Comparison of tiotropium plus fluticasone propionate/salmeterol with tiotropium in COPD: A randomized controlled study

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Summary

Background: The combination of tiotropium and fluticasone propionate/salmeterol (FSC) is commonly used to treat chronic obstructive pulmonary disease (COPD), but no study had evaluated the effectiveness of tiotropium plus FSC with 250 μg of fluticasone propionate. Our aim...
Tiotropium; Fluticasone propionate/salmeterol

was to assess whether tiotropium (18 μg once daily) plus FSC (250/50 μg twice daily) provides better clinical outcomes compared to tiotropium monotherapy.

Methods: In this 24-week, randomized, open label, multicenter two-arm parallel study, 479 patients received tiotropium plus FSC (n = 237) or tiotropium alone (n = 242).

Results: After 24 weeks of treatment, the triple-inhaled treatment group had a significant improvement in pre-bronchodilator FEV1 (L) compared to the tiotropium-only group (0.090 L vs. 0.038 L; P = 0.005). Regarding health-related quality of life, the mean change in total score on the St. George’s Respiratory Questionnaire for COPD patients (SGRQ-C) was –6.6 points in the tiotropium plus FSC group, but –1.5 points in the tiotropium-only group (P = 0.001). In the subgroup of GOLD stage II patients with COPD, treatment with tiotropium plus FSC also improved FEV1 compared to tiotropium alone (0.088 L vs. 0.030 L; P = 0.011) and improved the total SGRQ-C score than tiotropium alone (–4.5 points vs. –1.0 points, respectively). This triple-inhaled treatment approach did not induce more adverse events, such as pneumonia.

Conclusion: Over the course of 24 weeks, FSC (250/50 μg twice daily) added to tiotropium provided greater improvement in lung function and quality of life in patients with COPD (FEV1 ≤ 65%) than tiotropium alone.

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Introduction

The goals of chronic obstructive pulmonary disease (COPD) management are to control the symptoms of the disease, reduce the frequency and severity of exacerbations, and improve health in general. To achieve therapeutic goals, current guidelines for the diagnosis and treatment of patients with COPD recommend a combination of different classes of bronchodilators or that of an inhaled corticosteroid (ICS) and a bronchodilator. To maximize the benefits of combination therapy, particularly in moderate-to-very-severe COPD, the triple combination of the long-acting anticholinergic tiotropium plus an ICS and a long-acting β2-agonist (LABA) has been explored.

Recently, the Canadian Respiratory Research Group demonstrated that triple combination therapy of tiotropium and fluticasone propionate/salmeterol (FSC; 500 μg fluticasone propionate and 50 μg salmeterol, twice daily) provided greater improvement in hospitalization rates, health-related quality of life, and pulmonary function compared to tiotropium monotherapy. However, a reduced dose (250 μg) of fluticasone propionate in FSC twice daily has also shown efficacy in substantially improving symptoms and lung function, including airflow obstruction and hyperinflation in patients with COPD, and has a relatively low risk of inducing pneumonia compared to a higher dose of fluticasone propionate in FSC. So far, no study had evaluated the efficacy and safety of triple-inhaled therapy using tiotropium plus FSC with 250 μg instead of 500 μg of fluticasone propionate.

Therefore, this study was planned to evaluate whether the triple combination of tiotropium and FSC 250/50 μg twice daily provides clinical improvement in patients with COPD (FEV1 ≤ 65%) compared to tiotropium monotherapy.

Methods

Design

We conducted a randomized, open label, multicenter two-arm parallel study in 30 academic hospital-based pulmonary clinics in Korea. This study was approved by the institutional review board of all 30 institutes including Asan Medical Center (2009-0085), and all trial participants provided written informed consent.

Patients

We enrolled patients diagnosed with COPD, who had a post-bronchodilator forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio of less than 0.70 and FEV1 of less than 65% of the predicted value in the past 1 year or at screening. Eligible patients were 40–80 years of age and had a smoking history of at least 10 pack-years. The exclusion criteria were as follows: a history of physician-diagnosed asthma or a chronic respiratory disorder other than COPD that was clinically significant; any uncontrolled or serious disease that might affect participation in the study; use of systemic corticosteroids or immunosuppressant within 4 weeks prior to study entry; any malignant diseases; a history of severe glaucoma, urinary tract obstruction, or previous lung volume reduction surgery; women who were pregnant or lactating; and a known hypersensitivity or intolerance to tiotropium or FSC.

Randomization and interventions

After a 2-week run-in period, eligible patients were randomized to one of two treatment groups for 24 week treatment: tiotropium (Spiriva HandiHaler [Boehringer Ingelheim Pharma, Ingelheim, Germany]), 18 μg once daily; or tiotropium, 18 μg once daily plus FSC (Seretide Diskus [GlaxoSmithKline, UK]), 250/50 μg/puff, 1 puff twice daily.

Randomization was done in a 1:1 ratio through a computerized random-number generator. Neither research staff nor patients were aware of the treatment assignment until randomized.

All patients were provided with a salbutamol inhalation aerosol and instructed to use it when necessary to relieve symptoms. Before the run-in period, patients stopped their usage of inhaled corticosteroid and long-acting bronchodilators, but therapy with other regular medications such as...
Predicted IC in the SGRQ-C were analyzed. An exacerbation was defined as symptomatic deterioration requiring the short-term use of oral/intravenous steroids, antibiotics, or both, by the physician’s discretion. Safety evaluation

Safety was evaluated through the collection of reports of adverse events, serious adverse events, treatment related adverse events, and adverse events related to study discontinuation. In addition, research coordinators assessed adverse events at each visit by using the checklist of potential side effects. Physicians decided the expectedness, severity and causality to the study drugs of every event. Patients who experienced an adverse event were followed up until symptoms or signs of the adverse event subsided or returned to baseline.

Statistical analysis

One hundred eighty-six patients per group provided 90% power with a significance level of 0.05 to detect a treatment difference of 0.059 L in pre-bronchodilator FEV1 between the tiotropium plus FSC group and the tiotropium-only group, assuming a standard deviation of 0.194 L. In total, 466 patients (233 per treatment group) were recruited to allow a dropout rate of 20.16

The primary outcome and secondary outcomes for spirometry values and SGRQ-C were analyzed using analysis of covariance (ANCOVA) with baseline FEV1 values, gender, and pooled centers as covariates. A subgroup analysis with patients having moderate COPD was performed (post-bronchodilator FEV1 50% to <65% at screening) for mean changes in pre-bronchodilator FEV1, IC, or FVC from baseline to week 24.

Analyses were performed with SAS software, version 9.2 (SAS Institute, Inc., Cary, NC).

Results

Patients were enrolled from April 2009 to March 2010. Of the 534 patients recruited, 479 underwent randomization (Fig. 1). Twenty-four patients who were randomized without any outcome measurements were included only in the safety analysis. In total, 455 patients were included in the efficacy population.

The mean age was 67 years, with men comprising 98.0% of this population. The mean value of post-bronchodilator FEV1 was 1.31 L and % pred value was 50.8. A similar proportion of patients received theophylline, systemic corticosteroid, or anti-infective agents (Table 1).

The rate of adherence to treatment was high in both groups (94–96% of the prescribed doses taken).

Primary outcome

The tiotropium plus FSC group improved in pre-bronchodilator FEV1 (L) after 24 weeks of treatment significantly more than the tiotropium-only group (P = 0.005) (Fig. 2). Within the tiotropium plus FSC group, the value of pre-bronchodilator FEV1 (L) at week 24 was significantly higher compared to the baseline value (0.090 L, P = 0.010), whereas no significant improvement occurred within the tiotropium-only group (0.038 L, P = 0.283).

Secondary outcomes

Lung function

In the tiotropium plus FSC group, improvement in pre-bronchodilator FEV1 (L) was significant from week 4 to week 16 over baseline, whereas no significant differences were observed in the tiotropium-only group. At week 24, the pre-bronchodilator FEV1 % pred value increased by 4.57% in the tiotropium plus FSC group compared to 2.41% in the tiotropium-only group (P = 0.003) (Fig. 2).
Increase in pre-bronchodilator IC (L and %) by 0.13 L and 6.83% were observed at week 24 in the tiotropium plus FSC group compared to 0.079 L and 5.26% in the tiotropium-only group (P = 0.055 and P = 0.135, respectively) (Fig. 3).

Within the tiotropium plus FSC group, a pre-bronchodilator IC (L) at week 24 significantly increased over baseline (0.130 L, P = 0.010), whereas no significant difference was observed within the tiotropium-only group (0.079 L, P = 0.127) (Fig. 3).

Within the tiotropium plus FSC group, FVC (L) significantly improved at week 24 over the baseline (P = 0.044), but no significant differences were seen in the tiotropium-only group (P = 0.180) (Fig. 3).

Quality of life
Twenty-four-week combination therapy with tiotropium plus FSC significantly improved health-related quality of life compared to tiotropium monotherapy. Over the study period, the mean change in SGRQ-C total score was −6.6 points in the tiotropium plus FSC group compared to −1.5 points in the tiotropium-only group (P = 0.001). At week 24, differences in SGRQ-C scores between the two groups were 4.5 points, 6.1 points, and 4.5 points for subscores of symptoms, activity, and impact, respectively (Fig. 4).

Acute exacerbation
The number of patients with COPD exacerbations was numerically lower in the tiotropium plus FSC group compared to the tiotropium-only group, although the difference was not significant (17.5% vs. 20.3%, respectively; P = 0.462). No significant differences were observed in the rates of hospitalization, visits to the emergency room or outpatient clinics for COPD exacerbations, or the all cause hospitalization between the tiotropium plus FSC group and the tiotropium-only group.
Safety
Both treatments were well tolerated, and the overall incidence and severity of adverse events were comparable between the two groups. Twenty patients (8.7%) in the tiotropium plus FSC group and 16 patients (6.7%) in the tiotropium-only group experienced serious adverse events. Discontinuations due to adverse events were rare in both groups, with 4 patients (1.7%) in the tiotropium plus FSC group compared to 7 (2.9%) in the tiotropium-only group ($P = 0.545$). The most frequently reported adverse event was a productive cough in patients receiving tiotropium plus FSC (13.4%), whereas dyspnea was the most frequently reported event in the tiotropium-only group (12.6%). Two cases of pneumonia were reported in each treatment group, and one patient in the tiotropium group was withdrawn due to pneumonia.

Subgroup analysis with GOLD stage II (FEV$_1$ 50% to ≤65%) patients
Of the 479 patients randomized, 266 (55.5%) GOLD stage II patients with COPD at screening (FEV$_1$ 50% to ≤65%) were included for subgroup analysis (126 in the tiotropium plus FSC group and 140 in the tiotropium-only group).

Treatment with tiotropium plus FSC was superior to treatment with tiotropium alone for improvement of FEV$_1$ in the moderate COPD (FEV$_1$ 50% to ≤65%) group (Fig. 5). Over 24 weeks, the pre-bronchodilator FEV$_1$ increased significantly by 0.088 L in the tiotropium plus FSC group compared to 0.030 L in the tiotropium-only group ($P = 0.011$). Significant improvement of IC and FVC from the baseline was observed in the tiotropium plus FSC group; however, no significant difference existed in mean change between the two groups ($P = 0.183$ in IC and $P = 0.956$ in FVC between the groups).

In health-related quality of life, tiotropium plus FSC provided a greater improvement in the SGRQ-C total score than tiotropium alone (−4.5 points vs. −1.0 points, respectively). In the overall rate of exacerbation, no significant difference was observed between the two groups (19.0% for tiotropium plus FSC vs. 17.1% for tiotropium alone; $P = 0.750$).

Discussion
In our study, we observed that tiotropium and FSC with 250 μg of fluticasone propionate provided greater improvement of FEV$_1$ than tiotropium alone in patients with COPD (FEV$_1$ ≤ 65%), and the SGRQ-C score also increased in triple-inhaled therapy group with clinical significance throughout the study. Although the overall rate of exacerbations did not decrease, this treatment approach did not induce more adverse events such as pneumonia. This beneficial effect of triple-inhaled therapy was identical to the subgroup of GOLD stage II patients with COPD (FEV$_1$ 50% to ≤65%).

Although studies have demonstrated the beneficial impact of triple-inhaled therapy in patients with COPD, this is the first one using FSC with 250 μg of fluticasone propionate twice daily plus tiotropium to evaluate the efficacy and safety of triple-inhaled therapy. Adding FSC with 250 μg of fluticasone propionate to tiotropium showed superior improvement in pulmonary function, especially pre-bronchodilator FEV$_1$, than tiotropium alone. Over the treatment period, triple-inhaled therapy with FSC of 500/100 μg daily and tiotropium significantly increased pre-bronchodilator FEV$_1$ by 171 ml compared to tiotropium monotherapy at increments of 111 ml. These data are in line with the 12-month OPTIMAL study using FSC of 1000/100 μg daily, and the 3-month CLIME study using budesonide/formoterol plus tiotropium, presenting a difference of around 60 ml in the pre-bronchodilator FEV$_1$ between triple-inhaled therapy and tiotropium monotherapy.

Regarding total SGRQ-C score and subscores of symptoms, activity, and impact, patients undergoing triple-inhaled therapy improved more than 4 units after a 24-week treatment compared to baseline, which is clinically meaningful. They also showed a significant difference of more than 4 units compared to those treated with

![Figure 2](image-url)
tiotropium alone. Compared to the CLIME study reporting a total SGRQ score improvement of 3.8 units in the triple-inhaled therapy group using budesonide/formoterol and tiotropium, our findings show clinically meaningful improvements and suggest that adding FSC to tiotropium has substantial clinical benefits in health-related quality of life.

Triple-inhaled therapy using FSC of 500/100 mg daily and tiotropium in our study did not increase concerns or risks of pneumonia. Previous studies on triple therapy, including the OPTIMAL study, which used FSC 1000/100 mg daily, reported a significant increase in pneumonia compared to placebo or tiotropium monotherapy. Studies reporting the risk of pneumonia in conjunction with the use of ICS showed more risks of pneumonia with higher doses of ICS, which suggest a dose–response relationship of ICS and the risks of pneumonia. Thus, our study finding that a lower dose of FSC clinically improves lung function and health-related quality of life without raising the risks of pneumonia is meaningful for treating patients with COPD (FEV$_1$ $\leq$ 65%).

### Figure 3
Mean change in Inspiratory capacity and FVC from baseline to each visit using ANCOVA: (A) Inspiratory capacity (L), (B) Inspiratory capacity (%), (C) FVC (L), (D) FVC (%).

### Figure 4
Mean change in the SGRQ-C from baseline to week 24 using ANCOVA.

ANCOVA = Analysis of Covariance; FSC = fluticasone propionate/salmeterol combination; TIO = tiotropium. * p<0.05 FSC+TIO versus TIO
We had approximately half of the randomized patients categorized into GOLD stage II. The subgroup analysis of GOLD stage II (FEV1 50% to ≤65%) patients also demonstrated the benefits of FSC in combination with tiotropium in acquiring greater improvement of lung function compared with tiotropium monotherapy. Moreover, an increase of more than 4 points in total SGRQ-C score in this group indicates that triple-inhaled therapy is clinically beneficial to health-related quality of life. To date, the clinical evidence of triple-inhaled therapy for GOLD stage II patients is still necessary. This study, reporting beneficial effects of triple-inhaled therapy, could provide therapeutically important information for the treatment of GOLD stage II (FEV1 50% to ≤65%) patients.

Our study had several advantages compared to previous studies. First, specialists in respiratory medicine at each center cared for the enrolled patients. Second, since the primary outcome of our study was lung function improvement, the quality of pulmonary function tests at each center had been strictly controlled and monitored by a central institution via e-mail or fax. This verification process resulted in the maintenance of qualified lung function tests, which reduced potential performance bias that would possibly be apparent in multicenter studies. Last, our study had a low dropout rate of only 13% in both groups. This relatively low dropout rate attenuated the attrition bias, which could affect the validity of the study results. Thus, the statistical power obtained in our study is valid to demonstrate the beneficial effect of tiotropium plus FSC on the primary outcome.

The potential limitation of our study lies in its open-labeled design. Patients who received tiotropium plus FSC might subjectively have responded more actively to lung function tests and SGRQ-C than those who received tiotropium alone. Also, physicians might have been biased on the treatment of enrolled patients, which could have resulted in a nonsignificant change of pre-bronchodilator FEV1 in the tiotropium-only group. However, improvement in pre-bronchodilator FEV1 via tiotropium monotherapy was comparable to that in the study by Niewoehner et al., and bias could have been minimized since the technicians who performed lung function tests were not aware of the allocated medications of the patients. The other limitation is that generalizing our observations from the subgroup analysis to mild COPD is difficult since the upper limit for study eligibility mandated that post-bronchodilator FEV1 was less than 65% in post-bronchodilator FEV1 % pred.

In conclusion, FSC (500/100 μg per day) added to tiotropium provided greater improvement in lung function and quality of life in patients with COPD (FEV1 ≤ 65%) over the course of 24 weeks. Although the overall rate of exacerbation did not decrease, the treatment approach did not increase adverse events such as pneumonia. This study demonstrates that triple-inhaled therapy of FSC (500/100 μg per day) plus tiotropium was beneficial in the management of COPD (FEV1 ≤ 65%).

**Potential conflicts of interest**

Sang Do Lee serves as a consultant to GlaxoSmithKline and Nycome, and has participated as a speaker in scientific meetings organized and financed by various pharmaceutical companies (GlaxoSmithKline, AstraZeneca Korea, Boehringer, Nycomed, Altana Pahrma, Abbott).

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