

A 6-Month, Placebo-Controlled Study Comparing Lung Function and Health Status Changes in COPD Patients Treated With Tiotropium or Salmeterol*

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Background: Tiotropium, a once-daily anticholinergic, and salmeterol represent two inhaled, long-acting bronchodilators from different pharmacologic classes. A trial was designed to examine the efficacy and safety of both compounds with multiple outcome measures, including lung function, dyspnea, and health-related quality of life (HRQoL) in patients with COPD.

Methods: A 6-month, randomized, placebo-controlled, double-blind, double-dummy, parallel-group study of tiotropium, 18 µg once daily via dry-powder inhaler, compared with salmeterol, 50 µg bid via metered-dose inhaler, was conducted in patients with COPD. Efficacy was assessed by 12-h monitoring of spirometry, transition dyspnea index (TDI), and the St. George's Respiratory Questionnaire (SGRQ).

Results: A total of 623 patients participated (tiotropium, n = 209; salmeterol, n = 213; and placebo, n = 201). The groups were similar in age (mean, 65 years), gender (75% men), and baseline FEV₁ (mean, 1.08 ± 0.37 L; percent predicted, 40 ± 12% [± SD]). Compared with placebo treatment, the mean predose morning FEV₁ following 6 months of therapy increased significantly more for the tiotropium group (0.14 L) than the salmeterol group (0.09 L; p < 0.01). The average FEV₁ (0 to 12 h) for tiotropium was statistically superior to salmeterol (difference, 0.08 L; p < 0.001). Tiotropium improved TDI focal score by 1.02 U compared with placebo (p = 0.01), whereas there was no significant change in TDI focal score with salmeterol (0.24 U). Tiotropium was superior to salmeterol in improving TDI focal score (p < 0.05). At 6 months, the mean improvement in SGRQ total score vs baseline was tiotropium, - 5.14 U (p < 0.05 vs placebo); salmeterol, - 3.54 U (p = 0.4 vs placebo); and placebo, - 2.43 U. A statistically higher proportion of patients receiving tiotropium achieved at least a 4-U change in SGRQ score compared to patients receiving placebo. Both active drugs reduced the need for rescue albuterol (p < 0.0001).

Conclusions: Tiotropium once daily produces superior bronchodilation, improvements in dyspnea, and proportion of patients achieving meaningful changes in HRQoL compared to twice-daily salmeterol in patients with COPD. (CHEST 2002; 122:47-55)

Key words: bronchodilators; COPD; dyspnea; quality of life; salmeterol; spirometry; tiotropium

Abbreviations: AUC = area under the curve; BDI = baseline dyspnea index; HRQoL = health-related quality of life; MDI = metered-dose inhaler; PEFr = peak expiratory flow rate; SGRQ = St. George's Respiratory Questionnaire; TDI = transition dyspnea index

Several decades ago, the choices for the management of COPD were limited, but the last decade has been accompanied by meaningful options for patients, including lung transplantation, lung volume reduction surgery, and an increasing availability of

pulmonary rehabilitation programs. Smoking cessation is of paramount importance, and is the only option that has been shown to slow the accelerated

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decline in lung function in patients with COPD. Bronchodilator therapy has been advanced with the introduction of more convenient dosing for theophyllines, new devices for inhaled therapy, a combination product of anticholinergic plus short-acting β_2 -agonist, and long-acting β_2 -agonists. Guidelines for bronchodilator therapy have generally recommended anticholinergic therapy as first-line maintenance treatment for patients with regular symptoms of COPD.¹⁻³ The benefits seen with anticholinergic therapy are related to the increased cholinergic tone in the airways of patients with COPD.

Tiotropium represents a new chemical entity for the treatment of COPD.⁴ This novel compound is a once-daily inhaled anticholinergic, and provides sustained bronchodilation due to prolonged occupancy of M_3 -receptors.^{5,6} Both single-dose and multiple-dose studies using 18 μg once daily have confirmed a 24-h duration of action as assessed by spirometry.^{7,8} A placebo-controlled trial⁹ documented maintenance of the bronchodilator benefits throughout 3 months of treatment with tiotropium.

The long-acting β_2 -agonist salmeterol has been reported to be of therapeutic utility in patients with COPD.^{10,11} Studies have documented a 12-h effect on spirometry, although conflicting literature exists regarding benefits on health-related quality of life (HRQoL) and dyspnea indexes.¹²⁻¹⁶ To compare the benefits of tiotropium with salmeterol, a randomized, double-blind, placebo-controlled clinical trial was undertaken, which should assist health-care providers when considering these two medications in the management of patients with COPD.

MATERIALS AND METHODS

Study Design

This was a 6-month, placebo-controlled, multicenter, multinational, randomized, parallel-group study to compare the long-term efficacy of tiotropium dry-powder inhalation capsules with salmeterol inhalation aerosol in patients with COPD. The drugs were administered in a double-dummy design with tiotropium, 18 μg , or placebo capsules received once daily in the morning, and salmeterol, 50 μg , or placebo metered-dose inhaler (MDI) received twice daily (every 12 h). Capsules were administered using a dry-powder inhaler device (HandiHaler; Boehringer Ingelheim; Berkshire, UK). The placebo group received the placebo capsule once daily and the placebo MDI twice daily.

Patients

This study was conducted in 39 centers in 12 countries. Patients were required to have relatively stable airway obstruction with $\text{FEV}_1 \leq 60\%$ of predicted normal and $\text{FEV}_1 \leq 70\%$ of FVC.¹⁷ Patients were also required to be at least 40 years of age with a smoking history of > 10 pack-years. Patients with a history of asthma, allergic rhinitis or atopy, an elevated total eosinophil

count, or a recent respiratory tract infection were excluded. Patients receiving regular daytime supplemental oxygen for > 1 h/d or who had a significant disease other than COPD were also excluded. A significant disease was defined as a disease that in the opinion of the investigator would put the patient at risk because of participation in the study or a disease which would influence the results of the study. The protocol was approved by institutional review boards, and written, informed consent was obtained before any study procedure was undertaken.

Study Protocol

Following an initial screening to assess eligibility, patients entered a 2-week baseline period. Patients who successfully completed this phase were randomized into the double-blind portion of the study, during which they received tiotropium, salmeterol, or placebo for a period of 6 months. All previous inhaled anticholinergic or long-acting β_2 -agonist medication use was discontinued. All patients received salbutamol MDI and were instructed to use it as needed for symptom relief. Patients were permitted to continue the use of inhaled steroids and oral steroids (up to the equivalent of prednisolone, 10 mg/d) during the baseline period and throughout the entire study.

Spirometry was conducted prior to the start of therapy at -60 min and -10 min predose at the randomization visit, and at 30 min, 60 min, and 2, 3, 4, 6, 8, 10, and 12 h postdosing using the Ko-Ko spirometer (Pulmonary Data Services; Louisville, CO). Spirometry was repeated at the same time intervals after 2, 8, 16, and 24 weeks of therapy. Measurements were performed according to American Thoracic Society criteria.¹⁸ The highest values of FEV_1 and FVC measurements were retained. Short-acting theophyllines were withheld at least 24 h, long-acting theophyllines were withheld at least 48 h, and short-acting β_2 -agonists were withheld 8 h before spirometry. Patients received their morning dose of study drug on clinic days following the initial predose spirometry.

Additionally, morning and evening peak flow rate, and rescue medication use (salbutamol) were recorded by the patient daily throughout the 6-month treatment period. Peak expiratory flow rates (PEFRs) were collected twice daily (Personal Best Peak Flow Meter; Healthscan Products; Cedar Grove, NJ). Patients were requested to record the best of 3 efforts prior to study drug administration.

Questionnaires assessing dyspnea and HRQoL were administered at baseline and 8 weeks, 16 weeks, and 24 weeks following treatment. Dyspnea was evaluated using the baseline dyspnea index (BDI) and the transition dyspnea index (TDI).¹⁹ The BDI and TDI consist of three axes (functional impairment, magnitude of task, and magnitude of effort) that are summed to create a focal score. The BDI was administered at the end of the baseline period, and the TDI was administered at the follow-up visits indicated above. A higher TDI score represents improvement. A change of 1 U is considered clinically significant. HRQoL was determined using the St. George's Respiratory Questionnaire (SGRQ).²⁰ The SGRQ is a disease-specific instrument that contains 50 items in three subscales (symptoms, activity, and impacts). The total score can be calculated from responses to all 50 items. A lower score represents an improvement. A change of 4 U is considered clinically significant.

Adverse events were tracked throughout the entire baseline period and the 24-week treatment period. Laboratory testing, ECGs, and physical examinations were conducted at baseline and at the final visit.

Data Analysis

Analysis of covariance was performed with the baseline being used as a covariate. Baseline FEV_1 was defined as the mean of

the FEV₁ recordings 60 min and 10 min prior to the first dose of study medication. A similar calculation was performed on all other study days; however, the calculated value on these days will be referred to as the trough FEV₁ (ie, FEV₁ approximately 23 to 24 h after the previous dose of tiotropium, or 11 to 12 h after the previous dose of salmeterol). In order to be able to include the same patients at each time point in the spirometry summaries, missing values were estimated using other values recorded for the patient on that test day. Linear interpolation between the two adjacent measurements was used to estimate missing spirometry values from the middle of the profile. For values at the end of the profiles that were missing because rescue medication was used, the minimum observed FEV₁ value on that test day was used as the estimate. The last available value was used as the estimate for data that were missing for administrative reasons unrelated to the patient's response to treatment. For the analysis of mean weekly morning and evening PEFs and for as-needed salbutamol use, the mean of observations during the last week of the baseline period was used as covariate. Adjustments for multiple comparisons were not utilized. Unless otherwise specified, data are presented as means ± SD. Statistical significance was considered at $p < 0.05$.

RESULTS

A total of 623 patients were entered into the trial, with 209 patients receiving tiotropium, 213 receiving salmeterol, and 201 receiving placebo. A greater proportion of patients in the tiotropium group (88%) completed the 6-month treatment period compared with the salmeterol group (83%) and the placebo group (72%). The majority of premature discontinuations were secondary to adverse events, the most frequent of which were related to underlying respiratory disease. A significantly greater proportion of patients discontinued participation in the trial due to adverse events with the salmeterol group 0 (13.6%) and the placebo group (19.4%) compared with the tiotropium group (5.7%; $p < 0.001$). Exacerbations or worsening dyspnea were responsible for discontinuations in 5 of 10 patients, 15 of 20 patients, and 23 of 37 patients in the tiotropium, salmeterol, and placebo groups, respectively.

Demographics

The three groups were well balanced for all demographic and baseline data (Table 1). There were no significant differences in baseline demographic between the groups. The mean age of the population was 65 ± 8 years, with 75% being men. Mean FEV₁ was 1.08 ± 0.37 L ($40.2 \pm 12.1\%$ predicted). Mean FEV₁ for each treatment group at screening was as follows: tiotropium, 1.11 ± 0.39 L; salmeterol, 1.07 ± 0.37 L; and placebo, 1.06 ± 0.36 L. Virtually all patients received at least one respiratory medication. A high proportion of patients received inhaled corticosteroids (approximately 66%). Approximately 53% of patients received inhaled

Table 1—Baseline Demographics and Previous Respiratory Medication Use*

Variables	Tiotropium (n = 209)	Salmeterol (n = 213)	Placebo (n = 201)
Age, yr	64.5 ± 7.9	64.6 ± 8.1	65.6 ± 7.8
Gender, %			
Male	74	75	75
Female	26	25	25
Duration of COPD, yr	9.2 ± 7.8	10.4 ± 8.2	9.7 ± 7.9
Smoking, pack-yr	47 ± 25	48 ± 26	46 ± 24
FEV ₁ , L	1.11 ± 0.39	1.07 ± 0.37	1.06 ± 0.36
FVC, L	2.54 ± 0.71	2.57 ± 0.76	2.58 ± 0.74
FEV ₁ /FVC	43.6 ± 9.8	42.0 ± 9.5	41.3 ± 8.7
Prestudy, any pulmonary medication	191 (91.4)	195 (91.5)	187 (93.0)
Anticholinergic	116 (55.5)	109 (51.2)	106 (52.7)
β-Adrenergics, inhaled	135 (64.6)	142 (66.7)	135 (67.2)
β-Adrenergics, oral	1 (0.5)	0	0
Steroid, inhaled	137 (65.6)	144 (67.6)	133 (66.2)
Steroid, oral	10 (4.8)	10 (4.7)	14 (7.0)
Theophylline	45 (21.5)	49 (23.0)	35 (17.4)

*Data are presented as mean ± SD or frequency (%) unless otherwise indicated.

anticholinergics. Respiratory medication use was similar across treatment groups, as was the percentage of current smokers (42%).

Spirometry

The increase in FEV₁ during 12 h after the first dose of tiotropium and salmeterol was similar. Improvements in trough FEV₁ with the active medications were observed by the first follow-up spirometry testing on the 15th day of treatment. At 24 weeks, trough FEV₁ had improved significantly above placebo by 137 mL in the tiotropium group and by 85 mL in the salmeterol group. The difference between tiotropium and salmeterol was significant (52 mL, $p < 0.01$). Similar findings were noted for average FEV₁ from 0 to 3 h, average FEV₁ from 0 to 12 h, and peak FEV₁ where tiotropium was superior to salmeterol and both active treatments were better than placebo (Table 2). The differences between tiotropium and salmeterol during the 12-h observation period, including trough FEV₁, appeared to increase with study duration (Fig 1). As with FEV₁, the differences for FVC were significant for the active compounds over the placebo, but tiotropium was superior to salmeterol for all variables (Fig 2, Table 3). At the end of the study, trough FVC had improved significantly above placebo by 247 mL in the tiotropium group ($p < 0.0001$) and by 134 mL in the salmeterol group ($p < 0.001$). The difference between tiotropium and salmeterol was 112 mL ($p < 0.01$). As with FEV₁, the differences between tiotropium and salmeterol appeared to increase with study duration (Fig 2).

Table 2—Differences Between Treatment Groups for FEV₁ Values Following 24 Weeks of Treatment With Either Tiotropium, Salmeterol, or Placebo*

Variables	TIO vs PBO	TIO vs SAL	SAL vs PBO
Trough response, mL	137 ± 20 (0.0001)	52 ± 20 (0.0088)	85 ± 20 (0.0001)
Average 0–3 h, mL	222 ± 23 (0.0001)	77 ± 22 (0.0005)	145 ± 22 (0.0001)
Average 0–12 h, mL	215 ± 22 (0.0001)	77 ± 22 (0.0004)	138 ± 22 (0.0001)
Peak 0–3 h, mL	244 ± 24 (0.0001)	83 ± 23 (0.0004)	161 ± 24 (0.0001)

*Data are presented as mean ± SEM (p value). TIO = tiotropium; PBO = placebo; SAL = salmeterol.

PEFRs

Baseline morning PEFs were 238 L/min, 236 L/min, and 224 L/min for the tiotropium, salmeterol, and placebo groups, respectively. The weekly mean morning PEFs improved by 27.3 L/min, 21.4 L/min, and 0.3 L/min for the respective groups at the end of the study (Fig 3, top). Both active treatments were superior to placebo with a trend for tiotropium over salmeterol ($p < 0.001$ for tiotropium vs placebo at all weeks, and $p < 0.001$ for salmeterol vs placebo at all weeks except 15 and 16). Baseline evening PEFs were 248 L/min, 248 L/min, and 241 L/min for the tiotropium, salmeterol, and placebo groups, respectively. The weekly mean evening PEFs changed by 32.5 L/min, 14.6 L/min, and -5.7 L/min for the respective groups at the end of the study (Fig 3,

bottom). Both active treatments were superior to placebo ($p < 0.001$). Tiotropium was significantly better than salmeterol in improving evening PEF ($p < 0.05$).

Dyspnea

BDI focal scores were comparable between groups (tiotropium, 6.65; salmeterol, 6.62; and placebo, 6.21), and were consistent with a moderate degree of dyspnea. At 6 months, the improvement in TDI focal scores above placebo was 1.02 U for tiotropium ($p = 0.01$) and 0.24 U for salmeterol ($p = 0.56$). Tiotropium was superior to salmeterol in improving TDI focal score (difference, 0.78 U; $p < 0.05$). The proportion of patients within each group achieving a 1-U change was 42%, 35%, and 26% for the tiotropium, salmeterol, and placebo

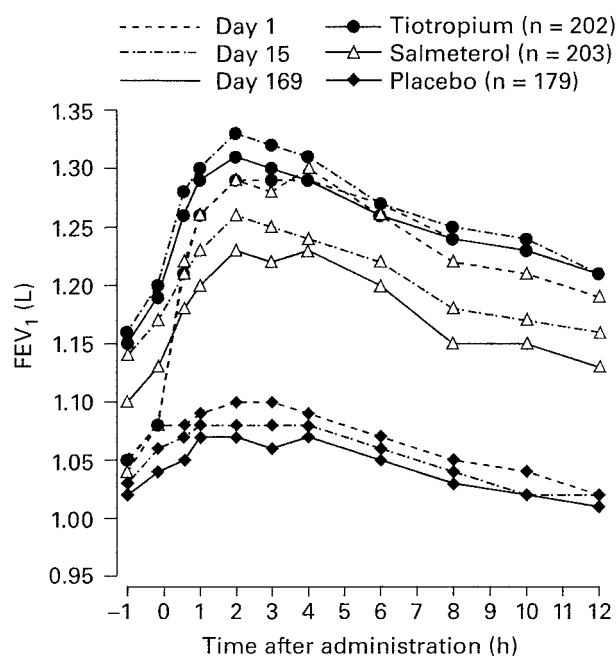


FIGURE 1. Mean FEV₁ before and after administration of tiotropium, salmeterol, and placebo on days 1, 15, and 169 of treatment. $p < 0.001$ for tiotropium vs placebo on all test days posttreatment; $p < 0.05$ for tiotropium vs salmeterol on all test days except day 1 and -1 h on day 15.

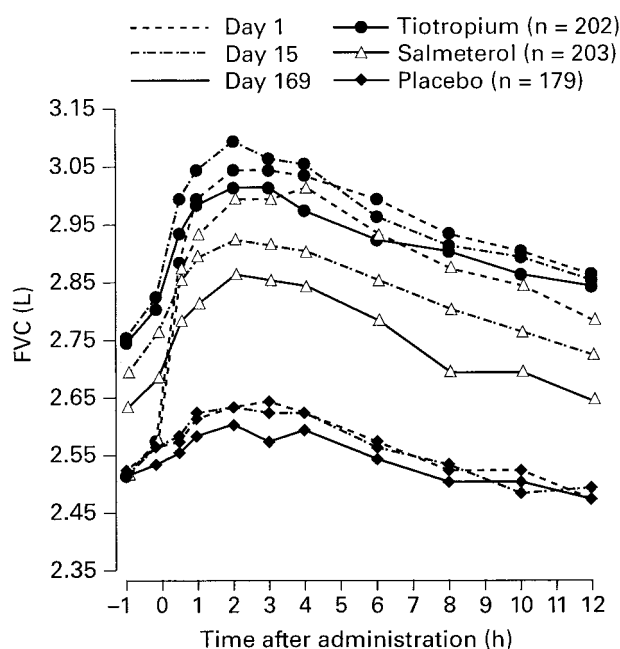


FIGURE 2. Mean FVC before and after administration of tiotropium, salmeterol, and placebo on days 1, 15, and 169 of treatment. $p < 0.001$ for tiotropium vs placebo on all test days posttreatment; $p < 0.05$ for tiotropium vs salmeterol on all test days except day 1 and -1 h and -10 min on day 15.

Table 3—Differences Between Treatment Groups for FVC Values Following 24 Weeks of Treatment With Either Tiotropium, Salmeterol, or Placebo*

Variables	TIO vs PBO	TIO vs SAL	SAL vs PBO
Trough response, mL	247 ± 39 (0.0001)	112 ± 38 (0.0031)	134 ± 39 (0.0007)
Average 0–3 h, mL	394 ± 43 (0.0001)	152 ± 41 (0.0002)	242 ± 43 (0.0001)
Average 0–12 h, mL	387 ± 42 (0.0001)	165 ± 41 (0.0001)	222 ± 42 (0.0001)
Peak 0–3 h, mL	416 ± 46 (0.0001)	166 ± 44 (0.0002)	250 ± 46 (0.0001)

*Data are presented as mean ± SEM (p value). See Table 2 for expansion of abbreviations.

groups, respectively. The differences were significant for tiotropium vs placebo ($p < 0.01$) but not for salmeterol vs placebo or for tiotropium vs salmeterol. Tiotropium appeared to improve dyspnea consistently over time, where there appeared to be a deterioration from the middle to the end of the trial for the other groups (Fig 4).

HRQoL

At 6 months, the mean improvement in SGRQ total score was as follows: tiotropium, -5.14 U ($p < 0.05$ vs placebo); salmeterol, -3.54 U ($p = 0.39$ vs placebo); and placebo, -2.43 U (Fig 5). The difference between tiotropium and salmeterol (-1.6 U) did not reach statistical significance. The mean improvement in SGRQ impacts score at 6 months was as follows: tiotropium, -5.24 ($p < 0.05$ vs placebo); salmeterol, -2.37 ($p = 0.98$ vs placebo); and placebo, -2.33 (Fig 5). The improvements observed with tiotropium appeared to increase over time (Fig 6). The proportion of patients within each group achieving a clinically meaningful change (at least 4 U) in the SGRQ total score was 51%, 40%, and 42% for the tiotropium, salmeterol, and placebo groups, respectively. Tiotropium was superior to placebo and salmeterol ($p < 0.05$) in the proportion of patients achieving a clinically meaningful change, whereas salmeterol was not statistically different from placebo.

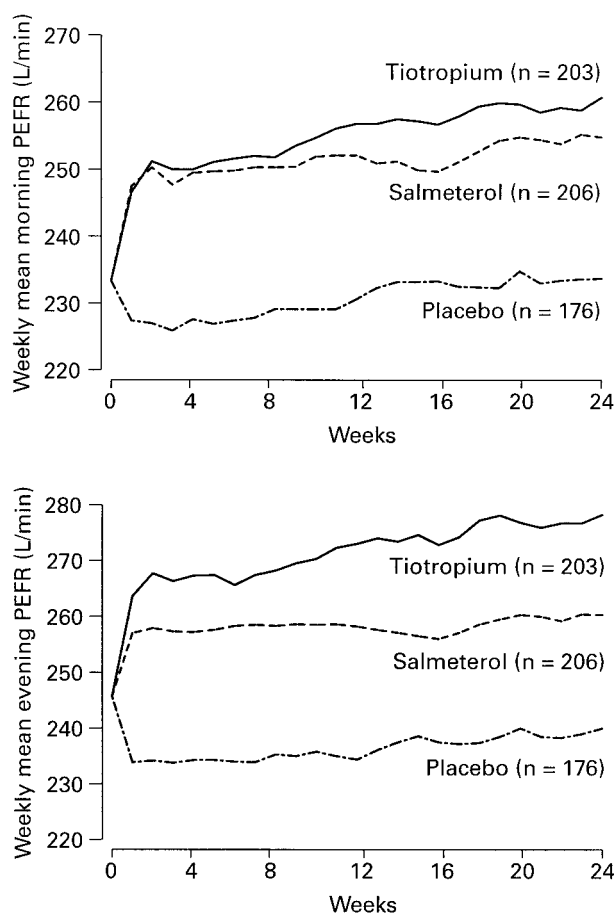


FIGURE 3. Mean of weekly means for morning (*top*) and evening (*bottom*) predose PEFR over 6 months for the tiotropium, salmeterol, and placebo groups. Morning PEFR = $p < 0.001$ for tiotropium vs placebo at all weeks. $p < 0.001$ for salmeterol vs placebo at all weeks except 15 and 16. Tiotropium vs salmeterol was not significant. Evening PEFR = $p < 0.001$ for tiotropium vs placebo at all weeks. $p < 0.001$ for salmeterol vs placebo at all weeks; $p < 0.05$ for tiotropium vs salmeterol at all weeks except week 6.

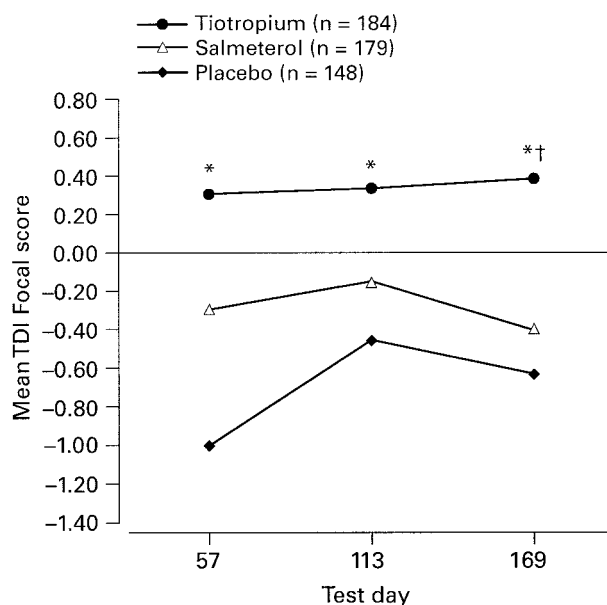


FIGURE 4. TDI focal scores at days 57, 113, and 169 for the tiotropium, salmeterol, and placebo groups. * $p < 0.05$ for tiotropium vs placebo. † $p < 0.05$ for tiotropium vs salmeterol.

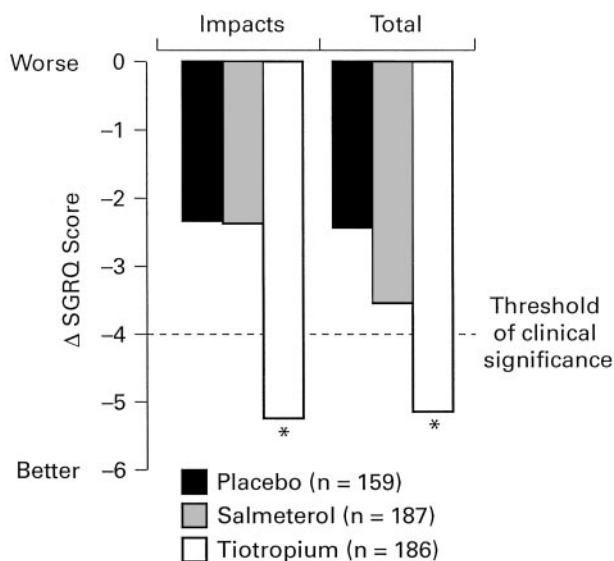


FIGURE 5. Change in SGRQ total and impacts scores from baseline to day 169 for the tiotropium, salmeterol, and placebo groups. * $p < 0.05$ for tiotropium vs placebo. Salmeterol vs placebo is not significant. Tiotropium vs salmeterol is not significant.

As-Needed Requirement For Salbutamol

Mean use of albuterol during the baseline run in period was 2.65 puffs per day. Compared with the placebo group, mean weekly requirement for salbutamol decreased equally with tiotropium (-1.45 puffs per day) and salmeterol (-1.44 puffs per day) [$p < 0.0001$, active vs placebo].

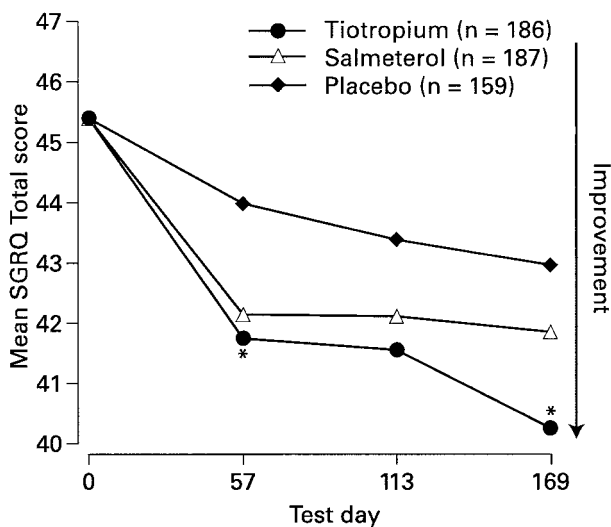


FIGURE 6. SGRQ total score at baseline and at days 57, 113, and 169 for the tiotropium, salmeterol, and placebo groups. * $p < 0.05$ for tiotropium vs placebo at day 57 and day 169. Salmeterol vs placebo is not significant. Tiotropium vs salmeterol is not significant.

Adverse Events

The most common adverse event related to tiotropium treatment was dry mouth (10%). None of the patients discontinued participation in the study due to dry mouth. Other than dry mouth, there were no significant differences among treatment groups. Exacerbations of COPD were experienced by a lower proportion of patients in the tiotropium group (36.8%) compared with salmeterol (38.5%) and placebo (45.8%); however, the differences were not statistically significant. There were no deaths in the tiotropium group. Three deaths occurred in the salmeterol group (sudden death, respiratory insufficiency, and pulmonary embolism), and four deaths occurred in the placebo group (respiratory insufficiency, cardiac arrest [$n = 2$], and unknown cause). None of the treatments were associated with laboratory or ECG abnormalities.

DISCUSSION

Bronchodilators are the mainstay of pharmacotherapy for patients with COPD.¹⁻³ Mechanism of action, route of administration, frequency of administration, onset of action, duration of action, symptomatic improvement, and side effect profile differentiates various bronchodilator medications. Generally, inhaled therapy has been preferred over oral therapy due to the targeted delivery to the lung, superior spirometric results, and superior tolerability. In addition, differential benefits have led to practical recommendations for a step approach to medication interventions.¹⁻³ The presently available bronchodilators have provided symptomatic benefit to patients and an increasing recognition that treatment intervention is useful in patients with COPD.

Tiotropium is a new, once-daily, anticholinergic bronchodilator that has its effect through prolonged M_3 -receptor antagonism.^{5,6} Single-dose and multiple-dose studies have documented a 24-h duration of action with once-daily administration.^{7,8} In addition, significant improvements were seen in bronchodilation over 3 months in a placebo-controlled study.⁹ In the present study, 6-month long-term treatment of COPD with tiotropium once daily was associated with superior bronchodilation compared with salmeterol administered twice daily. In addition, improvements in dyspnea and proportion of patients achieving meaningful changes in HRQoL were superior to salmeterol.

The spirometric response to drug administration has generally served as a useful initial standard to judge efficacy among bronchodilators. As clinical trials may differ somewhat in design, testing procedures, or population under study, direct comparisons

within a trial are of considerable assistance in determining when to prescribe therapy. Ipratropium has been considered the preferred first-line approach in patients with symptomatic COPD based on bronchodilator benefits.^{21,22}

Matera and colleagues¹² compared bronchodilator efficacy of ipratropium with salmeterol in 16 patients with COPD and noted that, while salmeterol had a superior FEV₁ area under the curve (AUC) [0 to 12 h], the differences were only significant between the 4-h to 12-h time period. However, ipratropium was only administered once in the morning (*ie*, less than the recommended dose of four times daily) during the 12-h spirometry studies, and persistence of efficacy with long-term dosing was not addressed. Mahler and colleagues¹³ conducted a larger trial comparing ipratropium and salmeterol in 411 patients with COPD. After 12 weeks, both treatment groups had similar peak FEV₁, but salmeterol had greater FEV₁ AUC (0 to 12 h). Ipratropium was administered twice during the 12-h observation period, and superiority in AUC was due to the significant differences at 4 h and 6 h (no significant differences were noted at other time points, including 30 min, 1 h, and 2 h following inhalation of drug). This was a finding similar to the study by Matera et al.¹² A recent large trial¹⁶ comparing ipratropium to salmeterol demonstrated that ipratropium and salmeterol had a similar AUC for both FEV₁ and FVC from 0 to 12 h.

The spirometric improvements with the novel anticholinergic tiotropium have now been evaluated in separate comparative trials with two commonly used maintenance inhaled bronchodilators prescribed for the treatment of COPD. A 3-month trial²³ with 288 COPD patients demonstrated that tiotropium therapy was superior to ipratropium in improving FEV₁ and FVC. Compared with ipratropium, tiotropium therapy produced higher predose trough FEV₁ (130 mL), peak FEV₁ (50 mL), and average FEV₁ (80 mL) over six serial measurements postdose. In the present trial, tiotropium was superior to salmeterol at all time points, and the difference between the two bronchodilators appeared to increase over the duration of the study. In addition, two other observations are notable: (1) FEV₁ and FVC measures approximately 24 h following tiotropium administration were superior to those observed 12 h following salmeterol administration, and (2) the onset of action following the first dose was similar for both drugs on day 1. The consistent spirometric superiority of tiotropium suggests that additional outcomes may follow a similar pattern.

Bronchodilator efficacy with tiotropium, as with other inhaled anticholinergic medications, is generally sustained with no evidence of tolerance. How-

ever in this 6-month trial, the bronchodilator efficacy with salmeterol declined over time. Tolerance to the effects of bronchodilation with salmeterol inhalation have been consistently observed in laboratory-based measurements of hyperresponsiveness in asthmatics.^{24–26} The phenomenon has not previously been demonstrated with long-term dosing of salmeterol in COPD clinical trials, although such studies have been limited to 12 to 16 weeks in duration. Whether there are long-term consequences related to diminished bronchodilator benefits from β -agonists remains to be seen.

Dyspnea is the most common complaint and most disabling symptom in patients with COPD. While progression of disease is often monitored through lung function by the physician, the patient will recognize the progression by the extent of disability from dyspnea. Hence, objective monitoring of dyspnea by health-care professionals should be considered as part of the evaluation process. COPD clinical trials have incorporated dyspnea as an outcome measure. In the aforementioned 12-week study of 411 patients with COPD reported by Mahler and colleagues,¹³ the TDI was assessed at weeks 2, 4, 6, 8, 10, and 12. Ipratropium therapy improved dyspnea compared with placebo at all time points beyond 2 weeks. While salmeterol therapy improved dyspnea at weeks 2, 4, 8, and 10, there was no difference compared with placebo at the end of the trial (12 weeks). Rennard et al¹⁶ observed no improvement in dyspnea with salmeterol therapy in recent, large, 12-week trial. In the present study, salmeterol therapy was not significantly different from placebo at any time point. Tiotropium therapy improved dyspnea at all measured intervals and was superior to salmeterol. In addition, the mean difference surpassed the clinically meaningful difference of 1 U. In the study by Mahler et al¹³ ipratropium therapy improved dyspnea more consistently than salmeterol. Therefore, for maintenance treatment of COPD, it appears that anticholinergics may be superior to β_2 -agonists in improving dyspnea.

For objective measurements of HRQoL, the SGRQ and the Chronic Respiratory Disease Questionnaire²⁷ appear to be the most commonly used in COPD clinical trials. An analysis of reliability, validity, and responsiveness to change suggested that there was no clear advantage with one instrument over the other.¹⁴ In the present study, tiotropium was the only treatment arm associated with significant improvements in the SGRQ total and impacts scores compared with placebo. In addition, the proportion of patients achieving at least a 4-U improvement was > 50%, and was significantly better than that seen in the other treatment groups ($p < 0.05$). As with other findings, the improvements

with tiotropium therapy were not only sustained over 6 months, but appeared to increase further over time. COPD clinical trials comparing salmeterol therapy with placebo have yielded inconsistent results with regard to changes in the SGRQ, with one trial with positive findings and two trials with negative findings.^{14–16} The present study is in agreement with the latter report in that salmeterol therapy did not improve SGRQ relative to placebo.

There are now multiple therapeutic options for the treatment of COPD. The choice of medication is based on the available information and the integration of efficacy, safety, and convenience. The standard approach to treatment of regular symptoms of COPD has been the prescription of an anticholinergic, which is most often ipratropium administered four times daily.^{1–3} Salmeterol represents an alternative, given the available data, and offers the advantage of twice-daily dosing. Tiotropium represents a new generation of inhaled therapy. No other inhaled product has demonstrated effectiveness with once-daily dosing, a unique advantage to patients. The present study followed up patients for 6 months and provides evidence that tiotropium, 18 µg once daily, via dry-powder inhaler results in 24-h bronchodilation as well as consistent and sustained improvements in dyspnea and HRQoL. The improvements observed were superior to salmeterol, 50 µg twice daily, with MDI. Given the benefits noted with tiotropium over other bronchodilators and the convenience of once-daily dosing, tiotropium can be considered as an appropriate first-line therapy for patients experiencing symptomatic COPD.

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APPENDIX

The following investigators participated in this study: Professor D. McKenzie, Dr. E. Beck, Dr. M.V. Middle, Professor D. Ruffin, Dr. T. Schaberg, Dr. J. M. Montserrat, Professor P. Thompson, Dr. C.F. Marchioni, Dr. M. Miravittles, Professor J. Aumann, Dr. C. Sanguinetti, Dr. J. Morera, Professor W. Vincken, Professor V. Brusasco, Dr. S.J. Langley, Dr. J. Verhaert, Dr. J.A. van Noord, Dr. R.J. White, Dr. N. Zamel, Dr. T.A. Bantje, Dr. A.J. Winning, Dr. R. Hodder, Dr. A.P.M. Greefhorst, Dr. K.R. Patel, Dr. R. Abboud, Dr. J.P.H.M. Creemers, Dr. J.F. Donohue, Dr. J. Bourbeau, Dr. J. Garrett, Dr. J. Ilowite, Professor R. Dahl, Professor H. Rea, Dr. J. Taylor, Professor R. Bonnett, Professor E.D. Bateman, Dr. R. Lapidus, Professor C-P. Crie, Professor J.R. Joubert, and Dr. I. Ziment.

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