Tiotropium in COPD patients not previously receiving maintenance respiratory medications

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**Summary**

*Introduction:* Use of maintenance bronchodilator therapy is currently recommended in symptomatic patients with Chronic obstructive pulmonary disease (COPD) and in those with Stage II or greater COPD as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Because no prospective data describe when rescue therapy alone is insufficient or the optimal time to start maintenance therapy, it is unclear whether maintenance therapy has benefits in milder disease. To explore potential benefits we asked: Does once-daily tiotropium improve lung function, health status, and/or symptoms in “undertreated” COPD patients (i.e., those who are not receiving maintenance bronchodilator therapy) or patients considered by their health care providers as having milder disease?

*Methods:* A post-hoc analysis of data from COPD patients participating in two, 1-year, placebo-controlled trials with tiotropium was performed. Patients were defined as “undertreated” if they received no respiratory medication or only as-needed short-acting \( \beta \)-agonists prior to enrollment. Measures included serial spirometry, Transition Dyspnea Index (TDI), and St. George’s Respiratory Questionnaire (SGRQ).

*Results:* Of 921 patients enrolled, 218 (23.7\%) were “undertreated”: 130 received tiotropium; 88 received placebo. Demographics for the two treatment groups were comparable. Tiotropium-treated patients had significantly improved forced expiratory volume in 1 s (FEV\(_1\)) and forced vital capacity (FVC) compared with patients
Introduction

Chronic obstructive pulmonary disease (COPD) is a disease that affects millions of people worldwide, is currently ranked as the fifth leading cause of death globally, and incurs significant health care expenditures. Recently, focus has been drawn to COPD as a public health issue through efforts such as the Global Initiative for Chronic Obstructive Lung Disease (GOLD), and organizations such as the American Thoracic Society (ATS) and European Respiratory Society (ERS), which have published recommendations to help optimize COPD diagnosis and management.

COPD begins with an asymptomatic phase in which lung function deteriorates without associated symptoms. The onset of the subsequent symptomatic phase is variable, but often does not occur until the forced expiratory volume in 1 s (FEV₁) has fallen to approximately 50% of the predicted normal value. Airflow obstruction is generally progressive over a period of years and is only partially reversible. Bronchodilators are important treatments to reduce symptoms in COPD. However, the optimal timing and the specific criteria (based on respiratory symptoms versus FEV₁) for initiating maintenance (i.e., regularly scheduled) bronchodilator therapy have not been addressed or clearly defined by clinical trials. Guidelines for COPD management suggest that maintenance therapy is indicated for those patients with at least moderate disease (GOLD Stage II or higher) or patients that are symptomatic. However, in clinical practice many patients (up to 45%) who have visits to a healthcare professional with the diagnosis of COPD have not ever had spirometry performed. Since healthcare professionals usually prescribe maintenance bronchodilators for COPD patients after an acute exacerbation of COPD or as a result of significant respiratory symptoms, one functional definition of "undertreated" disease may include patients who are not prescribed maintenance bronchodilator therapy.

To address whether once-daily tiotropium improves lung function, health status, and/or symptoms in undertreated COPD patients, we pooled the data from two large, 1-year, placebo-controlled studies of inhaled tiotropium 18 μg conducted in the United States. We evaluated the efficacy of once-daily tiotropium 18 μg given as a first-line maintenance therapy to patients with "undertreated" COPD. We defined subjects as having "undertreated" disease if they had previously received either no respiratory medications or only as-needed short-acting β-agonists. Additionally, we examined the effects of tiotropium 18 μg in two other subsets of subjects: (1) in the "undertreated" group according to baseline post-bronchodilator FEV₁ < 50% or ≥ 50% predicted, and (2) in a non-unique subset of subjects in the 1-year studies who were classified as having GOLD Stage I "mild" COPD by post-bronchodilator FEV₁ at day 8 (referred to as "mild by GOLD staging").

Methods

Study subjects

A post hoc analysis was performed on data from two identical, 1-year, randomized, double-blind, placebo-controlled, parallel-group studies of once-daily inhaled tiotropium 18 μg in patients with COPD (trials 205.117 and 205.128). Fifty clinical centers participated in these trials and each center’s institutional review board approved the protocol. All subjects provided written informed consent prior to participation.

The study groups consisted of outpatients of either gender who were at least 40 years of age with a clinical diagnosis of COPD, as defined by the ATS. Participants were required to have at least a 10-pack-year history of smoking, clinically stable airway obstruction, an FEV₁ less than 70% of the forced vital capacity (FVC) and an FEV₁ of less than 65% of the predicted normal value. Subjects were excluded if they had a history of asthma, allergic rhinitis, atopy, or a total blood eosinophil count of more than 600/mm³. Subjects were excluded if they required regular daytime supplemental oxygen, were on corticosteroid doses exceeding the...
equivalent of 10 mg of prednisone daily during the month prior to entering the study, had a recent history of myocardial infarction (1 year or less), hospitalization for heart failure (3 years or less), cardiac arrhythmias requiring drug therapy, symptomatic prostatic hypertrophy, or narrow angle glaucoma.

Study design

Following a 2-week baseline period, subjects were randomly assigned to receive either tiotropium (18 μg) or placebo. Subjects were randomized in 3:2 tiotropium:placebo ratios. Subjects were administered active medication (tiotropium in lactose) or placebo (lactose) by inhalation, one dose each morning in identical-appearing capsules via a dry-powder inhaler device (HandiHaler™, Boehringer Ingelheim GmbH & Co. KG, Ingelheim, Germany). Subjects were permitted to use an albuterol metered-dose inhaler, as needed, throughout the study. No other inhaled anticholinergics (other than study drug) or β-agonists (long-acting inhaled or oral) were allowed during the study. Investigators were permitted to prescribe any therapy that was medically necessary, including antibiotics and systemic corticosteroids, to treat acute exacerbations of COPD during the trial.

Spirometric testing was conducted according to ATS standards on treatment day 1 (baseline), on day 8, and at 6, 12, 24, 36, and 48 weeks of treatment. Drugs were to be administered at the same time each day (between 7 and 9 am). On test days, FEV₁ and FVC were measured and recorded at 1 h and at 5 min prior to dosing study medication and at 30, 60, 120 and 180 min post-dose. Trough values of FEV₁ and FVC were calculated as the mean of the two pre-dose measurements, i.e., approximately 23 and 24 h after the previous dose of study medication. The changes in lung function over time were evaluated by examining trough and peak FEV₁ and FVC from day 8 to day 344. As previously noted, a subgroup of subjects was defined as having “undertreated” disease if they had previously received either no respiratory medications or only as-needed short-acting β-agonists. An additional subset of (non-unique) subjects whose FEV₁ improved to greater than 80% of the predicted normal value on day 8, were analyzed and are referred to in this manuscript as “mild by GOLD staging.” As GOLD indicates that FEV₁ staging should be based on post-bronchodilator values and acute responses to short-acting bronchodilators was not assessed in the clinical trials, we used the post-tiotropium value on day 8 as a surrogate. Other than at day 8, the Transition Dyspnea Index (TDI) and the St. George’s Respiratory Questionnaire (SGRQ) were measured on the same days as the spirometry measurements.

Analysis

Data are presented as proportions or means (standard deviation or standard error). Data were analyzed using analysis of covariance (ANCOVA) at each visit to compare the change in response over the year in the two treatment groups of the “undertreated” COPD patients. The consistency of effects across subgroups based on severity or smoking status was assessed by testing treatment-by-subgroup interaction effects. For patients discontinued due to worsening of their disease (5% of patients), missing data were imputed using the least favorable data. For those who discontinued for other reasons, their missing data were imputed by carrying the last observation forward. A TDI Focal score of at least one unit was considered a clinically significant change in activity-related dyspnea. A change in SGRQ score of at least 4 units was considered to be a clinically significant change in quality of life. Statistical significance was considered at P < 0.05.

Results

Of 921 subjects enrolled in these two clinical trials, we identified a group of 218 (23.7%) subjects who were “undertreated,” defined as those who were not receiving maintenance respiratory medications (i.e., either no respiratory medications (N = 178) or only short-acting β-agonists (N = 40) upon entry). Within this subgroup of “undertreated” subjects, 130 received tiotropium and 88 received placebo. The subject characteristics at baseline were similar between groups (Table 1). The mean age was 64 years, they were predominantly male, smoked an average of 62 pack-years, and had a mean FEV₁ of 1.13 L (Table 1). Approximately 26% of placebo treated subjects and 19% of tiotropium treated subjects prematurely discontinued participation in the trial. The reasons for discontinuation are listed in Table 2.

Spirometry

The mean changes from baseline in trough FEV₁ and FVC over 1 year of treatment in this “undertreated” subgroup are shown in Figs. 1 and 2. These
subjects who were treated with tiotropium had significantly higher mean trough FEV₁ and FVC and peak FEV₁ and FVC on all study days compared with those who received placebo \((p < 0.001\) in all cases). At the end of the study, the mean trough FEV₁ was 190 mL greater and the mean FVC was 400 mL greater for the tiotropium treated subgroup than for the placebo group. In addition, the magnitude of difference in mean peak FVC was 540 mL larger in the "undertreated" subjects treated with tiotropium than those treated with placebo.

### Table 1 Baseline patient characteristics in the "undertreated" subgroup of those receiving tiotropium and placebo.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tiotropium</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>130</td>
<td>88</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.8 (8.9)</td>
<td>64.7 (9.5)</td>
</tr>
<tr>
<td>Males (%)</td>
<td>62.3</td>
<td>55.7</td>
</tr>
<tr>
<td>Duration of COPD (years)</td>
<td>7.6 (6.7)</td>
<td>6.1 (5.6)</td>
</tr>
<tr>
<td>Smoking history (pack-years)</td>
<td>65.1 (31.1)</td>
<td>58.5 (29.9)</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>49.2</td>
<td>47.7</td>
</tr>
<tr>
<td>Screening spirometry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>1.18 (0.47)</td>
<td>1.05 (0.44)</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>41.6 (13.8)</td>
<td>39.2 (14.5)</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>2.39 (0.83)</td>
<td>2.26 (0.83)</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>50.0 (11.1)</td>
<td>47.3 (12.3)</td>
</tr>
</tbody>
</table>

FEV₁ = forced expiratory volume in 1s; FVC = forced vital capacity.

* Data presented as mean (SD) or proportions.

\(p < 0.05.\)

### Table 2 Reasons for premature discontinuation in the placebo and tiotropium groups.

<table>
<thead>
<tr>
<th>Reasons</th>
<th>Tiotropium</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total discontinuations</td>
<td>25 (19.2)</td>
<td>23 (26.1)</td>
</tr>
<tr>
<td>Adverse event—worsening of COPD</td>
<td>1 (0.8)</td>
<td>4 (4.6)</td>
</tr>
<tr>
<td>Adverse event—worsening of pre-existing disease (not COPD)</td>
<td>1 (0.8)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Adverse event—other</td>
<td>5 (3.9)</td>
<td>8 (9.1)</td>
</tr>
<tr>
<td>Consent withdrawn</td>
<td>8 (6.2)</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>2 (1.5)</td>
<td>5 (5.7)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>4 (3.1)</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (3.1)</td>
<td>1 (1.1)</td>
</tr>
</tbody>
</table>

### Figure 1 Mean difference (Standard Error (SE)) from baseline in trough and peak FEV₁ response in the "undertreated" tiotropium group and placebo group between day 8 and day 344. (A) Trough FEV₁ response, and (B) peak FEV₁ response. * \(p < 0.001\) vs. placebo.

### Figure 2 Mean difference (SE) from baseline in trough and peak FVC response in the "undertreated" tiotropium group and placebo group between day 8 and day 344. (A) Trough FVC response, and (B) peak FVC response. * \(p < 0.001\) vs. placebo.
Dyspnea

Dyspnea assessed by the TDI Focal score for this “undertreated” subgroup improved 0.89 in the tiotropium treated group compared with placebo by the end of the year ($P < 0.05$) (Fig. 3). Upon further analysis, the differences in TDI Focal scores between tiotropium and placebo in the subgroup of active smokers within the “undertreated” subject group improved more than in the former smokers (active smokers [tiotropium $N = 54$, placebo $N = 37$] improved 1.14 and former smokers [tiotropium $N = 59$, placebo $N = 39$] improved 0.65); however, the difference between active vs. former smokers was not statistically significant ($P = 0.5$).

Health status

Health status as assessed by the SGRQ Total score improved $5.2$ units in the tiotropium treated subjects compared with placebo at the end of therapy in this “undertreated” subgroup ($P < 0.05$) (Fig. 4). At the end of the study, the differences from baseline for SGRQ Activity, Impact, and Total scores improved significantly more in subjects who received tiotropium than in those who received placebo. The mean Symptom scores improved by $5.1$ in the tiotropium group over the placebo; however, this difference was not statistically significant ($P = 0.07$). In addition, the differences in the SGRQ scores between the tiotropium and placebo groups were not different between those who were active vs. former smokers.

Use of rescue medication

In this “undertreated” group, the mean use of as-needed albuterol (2.6 doses/day at baseline) was reduced by 0.6 doses/day with tiotropium and was increased by 0.4 doses/day with placebo ($P = 0.0007$).

Analyses of other subsets of subjects

An analysis of the subset of “undertreated” subjects with a baseline FEV$_1 < 50\%$ predicted (tiotropium $N = 84$, placebo $N = 55$) compared with those with a baseline FEV$_1 \geq 50\%$ predicted (tiotropium $N = 35$; placebo $N = 23$) demonstrated that trough and peak FEV$_1$ and FVC significantly improved at all measured study days after day 50 with tiotropium vs. placebo in the subgroup with the lower lung function. The differences in lung function at day 344 between the tiotropium and the placebo groups are shown in Table 3 for these subgroups of patients based on their baseline FEV$_1$ values. In addition, the differences in TDI Focal scores between tiotropium and placebo significantly improved in the subset of subjects with the lower lung function (FEV$_1 < 50\%$ predicted, tiotropium $N = 79$, placebo $N = 53$) compared with those with higher lung function (FEV$_1 \geq 50\%$ predicted, tiotropium $N = 34$, placebo $N = 23$) ($1.32$ vs. $-0.12$, respectively, $P = 0.07$). Finally, the subjects with very low FEV$_1 (< 50\%$ predicted) demonstrated the most significant improvement in mean SGRQ total scores at each of the study days ($-7.48$ on day 344 for the subgroup with FEV$_1 < 50\%$ predicted vs. $0.15$ for the subgroup with FEV$_1 \geq 50\%$ predicted $P < 0.05$).

We analyzed another subset of 20 non-unique subjects with GOLD Stage I (Mild) disease by spirometry on day 8 (all from the tiotropium-treated group). Twelve of the 20 subjects in this “mild disease by GOLD staging” subset were also in the “undertreated” subgroup. The characteristics...
of this subset of 20 subjects with "mild disease by GOLD staging" are listed in Table 4. The trough, peak, and mean values for FEV₁ and FVC significantly improved from baseline on all study days in this "mild disease by GOLD staging" subset who all received tiotropium. At the end of the study, the mean (±se) percent improvements from baseline in trough (predose), peak and average FEV₁ were 15.4 (4.8), 26.0 (5.9) and 21.6 (5.2), respectively, and results for FVC were 7.6 (4.7), 18.7 (5.5) and 13.4 (4.9), respectively, showing that improvements in lung function were seen irrespective of "mild" severity and persisted over a period of 23–24 h after dosing. In addition, this subset of subjects had marked improvements in their SGRQ Total score (mean-6.1 units) at the end of the study (Day 344).

Finally, the mean use of as-needed albuterol with tiotropium (2.9 doses/day at baseline) was reduced by an average of 0.7 doses/day in this subset of subjects with "mild disease by GOLD staging."

**Discussion**

The present post hoc analysis of two 1-year, placebo-controlled trials suggests that tiotropium 18 µg once daily provides significant improvement in lung function, dyspnea, and health status when used by "undertreated" COPD subjects, defined clinically as those not previously receiving maintenance inhaler therapy. The subset of "undertreated" subjects with the lowest lung function (baseline FEV₁ <50% predicted) demonstrated the largest improvement in these outcomes. However, the subjects with severe obstruction to airflow were not the only subjects to benefit from tiotropium: the subset of non-unique subjects with "mild disease by GOLD staging" who were treated with tiotropium also demonstrated significant improvements in lung function and health status.

The observed differences from placebo within the "undertreated" subset of subjects with COPD were similar to or greater than those seen in the entire cohort. The absolute differences from placebo in the mean trough FEV₁ and FVC in the "undertreated" subgroup of subjects were larger than those seen in the full cohort (mean trough FEV₁ = 190 mL in the subgroup vs. 150 mL in the whole cohort, and mean trough FVC = 400 mL vs. 290 mL, respectively). The magnitude of difference from placebo in mean peak FVC was also
larger in the "undertreated" subjects than in the full cohort (540 mL vs. 440 mL). The improvement of the tiotropium group above the placebo group in the TDI Total score was similar for the "undertreated" subgroup and the full cohort (0.89 vs. 1.14, respectively). In addition, the improvement in SGRQ total score was greater in the "undertreated" subgroup than in the entire cohort (−5.2 vs. −3.7, respectively).12 Bronchodilators are usually prescribed to relieve symptoms, reverse airway obstruction and to improve the overall morbidity associated with COPD.3,9,10 As-needed short-acting β-agonists are currently recommended for the rapid relief of respiratory symptoms associated with COPD.3,7 The guidelines and current recommendations suggest however, that if short-acting bronchodilators do not control symptoms adequately, a long-acting bronchodilator can be added or substituted, but there are minimal data regarding the optimal timing of initiating maintenance therapy.3,7,20 For the "undertreated" subgroup of subjects with COPD described in this study, the absence of maintenance therapy could potentially indicate that their health care providers either considered these patients as having mild disease or were unaware of the options for maintenance airway medication.

COPD is frequently not recognized until the clinically advanced stages of the disease. Zaas et al.21 reported data from spirometry and questionnaires performed in 153 patients admitted to a general medicine service for any medical problems during a 7-month period in 2000. Fewer than 5% were admitted with either an asthma or COPD exacerbation. Overall, 26% had evidence of obstruction by spirometry; whereas, only 9% had the diagnosis of an obstructive lung disease at admission. At hospital discharge, 67–70% of patients with moderate to severe airway obstruction by spirometry were not diagnosed with COPD prior to, or during, their hospital stay and only 40% of these patients received bronchodilators at hospital admission and/or discharge.21 Surprisingly, 11% of the patients with very severe airway obstruction (FEV1 <30% predicted) did not have the diagnosis of COPD at discharge. Furthermore, there is a potential problem with relying on patients developing symptoms prior to initiating scheduled, maintenance bronchodilator therapy because patients with COPD often do not report symptoms to physicians until they have significantly reduced lung function. Depending on the population studied (routine screening of smokers vs. inpatients presenting with first episode of acute exacerbation of COPD), between 10% and 60% of newly diagnosed COPD patients have an FEV1 percent predicted of 50% or less.22–24 This current study supports the guideline recommendations to begin scheduled bronchodilator therapy for COPD patients with GOLD Stages II or higher (moderate to very severe). However, regularly scheduled bronchodilator therapy may be beneficial even in the patients who are not complaining of respiratory symptoms. Although the specific mechanism for the fact that the largest benefit in lung function with tiotropium is in the subgroup of "undertreated" COPD subjects with lower baseline lung function is unclear, one can speculate that utilizing a bronchodilator with a 24-h duration of action improves patient adherence and reduces hyperinflation throughout the day and night, which may influence long-term changes in spirometry, health status, and acute exacerbations.25,26

Our data support the need to identify patients with COPD early in the course of their disease. The consensus statement from the National Lung Health Education Program recommends the widespread use of spirometry for patients older than 45 years who have significant cigarette smoke exposure.27 Several investigators have demonstrated that spirometry is able to identify patients with COPD, who were not detected using a symptom related screening questionnaire.21 Although there is controversy in the literature regarding the value of screening spirometry, the guidelines clearly state that spirometry is required to diagnose and stage patients with COPD.3,7,28

There are several limitations to our study. We performed a retrospective, post hoc analysis of data collected prospectively from two clinical trials that were conducted in a rigorous fashion, but were not specifically designed to assess differences in lung function, dyspnea, rescue β-agonist use, or health status in the subgroups of COPD patients analyzed in the present report. Other data that are important in this patient population, such as type and duration of symptoms and access to health care, were not collected. Prospective epidemiologic studies have suggested that patients with respiratory symptoms are very likely to avoid medical treatment, which is why most of these patients are not identified until the advanced stages of the disease.29 In the present analysis, the tiotropium and placebo treated patients had similar baseline characteristics including a similar percent predicted FEV1, although the absolute (i.e., mL) FEV1 was statistically different which likely reflects a minor difference in gender distribution between groups. In addition, limiting the analyses to the "undertreated" and/or "mild by GOLD staging" subset results in a smaller sample size that may have inadequate power.


Furthermore, a higher discontinuation rate in the placebo arm may have also biased the results. However, one can argue that the more severely ill patients were not able to complete the study period and, as a consequence, the results may underestimate the tiotropium effect.

Conclusions

This study (1) demonstrates that tiotropium 18 μg once daily provides significant improvement in lung function, dyspnea, and health status when given to COPD subjects who previously received either no respiratory medications or only as-needed short-acting β-agonists and (2) supports the hypothesis that tiotropium should be used as a first-line maintenance therapy in COPD patients. Not surprisingly, the subgroup within this “undertreated” COPD population who appears to benefit the most from scheduled therapy with tiotropium is the group with very low lung function (FEV1 <50% predicted). Nevertheless, we also identified significant clinical benefits in lung function and health status in a subset of subjects with a post-bronchodilator FEV1 >80% predicted (i.e., GOLD mild disease). The present study indicates that health care providers need to be vigilant in their assessment of patients with COPD to insure that patients are receiving maintenance bronchodilators based on a consideration of symptoms and objective measures of airflow limitation. Future studies designed to identify the optimal time to initiate scheduled, maintenance therapy to potentially modify the clinical course for patients with COPD are indicated, particularly since some of the patients with FEV1 <50% predicted may have minimal to no respiratory symptoms at presentation and others may be symptomatic with mild airflow limitation.

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References


