion of emphysema was based on the following criteria: absence of low attenuation area on the chest HRCT, D_{LCO} within normal range, and absence of smoking history or ex-smoker with smoking secession at least 6 month prior to recruitment with a smoking history of less than 10 pack-years. Although ex-smokers with a light smoking history were included in the criteria, none of the "pure" asthmatics in the present study had any smoking history (Table 2). The patient background of each group is listed in Table 2. None of them used β-blockers.

2.2. Study design and conduct

To investigate the bronchodilating effects of a single-dose of inhaled tiotropium or placebo first, the study had a double-blind crossover placebo-controlled design. In this part of the study, subjects from both groups with and without emphysema were included. Each patient received two treatments on different study days with a washout period of 1–2 weeks between them; the patients in random order were allocated to tiotropium 18 μg or placebo (Fig. 1). Tiotropium and placebo were administered by HandiHaler. Patients were prohibited from inhalation of a short-acting β_2-agonist 12 h before and after the treatment. Lung function – FVC, FEV_1, peak expiratory flow rate (PEFR), and inspiratory capacity (IC) –, pulse oximetry (SpO_2), pulse rate, and blood pressure were taken at baseline condition and 30 min, 60 min, and 12 h after inhalation of the trial drug.

The primary efficacy outcome was the relative change in FEV_1 from baseline to 60 min after tiotropium inhalation. This was calculated as the absolute change in FEV_1 (volume in liters) from baseline to 60 min divided by the FEV_1 at baseline. The secondary outcome was the relative change in FEV_1 from baseline to 12 h after tiotropium inhalation. Spirometry was performed using a dry rolling-seal spirometer (Chestac-33, Chest Co., Tokyo, Japan).

For the subsequent open-label tiotropium treatment, the participants were prescribed tiotropium capsules and instructed inhalation of 18 μg of tiotropium once daily for 12 weeks. Lung function was assessed at least 12 h after the last tiotropium was given, before and after 1, 2, and 3 months of open-label tiotropium