Improvements with tiotropium in COPD patients with concomitant asthma

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Summary

Background: Chronic obstructive pulmonary disease (COPD) and asthma have different diagnostic criteria and treatment paradigms. Both are common and can occur in the same patient. We sought to determine the spirometric effects of tiotropium in COPD patients with concomitant asthma.

Methods: A 12-week randomized, double-blind, placebo-controlled, parallel group trial with tiotropium 18 mcg daily was performed. Patients continued usual respiratory medications except for inhaled anticholinergics. Inclusion criteria: Physician diagnosis of COPD and asthma, age \textgreater 40 years, smoking \textgreater 10 pack years, post-bronchodilator forced expiratory volume in 1s (FEV\textsubscript{1}) \textless 80% predicted, FEV\textsubscript{1}/forced vital capacity (FVC) \textless 70%, \textgreater 12%, and \textgreater 200 ml increase in FEV\textsubscript{1} following inhaled bronchodilator, treatment with inhaled steroids \textgreater 1 year. Spirometry was measured serially for 6 h on days 1, 29 and 85.

Results: Four hundred and seventy-two patients were randomized. Baseline characteristics were balanced. Mean age = 59.6 years, 61.4% were men, and FEV\textsubscript{1} = 1.55 l (53.0% predicted). Improvements at 12 weeks with tiotropium were observed for the primary endpoint FEV\textsubscript{1} area under the curve (AUC) from 0 to 6 h (difference = 186 ± 24 ml, \(p<0.001\)) and for morning pre-dose FEV\textsubscript{1} (difference = 98 ± 23 ml, \(p<0.001\)). Significant differences in favor of tiotropium were observed for pre-dose FVC (difference = 128 ± 34 ml, \(p<0.001\)) and FVC AUC 0–6 h (difference = 232 ± 35 ml, \(p<0.001\)). Compared to baseline, the mean weekly number of daily puffs of prn salbutamol was...
Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by airflow limitation that is not fully reversible.\(^1\) Asthma is defined as a chronic inflammatory disorder of the airways that is associated with airway hyperresponsiveness, which leads to recurrent symptoms that are usually associated with airflow obstruction within the lung that is often reversible either spontaneously or with treatment.\(^2\) Despite differing etiologies, pathophysiology, and clinical presentations, it is estimated that 10–20\% of patients have features of both diseases COPD and asthma.\(^3,4\)

Management strategies for asthma and COPD differ and current guidelines reinforce the need to determine a specific diagnosis and directing the subsequent treatment accordingly.\(^1,2\) Inhaled corticosteroids are well recognized as essential treatment in patients with asthma who have symptoms on a regular basis; however, in patients with COPD, inhaled steroids are considered only for patients with at least severe disease and repeated exacerbations.\(^1,2\) Anticholinergics such as ipratropium or tiotropium remain a first line treatment option in COPD, while their role in the treatment of asthma is limited. Studies indicate that anticholinergics may be additive to \(\beta\)-agonists in providing relief to patients with acute asthma.\(^5,6\) A recent trial suggested that ipratropium alone could be used for symptom relief in asthma.\(^7\)

While there is presently a large body of data supporting the efficacy of tiotropium in patients with COPD, to date, patients with COPD and concomitant asthma have been excluded from the long-term tiotropium COPD clinical trials.\(^8,10\) The objective of this trial was to evaluate the efficacy and safety of tiotropium inhalation capsules 18 mcg once daily administered via the HandiHaler\(^8\) in a subgroup of patients with COPD who have a concomitant diagnosis of asthma.

Methods and materials

The primary objective of this study was to demonstrate the superiority of tiotropium 18 mcg once daily administered via the HandiHaler\(^8\) compared to placebo in the treatment of patients with COPD and a concomitant diagnosis of asthma (trial 205.301). The primary efficacy endpoint was the change in forced expiratory volume in 1s (FEV\(_1\)) area under the curve over 6 h (FEV\(_1\) AUC\(_{0-6h}\)) after 12 weeks of randomized treatment.

Study design

The study was a 12-week, multi-center, multi-national, prospective, randomized, placebo-controlled, double-blind clinical trial. Following an initial screening, patients entered a 2-week run-in period. Patients treated with commercially available tiotropium were switched to ipratropium metered dose inhaler (MDI) qid 4 weeks prior to screening and continued treatment with ipratropium during the run-in period. Patients were allowed to continue treatment with long-acting inhaled \(\beta\)-agonists, inhaled corticosteroids, oral steroids (\(\leq 10\) mg/day prednisone or equivalent), theophyllines, leukotriene antagonists, and cromones as concomitant medication. Salbutamol was provided for as-needed acute symptom relief. At baseline, and 4 and 12 weeks post-randomization, spirometry was conducted 30 and 10 min prior to the administration of the study drug and 30, 60 min, 2, 3, 4, and 6 h post-dosing.

Patients were not allowed to take anticholinergic therapy other than study drug during the randomization period. Wash-out periods prior to spirometry on clinic days were as follows: long-acting inhaled \(\beta\)-agonists (including combination products) (24 h), theophylline preparations (24 h), and short-acting \(\beta\)-agonists (8 h).

The protocol was approved by ethics committees and/or institutional review boards for all participating centers. All patients signed written informed consent.

Patient population

Patients were required to have a physician diagnosis of asthma (before the age of 30 years), a diagnosis of COPD,\(^1,11\) post-bronchodilator FEV\(_1\) < 80\% predicted normal and a post-bronchodilator ratio of FEV\(_1\)/FVC (forced vital capacity) < 70\%. Other inclusion criteria were: smoking history > 10 pack-years, age ≥ 40 years, treatment with inhaled corticosteroids for ≥ 1-year prior to study entry, and an acute bronchodilator response ≥ 200 ml and ≥ 12\% of pre-bronchodilator FEV\(_1\) at the screening visit or documented during the past 5 years in the patient clinic records.

Spirometry

Spirometry equipment and techniques conformed to the criteria of the ATS.\(^12\) The highest FEV\(_1\) and the highest FVC obtained from three acceptable manoeuvres were recorded. For each patient, pulmonary function testing was to start between 7 and 10 a.m. At the beginning of the run-in period, spirometry was performed before and 30 min after 400 mcg inhaled salbutamol. At subsequent visits, FEV\(_1\) and FVC were obtained at 30 and 10 min prior to, and 30, 60 min, 2, 3, 4, and 6 h after drug administration.

Peak expiratory flow rates (PEFR) and symptom relief

Patients measured and recorded their PEFR in the morning (pre-dose) and in the evening. The patient took three readings per measurement and documented the highest in
the daily diary card. The patients recorded the number of actuations of salbutamol which he/she had needed per day in the daily diary card.

Data analysis

The area under the curve (AUC) for FEV\textsubscript{1} and FVC was calculated using the trapezoidal rule and normalized by division by 6 h. Baseline measurement was defined as mean of the two pre-dose measurements on day 1. For all diary endpoints, baseline was defined as the average of the data obtained in the week immediately preceding randomization. Testing was performed by comparing the least-square means, adjusted for treatment differences, pooled center differences, and baseline using the two sided t-test with the mean squared error as error term. The difference between the two treatment groups regarding the primary endpoint mean squared error as error term. The difference between differences, and baseline using the two sided means, adjusted for treatment differences, pooled center differences, and baseline values of the primary variable as covariate.

Continuous secondary efficacy endpoints were descriptively evaluated using, when appropriate, the models and methods described for the primary endpoint. The calculation of weekly means for PEFR and as-needed salbutamol were based on at least four data points. Imputations rules applied if fewer than four data points were available. For missing values, in general, the last observation was carried forward, or in case missing data was due to worsening of disease, than the worst observation was carried forward. Data are expressed as means ± SEM unless otherwise specified. Statistical significance was considered at \( p < 0.05 \).

According to sample size calculations (nQuery Advisor\textsuperscript{8} Version 4.0), a sample of 410 patients (205 per randomized treatment group) would be able to detect a 106 ml difference between the randomized treatment groups at 5% level of significance (two sided) with at least 90% power using a two-tailed t-test. Assumptions were based on previous clinical trials with tiotropium.\textsuperscript{9}

Results

The trial was conducted in 67 centers distributed within Belgium, Canada, Germany, Denmark, France, Italy, the Netherlands, and South Africa. A total of 566 patients were enrolled. Of those, 472 patients were considered eligible after the run-in period based on the inclusion and exclusion criteria and were randomized to either 18 \( \mu \)g tiotropium (228 patients) or matching placebo (244 patients). Ninety-four enrolled patients were not randomized. A total of 456 patients (96.6%) completed the entire planned observation time (placebo: 233 patients, 95.5%; tiotropium: 223 patients, 97.8%). Sixteen randomized patients (3.4%) discontinued prematurely (i.e., before day 85). The percentage of patients who withdrew was higher in the placebo group (11 patients, 4.5%) than in the tiotropium group (5 patients, 2.2%).

Patient characteristics

The mean age of the population was 59.6 years, 61.4% were men, and the mean FEV\textsubscript{1} was 1.55 l (53.0% predicted). The mean duration of COPD and asthma was 9.2 and 43.2 years, respectively. Baseline characteristics were similar between the treatment groups (Table 1). Mean baseline FEV\textsubscript{1} was 1.571 in the tiotropium group and 1.53 l in the placebo group. PEFR, as-needed salbutamol and concomitant maintenance pulmonary medications are recorded in Tables 1 and 2.

Spirometry

Improvements at 12 weeks with tiotropium were observed for the primary endpoint FEV\textsubscript{1} AUC 0–6 h (difference = 186 ± 24 ml, \( p < 0.001 \)) and for pre-dose FEV\textsubscript{1} (difference = 98 ± 23 ml, \( p < 0.001 \)). Significant differences in favor of tiotropium were observed for pre-dose FVC (difference = 128 ± 34 ml, \( p < 0.001 \)) and FVC AUC 0–6 h (difference = 232 ± 35 ml, \( p < 0.001 \)). Peak FEV\textsubscript{1} and peak FVC improvements relative to placebo were 188 ± 25 and 254 ± 37 ml, respectively (\( p < 0.001 \)). Increases in spirometry outcomes were observed with the first dose and at 4 weeks. Changes in spirometry over 6 h at baseline and at week 12 are displayed in Figures 1 and 2.

Peak expiratory flow rate

Weekly average PEFR improved on treatment with tiotropium. Daily dosing with tiotropium led to an increase in absolute morning and evening values. The mean difference to placebo in the change from baseline at week 12 was 20.3 ± 4.3 l/min (\( p < 0.0001 \)) for the morning measurement and 23.6 ± 4.2 l/min (\( p < 0.0001 \)) for the evening measurement (Figure 3).

Rescue requirement for salbutamol

Compared to baseline, mean weekly number of daily puffs of as-needed salbutamol was reduced by 0.05 ± 0.12 puffs/day in the placebo group and by 0.50 ± 0.12 puffs/day in the tiotropium group (difference = −0.45 ± 0.17, \( p < 0.05 \)) at week 12 (Figure 4).

Adverse events

Overall, 176 patients (37.3%) of the patients reported adverse events during the treatment period with a similar frequency for the two treatments (placebo: 36.5%; tiotropium: 38.2%). The most frequent adverse events on treatment were lower respiratory system disorders (placebo: 20.1%; tiotropium: 12.7%), upper respiratory system disorders (placebo: 5.7%; tiotropium: 13.2%), and gastrointestinal disorders (placebo: 5.7%; tiotropium: 9.6%). The most commonly reported gastrointestinal adverse event was dry mouth (placebo: 1.6%; tiotropium: 3.9%). Other system organ classes were noted with overall frequencies below 4%.

Within lower respiratory system disorders, the most common adverse events were exacerbations of the underlying diseases COPD and asthma (placebo: 28 patients, 11.5%; tiotropium: 15 patients, 6.6%). The frequency of patients with COPD exacerbations was lower in the tiotropium group (placebo: 26 patients, 10.7%; tiotropium:
13 patients, 5.7%). The number of patients with an asthma exacerbation was similar (placebo: 8 patients (3.3%), tiotropium: 6 patients (2.6%)). Two patients died during the trial, both were receiving placebo (COPD exacerbation, respiratory failure). A patient who had received tiotropium was reported to have died from a pneumothorax and COPD exacerbation approximately 6 months after the last dose of study drug.

### Discussion

The present 12-week trial is the first randomized, double-blind, controlled clinical study to have investigated the efficacy and safety of tiotropium 18 mcg once daily in patients with COPD and concomitant asthma. Tiotropium led to a significant improvement in FEV₁ measured over 6 h as well as FVC. Efficacy was further corroborated by the observed increase in PEFR and decrease in the use of rescue medication in patients treated with tiotropium. The results of the safety evaluation suggested a decrease in exacerbations with tiotropium, a finding consistent with previously reported clinical trials.⁸⁻¹⁰,¹³

Previously published reports indicate that there is likely a sizeable number of patients over the age of 50 years with obstructive airway disease to carry the dual diagnosis of asthma and COPD.⁴,¹⁴ Debate remains as to whether COPD develops from asthma (referred to as the Dutch hypothesis)¹⁵ or whether asthma and COPD are completely independent disorders (referred to as the British hypothesis).¹⁵⁻¹⁹ However, there is little debate that the diseases remain histologically different, have different physiologic abnormalities, differ in clinical manifestations and perhaps most importantly, have different responses to pharmacologic intervention.¹,²,²⁰,²¹,²³ One of the more relevant therapeutic differences is the recommended preference for inhaled corticosteroids as first-line maintenance treatment in asthma, and for long-acting inhaled bronchodilators in COPD.

Tiotropium is a once daily inhaled anticholinergic that has demonstrated improvements in spirometry, lung volumes, dyspnea, health-related quality of life, and exercise benefits in patients with COPD and concomitant asthma. The present 12-week trial is the first randomized, double-blind, controlled clinical study to have investigated the efficacy and safety of tiotropium 18 mcg once daily in patients with COPD and concomitant asthma. Tiotropium led to a significant improvement in FEV₁ measured over 6 h as well as FVC. Efficacy was further corroborated by the observed increase in PEFR and decrease in the use of rescue medication in patients treated with tiotropium. The results of the safety evaluation suggested a decrease in exacerbations with tiotropium, a finding consistent with previously reported clinical trials.⁸⁻¹⁰,¹³

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### Table 1  Baseline characteristics of patients in the tiotropium and placebo groups.

<table>
<thead>
<tr>
<th></th>
<th>Placebo, n = 244</th>
<th>Tiotropium, n = 228</th>
<th>Total, n = 472</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.2 (9.4)</td>
<td>59.1 (9.8)</td>
<td>59.6 (9.6)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>149 (61.1)</td>
<td>141 (61.8)</td>
<td>290 (61.4)</td>
</tr>
<tr>
<td>Duration of COPD (years)</td>
<td>9.1 (6.8)</td>
<td>9.2 (7.2)</td>
<td>9.2 (7.0)</td>
</tr>
<tr>
<td>Duration of asthma (years)</td>
<td>43.9 (13.9)</td>
<td>42.5 (14.3)</td>
<td>43.2 (14.1)</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>99 (40.6)</td>
<td>103 (45.2)</td>
<td>202 (42.8)</td>
</tr>
<tr>
<td>Smoking history (pack-years)</td>
<td>33.6 (16.8)</td>
<td>33.9 (17.3)</td>
<td>33.7 (17.0)</td>
</tr>
<tr>
<td>FEV₁ (l)</td>
<td>1.53 (0.48)</td>
<td>1.57 (0.53)</td>
<td>1.55 (0.51)</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>53.3 (13.7)</td>
<td>52.7 (13.5)</td>
<td>53.0 (13.6)</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>2.86 (0.86)</td>
<td>2.91 (0.87)</td>
<td>2.88 (0.86)</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>54.5 (11.4)</td>
<td>54.3 (11.3)</td>
<td>54.4 (11.3)</td>
</tr>
<tr>
<td>FEV₁ increase from baseline (%) to salbutamol 400 µg</td>
<td>19.5 (13.8)</td>
<td>19.8 (14.4)</td>
<td>19.6 (14.1)</td>
</tr>
<tr>
<td>AM PEFR (l/min)*</td>
<td>282.5 (85.8)</td>
<td>294.0 (102.3)</td>
<td>288.0 (94.2)</td>
</tr>
<tr>
<td>PM PEFR (l/min)*</td>
<td>292.8 (82.3)</td>
<td>307.1 (99.0)</td>
<td>299.7 (91.0)</td>
</tr>
<tr>
<td>Day time salbutamol use (puffs/day)</td>
<td>1.88 (2.08)</td>
<td>1.76 (1.97)</td>
<td>1.82 (2.03)</td>
</tr>
<tr>
<td>Night time use of salbutamol (puffs/night)</td>
<td>0.60 (1.12)</td>
<td>0.55 (1.04)</td>
<td>0.58 (1.08)</td>
</tr>
<tr>
<td>Total use of salbutamol (puffs/24 h)</td>
<td>2.47 (2.77)</td>
<td>2.31 (2.62)</td>
<td>2.40 (2.70)</td>
</tr>
</tbody>
</table>

Data are expressed as means (SD) or proportions.
*Weekly average.

### Table 2  Maintenance pulmonary medication (% of population) used prior to enrolment in the tiotropium and placebo groups.

<table>
<thead>
<tr>
<th></th>
<th>Placebo, n = 244</th>
<th>Tiotropium, n = 228</th>
<th>Total, n = 472</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total taking pulmonary medication*</td>
<td>99.6</td>
<td>98.2</td>
<td>98.9</td>
</tr>
<tr>
<td>β-Adrenergics (long-acting/inhaled)</td>
<td>68.4</td>
<td>75.0</td>
<td>71.6</td>
</tr>
<tr>
<td>Anticholinergics (short-acting/inhaled)</td>
<td>21.3</td>
<td>16.2</td>
<td>18.9</td>
</tr>
<tr>
<td>Theophyllines</td>
<td>19.7</td>
<td>16.2</td>
<td>18.0</td>
</tr>
<tr>
<td>Anticholinergics (long-acting/inhaled)</td>
<td>11.5</td>
<td>10.1</td>
<td>10.8</td>
</tr>
<tr>
<td>Leukotriene receptor antagonists</td>
<td>5.7</td>
<td>5.7</td>
<td>5.7</td>
</tr>
<tr>
<td>Steroids (oral)</td>
<td>5.3</td>
<td>3.5</td>
<td>4.4</td>
</tr>
<tr>
<td>β-Adrenergics (oral)</td>
<td>0.4</td>
<td>1.8</td>
<td>1.1</td>
</tr>
</tbody>
</table>

*Inhaled steroid use was an inclusion criteria.
In these trials, patients with a history of asthma were excluded from participation in an effort to assure that tiotropium was being evaluated in a patient population with COPD. Therefore, data on efficacy and safety in patients with both disorders have not been generated from randomized, blinded, controlled clinical trials. It could be argued that there it is obvious that these patients should be treated for both disorders and there is no need to study the benefits of an established treatment for a broad population of patients with COPD. Nevertheless, in the absence of specific data, the answer is based on indirect evidence. There may be unanticipated interactions of asthma and COPD along with other concomitant therapies that could diminish or possibly enhance responses to medications from another class. Ceiling effects are also unclear. It is therefore reasonable to conduct prospective trials specifically designed for such patients to confirm the supposition that COPD patients with asthma respond to tiotropium.

One of the critical factors in the present study is the accuracy of the diagnosis of asthma and COPD. The diagnosis of COPD appears to be easily defendable; patients with fixed airflow limitation, age of at least 40 years, history of smoking, and a physician diagnosis of COPD. The diagnosis is consistent with COPD guidelines. However, it is recognized that there may be some limitations regarding the diagnosis of asthma in this study. Challenge testing for airway hyperreactivity was not performed although patients were required to show acute responsiveness to a short-acting inhaled β-agonist. This in itself can be regarded as non-specific given that patients with COPD can demonstrate acute responsiveness to short-acting bronchodilators. In a retrospective analysis of 1 year clinical trials with tiotropium in COPD, tiotropium was efficacious irrespective of short-term improvements in FEV₁ of at least 12% and 200 ml, although those who did not achieve this definition for “response” appeared to have lower lung function. Markers of asthmatic inflammation, such as eosinophils and exhaled nitric oxide were not measured. In addition, skin testing for atopy and serum IgE was not requested. Nevertheless, the study had also sought to mirror what remains practical in terms of the standard diagnosis of asthma in the community. In this regard, patients were required to have a physician diagnosis of asthma before the age of 30 years, must have been receiving inhaled corticosteroids for at least 1 year prior to study entry, and must have had documentation of acute bronchodilator responsiveness.

A potential limitation may relate to the focus on lung function as an outcome rather than more in-depth measurements of patient-reported outcomes. The requirement for as-needed salbutamol, as observed, should be regarded as a relevant measure of symptom control. Indeed, in asthma...
In summary, tiotropium 18 mcg once daily appears efficacious and safe in patients with COPD and concomitant asthma. Tiotropium improved lung function and also provided symptomatic benefits as observed with a reduction in as-needed salbutamol and an observation suggesting a reduction in exacerbations. Whether tiotropium is only treating the COPD component or has some effect on the concurrent asthma diagnosis cannot be discerned from the present study. However, the data reinforces present guidelines for disease-specific treatments for asthma and COPD, which should be encouraged in the presence of concurrent obstructive diseases of the lung.

Disclosures

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References


