Tiotropium (Spiriva): a once-daily inhaled anticholinergic medication for chronic obstructive pulmonary disease

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Tiotropium represents a new generation of inhaled therapy. No other inhaled product has demonstrated effectiveness with once-daily dosing. Treatment has been associated with improved lung function, decrease in the number of exacerbations, increase in the time to first exacerbation, and improved quality of life. Adverse effects appear to be mild in nature, and the only significant adverse effect is dry mouth. Clinical trials show that tiotropium is more effective than placebo. When compared with current treatment for chronic obstructive pulmonary disease, tiotropium is at least as effective as salmeterol and more effective than ipratropium; moreover, the once-a-day dosing increases the likelihood of patient compliance. The guidelines of the Global Initiative for Chronic Obstructive Lung Disease recommend bronchodilator medications as first-line therapy in the symptomatic management of chronic obstructive pulmonary disease. Tiotropium, an anticholinergic bronchodilator, should be considered a first-line agent for patients with chronic obstructive pulmonary disease.

Chronic obstructive pulmonary disease (COPD) affects approximately 16 million people and is the fourth leading cause of chronic morbidity and mortality in the USA (1, 2). It is estimated that COPD consumes \$18 billion in direct health care costs each year (2). With further increases in morbidity and mortality predicted, the worldwide burden of this disease is expected to rank fifth in 2020. The National Heart, Lung, and Blood Institute and the World Health Organization developed the Global Initiative for Chronic Obstructive Lung Disease, which in turn developed a comprehensive overview of COPD, including treatment guidelines (1).

Characteristics of COPD include reduced expiratory airflow, cough, sputum production, and dyspnea. The breathlessness develops over many years and is the main reason for seeking medical care (3). The treatment guidelines specify bronchodilator medications as central to the management of COPD symptoms due to their ability to improve airflow and reduce breathlessness (1–3). Anticholinergic agents, a class of bronchodilators, have proven to be of particular value in the treatment of COPD since vagal cholinergic tone appears to be the only reversible component of airway narrowing (4).

A new anticholinergic agent, tiotropium (Spiriva), has been introduced and is likely to become the first-line anticholinergic agent in the treatment of COPD. The current mainstay of anticholinergic therapy, ipratropium (Atrovent), requires dosing 4 times a day, whereas tiotropium is dosed once daily (2). The Food and Drug Administration approved tiotropium on January 30, 2004.

INDICATION

Tiotropium is indicated for the maintenance treatment of COPD (5).

PHARMACOLOGY

Tiotropium is a long-acting, specific muscarinic receptor antagonist or anticholinergic drug. Tiotropium inhibits the cholinergic (bronchoconstrictive) effects of acetylcholine by binding to the muscarinic receptors (M_1 – M_5) in the bronchial smooth musculature (5). M_1 receptors in parasympathetic ganglia facilitate cholinergic neurotransmission and as a result enhance cholinergic bronchoconstriction, while M_3 receptors on airway smooth muscle cells and glands mediate bronchoconstriction and mucus secretion. M_2 receptors act as autoreceptors at cholinergic nerve endings by inhibiting the release of acetylcholine, which results in feedback inhibition. Therefore, blockade of M_2 receptors results in increased acetylcholine release. The currently available anticholinergic medications, atropine and ipratropium, are nonselective muscarinic antagonists that block M_{1-3} receptors. The increased acetylcholine release from the blockade of M_2 may overcome the blockade of other muscarinic receptors in the muscle (4).

Tiotropium displays a 6 to 20 times greater affinity for all subtypes of muscarinic receptors than ipratropium but dissociates rapidly from M_2 receptors. For the M_1 receptor complex, the muscarinic receptor-drug complex half-life is 14.6 ± 2.2 hours for tiotropium vs 0.11 ± 0.0005 hours for ipratropium. For the M_2 receptor complex, the values are 3.6 ± 0.5 hours and 0.035 ± 0.005 hours, and for the M_3 receptor complex, the values are 34.7 ± 2.9 hours and 0.26 ± 0.02 hours. Tiotropium's kinetic selectivity for longer blockade of M_1 and M_3 receptors and its slower dissociation from M_1 and M_3 receptors gives tiotropium a longer duration of action than ipratropium (2). Tiotropium's high potency and slow receptor dissociation correlate with significant and long-acting bronchodilation in patients with COPD (5). Because tiotropium contains a quaternary ammonium, the inhaled medication is associated with a lower degree of systemic absorption, a longer duration of action, and no penetration of the blood-brain barrier (2).

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PHARMACOKINETICS

Tiotropium demonstrates linear pharmacokinetics in its therapeutic range after dry powder inhalation (5).

Onset and duration

The time to a clinically significant increase in forced expiratory volume in 1 second (FEV_1) after inhalation is 30 minutes. The time to the peak increase in FEV_1 after inhalation is 1.5 to 3 hours. Tiotropium's duration of action is at least 24 hours (6).

Absorption

The absolute bioavailability following dry powder inhalation is 19.5%. Tiotropium is poorly absorbed from the gastrointestinal tract, with absorption of approximately 10% to 15% (5). Maximum plasma concentrations were observed 5 minutes after inhalation (4).

Distribution

The volume of distribution for tiotropium is 32 L/kg, and it is 72% bound to plasma proteins. The peak plasma level at steady state, measured 5 minutes after inhalation of an 18- μ g dose, was 17 to 19 μ g/mL; it decreased rapidly in a multicompartment manner. Steady-state trough plasma concentrations were 3 to 4 μ g/mL. The concentration of tiotropium in the lung is unknown at the present time. After long-term once-daily inhalation by COPD patients, pharmacokinetic steady state was reached after 2 to 3 weeks with no accumulation thereafter (5).

Metabolism

The extent of tiotropium biotransformation is small. The ester tiotropium is nonenzymatically cleaved to the inactive alcohol N-methylscopine and the inactive acid compound dithienylglycolic acid (5).

Elimination

The terminal elimination half-life is 5 to 6 days (4). After dry powder inhalation, 14% of the dose is eliminated via urinary excretion. The remainder is mainly nonabsorbed drug in the gastrointestinal tract, which is eliminated via the feces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine.

Special populations

Geriatric patients. Advanced age was associated with a decrease of tiotropium renal clearance after inhalation from 14% to about 7%, which could be explained by decreased renal function secondary to age. However, plasma concentrations increased with advancing age (43% increase in area under the curve $[AUC]_{0-4h}$ after dry powder inhalation), which was not significant when considered in relation to interindividual and intraindividual variability (5).

Renally impaired patients. Renal impairment was associated with increased plasma drug concentrations and reduced renal drug clearance. In mild renal impairment (creatinine clearance 50–80 mL/min), plasma concentrations increased slightly (39% increase in AUC_{0-4h}). COPD patients with moderate to severe renal impairment (creatinine clearance <50 mL/min) had dou-

bling of their plasma concentrations (82% increase in AUC_{0-4h}) after dry powder inhalation (5).

Hepatically impaired patients. Liver insufficiency is not expected to have any relevant influence on tiotropium pharmacokinetics because the medication is cleared primarily by renal elimination and simple nonenzymatic ester cleavage to pharmacologically inactive products (5).

CLINICAL TRIALS

Dose determination trial

Results of a multicenter, randomized, double-blind, parallel group, placebo-controlled study to evaluate the dose-response characteristics of tiotropium given once daily to patients in stable condition with COPD indicated that 18 μ g was the strength for use in long-term clinical trials. Patients were ≥ 40 years of age with a smoking history of at least 10 pack-years and a diagnosis of COPD defined as an $FEV_1 > 30\%$ and $< 65\%$ of predicted normal value and an FEV_1 -to-FVC (forced vital capacity) ratio $< 70\%$. This corresponds to moderate or severe COPD in accordance with the guidelines of the Global Initiative for Chronic Obstructive Lung Disease. Patients were excluded from the study if they had a clinical diagnosis of asthma, allergic rhinitis, or atopy; a total blood eosinophil count $> 600/\text{mm}^3$; other significant disease; or a viral infection within the 6 weeks prior to the screening visit. Treatments included placebo or tiotropium 4.5, 9, 18, or 36 μ g administered daily at noon. Concomitant medications allowed during the study included short-acting beta-agonists on an as-needed basis, theophylline and inhaled glucocorticosteroids if the patient's condition was stabilized on these medications 6 weeks prior to randomization, and anticholinergics during the baseline period only. Significant dose-related increases in FEV_1 and FVC were observed over time in response to the first dose of the study medication ($P < 0.05$), and all doses of tiotropium yielded significant improvements in FEV_1 compared with placebo (7) (Table 1).

Among the mean weekly FEV_1 trough responses over the course of treatment and during the posttreatment period, no significant differences were noted among the doses of tiotropium. All 4 doses of tiotropium provided a greater trough level and average response than placebo ($P < 0.05$). Trough FEV_1 increased after 1 week of daily administration and remained consistently greater than that for placebo through the treatment period. Two to three weeks after cessation of therapy, the FEV_1 response for all doses gradually returned to baseline; however, it never fell below baseline, so there was no evidence of rebound deterioration. The FVC responses paralleled the FEV_1 response, except that the increase in FVC in the 36- μ g group was smaller than that in the 18- μ g group. The FVC responses in the 36- μ g group were not significantly different from those in the placebo group at 29 days (7) (Table 2).

The adverse event profile revealed a low incidence of individual adverse events at all dose levels, and there were no dose-dependent increases in incidence or severity of an adverse event. The largest proportion of adverse events was seen in the group that received the highest dose, 36 μ g (50% of patients). The overall safety profiles for the 4 tiotropium doses were similar to that of placebo. The most frequent adverse event was dry mouth, which was reported in 2 patients in the 4.5- μ g treatment group, 2

Table 1. Mean peak and average FEV₁ and FVC response over 6 hours in liters (change from baseline) following first dose*

	Placebo		4.5 µg		Tiotropium bromide 9 µg		18 µg		36 µg	
	FEV ₁	FVC	FEV ₁	FVC	FEV ₁	FVC	FEV ₁	FVC	FEV ₁	FVC
Sample size	33	33	33	33	33	33	33	33	33	33
Baseline: mean	1.00	2.24	1.01	2.36	1.06	2.31	1.21	2.46	0.94	2.11
SE	(0.06)	(0.12)	(0.06)	(0.10)	(0.07)	(0.15)	(0.08)	(0.14)	(0.05)	(0.13)
Peak response† mean	0.05	0.17	0.15§	0.34§	0.22§	0.43§	0.24§	0.47§	0.23§	0.45§
SE	(0.01)	(0.04)	(0.02)	(0.04)	(0.03)	(0.06)	(0.03)	(0.07)	(0.04)	(0.06)
Average response‡ mean	-0.02	-0.01	0.05§	0.13§	0.12§	0.25§	0.13§	0.29§	0.16§	0.28§
SE	(0.01)	(0.03)	(0.02)	(0.04)	(0.02)	(0.06)	(0.02)	(0.06)	(0.03)	(0.05)

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†The largest value observed over the 6-hour measurement period minus the baseline FEV₁ or FVC.

‡The average change from baseline FEV₁ or FVC over the 6-hour observation period.

§P < 0.05 versus placebo.

FEV₁ indicates forced expiratory volume in 1 second; FVC, forced vital capacity; SE, standard error.

Table 2. Average FEV₁ and FVC response over the 6-hour postdosing interval in liters across the 4 weeks of treatment*

	Placebo		4.5 µg		Tiotropium bromide 9 µg		18 µg		36 µg	
	FEV ₁	FVC	FEV ₁	FVC	FEV ₁	FVC	FEV ₁	FVC	FEV ₁	FVC
End of week 1	-0.04	-0.08	0.13	0.28	0.11	0.24	0.12	0.35	0.19	0.26
SE	(0.03)	(0.07)	(0.03)	(0.07)	(0.03)	(0.07)	(0.03)	(0.07)	(0.03)	(0.07)
End of week 2	-0.02	-0.05	0.19	0.44	0.13	0.25	0.13	0.34	0.18	0.25
SE	(0.04)	(0.08)	(0.04)	(0.08)	(0.03)	(0.08)	(0.04)	(0.08)	(0.04)	(0.08)
End of week 4	0.00	0.03	0.18	0.40	0.11	0.28	0.15	0.40	0.20	0.21
SE	(0.04)	(0.07)	(0.04)	(0.07)	(0.04)	(0.07)	(0.04)	(0.07)	(0.04)	(0.07)

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FEV₁ indicates forced expiratory volume in 1 second; FVC, forced vital capacity; SE, standard error.

in the 9-µg group, and 3 in the 36-µg group. One subject withdrew from the placebo group because of an adverse event (anxiety). Two serious adverse events reported were a wrist fracture in the placebo group and a COPD exacerbation/respiratory failure in the 9-µg group (7).

Comparable bronchodilator responses were seen at doses from 9 to 36 µg. The spirometry values presented were higher for the 18-µg group than for the 9-µg group, but no direct statistical comparison between these was presented. These comparable results from the different dosing strengths combined with the trend toward a higher proportion of adverse events at the 36-µg dose level led to the selection of 18 µg as the dose for long-term clinical trials (7). Nevertheless, little explanation is given for why 18 µg was chosen instead of 9 µg.

The trial was well designed, with appropriate spirometric measures used to evaluate COPD severity and changes in lung capacity. No power analysis was presented, so the possibility of

into 2 groups, responders and nonresponders. A summary of the trials is presented in *Tables 3 and 4*.

Each study considered various secondary endpoints according to the study design. The preliminary 3-month study by Casaburi et al had no additional endpoints besides those listed in *Tables 3 and 4*. The incidence of side effects was low, and dry mouth was the most common at 9.3% (8).

The study by Casaburi et al used appropriate endpoints for COPD and was well designed. However, no power analysis was conducted. Recent studies in developed countries show that the prevalence of the disease is almost equal in men and women, but 65% of the subjects in this study were men, possibly limiting the applicability of these results to women (1, 8). Moreover, 92% of the subjects were white, which is not representative of the population suffering from COPD. While definitive data are lacking concerning the prevalence of COPD in individual ethnic groups, the percentage of smokers among the groups is more than likely

a type II error cannot be ruled out. Moreover, the results presented the standard error of the mean, which can artificially improve the results of a study. Unlike standard deviation, which is calculated from the sample, standard error of the mean is calculated from the whole population and thus may inflate the results. The beneficial results seen as early as 1 week after initiation of treatment could have been affected by the use of another anticholinergic drug (42% of patients used the anticholinergic drug ipratropium) during the baseline phase of the trial rather than representing the effect of tiotropium alone. Of the trial subjects, 57% were men, which strengthens the applicability of the results, as COPD is believed to affect men and women equally. However, 95% of the subjects were white, which limits the applicability of these data to other ethnic groups.

Tiotropium vs placebo

Three clinical trials have been published comparing tiotropium with placebo in the treatment of COPD. All are based on the same initial patient population. Casaburi et al first published a short trial comparing tiotropium with placebo over a treatment period of 92 days. They then recruited an additional 451 patients meeting the same inclusion and exclusion criteria and compared tiotropium and placebo in this combined sample for 1 year. Tashkin et al conducted a retrospective study using the same group of patients, dividing the group receiving tiotropium

Table 3. Design of published clinical trials of tiotropium versus placebo*

Author	Type of trial	Duration	N	Treatment groups
Casaburi et al (8)	R, DB, PC, MC	92 days	470	Tiotropium 18 µg (n = 279); placebo (n = 191)
Casaburi et al (3)	R, DB, PC, MC	1 year	921	Tiotropium 18 µg (n = 550); placebo (n = 371)
Tashkin et al (9)	Retrospective, DB, PC, MC, parallel-group	Retrospective; looked at 1 year of data	921	Tiotropium (n = 550), divided into responders (n = 263) and poor responders (n = 255); placebo (n = 371)

* The population for all trials consisted of patients aged ≥40 years with a clinical diagnosis of chronic obstructive pulmonary disease as defined by the American Thoracic Society, a smoking history >10 pack-years, clinically stable airway obstruction, a forced expiratory volume in 1 second ≤65% of predicted normal values, and a ratio of forced expiratory volume in 1 second to forced vital capacity ≤70%.

R indicates randomized; DB, double-blind; PC, placebo-controlled; MC, multicenter.

similar. As smoking is a major risk factor for COPD, the number of patients with COPD is probably similar among ethnic groups (1). Patients were permitted to use as-needed albuterol, stable doses of theophylline, inhaled corticosteroids, and ≤10 mg/day of oral prednisone during the study. As per the intention-to-treat analysis, if patients left this study secondary to worsening of COPD (<2%), the least favorable results for the patient were used to complete the study. For patients who missed study visits for

the tiotropium group and 29% to 34% in the placebo group ($P < 0.01$). The number of exacerbations was 0.76 events/patient-year in the tiotropium group and 0.95 events/patient-year in the placebo group ($P = 0.045$). The SGRQ assesses health status in various areas, and a clinically meaningful response is measured by a 4-unit improvement in score. The percentages of patients with a meaningful response were 49% in the tiotropium group and 30% in the placebo group. Results of the Global Assessment of

other reasons (6%), missing data were estimated by using the patient's last observed data (8).

Casaburi et al also conducted a randomized, double-blind, placebo-controlled 1-year study comparing tiotropium with placebo (3). Additional endpoints included in the study but not presented in Tables 3 and 4 include the transition dyspnea index (TDI) score, health outcomes as measured by number of exacerbations and by results of the St. George's Respiratory Questionnaire (SGRQ), and the physician's global assessment. In this study, 81.3% of subjects in the tiotropium group and 72.2% of subjects in the placebo group completed the study ($P < 0.05$). In the TDI, a score ≥1 reflects a clinically important difference. The proportions of patients who achieved this clinically important difference in TDI score were 42% to 47% in

Table 4. Comparative results of placebo-controlled trials of tiotropium

	Casaburi et al (8)	Casaburi et al (3)	Tashkin et al (9)
FEV ₁	All: significantly greater than placebo ($P < 0.001$). Trough: 10%–13% greater than baseline throughout treatment period. Peak: increased from 0.24–0.28 L. Average: increased 0.20–0.21 L over baseline.	Trough: T = 110–130 (±10) mL, $P = 120$ –150 (±10) mL ($P < 0.01$). Mean increase: T = 190–220 (±10) mL, $P = 140$ –220 (±10) mL.	Trough: R = 174 ± 13 mL, PR = 56 ± 13 mL ($P < 0.001$). Peak: R = 348 ± 14 mL, PR = 174 ± 15 mL ($P < 0.001$). Both R and PR trough and peak levels significantly greater than placebo ($P < 0.001$).
FVC	All: significantly greater than placebo ($P < 0.001$). Trough: 0.23 L (10.5%) greater than baseline after 13 weeks. Peak: 0.56–0.66 L (25%–30%) over baseline. Average: 0.49 L (22%) greater than baseline.	Mean increase in trough with T: 12%–13%, 260–290 (±20) mL. Mean increase: 19%–23%, 420–510 (±20) mL.	Trough: R = 345 ± 26 mL, PR = 175 ± 27 mL ($P < 0.001$). Peak: R = 717 ± 30 mL, PR = 439 ± 30 mL ($P < 0.001$). Both R and PR trough and peak levels significantly greater than placebo ($P < 0.001$).
PEFR	Morning—mean difference: 10–20 L/min, significantly greater ($P < 0.05$) in weeks 10–13. Evening—mean difference: 16–24 L/min, significant greater ($P < 0.01$) in all 13 weeks.	T group greater than P for both morning and evening ($P < 0.05$). Morning: range of differences over 1-year period: 11–25 ± 5 L/min.	Morning: R = 37.6 ± 5.6 L/min, PR = 36.3 ± 5.8 L/min. Evening: R = 34.8 ± 5.5 L/min, PR = 33.3 ± 5.7 L/min. R and PR AM and PM values not statistically different but both significantly greater than placebo ($P < 0.01$).
Albuterol use	Decreased by 30% from baseline after first week (3.7 to 2.6 doses) and remained at 2.6 doses for duration of 13-week treatment period ($P < 0.001$).	T = 3.2 ± 0.11 doses/day, $P = 4.1 ± 0.13$ doses/day ($P < 0.01$).	R = 3.1 ± 2.3 puffs/day, PR = 4.2 ± 3.0 puffs/day. Difference not statistically significant.

FEV₁, indicates forced expiratory volume in 1 second; FVC, forced vital capacity; PEFR, peak expiratory flow rate; T, tiotropium; P, placebo; R, tiotropium responders; PR, tiotropium poor responders.

Health revealed a significant difference favoring tiotropium over placebo ($P < 0.01$) for wheezing and shortness of breath but not for tightness of the chest or cough. The only adverse effect that was significantly more common for tiotropium than for placebo was dry mouth, which occurred in 16% of the tiotropium patients and in only 2.7% of placebo patients ($P < 0.05$). This study used an intention-to-treat analysis. Missing data were estimated as in the previous trial. The study reached the target sample size. Medications allowed were the same as in the 13-week study, with the following exception: after 13 weeks, patients could be prescribed glucocorticosteroids or theophylline preparations as necessary (3).

This study used appropriate endpoints for COPD. Sixty-five percent of the study subjects were men, with an average age of 65 years and an average smoking history of 61 pack-years. The study did not specify ethnicity. These demographics may limit the clinical applicability of these results. Unfortunately, P values were not available for some endpoints, and sometimes only a line graph was used rather than specific numbers to show a trend. This study does compare its results with those of other trials of salmeterol and fluticasone. Salmeterol was found to improve health status as measured by the SGRQ over a 16-week period, as was tiotropium over a 1-year period. In contrast, fluticasone was found to reduce the rate of deterioration compared with placebo, but the improvement was never significant.

Tashkin et al conducted a retrospective analysis of the data collected for the trial of Casaburi et al. They further subdivided the tiotropium group into responders and poor responders on the basis of their FEV₁ results. Tiotropium responders were defined as patients whose FEV₁ improved by $\geq 12\%$ and ≥ 200 mL compared with baseline within 180 minutes of the initial dose of tiotropium on the first study day. All other tiotropium users were classified as poor responders. The FEV₁ was 1.08 ± 0.41 L in the responder group and 0.95 ± 0.42 L in the poor responder group, a modest but statistically significant difference ($P < 0.05$). The percentage of tiotropium patients designated as responders was 51%.

At the end of the trial, the difference in the TDI scores of the responder and poor responder groups was significantly different (1.4 vs 0.94; $P < 0.05$). No statistically significant difference was identified in the SGRQ clinically meaningful total scores (score ≥ 4) for the responder and the poor responder groups. The difference in percentage of patients having ≥ 1 exacerbation during the course of the study was not statistically significant: 33.5% in the responder group and 40.4% in the poor responder group. However, the frequency of events per patient per year was significantly lower in the responder group than in the poor responder group (0.627 vs 0.885; $P < 0.05$). The only adverse event that occurred significantly more often in the tiotropium patients than in the placebo patients was dry mouth, which occurred in 16% of the subjects in the tiotropium groups and in 2.7% of the subjects in the placebo group (9). While this trial used data analyzed previously, the division of the tiotropium group into responders and poor responders provided more in-depth and possibly more clinically relevant data. The tiotropium group comprised a total of 550 patients, but the numbers of responders (263) and poor responders (255) do not add up to 550 patients. No explanation is given in the study for the discrepancy.

Tiotropium vs ipratropium

A randomized, double-blind, double-dummy, parallel-group trial comparing tiotropium with ipratropium demonstrated that tiotropium was significantly more effective than ipratropium as defined by assessing trough, average, and peak lung functions over a 13-week period. Patients in this study were at least 40 years old, were current or previous smokers (≥ 10 pack-years) with a clinical diagnosis of COPD according to the American Thoracic Society criteria, and had stable airway obstruction with an FEV₁ $< 65\%$ of predicted and a ratio of FEV₁ to FVC of $< 70\%$. Exclusion criteria included a history of asthma, allergic rhinitis, or atopy; increased total blood eosinophil count; significant disease other than COPD; recent myocardial infarction, heart failure, or cardiac arrhythmia requiring medication therapy; or required oxygen therapy. Patients received either tiotropium 18 μ g once daily plus placebo 4 times daily ($n = 191$) or ipratropium 40 μ g 4 times daily plus placebo once daily ($n = 97$). FEV₁ and FVC measurements were obtained 1 hour before and immediately before inhalation and at 0.5, 1, 2, 3, 4, 5, and 6 hours after inhalation of the trial drug on days 1, 8, 50, and 92 of treatment.

Thirty minutes after inhalation of the first dose, the baseline FEV₁ increased 15% in the tiotropium group and 18% in the ipratropium group ($P < 0.05$). The peak increase in FEV₁ for the tiotropium group was 23%, seen at 3 hours after dosing; at 6 hours, the improvement was still 21%. In the ipratropium group, the peak increase of 21% was achieved approximately 1 to 2 hours after dosing but the improvement had dropped to 9% after 6 hours. After 3 hours, the improvements in FEV₁ between tiotropium and ipratropium were significantly different ($P < 0.05$). FEV₁ responses, except at 0.5 and 1 hour on treatment days 8, 50, and 92, were all significantly greater after tiotropium than after ipratropium ($P < 0.05$). The FVC trough and average response were significantly better ($P < 0.05$) for tiotropium than for ipratropium at treatment days 1, 8, 50, and 92. Differences in peak FVC values were not significant. Improvement in morning peak expiratory flow rate (PEFR) was significantly better in the tiotropium group ($P < 0.05$) through week 10 of treatment, while improvement in evening PEFR was significantly better ($P < 0.05$) through treatment week 7. Both treatment groups used less rescue medication, but the reduction was greater in the tiotropium group. The tiotropium group used 1 puff/day, compared with 2.7 at baseline, and the ipratropium group used 1.5 puffs/day, compared with 2.2 at baseline ($P < 0.05$). No significant differences were seen in the incidence of adverse events. The only adverse event classified as drug related was dry mouth, which was reported in 28 patients (14.7%) in the tiotropium group and 10 patients (10.3%) in the ipratropium group (10).

The trial was well designed, with appropriate measures of COPD and lung function used as endpoints. Unfortunately, a power analysis was not presented, so neither the appropriateness of the sample size nor the reasoning for distributing two thirds of the patients in the tiotropium group and one third in the ipratropium group could be determined. This trial might have revealed more beneficial results if it had continued beyond 13 weeks and looked at issues concerning quality of life. Also, the highest FEV₁ value was used for analysis, which could have skewed the results. A mean value, as used in other trials of tiotropium, would have

been more appropriate. The subjects were primarily men (83%), limiting the applicability of these results to women.

Vincken et al compared the effects of tiotropium with those of ipratropium on lung function, dyspnea, exacerbation rate, and health-related quality of life in patients with COPD in 2 identical 1-year randomized double-blind, double-dummy trials. One trial was a continuation of the trial by van Noord et al already mentioned. The other trial recruited an additional 451 patients meeting the same inclusion and exclusion criteria as the van Noord et al study. Tiotropium showed consistently greater efficacy than ipratropium across all of the previously mentioned outcome measures. Patients received tiotropium 18 µg once daily in the morning (n = 356) or ipratropium 40 µg 4 times daily (n = 179). Spirometry was conducted 1 hour before and immediately after drug administration as well as at 30, 60, 120, and 180 minutes after dosing on day 1 of therapy and after 1, 7, 13, 26, 29, and 52 weeks of therapy. More patients in the tiotropium group, 302 (84.8%), completed the trial than in the ipratropium group, 141 (78.8%), although the difference was not significant ($P = 0.08$). The difference was largely due to fewer adverse events in the tiotropium group, including COPD exacerbations/worsening of COPD.

At the end of 1 year, trough FEV₁ was 120 mL above baseline in the tiotropium group but 30 mL less than baseline in the ipratropium group, a significant difference ($P < 0.001$). At the same time, FVC was 320 mL above baseline in the tiotropium group and 110 mL above baseline in the ipratropium group. Throughout the year, the morning and evening PEFR improved significantly more in the tiotropium group than in the ipratropium group ($P < 0.01$ at all collection intervals), with differences between the 2 groups of 10 to 18 L/min in the morning and 9 to 18 L/min in the evening. The proportion of patients who achieved a clinically meaningful difference in TDI focal score was greater in the tiotropium group (31%) than in the ipratropium group (18%, $P = 0.004$). Based on these results, the number needed to treat to obtain at least a 1-unit improvement in the TDI focal score over a population that would otherwise receive ipratropium would be 8. More patients in the tiotropium group (52%) than in the ipratropium group (35%) achieved clinically meaningful improvement in the SGRQ total score after 9 and 12 months ($P = 0.001$). The number needed to treat to obtain at least a 4-unit improvement in SGRQ total score over a population that would otherwise receive ipratropium would be 6. The number of exacerbations days per patient-year was 39% lower in the tiotropium group (10.8 vs 17.7; $P = 0.002$). On average, tiotropium patients took approximately 4 fewer inhalations of rescue medication per week than patients receiving ipratropium ($P < 0.05$ for 40 of the 52 weeks). Dry mouth was noted more frequently with tiotropium (12.1%) than with ipratropium (6.1%), $P = 0.03$ (11).

This trial was a combination of 2 trials, one being a continuation of a 13-week trial whose results were already presented. The target sample size was met, appropriate measures of COPD improvement were used, and number needed to treat was calculated for 2 of the endpoints. By comparing tiotropium with ipratropium, the standard of care for COPD, and powering the study to show a difference, the authors increased the clinical relevance of this trial. The population of the trial was 85% men, with an average 33 pack-year history and mild to moderate COPD, limiting the applicability of these results to various populations.

Tiotropium vs salmeterol

A 6-month, randomized, placebo-controlled, double-blind, double-dummy, parallel-group study of tiotropium and salmeterol demonstrated that tiotropium produced greater improvement in lung function, dyspnea, and health-related quality of life. The inclusion and exclusion criteria were consistent with the studies of tiotropium already described. Patients were randomized to receive tiotropium 18 µg once daily (n = 209), salmeterol 50 µg twice daily (n = 213), or placebo (n = 201). Spirometry was conducted 60 minutes and 10 minutes before dosing and at 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours after inhalation on day 1 and after 2, 8, 16, and 24 weeks of therapy. A greater number of patients in the tiotropium group (88%) completed the trial than in the salmeterol group (83%) or the placebo group (72%).

At the conclusion of the study, there was a statistically significant difference in trough FEV₁, 52 ± 20 ($P < 0.0085$), between the tiotropium and salmeterol groups. The differences in average FEV₁ (77 ± 22) and peak FEV₁ (83 ± 23) were statistically significant ($P < 0.0004$). Differences in FVC in the tiotropium and salmeterol groups were 112 ± 38 for the trough FVC, 165 ± 41 for the average FVC, and 166 ± 44 for the peak FVC; all differences were statistically significant. End-of-study improvements in morning PEFR were not significantly different in the tiotropium (27.3 L/min) and salmeterol (21.4 L/min) groups, but end-of-study improvement in evening PEFR was significantly better in the tiotropium group than in the salmeterol group (32.5 L/min vs 14.6 L/min; $P < 0.05$). The proportions of patients in the 2 groups with at least a 1-unit change in TDI focal score were not significantly different, but the proportion of patients achieving a change of at least 4 units on the SGRQ was significantly greater in the tiotropium group than in the salmeterol group (51% vs 40%; $P < 0.05$). The mean weekly requirement for albuterol decreased equally with tiotropium (−1.45 puffs/day) and salmeterol (−1.44 puffs/day). The most common adverse event related to tiotropium was dry mouth (10%) (12).

This trial compared tiotropium with a commonly used medication in COPD, salmeterol, and included a placebo arm. The report stated that patients in the salmeterol group received 50 µg twice daily via a metered-dose inhaler, but this is misleading as salmeterol in that strength is available only as a diskus. With that correction, dosing was appropriate. Endpoints for a trial on COPD also were appropriate, although the highest FEV₁ value was used for analysis, which could have skewed the results. Previous studies looked at the average or lowest FEV₁. Although using the highest values made it appear that tiotropium yielded the greatest improvement, in fact the lowest or average values of FEV₁ could have been similar among the 3 groups. The study was conducted over a 6-month period, which was appropriate, but long-term studies should be considered to determine if the superiority over salmeterol continues.

Patients with COPD were enrolled in two 6-month randomized, placebo-controlled, double-blind, double-dummy studies which demonstrated improvements in health outcomes with tiotropium that were similar to those with salmeterol. Tiotropium (n = 402), salmeterol (n = 405), and placebo (n = 400) were compared by time to onset of first exacerbation, assessment of dyspnea, and health-related quality of life. Spirometric tests were measured 60 and 10 minutes prior to treatment and 30, 60,

120, and 180 minutes following treatment on day 1 and after 2, 8, 16, and 24 weeks of treatment. The number of COPD exacerbations per patient-year and number of exacerbation days per patient-year did not differ significantly between the tiotropium (1.49, 25.0) and the salmeterol (1.23, 24.1) groups. The numbers of hospital admissions, days in the hospital, and unscheduled physician visits were not significantly different. The percentages achieving at least a 1-unit change in TDI score were 43.1% and 41.2% for tiotropium and salmeterol, respectively. The percentages of patients achieving an improvement of at least 4 units in the SGRQ total score were 48.9% for tiotropium and 43.2% for salmeterol. Dry mouth was the only adverse event that was significantly more common with tiotropium (8.2%) than with salmeterol (1.7%) (13).

The study design emphasized health outcomes over lung function improvement. Appropriate measurements of health outcomes in patients with COPD were measured, including numbers of exacerbations and hospital admissions. The population of this study was predominantly men (75%) but less so than some previous trials of tiotropium. A longer study would have been helpful to determine if the positive health outcomes seen with tiotropium continue beyond 6 months. As there is no cure for COPD, improved quality of life is imperative for all treatments.

ADVERSE EFFECTS

The most common adverse effect of tiotropium was dry mouth. In 1-year studies of 906 patients who received tiotropium, approximately 14% of patients experienced dry mouth. Onset of dry mouth typically occurred 3 to 4 weeks after starting therapy. Dry mouth was usually mild and often resolved with continued treatment (5). Various clinical trials of tiotropium reported dry mouth in 6% to 16% of the trial participants (2). The incidence of dry mouth with tiotropium is comparable to that with ipratropium, which is 3% to 25% (6). The most common adverse events (>3%) are listed in Table 5.

Isolated adverse reactions reported as severe and consistent in 1-year trials include constipation and urinary retention. Urinary retention was limited to elderly men with predisposing factors such as prostatic hyperplasia (5). Cardiovascular effects of tiotropium remain questionable. Supraventricular tachycardia and atrial fibrillation were reported, usually in susceptible patients, but causality is doubtful (5, 7).

DOSING AND ADMINISTRATION

The recommended dose is inhalation of one capsule (18 µg) at the same time each day. The recommended dose should not be exceeded and the medication should be taken only with the HandiHaler device.

Special populations

No dosage adjustment is necessary for geriatric patients or hepatically impaired patients. Among renally impaired patients (creatinine clearance <50 mL/min), tiotropium should be used only if the expected benefit outweighs the potential risk, because of the increased plasma concentration of the drug in these patients. There is no long-term

Table 5. Adverse events reported most frequently with tiotropium*

Adverse event	Rate
Dry mouth	6%–16%
Constipation	<10%
Respiratory system disorders COPD exacerbation/sinusitis	3%–9%
Dizziness	~3%
Headache	~3%

*From references 5 and 7.

experience in patients with severe renal impairment. The safety and effectiveness of tiotropium have not been established in children, and therefore the drug should not be used in patients younger than 18 years (5).

Tiotropium is a pregnancy category C drug. While no clinical data in humans are available, studies in animals have shown reproductive toxicity associated with maternal toxicity. Clinical data from nursing women are not available, but studies in lactating rodents showed that a small amount of tiotropium is excreted in milk (5).

Drug interactions

No formal drug interaction studies have been performed. However, tiotropium has been used concomitantly with other drugs, including sympathomimetic bronchodilators, methylxanthines, and oral and inhaled steroids, without adverse drug reactions. In vitro studies in liver microsomes found the metabolism of tiotropium was inhibited when used with the cytochrome 2D6 and 3A4 inhibitors quinidine and ketoconazole (5).

Dosage forms

Tiotropium is available as an 18-µg capsule for inhalation with the HandiHaler device. Approximately 10 µg leaves the mouthpiece and is available for delivery to the lungs. The capsule is light green and contains a white or yellowish white powder.

ECONOMIC ISSUES

The cost of various bronchodilators used in COPD is shown in Table 6. The daily cost difference is approximately \$1 between ipratropium or ipratropium/albuterol and tiotropium. Tiotropium

Table 6. Cost of bronchodilators used in the treatment of chronic obstructive pulmonary disease

Medication	Cost per inhaler*	Typical dose per day	Cost per day
Tiotropium	\$25.40 (6-day supply) \$93.78 (30-day supply)	1 inhalation daily	\$4.23 \$3.13
Ipratropium	\$43.36†	2 puffs every 6 hours	\$1.90
Ipratropium/albuterol	\$45.41†	2 puffs every 6 hours	\$1.99
Salmeterol	\$42.29‡	1 inhalation every 12 hours	\$1.41

*Cost data are based on Baylor University Medical Center pharmacy acquisition cost.

†Contains 200 inhalations/inhaler.

‡Contains 60 puffs/diskus.

is being packaged in a smaller “institutional pack,” which could be used for inpatients. This pack contains 6 doses. While the cost of tiotropium is higher than that of conventional therapy, the added benefit of increased compliance with a medication given once daily vs a medication given 4 times daily could result in lower overall health care costs for patients with COPD.

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