Tiotropium Bromide for the Maintenance of Chronic Obstructive Pulmonary Disease

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is associated with significant morbidity and mortality. It affects more than 10 million patients in the U.S. and accounts for approximately $14.7 billion in annual direct health care costs. COPD is characterized by progressive, irreversible airflow restriction and inflammation along with changes in lung compliance and elastic recoil that are manifested by hyperinflation. The diagnosis of COPD is based on a history of exposure to risk factors and the presence of airflow limitation that is not fully reversible, with or without the presence of symptoms. Patients who have chronic cough and sputum production (i.e., cigarette smoking, occupational dusts, and chemicals) should be tested for airflow limitation, even if they do not have dyspnea. The most important intervention for these patients is smoking cessation. It is the most cost-effective measure and the only option that has been shown to slow the accelerated decline in lung function in patients with COPD.

Because the available pharmacotherapeutic options for the management of COPD have not been shown to modify the long-term decline in lung function associated with the disease, the treatment options for COPD are used only to improve symptoms or to decrease complications. The bronchodilator medications, such as beta2-agonists and methylxanthines, are primarily directed toward the symptomatic relief of COPD manifestations. These medications should be given on an as-needed basis or on a regular schedule to prevent or reduce symptoms. Scheduled treatment with inhaled glucocorticosteroids should be prescribed only for symptomatic COPD patients with a documented spirometric response to them. COPD is associated with bronchial obstruction caused by hypersecretion of mucus and by increased bronchial muscle tone that is mediated by cholinergic mechanisms. Thus, decreased cholinergic tone results in reduced secretion of mucus in the airway and a reduced bronchial muscle tone. Because the cholinergic effects are the main reversible components of COPD, the inhaled anticholinergic agents are the first-line medications in the management of COPD.

PHARMACOLOGY

Tiotropium bromide (Spiriva®, Boehringer Ingelheim/Pfizer) is a new inhaled, dry-powder medication indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with COPD. It is a long-acting, dose-dependent, reversible, antimuscarinic (anticholinergic) agent. This quaternary ammonium compound is similar in structure to ipratropium bromide. At the binding sites in the human lung, tiotropium attaches to M1, M2, and M3 subtypes of the muscarinic receptor with equal affinity. It is approximately 10-fold more potent than ipratropium.

Although tiotropium binds to different subtypes of muscarinic receptors, it exerts its pharmacological effects via inhibition of the M3 receptors at the smooth muscle, resulting in bronchodilation. The antagonism of the M3 receptor is competitive and site-specific, causing bronchodilation that lasts more than 24 hours.

PHARMACOKINETICS

As with the inhalation of other therapies that include dry powder, after tiotropium is inhaled, most of the delivered dose is deposited in the gastrointestinal tract and, to a lesser extent, in the lung. The absolute bioavailability of 19.5% suggests that the fraction reaching the lung is high. Maximum tiotropium plasma concentrations were observed five minutes after inhalation. The volume of distribution is 32 liters/kg, indicating that the drug binds extensively to tissues. It is also bound by 72% to plasma proteins. The terminal elimination half-life of tiotropium is between five and six days after it is inhaled. The urinary excretion is 14% of the dose; the remainder, mainly nonabsorbed drug in the gut, is eliminated via the feces. After chronic once-daily inhalation by patients, the pharmacokinetic steady state is reached after two to three weeks, with no accumulation thereafter.

Efficacy Studies

Casaburi and colleagues compared the long-term efficacy of once-daily tiotropium with placebo in patients with clinical COPD. Overall, 921 patients (mean age, 65.2 years) were enrolled in the randomized, double-blind, placebo-controlled, one-year study. The patients inhaled tiotropium 18 mcg or placebo as a dry powder once daily. The mean
screening forced expiratory volume in one second (FEV₁) was 1.01 versus 0.99 liters, 39.1% and 38.1% of the predicted value, respectively. The primary spirometric outcome was trough FEV₁ or FEV₁ before dosing. The Transition Dyspnea Index (TDI) was used to measure changes in shortness of breath. The St. George’s Respiratory Questionnaire (a disease-specific instrument that accounts for symptoms, activity, and effects) and the generic Short Form 36 (SF-36) were used to assess the patients’ health status.

Tiotropium provided significantly superior bronchodilation compared with placebo for the trough FEV₁ response (approximately 12% over baseline) (P < .01) and mean response during the three hours following dosing (approximately 22% over baseline) (P < .001) over the 12-month period. Tiotropium recipients showed less dyspnea (P < .001), superior health status scores, and fewer COPD exacerbations and hospitalizations (P < .05).

The incidence of adverse drug events (ADEs) was comparable in patients receiving placebo, except for the incidence of dry mouth (tiotropium, 16.0%; placebo, 2.7%) (P < .05).

Overall, tiotropium therapy reduced the episodes of dyspnea in patients with exacerbations of COPD and improved their health status.

Casaburi et al., 2000¹⁵

Casaburi and associates investigated the efficacy and safety of tiotropium and placebo in a three-month, randomized, double-blind, comparative trial. The study group consisted of men and women 40 years of age or older with a clinical diagnosis of COPD, a smoking history of more than 10 pack-years, clinically stable airway obstruction, and an FEV₁ less than or equal to 70% of predicted normal values and an FEV₁/FVC ratio less than or equal to 70% of forced vital capacity (FVC). A total of 470 patients were randomly selected, in a 3:2 ratio, to receive either tiotropium 18 mcg (n = 279) or placebo (n = 191). Patients inhaled the study medication once a day between 8 A.M. and 10 A.M. Monitoring consisted of peak flow measurements twice daily and six visits to the study clinic.

Pulmonary function testing was performed during four visits, and the FEV₁ and FVC were recorded at various time intervals in relation to drug administration. The clinically significant increases in both FEV₁ and FVC occurred within 30 minutes after the first dose. Trough FEV₁ was measured 24 hours after the first dose reached a steady state one week after treatment was started—the next testing day—and remained 10% to 13% greater than baseline values throughout the 13-week treatment period.

All FEV₁ responses were significantly greater than with placebo (P < .001). All FVC comparisons of tiotropium and placebo were also statistically significant (P < .001). The improvement of morning peak expiratory flow rates (PEFRs) was significantly greater in the tiotropium patients from weeks 10 to 13 (P < .005); the mean difference between the two groups ranged from 10 to 20 liters/minute. Evening PEFRs were significantly higher in the tiotropium group during all 13 weeks (P < .001) and ranged from 16 to 24 liters/minute during treatment.

Physicians’ global assessments on test days were significantly improved (P < .001) for patients receiving tiotropium compared with those receiving placebo for all 13 weeks. Symptom scores for the tiotropium patients were statistically improved for wheezing and shortness of breath (P < .01) but not for tightness of the chest or cough in the placebo patients.

Supplementation with albuterol (e.g., Proventil®, Schering) was also evaluated. Albuterol therapy was maintained in the placebo group but was significantly decreased by approximately 30% in the first week (from 3.7 to 2.6 doses) and remained at this level for the 13 weeks. The difference between the two groups was significant at all 13 weeks (P < .001).

In this study, once-daily tiotropium improved pulmonary function based on FEV₁, FVC, and PEFR measurements. Overall improvements were also noted based on the physician’s global assessment.

Littner et al., 2000¹⁶

The dose–response effects of tiotropium were evaluated in a multicenter, randomized, double-blind, parallel group, placebo-controlled study. A total of 252 patients with COPD were screened, and 169 were randomly divided into five treatment groups: placebo or once-daily tiotropium 4.5, 9, 18, or 36 mcg at noon for four weeks. Patients were monitored for 10 visits.

Spirometry was the main assessment of efficacy and was performed before and hourly for six hours after administration. The concomitant medications that were allowed were short-acting beta-agonists, as needed; theophylline; and inhaled glucocorticosteroids—but only if COPD in the patients taking these drugs was stabilized for at least six weeks before the randomized trial. Oral glucocorticosteroids were prohibited for at least three months before the trial and throughout the study period.

When the single-dose responses of FEV₁ and FVC were measured, the FEV₁ was significantly increased over time in response to the first dose of the study medication (P < .05). All doses brought about significant improvements in FEV₁ compared with placebo (P < .05). Mean peak and average changes from baseline FEV₁ and FVC over the six-hour observation period were significantly greater in the patients receiving the drug than in those receiving placebo (P < .005).

The multiple-dose response, when compared with the mean weekly FEV₁ trough response over the course of treatment and post-treatment periods, showed no significant differences for the various doses of tiotropium; however, all four doses provided a greater trough response than placebo (P < .05). Trough FEV₁ increased by the fourth visit (after one week of daily administration); it remained consistently greater than in the patients receiving placebo through the treatment period, suggesting that a steady state had been reached by the end of one week of treatment.

Within two to three weeks of treatment cessation, the FEV₁ returned to the baseline value but never fell below it, signifying that all doses of tiotropium showed no evidence of rebound deterioration. The FEV₁ response paralleled the FVC responses, except in the patients taking 36 mcg of tiotropium, who showed no significant difference from patients receiving placebo at the 29th day.

In summary, patients receiving all doses of tiotropium once daily experienced significant improvements in FEV₁ and FVC compared with patients receiving placebo over the one-month trial period.
Van Noord et al., 2000\textsuperscript{17}

A multicenter, double-blind, double-dummy, parallel group study enrolled 288 patients with COPD to compare the efficacy of tiotropium and ipratropium. After a two-week run-in period, 191 patients were randomly assigned to receive tiotropium 18 mcg once daily, and 97 patients received ipratropium 40 mcg four times daily for 13 weeks. Outcome measures were lung function; daily records of PEFR, FEV\textsubscript{1}, FVC; and the use of concomitant salbutamol.

Baseline FEV\textsubscript{1} at the start of treatment did not differ between the two treatment groups, but three hours after inhalation, the improvement in FEV\textsubscript{1} was greater after tiotropium than after ipratropium (\(P < .05\)). At all time points on days 8, 50, and 92 (except at one-half hour and at one hour after inhalation), the FEV\textsubscript{1} response was significantly better with tiotropium than with ipratropium (\(P < .05\)). The results for FVC closely reflect those obtained for FEV\textsubscript{1}.

Baseline PEFRs did not differ between the groups (\(P > .05\)). An improvement was seen in both treatment groups, but it was greater in the tiotropium group. The difference in morning and evening PEFRs between the groups was significant through weeks 10 and 7, respectively (\(P < .05\)).

Concomitant medication use was also similar in both groups at baseline. A decrease in the use of salbutamol as a rescue treatment was noted in both groups, but a greater reduction was seen in the tiotropium group (\(P < .05\)).

In this comparative trial, tiotropium 18 mcg once daily was significantly more effective than ipratropium 40 mcg four times a day in trough, average, and peak lung function over 13 weeks.

Donohue et al., 2002\textsuperscript{18}

Donohue et al. conducted a multicenter, randomized, placebo-controlled, double-blind, double-dummy, parallel-group study to compare tiotropium 18 mcg once daily (\(n = 209\)), salmeterol xinafoate (e.g., Advair\textsuperscript{®} or Serevent Diskus\textsuperscript{®}, GlaxoSmithKline) 50 mcg twice daily (\(n = 213\)), and placebo (\(n = 201\)) for six months in patients with COPD. The demographics, including age, sex, and baseline FEV\textsubscript{1} were similar in all three groups. Twelve-hour spirometric monitoring, the TDI, and the St. George’s Respiratory Questionnaire were used to measure efficacy.

After the first dose of tiotropium and salmeterol, the increase in FEV\textsubscript{1} was similar; at 24 weeks trough, FEV\textsubscript{1} had improved significantly over placebo by 137 ml in the tiotropium group and by 85 ml in the salmeterol group. The difference of 52 ml between the treatment-active groups was statistically significant (\(P < .01\)).

The differences for FVC for the active groups were superior to placebo, and tiotropium was superior to salmeterol for all measured variables. At the end of the study, trough FVC for the tiotropium group improved over that for the placebo group by 247 ml (\(P < .0001\)), whereas trough FVC for salmeterol improved by 134 ml over placebo (\(P < .001\)). The difference between tiotropium and salmeterol was 112 ml (\(P < .01\)).

PEFRs were superior in both of the active-treatment groups compared with the placebo groups and showed a trend favoring tiotropium over salmeterol, with \(P < .001\) for tiotropium vs. placebo at all weeks and \(P < .001\) for salmeterol versus placebo at all weeks except at the 15th and 16th weeks. Tiotropium was also significantly superior to salmeterol in improving evening PEFRs (\(P < .05\)).

The Baseline Dyspnea Index (BDI) and the TDI were used. A higher TDI score represents improvement in dyspnea; a change of one unit is considered clinically significant. The BDI focal scores were comparable between groups and were consistent with moderate dyspnea. At six months, the improvements in TDI scores above placebo were 1.02 units for tiotropium (\(P = .01\)) and 0.24 units for salmeterol (\(P = .56\)). The difference between the two active-treatment groups was 0.78, indicating that tiotropium was superior to salmeterol (\(P < .05\)). The tiotropium patients also appeared to have less dyspnea steadily over time, whereas dyspnea in the patients in the salmeterol and placebo groups seemed to worsen from the middle to the end of the trial.

The St. George’s Respiratory Questionnaire revealed no statistical difference between the two active-treatment groups at six months; however, tiotropium was superior to placebo and to salmeterol (\(P < .05\)) in achieving a clinically meaningful change in disease state in terms of symptoms, activity, and impacts.

Mean weekly requirements for salbutamol decreased equally with tiotropium and salmeterol (~1.45 and ~1.44 puffs per day, respectively) (\(P < .0001\), active treatment vs. placebo).

In summary, tiotropium 18 mcg once daily produced superior improvements in FEV\textsubscript{1}, FVC, PEFRs, and dyspnea in patients with COPD compared with salmeterol 50 mcg twice daily and placebo.

Tashkin et al., 2003\textsuperscript{19}

In a retrospective analysis of two identical one-year, placebo-controlled trials, the use of tiotropium 18 mcg once daily for long-term health benefits was reviewed. In the two combined trials, 921 patients were enrolled (550 patients receiving tiotropium and 371 receiving placebo). All patients had similar baseline demographics, including lung function and medications used. The patients were subdivided into tiotropium-responsive (TIO-R) and partially responsive (TIO-PR) groups. Responsiveness was demonstrated by an increase of FEV\textsubscript{1} of both 12% or more and 200 ml from baseline within three hours of the first dose.

Both TIO-R and TIO-PR patients experienced a significant improvement in mean peak change in FEV\textsubscript{1} from the first day’s baseline value compared with the placebo group (\(P < .001\)). Trough FEV\textsubscript{1} and FVC in the tiotropium groups also improved at the end of the study, in comparison to the placebo group (\(P < .001\)); FVC was continually increased after tiotropium therapy in the TIO-R and TIO-PR groups during the year of observation.

PEFR was significantly higher in both TIO-R and TIO-PR groups than in the placebo groups in both mornings and evenings (\(P < .01\)). There was a statistically significant difference between drug and placebo but not between the TIO-R and the TIO-PR groups.

The incidence of dyspnea was similar among all three groups at baseline and at the end of the trial. Patients in both tiotropium groups showed significant improvement over the placebo group (\(P < .001\)), whereas the TIO-R group showed significant improvement over the TIO-PR group (\(P < .05\)).

The number of inhalations of albuterol per day at baseline was comparable: for
the TIO-R group, 3.1 ± 2.3 puffs/day; for the TIO-PR group, 4.2 ± 3.0 puffs/day; and for the placebo group, 3.5 ± 2.6 puffs/day. Fewer inhalations of albuterol were administered to the patients in the tiotropium groups at the end of the trial than to those in the placebo group (P < .001); however, no differences between the two tiotropium groups were noted.

Improvements occurred over the one-year period and were achieved irrespective of the patient’s first-dose bronchodilator response. Patients without the first-dose improvement of FEV₁ of at least 12% and 200 ml benefited from tiotropium 18 mcg once daily and showed statistically significant improvements in lung function, dyspnea, and health status.

Vincken et al., 2002

The effects of tiotropium on health outcomes in patients with COPD were investigated over the course of one year. The findings were assessed in two identical one-year randomized, double-blind, double-dummy studies of tiotropium 18 mcg once daily (n = 356) compared with ipratropium 40 mcg four times a day (n = 179). The screening FEV₁ was 1.25 ± 0.43 liters (41.9 ± 12.7% of the predicted value) in the tiotropium group and 1.18 ± 0.37 liters (39.4 ± 10.7% of the predicted value) in the ipratropium group. The trough FEV₁ at one year improved by 0.12 ± 0.01 liters with tiotropium and declined by 0.03 ± 0.02 liters with ipratropium (P < .001).

Significant improvement in PEFR, salbutamol use, TDI focal score, and the St. George’s Respiratory Questionnaire total and impact scores were seen with tiotropium (P < .01). Tiotropium reduced the number of COPD exacerbations by 24% (P < .01) and increased the time to first exacerbation (P < .01) and the time to first hospitalization for a COPD exacerbation (P < .05) compared with ipratropium.

Overall, tiotropium was effective in improving dyspnea, exacerbations, and lung function in patients with COPD, and it provided sustained benefits compared with ipratropium.

SAFETY

In clinical trials, the most commonly reported ADE was dry mouth. For the majority of patients, the severity was mild and was reported by 9.3% to 16% of patients taking tiotropium. Other ADEs included constipation, blurred vision, an increased heart rate, glaucoma, urinary difficulty, and urinary retention. The most common side effect being dry mouth.

Although tiotropium improved lung function, its effects on long-term morbidity and mortality in patients with COPD have not been studied. Overall, this agent may prove to be safe and efficacious as a long-term treatment option for patients with COPD.

REFERENCES