

# Improvement in Exercise Tolerance With the Combination of Tiotropium and Pulmonary Rehabilitation in Patients With COPD\*

Richard Casaburi, MD, PhD, FCCP; David Kukafka, MD, FCCP;  
Christopher B. Cooper, MD, FCCP; Theodore J. Witek, Jr, DrPH; and  
Steven Kesten, MD, FCCP

**Study objectives:** Pulmonary rehabilitation (PR) improves exercise tolerance in COPD patients. Tiotropium is a once-daily, inhaled anticholinergic bronchodilator that provides sustained 24-h improvements in airflow and lung hyperinflation reduction. We hypothesized that ventilatory mechanics improvements from tiotropium would permit enhanced ability to train muscles of ambulation and therefore augment exercise tolerance benefits of PR.

**Design:** In a randomized, double-blind, placebo-controlled trial (tiotropium, n = 47; placebo, n = 44), tiotropium (18 µg qd) was administered to COPD patients participating in 8 weeks of PR (treadmill training three times a week; ≥ 30 min per session) at 17 sites. Study drug was administered 5 weeks prior to, 8 weeks during, and 12 weeks following PR. The primary end point was treadmill walking (0% incline) endurance time at 80% of maximum speed attained in an initial incremental test. The transition dyspnea index (TDI), St. George's respiratory questionnaire (SGRQ), and rescue albuterol use were secondary end points.

**Participants:** Mean age of the 93 participants was 67 years, 57% were men, and mean FEV<sub>1</sub> was 0.88 L (34% predicted).

**Results:** Mean endurance time differences (tiotropium minus placebo) prior to PR, at the end of PR, and 12 weeks after PR were 1.65 min (p = 0.183), 5.35 min (p = 0.025), and 6.60 min (p = 0.018), respectively. Mean TDI focal scores at the end of PR were 1.75 for tiotropium and 0.91 for placebo (p > 0.05). At 12 weeks after PR, TDI focal scores were 1.75 for tiotropium and 0.08 for placebo (p < 0.05). Relative to placebo, tiotropium improved SGRQ total scores by 3.86 at the end of PR and 4.44 at 12 weeks after PR (p > 0.05). Mean albuterol use declined following PR plus tiotropium, compared to PR alone (p ≤ 0.05 for 17 of 25 weeks).

**Conclusions:** Tiotropium in combination with PR improved endurance of a constant work rate treadmill task and produced clinically meaningful improvements in dyspnea and health status compared to PR alone. Improvements with tiotropium were sustained for 3 months following PR completion. (CHEST 2005; 127:809–817)

**Key words:** COPD; exercise; pulmonary rehabilitation; tiotropium

**Abbreviations:** CWR = constant work rate; mph = miles per hour; PEFR = peak expiratory flow rate; PR = pulmonary rehabilitation; Sao<sub>2</sub> = arterial oxygen saturation; SGRQ = St. George's respiratory questionnaire; TDI = transitional dyspnea index

COPD is a progressive disorder leading to increasing symptoms of dyspnea on exertion. These symptoms impair exercise tolerance and result in limitation or avoidance of activity. Reducing dyspnea and improving a patient's exercise tolerance and ability to engage in activities are therefore important goals of therapy in COPD.

The impairment of exercise tolerance occurs as a result of both ventilatory limitation, and deconditioning and distinct abnormalities in the muscles of ambulation. Pulmonary rehabilitation (PR) has repeatedly and consistently been shown to enhance

exercise tolerance as well as improve dyspnea without necessarily improving the mechanics of the respiratory system.<sup>1–3</sup> Bronchodilators have been shown to improve airflow limitation but have had an inconsistent effect on various measures of exercise capacity.<sup>4,5</sup>

Data suggest, however, that tiotropium, an inhaled anticholinergic, provides sustained 24-h improvement in airflow limitation and reduces hyperinflation with once-daily dosing.<sup>6–8</sup> In addition, data have shown that exercise tolerance can be improved with tiotropium as measured by constant work rate

(CWR) cycle ergometry.<sup>9</sup> It seemed likely, therefore, that improvements in ventilatory mechanics from tiotropium would permit an enhanced ability to train and augment the exercise tolerance benefits observed with PR.

Tiotropium yields sustained bronchodilation throughout the day due to prolonged M<sub>3</sub> muscarinic receptor antagonism and has superior spirometric outcomes in morning flow rates in comparison to placebo or ipratropium bromide.<sup>6,7</sup> In terms of aerobic conditioning, these effects may provide advantages when tiotropium is administered during a period of exercise training. Patients may be able to exercise longer or with a higher intensity, thereby inducing an improved physiologic training effect on the muscles of ambulation. This may yield superior gains in exercise tolerance.

Theoretically, other benefits may also be provided when tiotropium is used during rehabilitation. The frequent troughs associated with short-acting agents may not allow for sustained improvements in lung volumes. Investigators have shown that hyperinflation and reduced inspiratory capacity can significantly limit the duration of physical activity.<sup>10,11</sup> It is likely that the sustained effects of tiotropium may lead to alterations in lung volumes and may be partially responsible for improvements in dyspnea.

The present study was designed to determine whether tiotropium can enhance improvements in exercise tolerance, dyspnea, and health-related quality of life compared to placebo in patients with COPD who participate in PR. The study also assessed whether improvements were maintained with tiotropium after the conclusion of the PR program.

---

\*From the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center (Dr. Casaburi), Torrance, CA; North Colorado Pulmonary Consultants PC (Dr. Kukafka), Fort Collins, CO; David Geffen School of Medicine (Dr. Cooper), University of California, Los Angeles, CA; and Boehringer Ingelheim Pharmaceuticals, Inc. (Drs. Witek and Kesten), Ridgefield, CT. Dr. Casaburi holds the Alvin Grancell/Mary Burns Chair in the Rehabilitative Sciences.

Dr. Casaburi is a consultant of Boehringer-Ingelheim Pharmaceuticals and Pfizer and serves on their Academic Advisory Board. Dr. Cooper receives research support from Boehringer-Ingelheim Pharmaceuticals and is a member of their Speaker's Bureau and Scientific Advisory Board. Drs. Witek and Kesten are employees of Boehringer-Ingelheim Pharmaceuticals.

This study was supported by Boehringer-Ingelheim Pharmaceuticals Inc. and Pfizer Inc.

Manuscript received March 15, 2004; revision accepted August 31, 2004.

Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (e-mail: [permissions@chestnet.org](mailto:permissions@chestnet.org)).

Correspondence to: Richard Casaburi, PhD, MD, FCCP, Chief, Division of Respiratory and Critical Care Physiology and Medicine, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, 1124 W Carson St, Building RB-2, Torrance, CA 90502; e-mail: [casaburi@ucla.edu](mailto:casaburi@ucla.edu)

## MATERIALS AND METHODS

### Study Design

This study is a 25-week, multicenter, single-country, randomized, double-blind, parallel-group clinical trial to determine the efficacy of tiotropium inhalation capsules compared to placebo on exercise tolerance in patients with COPD participating in a PR program. Randomization to tiotropium, 18 µg qd, or placebo occurred in a 1:1 ratio. Tiotropium or matching placebo were supplied as a dry-powder capsule and inhaled (HandiHaler device; Boehringer Ingelheim; Ingelheim, Germany) in the morning. Patients were allowed to use inhaled steroids, theophylline preparations, and oral steroids as previously prescribed by their physician. All patients were supplied with an albuterol metered-dose inhaler to use as needed for acute symptom relief. Other β-agonists (long and short acting) and inhaled anticholinergic medications (other than study drugs) were not permitted. The study was conducted in 17 sites in the United States. The protocol was approved by institutional review boards; written informed consent was obtained from all patients. The procedures used were in accordance with the recommendations of the Helsinki Declaration of 1975.

### Patients

Patients were required to have a clinical diagnosis of COPD,<sup>12</sup> FEV<sub>1</sub> ≤ 60% of predicted normal,<sup>13</sup> and FEV<sub>1</sub> ≤ 70% of FVC. Patients were also required to be at least 40 years of age and to have a smoking history > 10 pack-years. All patients needed to be candidates for PR and to meet local requirements for enrollment in a PR program. Patients with a history of asthma, allergic rhinitis, atopy, or an elevated total blood eosinophil count were excluded, as were patients with recent respiratory tract infections. Other exclusion criteria included orthopedic, muscular, or neurologic disease that would interfere with regular participation in aerobic exercise or with exercise testing as well as a body mass index > 30 or < 18 kg/m<sup>2</sup>. Patients with a significant disease other than COPD (defined as a disease that in the opinion of the investigator would either put the patient at risk because of participation in the study, or a disease that may influence the results of the study or the patient's ability to participate in the study) or a recent history of myocardial infarction, hospitalization for cardiac failure, and cardiac arrhythmia requiring drug therapy were excluded from the study.

### Study Protocol

The study protocol is outlined in Figure 1. An incremental treadmill exercise test was performed at the initial screening visit (visit 1). Patients did not receive study medications during the week (± 3 days) prior to the second visit. One week following the initial screening (visit 2), patients performed a CWR treadmill exercise test at 80% of the maximum treadmill speed in the incremental treadmill test and were randomized to tiotropium or placebo inhalation capsules to be taken once daily in the morning for the subsequent 25 weeks. Patients then entered a 4-week run-in period. At the end of the 4-week run-in period (visit 3), patients completed a CWR treadmill test. After completion of the run-in period of study drug administration, patients entered PR (visit 4). PR included aerobic lower-limb exercise three times weekly for 8 weeks. After the last PR session (visit 6), patients continued on study medication for a 12-week follow-up period. CWR treadmill tests were performed at the conclusion of the 8 weeks of PR (visit 6) and after the 12-week follow-up period (visit 9). Except for visit 2, all CWR tests commenced 90 min after inhalation of the study drug.

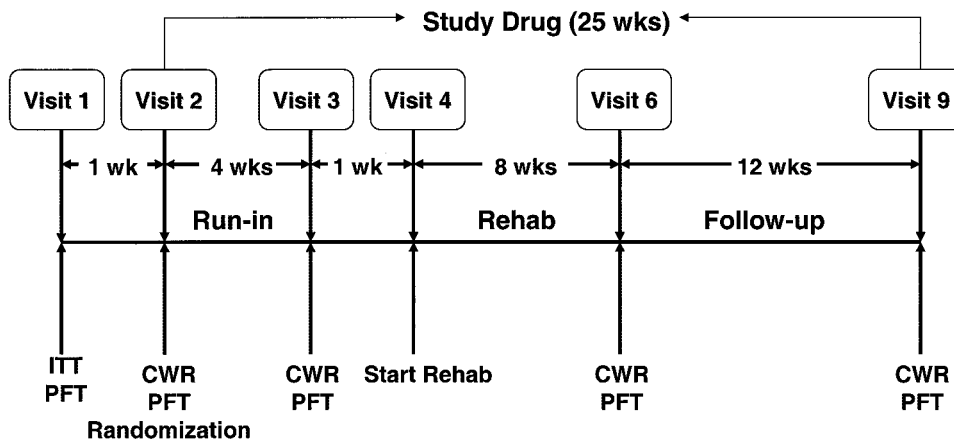


FIGURE 1. Outline of trial protocol. ITT = incremental treadmill test; PFT = pulmonary function test; Rehab = rehabilitation.

### Study Procedures

**Incremental Exercise Test:** The initial treadmill speed was set at 0.8 miles per hour (mph) with no incline on the treadmill. The patient walked for 3 min at this speed prior to increasing the speed. At the end of each subsequent minute, the speed was increased by 0.5 mph. The patient was encouraged to continue exercising for as long as possible. The test was terminated at symptom limitation or if there was a safety concern (*ie*, ischemic ECG changes). For patients suspected of having extremely poor exercise tolerance, the treadmill speed was increased in increments of 0.25 mph. During recovery, the patient was asked to continue to walk at the lowest speed (0.8 mph) for at least 2 min.

**CWR Treadmill Test:** The initial treadmill speed was set at 0.8 mph. The patient walked for 3 min at 0.8 mph prior to increasing the work rate to 80% of the peak treadmill speed determined during the incremental treadmill test. The patient was encouraged to continue exercising for as long as possible. The test was terminated at symptom limitation or if there was a safety concern. Patients were asked to rate the intensity of dyspnea using the modified Borg scale at the end of the 3-min period at 0.8 mph, every 2 min thereafter, and at the end of exercise. Patients were also asked to rate the intensity of leg discomfort using the modified Borg scale at the end of the 3-min walking period at 0.8 mph and at the end of exercise. Arterial oxygen saturation ( $\text{SaO}_2$ ) was measured by pulse oximetry continuously throughout testing. The duration of exercise was recorded to the nearest second. During recovery, the patient was told to continue walking slowly with the treadmill speed set at 0.8 mph. Immediately following completion of the exercise test, patients were asked to indicate why they stopped exercise.

**PR:** The PR programs were standardized according to a prespecified lower-limb training procedure and schedule (Table 1). Other exercise modalities were strongly encouraged. All patients were encouraged to exercise at home on days when they were not participating at the rehabilitation center. The rehabilitation coordinator recorded the frequency, type, and duration of home exercise between sessions. The rehabilitation programs were requested to provide upper-limb activities as well as education to all patients enrolled.

**Lung Function:** Spirometry was conducted at the initial screening (visit 1); randomization (visit 2), which served as the baseline measurement; after 4 weeks of treatment (visit 3); after PR (visit 6); and after the 12-week follow-up period (visit 9). The best of three efforts was defined as the highest  $\text{FEV}_1$  and the highest

FVC each obtained on any of three efforts meeting the American Thoracic Society criteria (with a maximum of five attempts).<sup>14</sup> Peak expiratory flow rates (PEFRs) were self-measured by patients twice daily (on rising and at bedtime) with a peak flowmeter (Mini-Wright; Clement Clarke International; Harlow, UK). Patients recorded the best of three efforts.

**Dyspnea, Health-Related Quality of Life, and Albuterol Use:** Dyspnea was evaluated using the baseline dyspnea index (visit 2) and the transition dyspnea index (TDI) [visits 3, 6, and 9].<sup>15</sup> Health-related quality of life was determined using the St. George's respiratory questionnaire (SGRQ) [visits 2, 3, 6, and 9].<sup>16</sup> Patients recorded the number of doses of albuterol, taken as required, in a diary.

### Data Analysis

The statistical model was an analysis of variance or covariance, depending on end points, with terms for treatment and center.

**Table 1—Protocol for Lower-Limb Exercise During PR Sessions**

1. Attendance and participation three times each week.
2. Treadmill exercise training.
3. Treadmill speed at the first training session should be set to 70% of the treadmill speed obtained during the incremental exercise test at visit 1.
4. The treadmill speed should be lowered as necessary to obtain at least 30 min of continuous walking. The treadmill speed at sessions subsequent to the first session may begin at < 70% of that obtained during the incremental test at the discretion of the rehabilitation coordinator.
5. Adjust supplemental oxygen (if required) to maintain  $\text{SaO}_2 \geq 90\%$ .
6. Train for as long as tolerated for at least 30 min. The patient may exercise > 30 min if tolerated.
7. If the patient is able to complete 30 min of continuous lower-extremity exercise, increase intensity of training as tolerated.
8. If unable to complete 30 min of continuous lower-limb exercise, break the session into as many as four parts with 5- to 10-min rests in between. Conclude session if more than three rests are required.

For the analysis of the covariance model, the predosing data at the end of the screening period (visit 2) was used as a covariate. The analysis included an adjustment for any differences at baseline. All randomized patients with complete CWR treadmill exercise tests at visits 2, 3, and 6 were used for the analyses of exercise endurance time and the analyses of variables to be collected during the exercise tolerance test. For all other analyses, all randomized patients with baseline (visit 2) and adequate datum following multiple administrations of study medications were included. Other secondary analyses included the morning predose and postdose FEV<sub>1</sub> and FVC at visits 3, 6, and 9; the PEFR from the patient's diary; TDI scores; SGRQ scores; and rescue albuterol use. Analysis of covariance was conducted to compare FEV<sub>1</sub> and FVC between tiotropium and placebo. For this analysis, baseline datum (visit 2 prior to dosing) was used as the covariate. For the analysis of PEFR and as-needed albuterol use, the weekly mean of observations during the screening period was used as a covariate. Results are described as mean ± SE with statistical significance considered at  $p < 0.05$ .

## RESULTS

A total of 108 patients were randomized and received at least one dose of study medication. The full analysis data sets included all randomized patients who had adequate baseline measurements and at least one efficacy measurement after the multiple administration of study medication. By this definition, 12 patients (6 in each treatment group) were excluded from all efficacy analyses. In addition to the 12 patients excluded from all efficacy analyses, 5 additional patients were excluded from the primary efficacy analysis (2 patients in the tiotropium group, and 3 patients in the placebo group) due to significant protocol violations.

### Demographics

The mean age of the population was 66.6 years (range, 42 to 83 years) with 61 (57%) being men (Table 2). There were approximately 10% more current smokers in the tiotropium group compared to the placebo group. Other demographic data were balanced between the two groups. The mean duration of COPD was approximately 9 years (range, 1 to 31 years).

### Baseline Lung Function and Incremental Treadmill Testing

The tiotropium group had mildly lower mean FEV<sub>1</sub> and FVC values compared to the placebo group (Table 2). The mean FEV<sub>1</sub> and FVC were 0.82 L and 2.01 L, respectively, in the tiotropium group, vs 0.94 L and 2.14 L in the placebo group. The percentage of predicted FEV<sub>1</sub> was 33% in the tiotropium group, vs 36% in the placebo group. The exercise endurance time in the incremental exercise test was similar in the two groups and averaged

**Table 2—Baseline Characteristics of the Tiotropium and Placebo Groups\***

Characteristics	Tiotropium	Placebo	Total
Patients treated, No.	55	53	108
Male/female gender, %	54.5/45.5	58.5/41.5	56.5/43.5
Age, yr	65.9 (8.8)	67.3 (6.9)	66.6 (7.9)
Body mass index	25.0 (4.6)	26.8 (5.6)	25.9 (5.2)
Smoker/ex-smoker, %	29.1/70.9	18.9/81.1	24.1/75.9
Smoking history, pack-yr	58.7 (34.6)	58.8 (31.4)	58.7 (32.9)
COPD duration, yr	9.7 (7.6)	8.9 (6.6)	9.3 (7.1)
FEV <sub>1</sub> , L	0.82 (0.31)	0.94 (0.40)	0.88 (0.36)
FEV <sub>1</sub> , % predicted	32.6 (12.4)	36.2 (12.2)	34.4 (12.4)
FEV <sub>1</sub> /FVC, %	41.5 (10.4)	44.6 (11.2)	43.0 (10.9)
FVC, L	2.01 (0.68)	2.14 (0.85)	2.08 (0.77)
Incremental treadmill test			
Duration, min	9.0 (2.8)	8.8 (3.6)	8.9 (3.2)
Maximum speed, mph	2.98 (0.87)	2.81 (0.98)	2.90 (0.92)

\*Data are presented as mean (SD) unless otherwise indicated.

approximately 9 min, with a maximum speed averaging approximately 2.9 mph.

### CWR Treadmill Testing

The changes in endurance time over the study are displayed in Figure 2. The observed mean baseline endurance times were 10.85 min (SE 0.67) and 8.51 min (SE 0.55) for the tiotropium and placebo groups, respectively, with a group mean endurance time of 9.72 min (SE 0.45) minutes. As the tiotropium group showed a higher mean endurance time at baseline, on-treatment values were adjusted for baseline differences. At visit 3 after 29 days of treatment, patients receiving tiotropium showed longer exercise endurance time than patients receiving placebo. The difference between treatments was 1.65 min ( $p = 0.183$ ). Patients receiving tiotropium showed significantly longer exercise endurance times compared to placebo both after 13 weeks of treatment including 8 weeks of PR (visit 6, day 92) and at 12 weeks following the termination of the PR program after 25 weeks of treatment (visit 9, day 176). The mean differences were 5.35 min ( $p = 0.025$ ) and 6.6 min ( $p = 0.018$ ), respectively (Table 3).

Four patients had a prolonged endurance time (> 50 min) on day 92. All four patients had received treatment with tiotropium. Since the distributions of the endurance times appeared to be skewed, additional analyses were performed to evaluate the median endurance times. The difference between groups in median change from baseline to day 92 in endurance time was approximately 3.6 min. The rank analysis of covariance showed that the difference in the endurance time between the two groups on day 92 approached statistical significance ( $p = 0.053$ ) and achieved statistical significance on day 176



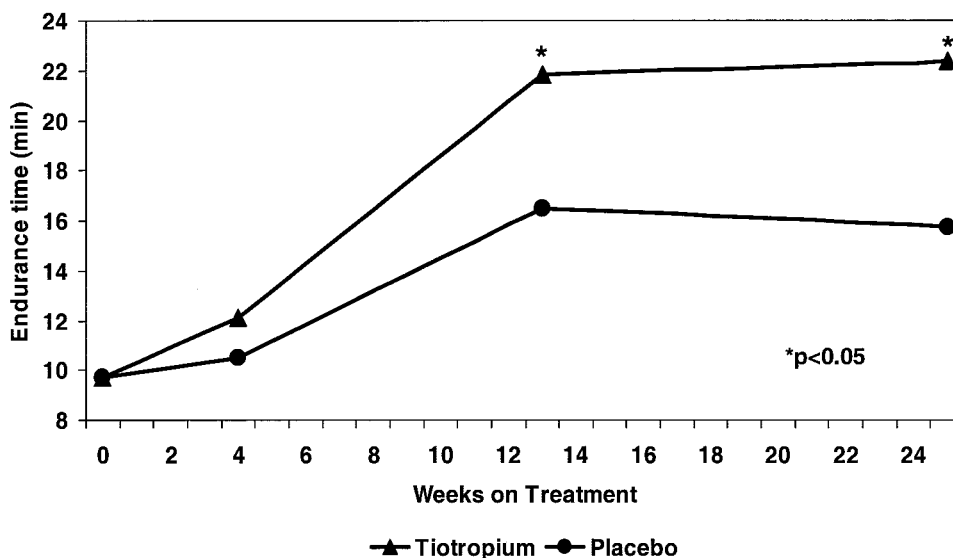


FIGURE 2. Treadmill endurance time at baseline and at all post-treatment clinic visits in the tiotropium and placebo groups.

( $p = 0.018$ ). The results from the analysis of covariance of the endurance time with the four patients excluded on all the test days also indicated that patients receiving tiotropium exercised longer on all the test days. The mean differences were 1.43 min, 3.0 min, and 6.13 min on days 29, 92, and 176, respectively. The difference in the endurance time between the tiotropium and the placebo groups on day 176 was statistically significant ( $p = 0.01$ ).

The mean increase in endurance time from day 29 (visit 3) before PR to day 92 (visit 6) after PR was 80% in the tiotropium group but only 57% in the placebo group, suggesting that tiotropium amplifies the effectiveness of PR. Further evidence of this was seen in the ratio of the mean endurance time (tiotropium/placebo), which increased from 1.16 at day 29 to 1.32 at day 92.

The Borg dyspnea scores at the end of the constant speed exercise were similar in the two treatment groups on all test days despite the tiotropium group exercising for a longer time. Mean Borg end-exercise dyspnea scores for tiotropium and placebo were 4.36 and 4.69, respectively ( $p = 0.42$ ), on

day 92, and 4.34 and 4.38, respectively, on day 176 ( $p = 0.91$ ). The Borg leg discomfort scores were also similar in the two treatment groups on all test days. Mean Borg leg discomfort scores for tiotropium and placebo were 2.67 and 3.04, respectively, on day 92, and 3.01 and 3.52, respectively, on day 176. In addition, there were no relevant differences between treatment groups in reasons for stopping exercise (breathing discomfort, leg discomfort, or both) on any test day.

SaO<sub>2</sub> at the peak of the constant rate exercise on each test day was similar in the two treatment groups on all test days despite the tiotropium group exercising for a longer time. Mean SaO<sub>2</sub> levels for tiotropium and placebo were 92.6% and 92.1%, respectively ( $p = 0.35$ ), on day 92, and 91.6% and 91.9%, respectively, on day 176 ( $p = 0.64$ ).

#### Lung Function

Tiotropium treatment significantly increased post-dose FEV<sub>1</sub> on all test days compared to placebo. The mean differences in postdose FEV<sub>1</sub> between the two

Table 3—Endurance Time From the CWR Exercise Test on the Test Days\*

Variables	Time, min		Difference†		
	Tiotropium (n = 47)	Placebo (n = 44)	Mean (SE)	p Value	95% CI
Before PR (day 29)	12.14 (0.83)	10.50 (0.86)	1.65 (1.22)	0.183	- 0.79–4.09
After PR (day 92)	21.86 (1.58)	16.51 (1.64)	5.35 (2.34)	0.025	0.69–10.00
12 wk after PR (day 176)	22.36 (1.84)	15.76 (1.91)	6.60 (2.72)	0.018	1.18–12.02

\*Data are presented as mean (SE). Mean adjusted baseline was 9.72 min.

†Analysis of covariance.

groups were 0.11 L, 0.12 L, and 0.12 L on days 29, 92, and 176, respectively ( $p < 0.0025$  on all test days). Patients receiving tiotropium had higher morning predose FEV<sub>1</sub> than patients receiving placebo on all test days. The mean difference between the tiotropium and the placebo group was 0.07 L on day 92 ( $p = 0.023$ ). The mean differences on the other two test days (0.04 and 0.06 on days 29 and 176, respectively) did not achieve statistical significance. Tiotropium treatment significantly increased post-dose FVC on all the test days compared to placebo. The treatment differences were 0.23 L, 0.31 L, and 0.27 L on days 29, 92, and 176, respectively ( $p < 0.001$  on all test days). Treatment with tiotropium increased morning predose FVC compared to the placebo. The differences between the two groups were 0.10 L, 0.21 L, and 0.19 L on days 29, 92, and 176, respectively. The differences on the test days 92 and 176 were statistically significant ( $p < 0.05$ ). The improvements in spirometry were supported by corresponding improvements in morning and evening PEFr.

#### Dyspnea and Health-Related Quality of Life

The baseline dyspnea index focal scores averaged 5.7 U and were similar in the tiotropium and placebo groups. Before PR (visit 3, day 29), the TDI focal scores were similar in the tiotropium and the placebo groups. On day 92 (8 weeks after the PR program), both treatment groups showed increases in the mean TDI focal scores. The mean TDI focal score for tiotropium was 1.75, and for placebo was 0.91. On day 176 (12 weeks after the termination of the PR

program), the placebo group showed a decline in the TDI focal score to 0.08 while the improvement in the tiotropium group was maintained at 1.75. At 12 weeks following PR, the difference between treatments in the TDI focal score was 1.67 U ( $p = 0.03$ ). The differences at the end of PR and in the follow-up period exceeded the value of 1 U, which is regarded as a clinically meaningful difference.<sup>17,18</sup>

The SGRQ total score in the tiotropium group was lower (*ie*, improved) on each test day compared to the placebo group. After PR (day 92), the SGRQ total scores improved by 7.27 U in the tiotropium group and 3.41 U in the placebo group. The difference between treatments was not statistically significant. At 12 weeks following PR (day 176), the total score in the tiotropium group was 6.06 U lower than at baseline as compared with 1.63 in the placebo group. The difference (tiotropium minus placebo) on day 176 exceeded the minimally clinically important difference of 4 U ( $-4.44$ ) and approached statistical significance ( $p = 0.055$ ).<sup>16</sup>

#### Rescue Requirement for Albuterol

The weekly mean rescue medication use during the 25-week treatment period including the 8 weeks of PR is displayed in Figure 3. On average, patients receiving tiotropium used approximately one dose less of albuterol rescue medication per day when compared to patients receiving placebo during the 25 weeks of treatment. The difference in the rescue medication use between the two treatment groups was statistically significant ( $p < 0.05$ ) in 17 of the 25 weeks.

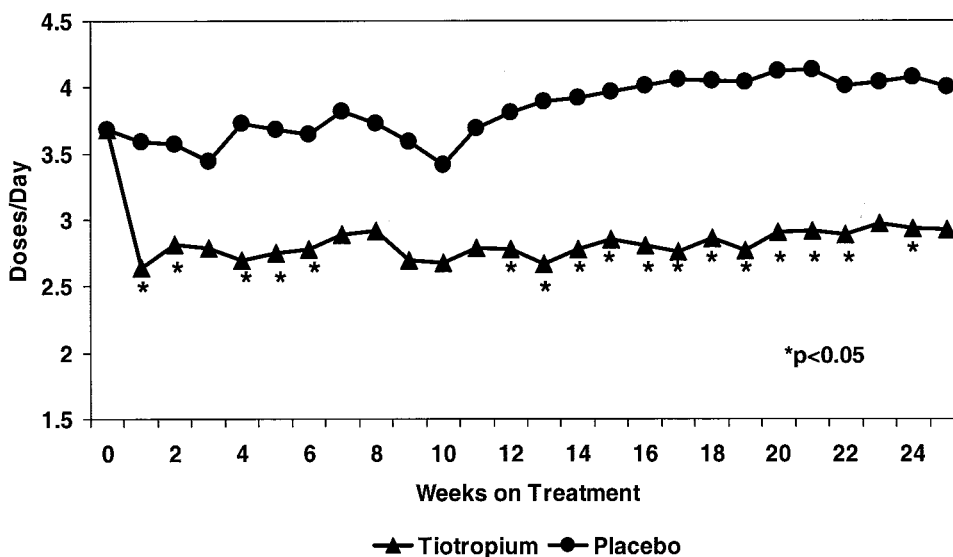


FIGURE 3. Mean of weekly mean number of doses per day of as-needed (rescue) albuterol use over the full treatment period for the tiotropium and placebo groups.

## Adverse Events

Adverse events were reported in 72.2% of the patients. There were 36 patients (65.5%) reporting adverse events while receiving tiotropium, and 39 patients (73.6%) reporting adverse events while receiving placebo. One patient (in the tiotropium group) died of lung cancer during this trial. Serious adverse events were experienced by 17 patients (15.7%, including screening period), with 7 patients (12.7%) during treatment in the tiotropium group and 8 patients (15.1%) during treatment in the placebo group. The most frequent serious adverse events were lower respiratory events such as exacerbations of COPD and pneumonia. Overall, individual serious adverse events occurred with a low frequency with similar proportions of patients experiencing such events in the two treatment groups.

## DISCUSSION

The purpose of the present study was to determine whether tiotropium enhances exercise training benefits in PR programs in COPD patients. In addition, this study sought to assess the impact of tiotropium on dyspnea and health-related quality of life following PR. Finally, the inclusion of a 12-week postrehabilitation period was used to determine whether benefits of PR are better maintained with tiotropium. Patients receiving tiotropium showed significantly longer exercise endurance time at the conclusion of PR compared to patients in the control group. The tiotropium group maintained improvements in endurance time 12 weeks after conclusion of PR, while there was a slight decline in the placebo-treated group. Improvements in spirometry, dyspnea, and health status were observed with tiotropium, and these improvements were sustained in the postrehabilitation period.

Several reviews and conferences<sup>1-3</sup> have been published giving guidance on PR program components. Although all mention exercise, education, nutrition, and counseling, there is infrequent mention of the importance of improving airways obstruction through the use of bronchodilators. By improving airflow limitation and reducing airways resistance, hyperinflation and gas trapping can be reduced. Reductions in hyperinflation permit tidal volume expansion during exertion such that the ventilatory limitation to the performance of work is reduced.<sup>10</sup> Indeed, O'Donnell and Webb<sup>10</sup> documented that improvements in dyspnea and exercise tolerance correlate better with changes in inspiratory capacity than in FEV<sub>1</sub> in a study of 29 patients who had constant load cycle exercise testing before and after ipratropium bromide, 500 µg.<sup>10</sup>

While the rationale for the use of bronchodilators as a means to lessen dyspnea and improve exercise appears obvious, data from controlled clinical trials are inconsistent. In a review of exercise outcomes in bronchodilator trials, Liesker et al<sup>4</sup> noted that, while approximately two thirds of studies with short-acting β-agonists showed benefits, the most consistently positive effects are observed with anticholinergics. The authors<sup>4</sup> also noted that results of clinical trials with long-acting β-agonists are less clear and that the majority of study findings with theophyllines are negative. In general, previous bronchodilator trials have suffered from small sample sizes, open study designs, and a multitude of different testing procedures (*ie*, 6-min walk distance, 12-min walk test, shuttle walk test, incremental work test, CWR test, treadmill vs cycle) with no accepted standard. The CWR test on cycle ergometer, however, is increasingly being accepted as the most appropriate and responsive instrument.<sup>19</sup>

Tiotropium is a once-daily, inhaled anticholinergic medication that provides benefits through prolonged M<sub>3</sub>-receptor blockade. Clinical trials<sup>6,7,20</sup> have documented improvements in lung function, dyspnea, and health status. In addition, tiotropium has been shown to improve hyperinflation over 24 h and improve CWR endurance on cycle ergometry.<sup>8,9</sup> In terms of aerobic conditioning, there may be an advantage of tiotropium administered during a period of exercise training. Improvements in lung volumes might be sufficient to allow patients to exercise (*ie*, train) longer or with higher intensity, thereby leading to augmented benefits from exercise training programs. Given the 24-h duration of volume reduction, patients may engage in daily activities for longer periods of time, which may also contribute to benefits observed from formal exercise training. Furthermore, benefits gained may have a longer-lasting effect due to the higher exercise tolerance attained.

Several issues arise in prospectively studying PR programs. A minimum program duration is necessary. Green et al<sup>21</sup> demonstrated that 7 weeks of PR provides greater benefits than a 4-week program. The present study incorporated an 8-week program, which is consistent with the recommended duration from the 2003 Global Initiative for Chronic Obstructive Lung Disease update.<sup>22</sup> The exercise program was standardized across centers for lower-limb activity but was not standardized for either upper-limb activity or the educational component. Given that the primary outcome involved lower-limb activity (*ie*, treadmill endurance time), standardization for the lower-limb component can be considered reasonable. Although there are advantages to cycle ergometry, treadmill exercise was chosen as the procedure

to evaluate the primary outcome due to concerns regarding availability of electronically braked and appropriately calibrated equipment across a multicenter trial. While the outcome measurement was simple to standardize across multiple sites, the design resulted in several subjects having prolonged endurance times and, in retrospect, a protocol incorporating treadmill inclination may have been preferable. The duration of follow-up may be considered somewhat brief given the gradual decline in function over time after rehabilitation. Nevertheless, changes could be observed at 12 weeks, with the placebo group showing a slight decline in endurance time and more pronounced deterioration in dyspnea scores and health status.

The changes over the course of the clinical trial bring forward several observations. There were trends toward improvement in exercise tolerance after 4 weeks of tiotropium without instructions for regular exercise; though nonsignificant, this improvement was of similar magnitude to that seen in a larger trial<sup>8</sup> studying the effect of tiotropium on exercise tolerance. Rehabilitation induced substantial improvements in exercise tolerance in both groups, but the tiotropium group obtained significantly greater benefit. This suggests that tiotropium amplified the effectiveness of the rehabilitative exercise program. Both groups maintained exercise tolerance benefits at 12 weeks after rehabilitation, with the tiotropium group continuing to demonstrate better exercise tolerance than the placebo group.

In the present study, dyspnea did not improve significantly until patients participated in PR. The lack of trends toward improvement on day 29 is different from a previous study in which improvements with tiotropium appeared relatively early<sup>9</sup>; however, this may relate to the relatively small sample and the airflow obstruction severity of the population. Prior to rehabilitation, the group was likely sedentary, avoiding activity and hence avoiding dyspnea. It seems plausible that only with training might dyspnea reduction benefits be appreciated in this population.

Another consideration relates to skeletal muscle. Improvement in airflow and static lung volumes may not lead to exercise improvements if there are peripheral muscle abnormalities. Saey et al<sup>5</sup> noted significant improvements in endurance time following nebulized ipratropium in patients with COPD but not in the subgroup with contractile fatigue of the quadriceps muscles.

In the present study, following a standardized training program, TDI focal scores improved in both groups; however, at the end of rehabilitation there was a 1.7-U improvement with tiotropium but a <1-U improvement in the placebo group. The

changes in the tiotropium group are regarded as clinically meaningful.<sup>17,18</sup> Comparatively, improvements with rehabilitation in this study are less than those documented by others<sup>23–25</sup> (occasionally seen as 2- to 3-U improvements). Nevertheless, at the end of the 12-week follow-up, the TDI focal score in the placebo group declined to approximately zero while improvements in the tiotropium group were maintained at 1.75 U. This suggests that rehabilitation benefits are more likely to be maintained if long-acting bronchodilators such as tiotropium are prescribed. Improvements in dyspnea are supported by the observations that patients receiving tiotropium used approximately one dose less of albuterol rescue medication per day when compared to patients receiving on placebo during 25 weeks of treatment. Furthermore, it indicates that improvements in dyspnea were not a result of increased  $\beta$ -agonist use.

The SGRQ total score in the tiotropium group was lower (*ie*, improved) on each test day compared to the placebo group; however, the differences were not statistically significant. Improvement on day 176 exceeded the minimal clinically important difference of 4 U ( $-4.44$ ) and approached statistical significance ( $p = 0.055$ ). In addition, improvement from baseline to trial end in the tiotropium group was 6.06 U, with the largest difference occurring during the period immediately before to immediately after PR. The findings are supportive of benefits observed with the combination of both sustained bronchodilation and exercise.

In summary, combining PR with tiotropium resulted in superior outcomes than utilizing PR alone. With the addition of tiotropium, the efficacy of PR was maintained for at least 3 months, while the control group showed a decline, particularly with regard to the perception of breathlessness. Further studies are necessary to evaluate whether similar results can be observed with other long-acting bronchodilators or if combination long-acting bronchodilators may further augment the effects of PR.

**ACKNOWLEDGMENT:** We acknowledge our co-investigators for their contributions: Dr. S. Brazinsky, Dr. B. Carlin, Dr. J. Fine, Dr. E. Jimenez, Dr. L. Lapidus, Dr. N. MacIntyre, Dr. F. Martinez, Dr. C. Piquette, Dr. S. Stuart, Dr. S. Smith, Dr. J. Hodgkin, Dr. A. Silverthorn, Dr. R. Irwin, Dr. R. Zuwallack, Dr. E. Diamond, Dr. D. Briggs Jr., Dr. G. Criner, and Dr. I. Leech.

## REFERENCES

- 1 British Thoracic Society. Pulmonary rehabilitation. *Thorax* 2001; 56:827–834
- 2 Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based guidelines. ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel. *Chest* 1997; 112:1363–1396
- 3 American Thoracic Society. Pulmonary rehabilitation 1999. *Am J Respir Crit Care Med* 1999; 159:1666–1682
- 4 Liesker JWJ, Wijstra PJ, Ten Hacken NHT, et al. A system-



- atic review of the effects of bronchodilators on exercise capacity in patients with COPD. *Chest* 2002; 121:597–608
- 5 Saey D, Debigare R, LeBlanc P, et al. Contractile leg fatigue after cycle exercise. *Am J Respir Crit Care Med* 2003; 168:425–430
  - 6 Casaburi R, Mahler DA, Jones PW, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002; 19:217–224
  - 7 Vincken W, van Noord JA, Greefhorst APM, et al. Improvement in health status in patients with COPD during one year treatment with tiotropium. *Eur Respir J* 2002; 19:209–216
  - 8 Celli B, ZuWallack R, Wang S, et al. Improvements in resting inspiratory capacity and hyperinflation with tiotropium in COPD with increased static lung volumes. *Chest* 2003; 124:1743–1748
  - 9 O'Donnell DE, Fluge T, Gerken F, et al. Effects of tiotropium on lung hyperinflation, dyspnea and exercise tolerance in COPD. *Eur Respir J* 2004; 23:832–840
  - 10 O'Donnell DE, Webb KA. Exertional breathlessness in patients with chronic airflow limitation. *Am Rev Respir Dis* 1993; 148:1351–1357
  - 11 O'Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160:542–549
  - 12 American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1995; 152:S77–S120
  - 13 Morris JF, Koski A, Temple WP, et al. Fifteen year interval spirometric evaluation of the Oregon predictive equations. *Chest* 1988; 93:123–127
  - 14 American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995; 152:1107–1136
  - 15 Mahler DA, Weinberg DH, Wells CK, et al. Baseline dyspnea index and transitional dyspnea index: the measurement of dyspnea. *Chest* 1984; 85:751–758
  - 16 Jones PW, Quirk FH, Baveystock CM, et al. A self-complete measure of health status for chronic airflow limitation. *Am Rev Respir Dis* 1992; 145:1321–1327
  - 17 Witek TJ Jr, Mahler DA. Minimal important difference of the transition dyspnoea index in a multinational clinical trial. *Eur Respir J* 2003; 21:267–272
  - 18 Witek TJ Jr, Mahler DA. Meaningful effect size and patterns of response of the transition dyspnea index. *J Clin Epidemiol* 2003; 56:248–255
  - 19 ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003; 167:211–277
  - 20 Brusasco V, Hodder R, Miravittles M, et al. Health outcomes following six months treatment with once daily tiotropium compared to twice daily salmeterol in patients with COPD. *Thorax* 2003; 58:399–404
  - 21 Green RH, Singh SJ, Williams J, et al. A randomized controlled trial of four weeks versus seven weeks of pulmonary rehabilitation in chronic obstructive pulmonary disease. *Thorax* 2001; 56:143–145
  - 22 Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: updated 2004. Available at: <http://www.goldcopd.org>. Accessed February 8, 2005
  - 23 O'Donnell DE, McGuire MA, Samis L, et al. The impact of exercise reconditioning on breathlessness in severe chronic airflow limitation. *Am J Respir Crit Care Med* 1995; 152:2005–2013
  - 24 Foglio K, Bianchi L, Bruletti G, et al. Long-term effectiveness of pulmonary rehabilitation in patients with chronic airway obstruction. *Eur Respir J* 1999; 13:125–132
  - 25 Ramirez-Venegas A, Ward JL, Olmstead EM, et al. Effect of exercise training on dyspnea measures in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 1997; 17:103–109