Title

Treadmill Endurance during Treatment with Tiotropium for Two Years in Patients with COPD: A Randomized Trial

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Treadmill Endurance during Treatment with Tiotropium for Two Years in Patients with COPD: A Randomized Trial

A thesis submitted in partial satisfaction

Of the requirements for the degree Master of Science

in Clinical Research

by

Christopher Brian Cooper

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Abstract of the Thesis

Treadmill Endurance during Treatment with Tiotropium for Two Years in Patients with COPD: A Randomized Trial

by

Christopher Brian Cooper

Master of Science in Clinical Research

University of California, Los Angeles, 2013

Professor Robert M Elashoff, Chair

Background: Disease progression in chronic obstructive pulmonary disease (COPD) is associated with decline in exercise performance over time. We assessed whether tiotropium might mitigate this by determining its effect on treadmill endurance time (ET) over 2 years.

Methods: Randomized, double-blind, placebo-controlled trial of tiotropium 18 µg daily in patients with COPD (forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) < 70%; postbronchodilator FEV_1 < 65%). Primary endpoint: ET at 90% of baseline maximum work rate at 96 weeks. Secondary endpoints: ET at other visits, ET by smoking status, spirometry, St George Respiratory Questionnaire (SGRQ).

Results: 519 patients randomized (tiotropium 260, placebo 259), mean 65 years, 77% men, 34% continuing smokers, FEV_1 1.25 L (44% predicted). Significantly more patients discontinued placebo: hazard ratio (95% CI) 0.61 (0.44, 0.83). Baseline ET was 301 s (improvement tiotropium/placebo: 13% overall, $P = 0.009$; 18% at 48 weeks, $P = 0.004$; 13% at 96 weeks,

P = 0.106). In patients with baseline ET between 2-10 minutes (n = 404), improvement at 96 weeks was 19% (*P* = 0.04). Current smokers had higher ET with tiotropium vs placebo (*P* = 0.018). FEV_1/FVC improved with tiotropium (*P* < 0.01). SGRQ total score at 96 weeks improved with tiotropium versus placebo by 4.03 units (*P* = 0.007).

Conclusions: Treadmill ET was numerically greater over 2 years with tiotropium versus placebo. However, 96-week difference was not statistically significant. Spirometry and health status also improved with tiotropium over 2 years, attesting to the benefits of long-acting bronchodilator therapy.

ClinicalTrials.gov: NCT00525512

Committee

The thesis of Christopher Brian Cooper is approved.

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Donald P Tashkin

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Elliot M Landaw

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Robert M Elashoff, Committee Chair

University of California, Los Angeles

2013

Dedication

This thesis is dedicated to my wife Nancy for her tremendous support during the completion of the MS degree work.

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Abbreviations, Symbols, and Definitions

COPD	chronic obstructive pulmonary disease
CWR	constant work rate
Disc	discontinued
ET	endurance time
FEV_1	forced expiratory volume in 1 s
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
IR	incidence rate
MET	metabolic equivalents
MMRM	mixed-model repeated measurement
RR	rate ratio
SGRQ	St George Respiratory Questionnaire
SOC	system organ class
TORCH	Towards a Revolution in COPD Health

List of Appendices and Supplementary Materials

Acknowledgements

The basis of this thesis is an international, multi-center clinical trial that, at the time of filing, is published on-line pending print publication in the journal Chest. The digital identifier of this publication is *Chest* 2013 Apr 4. doi: 10.1378/chest.12-2613. I was the lead investigator in this clinical trial and performed prior experimental work that led to the development of the experimental protocol. The prior publication describing the protocol is *Int J Chron Obstruct Pulmon Dis* 2010; 5: 375-385 and this is included with permission from the journal as Appendix B. I was involved with the statistical analyses and wrote the manuscripts for both papers.

I would like to acknowledge the contributions of several co-authors. These include Bartolome R Celli, MD, José R Jardim, MD and Robert A Wise, MD who were principal investigators at their individual study sites at Brigham and Women's Hospital, Boston, MA, Federal University of Sao Paulo, Sao Paulo, Brazil and Johns Hopkins Asthma and Allergy Center, Baltimore, MD. These colleagues contributed to the edited manuscript. The other co-authors I wish to acknowledge are Daniel Legg, MPH who acted as the liaison between study sites, Junhai Guo, PhD who provided guidance and support with the statistical analysis and Steven Kesten, MD who assisted with editing the manuscript and provided physician oversight of the entire study during its progress. Mr Legg and Dr Guo are employees of Boehringer Ingelheim Pharmaceuticals which provided financial and logistical support to the study sites for the execution of the clinical trial. Dr Kesten was also employed by Boehringer Ingelheim at the time of this study.

Finally, I would like to acknowledge the dedicated work of the staff of the UCLA Exercise Physiology Research Laboratory where the experimental work for this clinical trial was carried out, in particular Marlon Abrazado, MS who was also a co-author on the methodology paper.

Statement of Ethical Approval

Ethical approval for the study described in this thesis was obtained in advance from the Human Subjects in Research Protection Committee (IRB) of the David Geffen School of Medicine, University of California, Los Angeles and maintained for the duration of the studies. Similar ethical approval was also obtained by other participating sites. All subjects gave written informed consent using an approved form. They were able to withdraw themselves from the studies at any time and for any reason. Subjects were withdrawn at the discretion of the investigator if there was any reason why continuing the study would pose any undue risk to the subjects.

Introduction

Chronic obstructive pulmonary disease (COPD) affects about 8% of the world population and currently ranks as the third leading cause of death worldwide. The clinical, social and economic consequences of this disease are enormous. Disease progression in COPD is characterized by progressive airflow limitation, hyperinflation, worsening exertional dyspnea and activity limitation.[1] Long-acting inhaled bronchodilators are recommended for symptomatic patients to improve airflow, reduce hyperinflation, and improve exercise performance.[2] Tiotropium results in sustained bronchodilation as well as improvements in spirometry, lung volumes, dyspnea, COPD exacerbations, and health status. Tiotropium also improved exercise endurance during constant work rate cycle ergometry in two 6-week trials in moderate to very severe COPD (GOLD stages II to IV).[3,4] A 6-month trial documented improved constant-speed treadmill time in patients who also received pulmonary rehabilitation;[5] however, this population had predominantly severe and very severe disease (GOLD stages III and IV). Data are lacking on the sustainability of exercise performance benefits with tiotropium in symptomatic patients not engaged in regular pulmonary rehabilitation. Therefore, a 2-year randomized study was designed to evaluate the effect of tiotropium versus placebo on exercise endurance in patients with stage II to IV COPD. Baseline characteristics and methodology of this study have been reported previously.[6]

Materials and Methods

Study Design

This randomized, placebo-controlled, double-blind, parallel-group study compared 96 weeks of treatment with tiotropium 18 µg via HandiHaler® versus placebo on exercise duration in COPD patients.[6] Patients continued all respiratory medications other than inhaled

anticholinergics. An incremental treadmill protocol was conducted during screening (Visit 1). During a 2-week baseline period (3 weeks for patients taking tiotropium in the 2 weeks prior to Visit 1), a practice constant work rate (CWR) test was performed at 90% of maximum work rate (Visit 2). Patients were randomized 1:1 into the double-blind portion of the study after the baseline CWR test at Visit 3. Patients, investigators and others involved in data analysis remained blinded. Subsequent visits were 8 weeks apart (Visits 4 and 5) for 4 months and then 16 weeks apart (Visits 6 to 10) with exercise tests performed using the same CWR as at baseline. After 96 weeks (Visit 10), patients received open-label tiotropium for 4 weeks. Patients discontinuing the double-blind portion with at least 6-months' double-blind therapy were offered the open-label portion if medically appropriate; these included 22 discontinuing from the tiotropium group and 15 discontinuing from the placebo group.

Study Population

Patients with a COPD diagnosis were enrolled from 60 study sites across 11 countries. They were at least 40 years old, with at least 10 pack-years smoking history, forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) < 0.70, post-bronchodilator $FEV_1 \leq 65\%$ of predicted[7] (Visit 1), plus pre-bronchodilator $FEV_1 \leq 60\%$ (Visit 3) and a Medical Research Council dyspnea score ≥ 2 (1-5 scale). The protocol was approved by respective institutional review boards and all patients provided informed consent.

The exclusion criteria were as follows: history of asthma, frequent exacerbations (at least three in the preceding year), or a recent exacerbation, pulmonary resection, long-term use of supplemental oxygen, or unstable doses of systemic steroids. We excluded subjects with symptomatic or unstable cardiovascular (CV) disease; specifically those with a recent history of a myocardial infarction, hospitalization for congestive heart failure, or unstable or life-threatening dysrhythmia; as well as subjects with electrocardiogram abnormalities during the initial maximal

incremental treadmill testing. We also excluded subjects who had participated in a rehabilitation program within 13 weeks of the first study visit, and those with conditions that would interfere with the conduct of exercise tests (i.e. certain orthopedic, muscular, or neurologic diseases), oxygen desaturation ≤ 85% during the constant work rate (CWR) test prior to randomization.

Exercise Testing

The details of the exercise protocol used in the current study were previously published as shown in Appendix B.[6] The incremental treadmill test incorporated increases in speed and incline to produce a near-linear increase in work rate (adapted from Porszasz et al[8]). The CWR was 90% of maximum from the incremental test. A repeated CWR test was performed (Visit 3) with adjustment to target work rate if the exercise duration was ≤ 2 or ≥ 15 min.

Other Outcome Measures

At each visit after randomization, FEV_1 and FVC were measured before and after administration of study drug according to American Thoracic Society criteria using identical equipment at each site. A modified Borg scale was completed during exercise tests (baseline, every 2 min, peak exercise). At end-exercise, patients gave the reason for stopping (breathing discomfort, leg discomfort, both breathing and leg discomfort, other). The St George Respiratory Questionnaire (SGRQ) was completed at Visits 3 to 11 prior to spirometry and exercise testing. The number of exacerbations and time to first exacerbation were recorded. An exacerbation was defined as an increase or new onset of more than one of the following: cough, sputum, wheezing, dyspnea, chest tightness, with a duration of at least 3 days and requiring treatment with antibiotics, or systemic steroids, or hospital admission.

Data Analysis

The primary efficacy outcome measure was the difference between treatment groups in treadmill endurance time (ET) at 96 weeks. Differences in ET between groups at all time points and the overall treatment effect were compared using the mixed-model repeated measurement (MMRM) with variables of treatment group, center, and visit as fixed effects, patient as random effect, and baseline CWR treadmill time as a covariate. This analytical approach accounts for missing data without need for imputation such as last observation carried forward. Further details of the statistical analysis plan can be reviewed in Appendix A.

Results

A total of 713 patients were screened and 519 patients were randomized (placebo, n = 259; tiotropium, n = 260) (Fig 1). Altogether, 464 patients were analyzed for the primary endpoint. Premature discontinuation was more frequent with placebo (96 versus 66 patients, hazard ratio for tiotropium/placebo [95% CI], 0.61 [0.44, 0.83]; *P* = 0.002) (Fig 2), with a difference in mean treatment exposure of approximately 2 months (506 ± 252 versus 572 ± 209 days). Adverse events leading to discontinuation occurred in 28 tiotropium and 48 placebo-treated patients, the most common being worsening of COPD (8 tiotropium versus 16 placebo).

Baseline Characteristics

Baseline subject characteristics were balanced: mean age 64.6 ± 8.3 years, 77% men, and 34% continuing smokers (Table 1). Mean screening FEV_1 was 1.25 ± 0.42 L (44.3 ± 11.9% predicted). The mean baseline CWR ET was 336 ± 175 and 344 ± 192 s in the tiotropium and placebo groups, respectively (Table 2). More patients in the tiotropium group cited leg discomfort as the reason for stopping the baseline exercise test (13.8% tiotropium versus 7.3% placebo). The baseline ET of patients completing the study was 351 ± 194 s (tiotropium 332 ±

176; placebo 374 ± 211) compared with 316 ± 157 s (tiotropium 349 ± 175; placebo 294 ± 140) for those who dropped out, indicating nonrandom discontinuation.

Exercise Endurance

At 96 weeks (primary endpoint), the ratio (95% CI) of ETs (tiotropium/placebo) was 1.13 (0.97, 1.32), *P* = 0.106. The ratio by MMRM throughout the trial was 1.13 (95% CI: 1.03, 1.24), *P* = 0.009. The difference in ET between treatment groups was approximately 40 s throughout the trial favoring tiotropium versus placebo by 10-18% (Table 3). The adjusted mean ET during the open-label period increased by approximately 10 and 31 s in the tiotropium and placebo groups (*P* = 0.44), respectively. The differences were greater for GOLD stages II and III (n = 398; ratio [95% CI], 1.16 [0.99, 1.36]) versus GOLD stage IV (n = 66; ratio [95% CI], 1.00 [0.65, 1.54]). Larger differences were observed at 96 weeks in patients with baseline ETs in the range of 2-10 min (n = 404; ratio [95% CI], 1.20 [1.01, 1.43]).

An analysis of ET data by smoking status revealed interesting differences. ET data were available in 308 subjects who were ex-smokers (156 receiving tiotropium and 152 receiving placebo), while 156 were current smokers (83 receiving tiotropium and 73 receiving placebo). There was no difference in mean exercise ET between the two groups of ex-smokers receiving tiotropium or placebo (332 s). However, in current smokers receiving tiotropium, the mean exercise ET was 345 versus 244 s for current smokers in the placebo group (*P* = 0.018).

Lung Function

The mean morning pre-dose difference in FEV_1 ranged from 75 ± 27 to 116 ± 22 mL with the difference, favoring tiotropium, being 75 ± 27 mL at 96 weeks (*P* < 0.01 for all differences). For FVC, the difference ranged from 157 ± 50 to 241 ± 58 mL; the difference, favoring tiotropium, was 241 ± 58 mL at 96 weeks (*P* < 0.01 for all differences).

Other Outcomes

Compared with baseline, SGRQ scores improved with tiotropium (Fig3). Group differences at 96 weeks, in favor of tiotropium, were: SGRQ total score, 4.03 units ($P = 0.007$); symptoms, 8.94 units ($P < 0.0001$); activity, 2.33 units ($P = .203$); impact, 3.58 ($P = 0.031$). There were no statistically significant differences for Borg dyspnea score at iso-time (shortest comparable exercise time within a patient) or in the risk for an exacerbation. The locus of symptom limitation at the first post-randomization visit was dominated by breathing discomfort, but shifted towards leg discomfort over time (Figure 4).

Safety

A total of 4919 treadmill exercise tests were performed across 60 centers. Adverse events were reported in 127 (2.6%) tests, with only one serious adverse event (hypotension, which recovered promptly). The most common adverse events associated with treadmill testing were dizziness (n = 16) and musculoskeletal discomfort (n = 11).

The incidence of other adverse events and serious adverse events was balanced between groups (Table 4). A lower proportion of patients experienced an adverse event leading to discontinuation in the tiotropium group (8.5%) compared with the placebo group (15.1%). The most frequently reported serious adverse events were COPD exacerbations and pneumonia. There were no serious anticholinergic effects reported.

There were 12 deaths during the trial, 6 in each group. The most common cause of death was malignant neoplasms (placebo n=4, tiotropium n=2), followed by cardiac disorders (myocardial infarction in one placebo patient, cardiac arrest in one tiotropium patient) and respiratory (lower respiratory tract infection and pneumonia each in one tiotropium patient). For

the two remaining patients, there was a death from alcohol poisoning in the placebo group, while the cause was not specified for one tiotropium patient.

Discussion

This longitudinal study of exercise ET in moderate to very severe COPD found that tiotropium resulted in consistently longer ETs than placebo at 90% of maximum work rate (approximately 40 s) over 2 years. However, the primary endpoint of the difference in ET between treatment groups at 96 weeks was not statistically significant. Lung function (FEV_1 and FVC) was improved along with health status, as measured by the SGRQ.

Sustained bronchodilation with tiotropium reduces static and dynamic hyperinflation, increasing performance at constant load in shorter studies.[3,4,9] Another study[5] of COPD patients enrolled in an 8-week program of pulmonary rehabilitation found that tiotropium increased submaximal treadmill ET at 75% of maximum work rate. This effect was maintained for 12 weeks after the end of the exercise program. Our study expands on these findings by showing a prolonged improvement in exercise endurance with tiotropium over 2 years. Our study protocol cannot account for any possible changes in power duration characteristics over the 2-year period that might have occurred as a result of changed work efficiency.[10-12] However, we believe that our schedule or repeated testing would minimize the influence of such an effect.

We chose treadmill exercise testing because this is representative of the everyday activities in COPD patients,[13] and test performance is probably less restricted by leg fatigue than with cycle ergometry.[6,14] ET is particularly sensitive to changes with inhaled bronchodilator therapy.[15] Our rationale for selecting a constant workload 90% of maximum work rate has been described.[6] This approach avoids the need to stop a test because a patient is insufficiently limited by lower intensity work rates (e.g. 75% of maximum).[5]

The mean improvement in exercise ET over all time points compared with baseline was 46.2 s (15.3%) with tiotropium versus 5.7 s (1.2%) with placebo. Although endurance exercise tests are considered to be appropriate for repeated testing in COPD and sensitive to changes induced by a bronchodilator, the minimum clinically important difference (MCID) for this type of test has not been determined. Puente-Maestu et al[16] analyzed changes in ET at 75% of maximum work rate following 8 weeks of structured rehabilitative exercise in COPD and suggested that > 33% increase was clinically meaningful. Our protocol was different and we would expect patients to have significantly shorter ETs at 90% of maximum work rate and smaller clinically meaningful changes with interventions.[10] The average between-group difference throughout our study was 40 s and the average constant work rate was 60 watts (treadmill speed 1.5 mph, grade of 6%). Based on mean body weight (76.4 kg), the oxygen uptake for this level of exertion would be 0.92 L/min (11.9 mL/kg/min or 3.4 metabolic equivalents [METs]). This is equivalent to walking on level ground at 3.1 mph (83 m/min) which would equate to a difference in 6-min walking distance of 56 m, considered clinically meaningful.[17-19] This extrapolation to walking ability is speculative and indeed one limitation of the study was that we did not define a minimum clinically important difference in ET *a priori*.

The study results may be biased by higher withdrawal of patients in the placebo group, as was also seen in the ISOLDE[20] and TORCH[21] studies. Like Vestbo et al,[21] we found that withdrawal was associated with more frequent exacerbations (annualized rate per patient/year during the first 6 months: 0.63 with placebo vs 0.39 with tiotropium). However, at 96 weeks, the rate was similar (0.52 for placebo and 0.50 for tiotropium). We compared other baseline characteristics of the patients who dropped out versus those of completers. Baseline FEV_1 values were similar (38.3% versus 38.1% of predicted, respectively). However, dropouts had lower baseline exercise ETs compared with completers (316 versus 351 m) and more

breathlessness. Thus, patients completing the study were, on average, healthier than the population at enrolment; differential withdrawal could have reduced the difference between active and placebo groups and underestimated the treatment effect. The tiotropium benefit could be further underestimated without inclusion of post-treatment data.[22]

Exploratory analysis showed that patients with less severe COPD (GOLD stages II and III) experienced greater improvements in treadmill ET than those with severe COPD. In very severe disease, exercise is limited by skeletal muscle dysfunction,[2,23] peripheral vascular disease, and oxyhemoglobin desaturation due to gas exchange failure.[24] Our findings suggest that potential improvement from reconditioning exercise is greater in early disease stages, and timely intervention is important to maintain a higher level of exercise performance. More severe patients do improve with pulmonary rehabilitation, but different mechanisms are probably involved.[25,26] Participation in a formal pulmonary rehabilitation program was discouraged during the study, although five patients (four in the placebo group and one in the tiotropium group) had done so. The use of pulmonary rehabilitation was low and would not have influenced the primary endpoint significantly.

We found that current smokers were more likely to have increased exercise ET with tiotropium compared with placebo, similar to the results of the short, crossover study comparing the effects of indacaterol with placebo on exercise endurance and hyperinflation in COPD patients.[27] The reason for this is unknown.

This study offers the opportunity to evaluate changes in exercise endurance in COPD patients over time. Our data suggest that endurance time increased above a common baseline of 301 m by about 40 meters in the tiotropium-treated group at 8 weeks and thereafter declined by only 7 m over 2 years. However, endurance time also appeared to decline by 7 m over 2

years in the placebo group as well. Unfortunately, these calculations are influenced by differential discontinuation and perhaps should not be taken at face value. Other non-interventional studies have shown declines in aerobic capacity over 5 years[28] and 6-minute walking distance.[29] Although the changes in endurance time over 2 years in our study were small, it is possible that tiotropium manifests an immediate effect of improved exercise endurance but does not influence the effects of disease progression on exercise endurance over time, rather like its effects on pulmonary function (UPLIFT).

The changes in exercise endurance with tiotropium in this study were associated with statistically significant and clinically meaningful improvement in health status, supporting the link between these outcomes.[30] Interestingly, the greatest difference in SGRQ score was seen for symptoms (–8.94; $P < 0.001$), whereas there was no appreciable difference in the activity domain (–2.33; $P = 0.203$). The dyspnea differences are consistent with those previously reported with tiotropium[31] and could help to explain the shift in the locus of symptom limitation. However, the lack of correlation between the exercise ET changes and the activity score of the SGRQ as well as Borg scores for dyspnea and leg fatigue challenges this interpretation. This may be because the SGRQ is unable to capture true activity levels accurately, or because patients did not change habitual physical activity.

The submaximal treadmill endurance test was successfully implemented at all sites and 4,919 tests were very well tolerated. Adverse events such as dizziness and musculoskeletal discomfort were reported in 127 tests (2.6%) with only one serious adverse event (hypotension which resolved promptly).

In summary, we utilized a novel treadmill protocol to demonstrate sustained improvements in exercise ET with tiotropium in patients with moderate to very severe COPD

over 2 years. The treadmill protocol was successfully implemented and well tolerated. Improvements in exercise performance were associated with improved lung function and health status. The fact that ET did not deteriorate over 2 years in those randomized to tiotropium and that pulmonary function and perceived health status actually improved, testifies to the sustained beneficial effects of long acting bronchodilators.

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Figures

Figure 1: Disposition of patients during the study. COPD = chronic obstructive pulmonary disease; ET = endurance time.

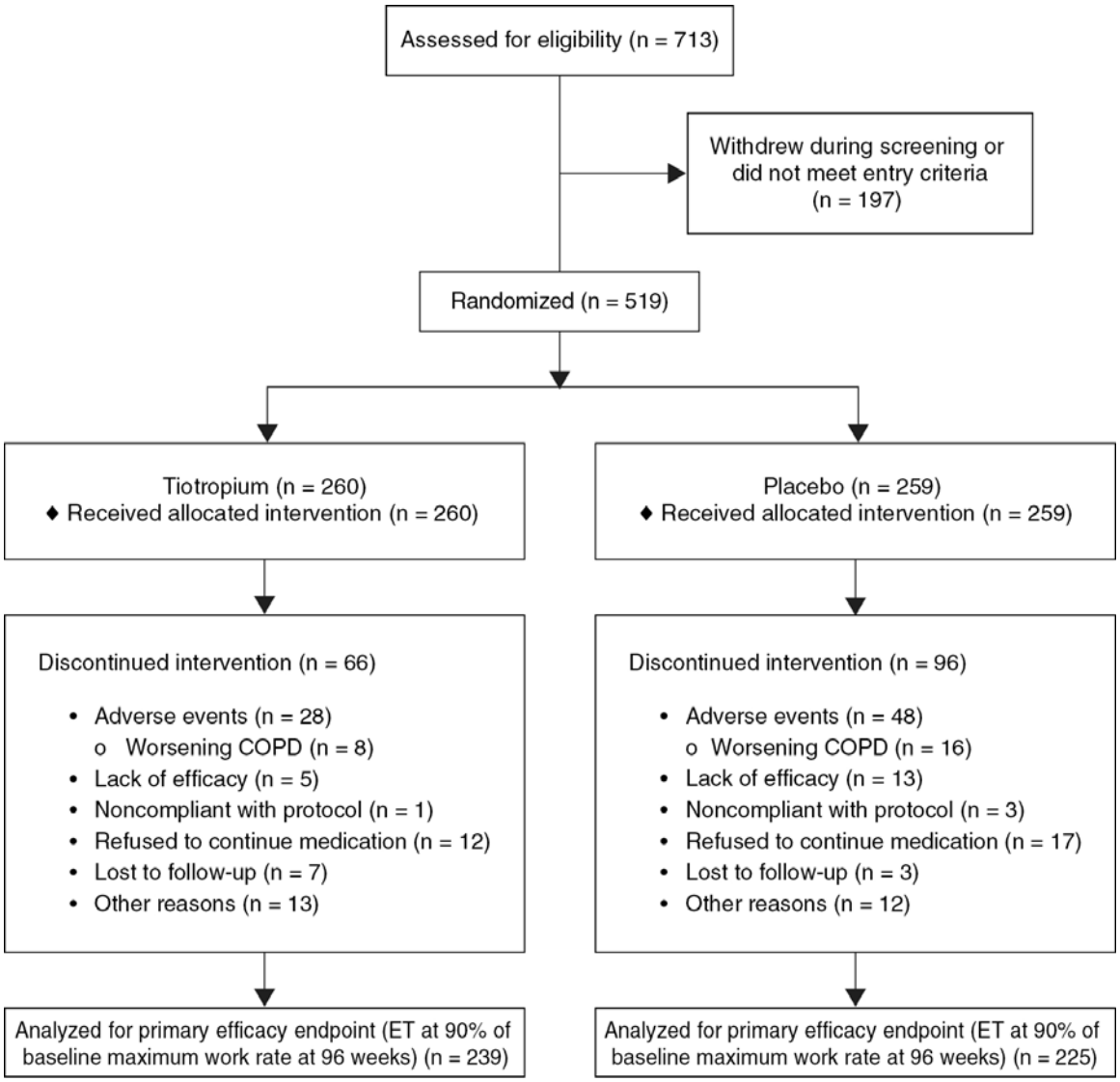
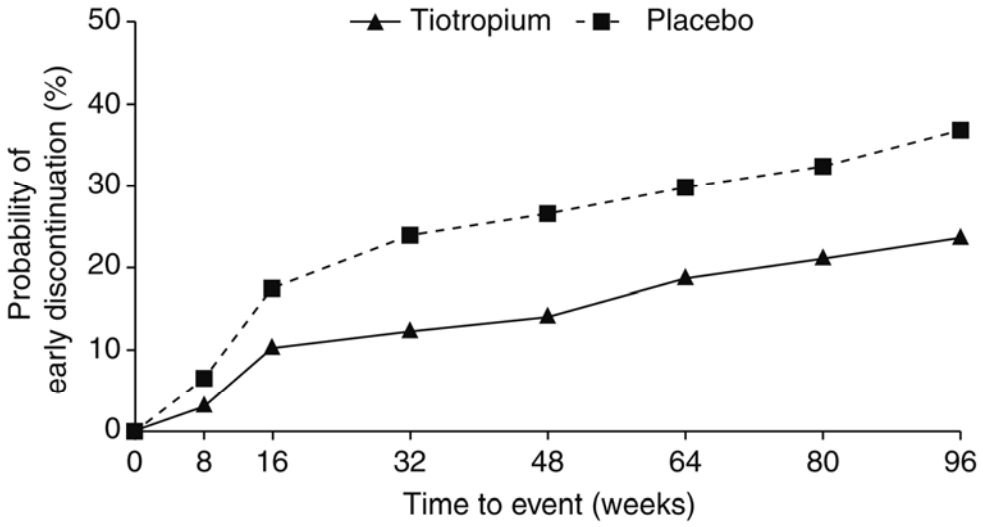


Figure 2: Kaplan-Meier estimates of the probability of early discontinuation in the tiotropium and placebo groups.



No. patients at risk:

Tiotropium	260	252	233	229	223	211	204	141
Placebo	259	243	214	199	191	182	175	108

The Kaplan-Meier method considers Week 96 as exactly 672 days. However, some patients completed the Week 96 visit slightly before 672 days and were not considered part of the “at-risk” group at this time point. This explains the differences in patient numbers in Figures 1 and 2.

Figure 3: Change from baseline to 96 weeks in the SGRQ total score and domains in the tiotropium and placebo groups. SGRQ = St George Respiratory Questionnaire.

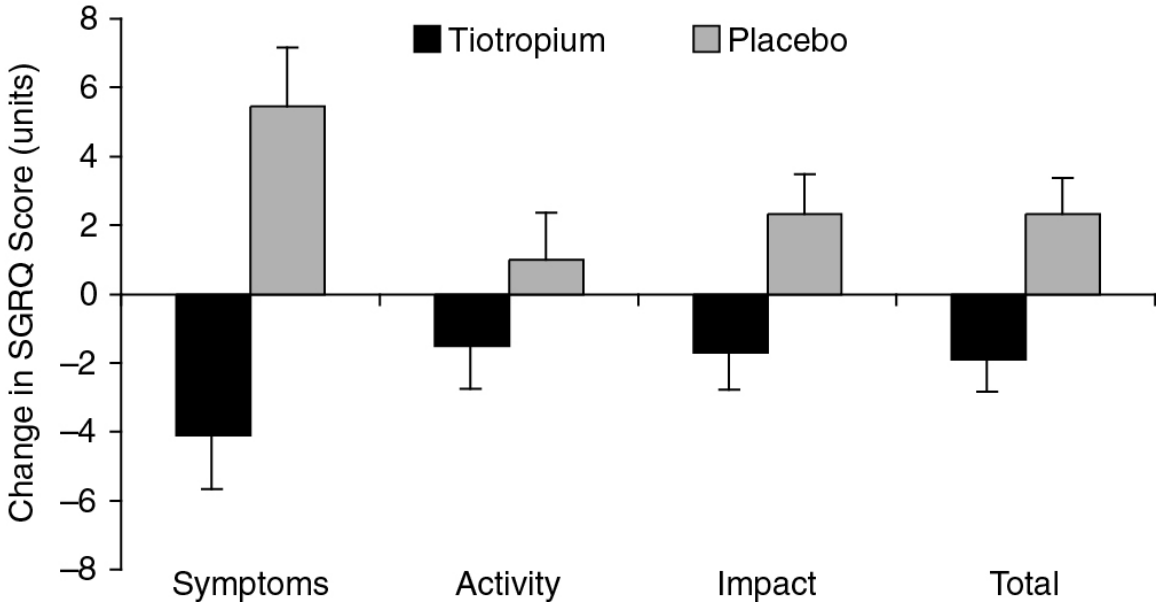
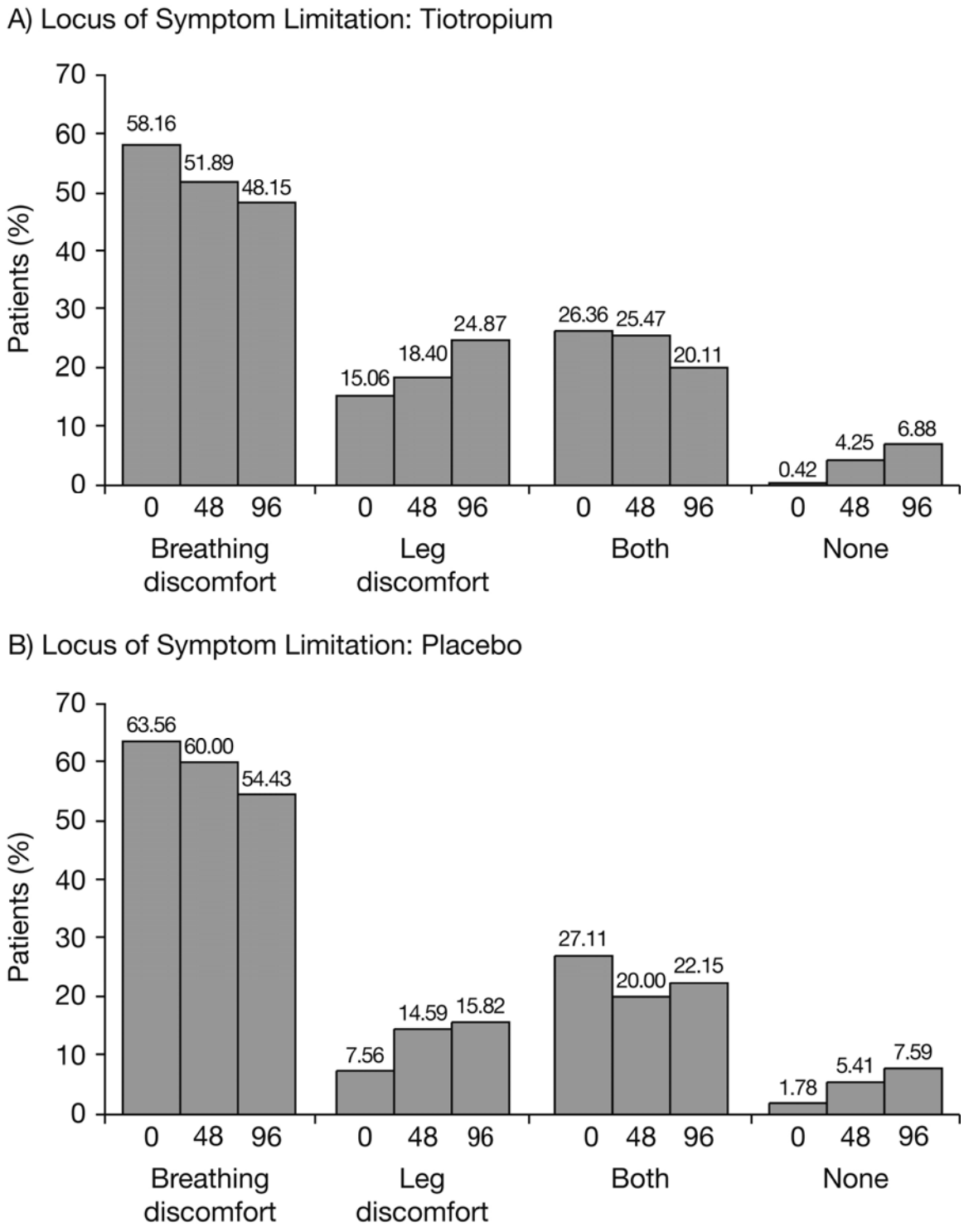


Figure 4: Locus of symptom limitation throughout the trial in the tiotropium (A) and placebo (B) groups.



Tables

Table 1: Baseline Characteristics of Patients in the Tiotropium and Placebo Treatment

Characteristic	Tiotropium(n = 260)	Placebo(n = 259)
Male, %	76.5	78.0
Age, y[a]	64.7 ± 8.2	64.5 ± 8.5
Body mass index[a]	26.0 ± 4.4	26.8 ± 4.2
Smoking status		
Current smoker, %	35.0	32.8
Smoking history, pack-years[a]	52.2 ± 29.0	51.0 ± 26.3
Postalbuterol spirometry[a]		
FEV_1, L	1.25 ± 0.41	1.25 ± 0.42
FEV_1, % predicted	44.5 ± 11.7	44.2 ± 12.1
FVC, L	2.75 ± 0.84	2.71 ± 0.80
FEV_1/FVC, %	46.7 ± 11.4	46.7 ± 11.1
GOLD Stage II/III/IV, %	37/50/13	35/51/14
SGRQ total score, units[a]	43.2 ± 17.0	41.8 ± 17.4
Respiratory medications, %		
Short-acting inhaled anticholinergics[b]	26.5	25.9
Long-acting inhaled anticholinergics	21.5	22.8
Short-acting inhaled β_2-agonists[b]	47.3	43.2
Long-acting inhaled β_2-agonists[b]	58.1	60.2.
ICS[†b]	60.8	59.1
Oral steroids	3.1	3.1
Theophylline compounds	11.9	8.5
Leukotriene receptor antagonists	1.2	0

FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroids; SGRQ = St George Respiratory Questionnaire

[a]Mean ± SD

[b]Used alone or as a fixed combination

Table 2: Baseline Constant Work Treadmill Test in the Tiotropium and Placebo Groups

	Tiotropium (n = 260)	Placebo (n = 259)
Locus of symptom limitation, %		
Leg discomfort	13.8	7.3
Breathing discomfort	60.4	63.7
Both	25.4	27.0
None	0.4	1.9
Baseline endurance time, s		
Mean, SD	335.9 (175.1)	344.2 (191.6)
Median	290.0	290.0
Max	900	896
Min	42	46
Workload, watts		
Mean	58.0 (31.9)	63.4 (33.2)
Median	53.9	60.0
Maximum	146.1	177.1
Minimum	1.8	3.4

Table 3: Endurance Time during Constant Work Treadmill Exercise in the Tiotropium and Placebo Groups

	Tiotropium (n = 260)		Placebo (n = 259)		Tiotropium/Placebo	*P*-value
	Time (s)	Disc[a]	Time (s)	Disc[a]	Ratio (95% CI)	
Baseline[b]	305.0	–	297.7	–		
Week 8	343.0	8	304.9	16	1.12 (1.03, 1.23)	0.008
Week 16	338.6	27	308.6	45	1.10 (1.00, 1.21)	0.060
Week 32	358.7	31	311.8	60	1.15 (1.03, 1.29)	0.013
Week 48	365.7	37	309.8	68	1.18 (1.05, 1.32)	0.004
Week 64	349.0	49	313.4	77	1.11 (0.98, 1.26)	0.095
Week 80	340.1	56	302.8	84	1.12 (0.98, 1.28)	0.090
Week 96	336.6	60	297.1	94	1.13 (0.97, 1.32)	0.106
Overall[b]	347.5	60	306.9	94	1.13 (1.03, 1.24)	0.009
Open label	358.8	82	337.3	109	1.06 (0.91, 1.25)	0.444

ETs shown are geometric mean values in s; Disc = discontinued; ET = endurance time

[a]Cumulative number of discontinued patients

[b]Overall baseline geometric mean across groups=301.2

[c]Average over the blinded period of the trial

Table 4: Adverse Events

	Tiotropium(n = 260)		Placebo(n = 259)		
Any adverse event, n(%)	195 (75.0)		193 (74.5)		
Adverse event leading to treatment discontinuation, n (%)	22 (8.5)		39 (15.1)		
Serious adverse event, n (%)	63 (24.2)		59 (22.8)		
Fatal adverse event, n (%)	6 (2.3)		6 (2.3)		
Serious adverse events[b,c]	**n (%)**	**IR[d]**	**n (%)**	**IR[d]**	**RR (95% CI)[e]**
System organ class:					
Total with serious adverse events	63 (24.2)	17.42	59 (22.8)	18.21	1.0 (0.67, 1.36)
Infections	18 (6.9)	4.55	16 (6.2)	4.59	1.0 (0.50, 1.94)
Neoplasms	7 (2.7)	1.74	15 (5.8)	4.22	0.4 (0.17, 1.01)
Respiratory disorders	24 (9.2)	6.19	21 (8.1)	6.05	1.0 (0.57, 1.84)
Preferred term:					
Pneumonia	11 (4.2)	2.75	12 (4.6)	3.4	0.8 (0.36, 1.83)
COPD	21 (8.1)	5.37	15 (5.8)	4.29	1.3 (0.65, 2.43)

COPD = chronic obstructive pulmonary disease; IR = incidence rate; RR, rate ratio; SOC = system organ class.

[a]Treated set. Events occurring during blinded treatment phase

[b]SOC and preferred terms according to the Medical Dictionary for Regulatory Authorities. Cardiac disorders occurred in 2.7% of patients in both treatment and placebo groups

[c]Serious adverse events occurring with incidence > 3% in either treatment group: Primary SOC and preferred term

[d]IR = per 100 patient years

[e]Tiotropium versus placebo

Appendix A. Statistical Analysis Plan

Statistical Design—Model

The primary efficacy end point was the difference between treatment groups in exercise duration during CWR treadmill exercise after 96 weeks. A mixed-effects model was used for the analyses of efficacy end points. The absolute log-transformed values adjusting for baseline were analyzed using a restricted maximum likelihood-based repeated measures approach. Analyses included the fixed, categorical effects of treatment, investigative site, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction. An unstructured (co)variance structure was used to model the within-patient errors. If convergence was not achieved, the following structures were planned to be tested: compound symmetric and autoregressive. The (co)variance structure converging to the best fit, as determined by Akaike's information criterion, was used as the primary analysis. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Significance tests were based on least-squares means using a two-sided test, $\alpha = 0.05$ (two-sided 95% CIs). Analyses were implemented using SAS software version 9.2 (SAS Institute; Cary, North Carolina). The primary treatment comparisons were the contrast between treatments at the week 96 visit.

Null and Alternative Hypotheses

The null hypothesis for the primary end point was:

- Mean exercise duration from CWR treadmill testing at week 96 for the tiotropium group ≤ mean exercise duration at week 96 for the placebo group.

The alternative hypothesis for the primary end point was:

- Mean exercise duration from CWR treadmill testing at week 96 for the tiotropium group > mean exercise duration at week 96 for the placebo group.

Planned Analyses

All randomized patients with baseline and any post-dosing exercise duration data were included in the full analysis set (FAS). An additional set was defined, using all patients treated for ≥ 48 weeks.

All patients who were randomized and treated were included in the safety analysis. All individual data were listed. Adherence to the protocol (eg, inclusion/exclusion criteria, times of measurement, completeness and consistency of data) was checked using the data recorded. Standard statistical parameters (number of non-missing values, mean, standard deviation, median, quartiles, minimum, and maximum) or frequency tables were calculated where appropriate. In general, these parameters or frequencies were calculated separately for each treatment, but jointly for all study centers.

Primary Analyses

The primary efficacy end point was the exercise duration from CWR treadmill testing at week 96. Exercise duration between tiotropium and placebo groups at week 96 was compared using the mixed-effects model with terms of treatment, center, and visit as fixed effects, patient as random effect, and baseline as a covariate. Baseline was defined as CWR treadmill time measured at the randomization visit just prior to first treatment administration. The ET was log-transformed in the analysis. The primary analysis was performed on the FAS.

Secondary Analyses

The mixed-effects model was used for all other secondary efficacy end points at each time point as well as for the other time points for exercise duration. Baseline was defined as the value measured at the randomization visit just prior to first treatment administration.

No correction for multiple hypotheses testing was made. All secondary analyses were exploratory and the results were to be interpreted in a descriptive manner. All tests were two-sided; unless otherwise stated, $\alpha = 0.05$.

The secondary end points were:

1. Forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) measurements at each time point.
2. St. George Respiratory Questionnaire (SGRQ). The total SGRQ score as well as the three component (impacts, activities, and symptoms) scores were analyzed as described above.
3. Modified Borg scale. Descriptive statistics were collated.
4. Number (%) of patients with at least one chronic obstructive pulmonary disease (COPD) exacerbation and time to first exacerbation. For the analysis of number (%) of patients with at least one COPD exacerbation, the Cochran-Mantel-Haenszel test was used, with center as a stratum. The risk ratios and corresponding 95% CIs were provided. The time to first exacerbation was compared across treatment groups using stratified Cox regression with center as a stratum. Cox regression provides relative risk (hazard ratio) and corresponding 95% CI, and therefore was preferred to simple log-rank test. The number of exacerbations was compared across treatment groups using negative

binomial regression with (natural) logarithm of extent of exposure as offset and correction for overdispersion.

5. Physician and Patient Global Evaluation. Descriptive statistics only were used to describe these end points.
6. The CWR test duration at all visits other than week 96 was analyzed in the same way as the primary end point.

Safety Analyses

All randomized and treated patients were included in the safety analysis. In general, the safety analysis was descriptive in nature and was based on Boehringer Ingelheim standards. No hypothesis testing was planned prospectively.

Statistical analysis and reporting of adverse events concentrated on “treatment-emergent” adverse events. To this end, all adverse events occurring between the first drug intake and until 30 days after last drug intake were considered “treatment-emergent.” Adverse events that started before first drug intake and deteriorated under treatment were also considered as “treatment-emergent.” Adverse events not considered “treatment-emergent” were listed, but not included in frequency tables. Patients treated for 96 weeks with tiotropium or placebo were compared.

Frequency, severity, and causal relationship of adverse events were tabulated by system organ class and preferred term after coding to the current version of the Medical Dictionary for Regulatory Activities.

Handling of Missing Data

For missing exercise durations or questionnaire data, if the missing value was caused by early discontinuation due to worsening of COPD disease, it was replaced by the least favorable observation from the prior visits excluding baseline. The last visit carried forward was used to replace all other missing visits. Baseline values were not carried forward.

FEV_1 and FVC were imputed using the pre-study drug values on the same test day. If the pre-study drug FEV_1 and FVC were missing and the post-study drug FEV_1 and FVC were available, the missing pre-study drug FEV_1 and FVC was replaced using the pre-study drug values from the prior visits. This included the baseline value.

For missing both pre- and post-study drug FEV_1 and FVC (the entire visit missing), if the missing was caused by intake of rescue medication or early discontinuation due to worsening of COPD disease, the missing value was replaced by the least favorable observation from the prior visits excluding baseline. The last visit carried forward was used to replace all other missing visits.

For the analysis of quality of life (SGRQ), missing responses to individual questionnaire items were imputed by the rules specified by the developer (Dr. P. Jones) to be consistent with the methods used in validating these questionnaires.

For all other end points, the value of the last visit was carried forward to replace missing values. Baseline values were not carried forward.

Determination of Sample Size

Based on the previous tiotropium exercise trials using CWR cycle ergometry,[1,2] the standard deviation of exercise duration was assumed to be around 300 s. It can be assumed that the variability with the treadmill was similar, and the effect size at least as large as with

cycle exercise. The trials suggest that the difference between tiotropium and placebo for the CWR test can be estimated to be 105 s at 75% of maximum work rate on a cycle ergometer. The assumed effect size for EXercise endurance And COPD Treated with Tiotropium (EXACTT) was based on these data and supported by a study by Pepin, in which an approximately 40-s greater response to ipratropium was seen with a walking test compared with a cycle test.[3] Whereas these were 6-week trials, a similar size of effect was expected after 96 and 100 weeks' treatment. With 173 patients in each treatment group, the trial would have 90% power to detect a 105-s difference in CWR treadmill time at a 0.025 significance level. As the primary end point might not be normally distributed, a sample size of 184 in each group was needed using a Wilcoxon (Mann-Whitney) rank-sum test. To ensure enough power for analyzing the primary end point in the set of patients treated for ≥ 48 weeks and assuming a discontinuation rate of ~ 20%, the sample size was set at 230 patients per group.

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Appendix B. Previously Published Methodology

International Journal of Chronic Obstructive Pulmonary Disease

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ORIGINAL RESEARCH

Development and implementation of treadmill exercise testing protocols in COPD

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Background: Because treadmill exercise testing is more representative of daily activity than cycle testing, we developed treadmill protocols to be used in various clinical settings as part of a two-year, multicenter, chronic obstructive pulmonary disease (COPD) trial evaluating the effect of tiotropium on exercise.

Methods: We enrolled 519 COPD patients aged 64.6 ± 8.3 years with a postbronchodilator forced expiratory volume in one second (FEV_1) of 1.25 ± 0.42 L, 44.3% ± 11.9% predicted. The patients performed symptom-limited treadmill tests where work rate ($\dot{W}$) was increased linearly using speed and grade adjustments every minute. On two subsequent visits, they performed constant $\dot{W}$ tests to exhaustion at 90% of maximum $\dot{W}$ from the incremental test.

Results: Mean incremental test duration was 522 ± 172 seconds (range 20–890), maximum work rate 66 ± 34 watts. For the first and second constant $\dot{W}$ tests, both at 61 ± 33 watts, mean endurance times were 317 ± 61 seconds and 341 ± 184 seconds, respectively. The mean of two tests had an intraclass correlation coefficient of 0.85 ($P < 0.001$). During the second constant $\dot{W}$ test, 88.2% of subjects stopped exercise because of breathing discomfort; 87.1% for Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stage II, 88.5% for GOLD Stage III, and 90.2% for GOLD Stage IV.

Conclusion: The symptom-limited incremental and constant work treadmill protocol was well tolerated and appeared to be representative of the physiologic limitations of COPD.

Keywords: chronic obstructive pulmonary disease, exercise testing, endurance, tiotropium

Introduction

Patients with chronic obstructive pulmonary disease (COPD) have limited exercise capacity due to complex pathophysiology, and evaluation of exercise performance at all stages of COPD is important if we are to understand disease progression better.[1] One approach would be to measure aerobic capacity ($\dot{V}O_2$ max) periodically. However, there has been limited development of maximal incremental protocols specific for patients with COPD. Furthermore, maximal incremental exercise testing is effort-dependent and not representative of everyday activity. Functional exercise tests, such as six-minute walking distance, vary significantly in how they are performed from center to center, despite guidelines.[2,3] Six-minute walking distance may not reflect maximal ability, because it is self-paced and also may not be sensitive to pharmacologic intervention.[3,4] Oga et al[5] reported that among the different types of exercise test, the submaximal constant work rate endurance test was the most sensitive in detecting improvements after bronchodilator therapy. Other investigators have successfully used this type of test to elucidate physiologic impairments in COPD.[6,7]

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A similar type of test, the endurance shuttle walk, was tested at approximately 75%, 85%, and 95% of maximum intensity and found to be both repeatable and sensitive to therapeutic changes.[8]

Cycle ergometry testing has traditionally been used to assess the efficacy of treatments. However, walking is less likely to induce quadriceps fatigue and is more often limited by breathlessness compared with cycling,[9] and therefore may better reflect the impact of pharmacologically induced changes in lung function on exercise tolerance.[10,11] Computer control enables electronically braked cycle exercise to be implemented with a continuous linear increase in work rate, but now linear treadmill protocols have also been described.[12] Furthermore, it has been shown that treadmill versus cycle exercise elicits higher levels of ventilation and is more likely to be associated with oxyhemoglobin desaturation.[13] Thus, exercise testing using a treadmill may better reflect the activities of daily living than cycle ergometry.

In order to overcome some of the problems associated with cycle ergometry, we developed symptom-limited, incremental, and constant work rate ($\dot{W}$) protocols using a treadmill to measure exercise performance in patients with COPD. The maximal incremental treadmill protocol was designed with an approximate linear increase in work rate with respect to time. We then implemented duplicate constant load exercise tests at 80% and 90% of the maximum work rate achieved in the preceding incremental test. The repeatability of these constant load exercise tests was evaluated in a small pilot study. The objective was to standardize a treadmill protocol that would be acceptable to COPD patients with a wide range of disease severity and would be suitable for use in diverse clinical settings, including an international, multicenter, interventional clinical trial called EXACTT (a randomized, double-blind, placebo-controlled two-year trial to examine the changes in exercise endurance and COPD treated with tiotropium once daily).

Tiotropium has been documented to improve constant work cycle exercise duration in two six-week trials and to improve constant speed treadmill exercise in a six-month trial in a pulmonary rehabilitation setting.[6,7,14] With the EXACTT trial, we are seeking to evaluate whether improvements in exercise duration with tiotropium in a relatively broad selection of COPD patients could be sustained over two years using a COPD-specific novel constant work treadmill exercise protocol.

Methods

Exercise protocol development

The maximal incremental treadmill exercise protocol was developed by increasing the work rate at one-minute intervals, with the target being symptom limitation in approximately 8–12 minutes.[15] In order to achieve a near-linear increase in work rate, a calculated sequence of speed and grade adjustments was developed from basic principles.[16,17] We incorporated a more gradual work rate incrementation early in the test specifically designed for impaired subjects. The speed and grade adjustments, shown in Table 1, were standardized across subjects to maintain the linearity of the incremental protocol, but the actual work rates varied according to body weight. The work rates shown as an example in Table 1 assume a subject weighing 70 kg.

A small feasibility study was performed with 12 COPD patients at the UCLA Exercise Physiology Research Laboratory. Each subject attended at the same time of day on three occasions. On the first visit, they performed an incremental treadmill test using the adjustments of speed and grade as shown in Table 1. On two subsequent visits, they performed constant $\dot{W}$ tests to exhaustion either at 80%

Table 1 Speed and grade adjustments used in incremental treadmill exercise

Time (min)*	Speed (mph)	Speed (m/sec)	Grade (%)	Work (watts)**
W1	1	0.45	0	"0"
W2	1	0.45	0	"0"
W3	1	0.45	0	"0"
E0	1	0.45	1	3
E1	1	0.45	2	6
E2	1	0.45	3	9
E3	1	0.45	5	15
E4	1.5	0.67	5	23
E5	1.5	0.67	7	32
E6	2	0.89	7	43
E7	2	0.89	8	49
E8	2.5	1.12	8	61
E9	2.5	1.12	9	69
E10	3	1.34	9	83
E11	3.5	1.56	9	96
E12	4	1.79	9	110
E13	4.5	2.01	9	124
E14	5	2.24	9	138
R1	1	0.45	0	"0"
R2	1	0.45	0	"0"

Notes: *W1–W3 represents a three-minute warm-up period. E0–E14 represents a 15-minute incremental exercise phase. R1–R2 represents a two-minute cool-down period; **Work rate is calculated based on treadmill speed and grade for a subject weighing 70 kg. "0" is notionally "zero watts" for the warm-up and cool-down phases.

or 90% of maximum $\dot{W}$ determined from the incremental test. During each test, minute ventilation ($\dot{V}_E$) and heart rate (f_c) were continuously monitored. Oxygen uptake ($\dot{V}O_2$) and carbon dioxide output ($\dot{V}CO_2$) were derived from exhaled gas analysis using a metabolic measurement system (Vmax; VIASYS Healthcare, Yorba Linda, CA). This system was calibrated using standard routines prior to each exercise test. Subjects received standard encouragement during the tests using a novel instrument (Figure 1). At the end of the tests, rating of perceived exertion was obtained using the original Borg RPE scale,[18] and breathlessness was evaluated using a 100 mm visual analog scale.

For the purpose of endurance testing, a fixed percentage of the maximum work rate was applied as a constant work rate, and time to exhaustion was measured as the outcome of interest. The standard approach to constant work rate cycle ergometry has been to initiate the test at 75% or 80% maximum work rate.[6,7] In the feasibility study, we therefore used 80% as a starting point for constant work treadmill testing. However, it became apparent that 80% of maximal work during a treadmill test resulted in a prolonged exercise time beyond the target range in a number of patients. Hence the constant work was reset to 90% of maximum work. The chosen constant work rate (eg, 80% or 90% of maximum) is easily derived by proportional reduction of the final speed from the incremental test, leaving the final grade unchanged. For example, if one desired 90% of maximum work rate in a subject whose maximal incremental treadmill settings were a speed of 1.34 m/sec (3 mph) and grade of 9%, then the appropriate settings would be a speed of 1.21 m/sec (2.7 mph), ie, 90% of maximum speed, and the same grade of 9%.

EXACTT protocol

The maximal incremental and 90% constant work rate treadmill exercise testing protocols described above were incorporated into the design of the EXACTT study, which aimed to examine the effects of tiotropium on exercise endurance in COPD patients over two years. The goal of EXACTT was to recruit over 500 subjects and this has been achieved using 61 sites in 11 different countries. EXACTT included men and women, aged 40–80 years, with a clinical diagnosis of COPD, ratio of the forced expiratory volume in

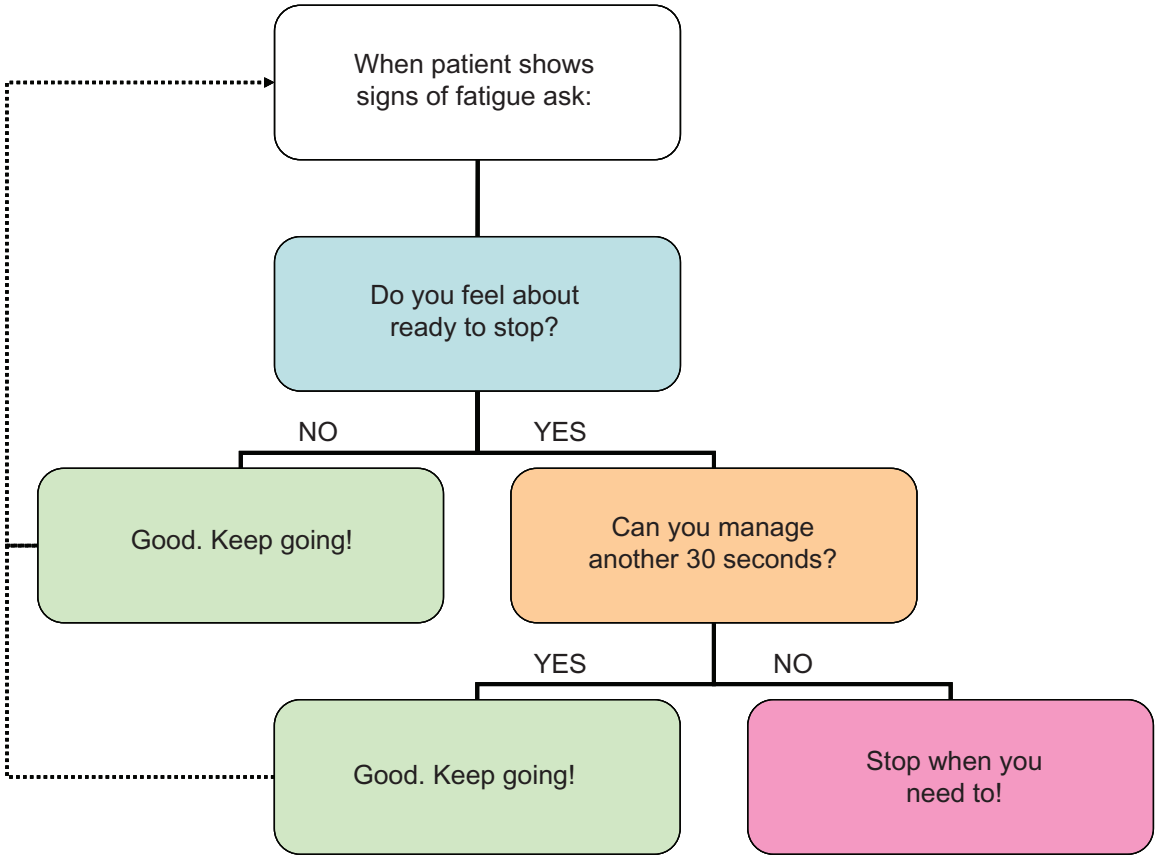

Figure 1 EXACTT instrument used to optimize maximal effort during incremental and endurance exercise tests.

the first one second to the forced vital capacity of the lungs (FEV_1/FVC) < 70% and a smoking history greater than 10 pack-years. Spirometry was performed in accordance with American Thoracic Society/European Respiratory Society standards.[19,20] Measures of FEV_1 and FVC were compared with reference values from the Third National Health and Nutrition Examination Survey (NHANES III).[21] Patients with pulmonary disease other than COPD, including asthma, clinically significant bronchiectasis, interstitial lung disease, pleural disease, and previous history of thoracic surgery, such as lung resection or lung volume reduction surgery, were excluded. Patients requiring supplemental oxygen at rest or during exercise to prevent desaturation (<85%) were also excluded. Patients with disorders that could impact their ability to participate in exercise testing, such as obesity (body mass index >30 kg/m^2), and cardiovascular or musculoskeletal disease were excluded. Patients were allowed to continue taking other prescribed medications, including long-acting β-sympathomimetic bronchodilators and inhaled corticosteroids, with the same timing and dosage throughout the study. The following respiratory medications were washed out prior to each clinic visit for exercise testing: short-acting theophylline (24 hours), long-acting theophylline (48 hours), inhaled corticosteroids (12 hours), long-acting inhaled beta-agonists (24 hours), combination inhaled corticosteroid-long-acting beta-agonists (24 hours), and short-acting beta-agonists (eight hours). At the beginning of the EXACTT study, subjects had treadmill exercise testing on three visits. At visit 1, they performed the incremental protocol. At visits 2 and 3, constant work rate protocols were performed at 90% of the initial maximum work rate. Visits 1, 2, and 3 were separated by seven or 14 days, depending on tiotropium use at consent as specified in the protocol. The exercise tests on visits 2 and 3 were separated by a minimum of three days. The only data captured from these tests were for endurance time. Gas exchange measurements were not included in the protocol for the EXACTT study. Subjects were permitted to use the rails for balance but were requested not to hold onto the rails. Standardization was achieved through a central training and an interactive DVD/web-based training system. Successful completion of training was required for all study staff conducting exercise testing. Treadmills were calibrated annually according to the procedures described in the National Aeronautics and Space Administration manual entitled "Procedures for Exercise Laboratories" (http://ston.jsc.nasa.gov/collections/TRS/_techrep/TM-1998-104826.pdf). After baseline testing, the subjects are being followed for two years with three-monthly measurements of constant work rate treadmill exercise endurance time at 90% of the initial maximum work rate. This paper presents data from the pilot feasibility study, as well as the baseline characteristics, before randomization, of the subjects recruited into the EXACTT study.

Statistical analysis

Data were analyzed using the SAS software package (version 9.2; SAS Institute, Cary, NC). The subject characteristics, including endurance times for the incremental tests (visit 1) and paired constant $\dot{W}$ tests (visits 2 and 3), are presented as mean values with standard deviations (SD). The reproducibility of exercise tests was assessed by computing intraclass correlation coefficient for the mean of two tests.[22] Intraclass correlation scores are based on Shrout and Fleiss and present the two-way mixed average.[23]

Based on two previous tiotropium exercise trials using constant work rate cycle ergometry, the SD of exercise duration was assumed to be around 300 seconds.[6,7] The difference between tiotropium and placebo for the constant work rate test was approximately 105 seconds. A total of 173 patients in each group would provide 90% power to detect a 105-second difference in exercise duration at the 0.025 significance level. Given that the primary endpoint might not be normally distributed, a sample size of 184 in each group would be needed using a Wilcoxon (Mann–Whitney) rank-sum test. To ensure sufficient power for analyzing the primary endpoint in the set of patients treated for at least 48 weeks and assuming a discontinuation rate of about 20%, the sample size was set at 230 patients per group.

Results

Feasibility study

For the feasibility study, we recruited 12 clinically stable COPD patients (nine men, three women), mean age 69.5 ± 7.8 years, FEV_1 1.44 ± 0.38 L (33%–70% of reference). The important parameters of their exercise tests are summarized in Table 2. The mean incremental test duration approximated 10 minutes. Plots of $\dot{V}O_2$ versus time indicated linear increases in $\dot{V}O_2$ during incremental testing, with a mean gradient of $\dot{V}O_2$ versus $\dot{W}$ of 10.7 ± 4.3 mL/min/watt, indicating work efficiency similar to that of cycle ergometry.[24] Seven patients demonstrated a $\dot{V}O_2$ plateau at the end of the test, confirming maximal effort. A metabolic threshold ($\dot{V}O_2\theta$), above which lactic acid was deduced to have accumulated, was identified in 11/12 subjects by noninvasive gas exchange measurements using the method of Beaver et al[25] in conjunction with analysis of the ventilatory equivalents

Table 2 Physiologic data from the pilot feasibility study

Parameter	Maximal incremental	Constant 80% $\dot{W}$max		Constant 90% $\dot{W}$max	
	Visit 1	Visit 2	Visit 3	Visit 2	Visit 3
Time (seconds)	575 (170)	599 (221)	713 (267)	308 (180)	388 (235)
Speed (mph)	2.7 (1.0)	2.2 (0.7)	2.2 (0.7)	2.6 (0.8)	2.6 (0.8)
Grade (%)	8.2 (1.6)	8.4 (1.4)	8.4 (1.4)	8.1 (1.5)	8.1 (1.5)
$\dot{W}$ (watts)	80 (38)	67 (29)	68 (30)	77 (34)	77 (34)
$\dot{V}O_2$ max (L/min)	1.34 (0.36)	1.28 (0.35)	1.26 (0.37)	1.41 (0.39)	1.40 (0.43)
$\dot{V}O_2$ max (% reference)	86 (23)	81 (22)	79 (21)	96 (29)	95 (26)
$\dot{V}O_2$ max (mL/kg/min)	16.7 (4.2)	15.2 (2.9)	14.9 (2.9)	17.6 (4.3)	17.3 (3.9)
$\dot{V}O_2/\dot{W}$ (mL/min/watt)	10.7 (4.3)	–	–	–	–
$\dot{V}O_2\theta$ (L/min)	0.98 (0.17)	–	–	–	–
$\dot{V}O_2$ (6'–3') (L/min)	–	0.05 (0.08)	1.22 (0.41)	0.13 (0.03)	0.12 (0.08)
$\dot{V}CO_2$ max (L/min)	1.29 (0.40)	1.22 (0.37)	1.22 (0.41)	1.41 (0.51)	1.35 (0.50)
f_c max (/min)	119 (17)	113 (14)	112 (13)	122 (17)	119 (13)
f_c max (% reference)	80 (13)	75 (11)	74 (11)	81 (10)	79 (8)
$\dot{V}_E$ max (L/min)	43.7 (11.6)	44.2 (13.2)	45.1 (15.4)	46.8 (14.6)	48.4 (17.4)
$\dot{V}_E$ max/MVV (%)	77 (18)	68 (16)	69 (20)	85 (11)	87 (11)
RPE (Borg 6–20)	15.0 (1.8)	–	–	14.8 (2.1)	15.1 (2.2)
Dyspnea (VAS 0–100)	50 (20)	–	–	52 (28)	58 (28)

Note: Values are mean (± standard deviation).

Abbreviations: $\dot{W}$, work rate; $\dot{V}O_2$, oxygen uptake; $\dot{V}O_2$(6'–3'), change in oxygen uptake between the third and sixth minutes of the test (oxygen uptake drift); $\dot{V}CO_2$, carbon dioxide output, f_c, heart rate; $\dot{V}_E$, minute ventilation; *MVV*, maximum voluntary ventilation; RPE, rating of perceived exertion (on original Borg 6–20 scale); VAS, visual analog scale (with terminal anchors of "not at all breathless" and "extremely breathless").

and end-tidal gas tensions for oxygen and carbon dioxide.[26] The $\dot{V}O_2\theta$ was compared with the lower limit of normal.[27] Five patients reached a $\dot{V}_E$ max > 85% of their ventilatory capacity (as measured by maximum voluntary ventilation over 12 seconds) and might thus have been considered to be ventilation limited. For the constant $\dot{W}$ tests, $\dot{V}O_2$ max, f_c max and $\dot{V}_E$ max were higher, with 90% of $\dot{W}$max rather than 80%, suggesting that the 90% tests were more successful at eliciting a true maximal effort (see Table 2). Ratings of perceived exertion and breathlessness were similar for the incremental and 90% constant work rate tests. Comparing 80% and 90% tests, coefficients of variation were endurance time 16% versus 17%, $\dot{V}O_2$ max 10% versus 7%, $\dot{V}CO_2$ max 10% versus 8%, f_c max 6% versus 3%, and $\dot{V}_E$ max 10% versus 7%. We concluded from these data that the symptom-limited incremental treadmill protocol was well tolerated in patients with moderate to very severe COPD. Constant $\dot{W}$ tests at 90% compared with 80% of $\dot{W}$max resulted in a narrower range of endurance times and slightly more repeatable physiologic measures. However, the 90% tests always followed the 80% tests and so there could have been a sequence effect related to familiarization with the exercise protocol.

EXACTT study

Subjects

Five hundred nineteen patients were randomized into the EXACTT study. The demographics and baseline characteristics of these subjects are shown in Table 3. There were 401 men and 118 women with a mean age of 64.6 ± 8.3 years. The mean postbronchodilator FEV_1 was 44.3% ± 11.9% of predicted. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria,[28] 187 patients had moderate (Stage II) COPD, 261 had severe (Stage III) COPD, and 71 patients had very severe (Stage IV) COPD. The cohort comprised 34.3% current smokers and 65.7% former smokers. On average, they had smoked for approximately 51.7 ± 27.7 pack years and

Table 3 EXACTT patient demographics and baseline characteristics

Parameter	Result
Men/women, n	401/118
Age (years)	64.6 (8.3)
Body mass index (kg/m^2)	26.4 (4.2)
Current/former smokers	178/341
Smoking history (pack-years)	51.7 (27.7)
Duration of COPD (years)	8.8 (6.7)
Prebronchodilator FEV_1 (L)	1.08 (0.40)
Prebronchodilator FEV_1 (% predicted)	38.2 (11.2)
Postbronchodilator FEV_1 (L)	1.25 (0.42)
Postbronchodilator FEV_1 (% predicted)	44.3 (11.9)
FVC (L)	2.93 (0.72)
FEV_1/FVC (%)	50.7 (13.5)
Concurrent LABA, n (%)	300 (57.8)
Concurrent ICS, n (%)	311 (59.9)

Note: Values are mean (SD) unless otherwise stated.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; LABA, long-acting β-agonist; ICS, inhaled corticosteroid.

were known to have COPD for 8.7 ± 6.6 years. The number of patients with evaluable data at visits 1, 2, and 3 were 512, 459, and 463, respectively.

Incremental test

The mean ± SD exercise endurance time for the incremental exercise test at visit 1 was 522 ± 172 seconds. Individual exercise endurance times ranged from 20 seconds to 890 seconds (see Figure 2). The maximum work rate was 66.3 ± 33.9 watts. Values of endurance time and work rate for different stages of COPD severity are shown in Table 4.

Constant work rate tests

The mean ± SD and median endurance times for the constant $\dot{W}$ tests were 316 ± 200 and 260 seconds, respectively, on visit 2 compared with 341 ± 184 and 290 seconds on visit 3 (see Figures 3 and 4). The range of values for visit 2 was 42–1096 seconds and for visit 3 or visit 3r (with work rate adjustment) the range was 42–900 seconds. The constant work rates for the two visits were 61.0 ± 32.4 and 60.4 ± 32.6 watts. Values of endurance time and work rate for the different stages of COPD severity are shown in Table 4. Data were available for identical constant $\dot{W}$ tests at visits 2 and 3 in 470 subjects. The target endurance time for the constant work rate tests was 120–900 seconds. If endurance time was >900 seconds, the work rate was increased, whereas if endurance time was <120 seconds, the work rate was reduced. Increases or reductions in the constant work rate were obtained using speed and grade from either the previous or next stage of the standard protocol. Constant work rate was modified 56 times in 52 subjects, being reduced 32 times in 31 subjects and increased 24 times in 21 subjects. There was good repeatability of endurance times between two identical tests (n = 470), with an intraclass correlation coefficient of 0.85 ($P < 0.001$) for the mean of two tests (see Figure 5).

Locus of symptom limitation

The reasons for stopping exercise during the constant $\dot{W}$ exercise tests are shown in Table 5. At visit 2, 402 (85.4%) of the patients stopped exercise due to breathlessness with or without leg fatigue compared with 416 (88.3%) at visit 3. There was a high degree of consistency (79.0%) in the reasons given for stopping exercise, with few patients switching reasons between these two visits.

Safety

At the time of this analysis, 422 (81%) of subjects have been retained in the EXACTT trial. Overall, 50 subjects experienced 76 adverse events. Events which occurred in >1% of patients were COPD exacerbation (seven patients) and cough (five patients). Two patients experienced serious adverse events, ie, COPD exacerbation and hypotension. The hypotension occurred shortly after exercise testing, but no other serious

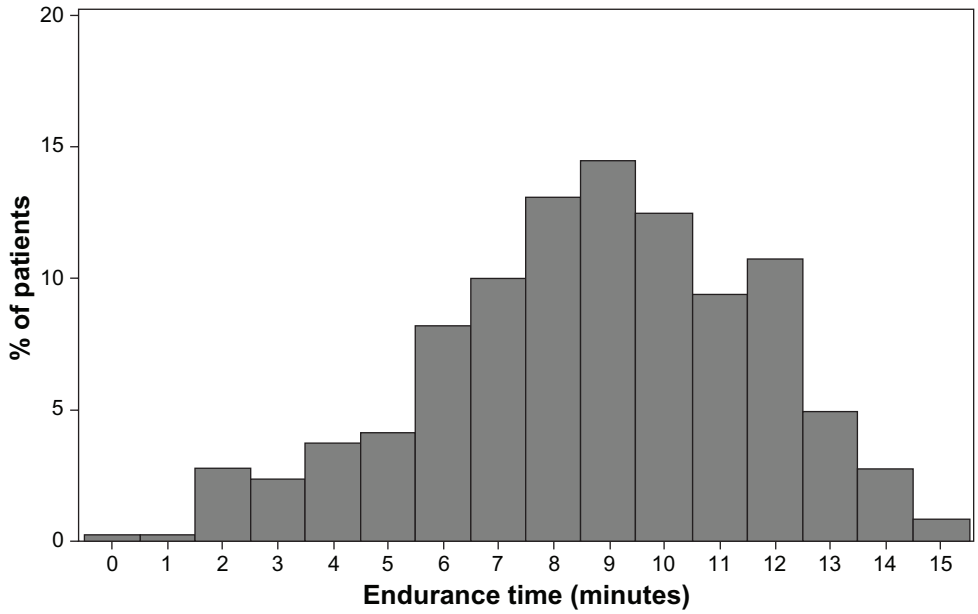

Figure 2 Distribution of patients by endurance time for the incremental exercise tests at visit 1 (n = 512). The mean ± standard deviation exercise endurance time was 522 ± 172 seconds.

Table 4 Duration and work rate from the EXACTT incremental and constant work rate exercise tests

GOLD stage	Visit 1		Visit 2		Visit 3	
	Time sec	$\dot{W}$max watts	Time sec	$\dot{W}$con watts	Time sec	$\dot{W}$con watts
Stage II: moderate (n = 185)	557 (168)	74 (34)	340 (209)	69 (34)	361 (178)	68 (34)
Stage III: severe (n = 260)	517 (179)	65 (34)	305 (197)	60 (32)	321 (180)	59 (33)
Stage IV: very severe (n = 71)	443 (128)	50 (22)	295 (182)	45 (21)	362 (207)	45 (22)
All stages (n = 516)	522 (172)	66 (34)	317 (201)	61 (33)	341 (184)	61 (33)

Note: Values are means (± standard deviations).
Abbreviations: Visit 1, incremental work rate test; visit 2, constant work rate test at 90% of maximum work rate from visit 1; visit 3, repeat identical constant work rate test; time, endurance time in seconds; $\dot{W}$max, maximum work rate for the incremental exercise test at visit 1; $\dot{W}$con, constant work rate for the exercise tests at visits 2 and 3; GOLD, global initiative for chronic obstructive lung disease.

events were associated with exercise testing. Electrocardiograms were monitored and there were only two reports of premature ventricular contractions and one report of self-limiting ventricular tachycardia. Nonserious advents which occurred on more than one occasion during exercise testing were vertigo (three patients), dizziness or lightheadedness (four patients), and abdominal pain (two patients). There have been no reports of accidental falls or problems with instability.

Discussion

The purpose of the present study was to develop incremental and constant work rate treadmill exercise testing protocols and then to implement them in the international, multicenter EXACTT study. The primary outcome measure in EXACTT will be endurance time at 90% of maximum work rate. All patients enrolled were able to complete the incremental and constant work exercise tests, and no subjects were lost to follow-up because of technical difficulties with test administration. Determination of exercise endurance time does not depend upon gas exchange measurements, thus simplifying the test protocols and allowing them to be performed quickly and cost effectively.

The incremental treadmill test was designed based on calculated increases in speed and grade to obtain a linear

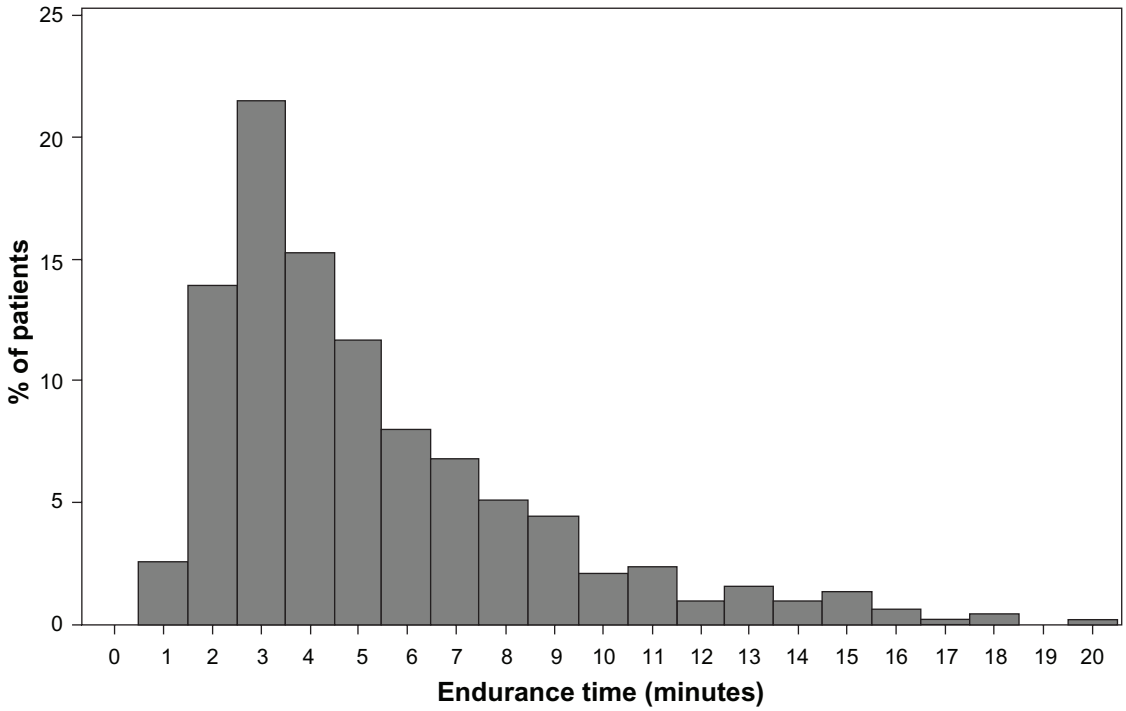

Figure 3 Distribution of endurance time for constant $\dot{W}$ exercise tests at visit 2 (n = 459). The mean ± standard deviation and median endurance times were 316 ± 200 and 260 seconds, respectively.

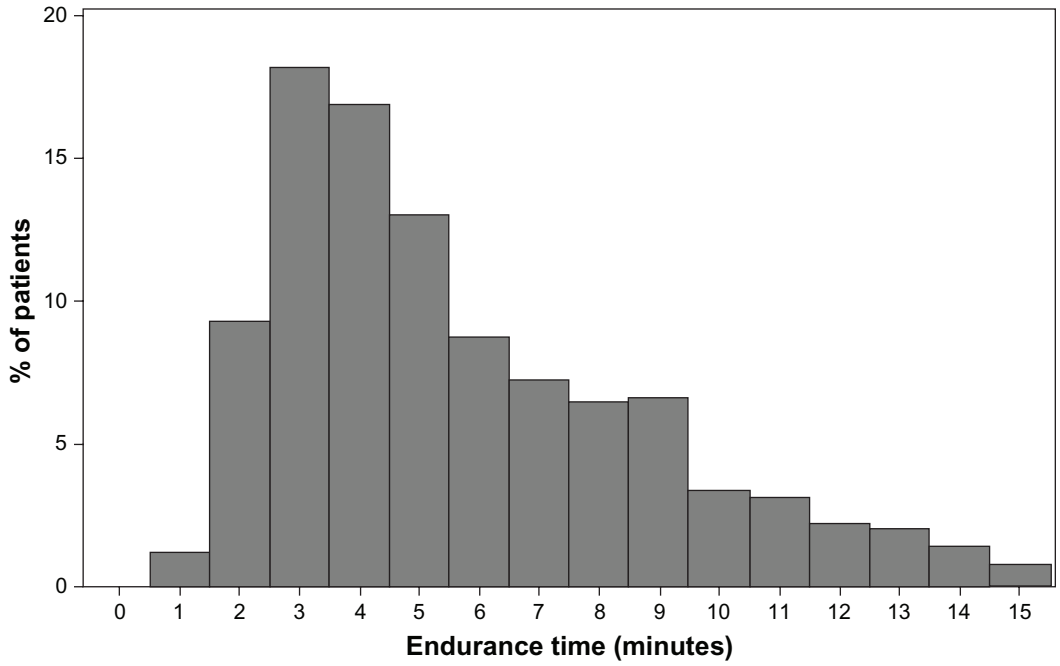

Figure 4 Distribution of endurance time for constant $\dot{W}$ exercise tests at visit 3 (n = 463). The mean ± standard deviation and median endurance times were 341 ± 184 and 290 seconds, respectively.

increase in $\dot{V}O_2$ suitable for patients with COPD. Plots of $\dot{V}O_2$ versus time from the subjects in the pilot study confirm that this objective was achieved. The data also show a mean incremental test time of approximately 10 minutes, with most tests falling within the target range of 8–12 minutes. In the pilot study, subjects attained 80% of predicted maximum heart rate, and $\dot{V}O_2$ max was 86% of that predicted for sedentary individuals.[16] Furthermore, 7/12 subjects had evidence of a plateau in $\dot{V}O_2$ despite further increase in $\dot{W}$, suggesting a true maximal test. Work efficiency was, on average, similar

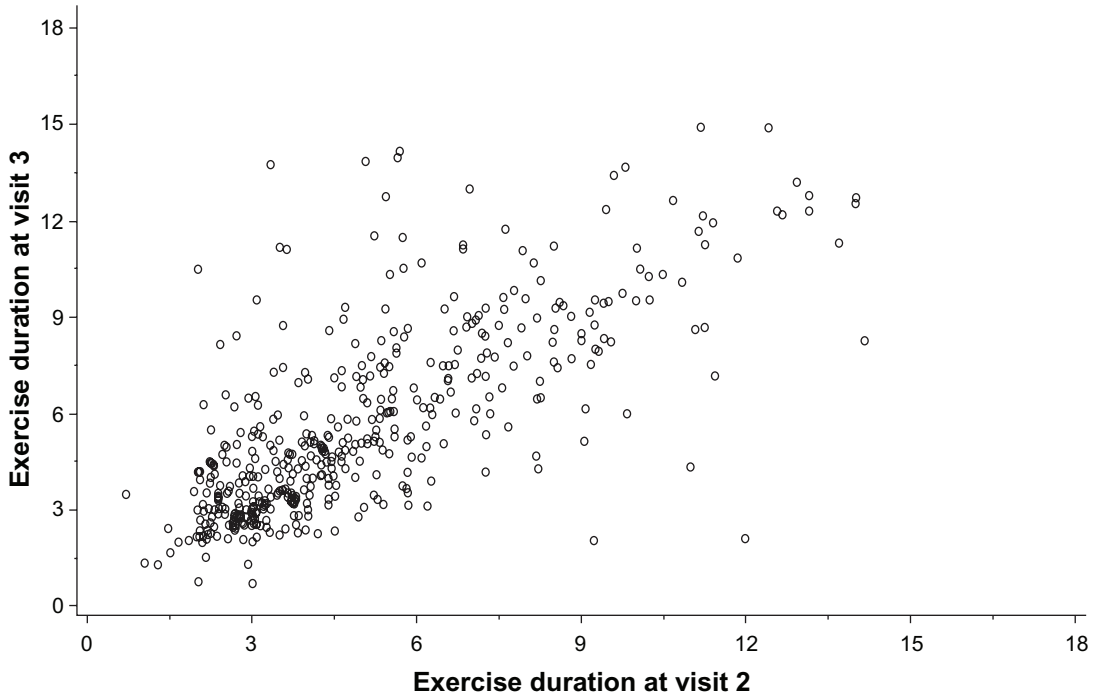

Figure 5 Comparison of endurance times for constant $\dot{W}$ exercise tests at visits 2 and 3. The means of the two tests had an intraclass correlation coefficient of 0.85 ($P < 0.001$).

Table 5 Reason for stopping the constant work rate exercise test at randomization in EXACTT (visit 3)

GOLD stage	Reason for stopping	Number	Percentage within stage
Stage II: moderate (n = 187)	Breathing discomfort	107	57.2
	Leg discomfort	23	12.3
	Both	56	29.9
	Neither	1	0.5
	Any breathing	163	87.1
Stage III: severe (n = 261)	Breathing discomfort	170	65.1
	Leg discomfort	26	10.0
	Both	61	23.4
	Neither	4	1.5
	Any breathing	231	88.5
Stage IV: very severe (n = 71)	Breathing discomfort	45	63.4
	Leg discomfort	6	0.1
	Both	19	26.8
	Neither	1	1.4
	Any breathing	64	90.2
All stages (n = 519)	Breathing discomfort	322	62.0
	Leg discomfort	55	10.6
	Both	136	26.2
	Neither	6	1.1
	Any breathing	458	88.2

Notes: Values are absolute numbers in each category followed by the percentage of all patients with the same stage of chronic obstructive pulmonary disease severity. "Any breathing" refers to the combined number of patients in the "breathing discomfort" and "both" categories.

to what would be expected with incremental cycle ergometry.[24] Only 5/12 subjects exhibited ventilatory limitation ($\dot{V}_E$max > 85% of maximum voluntary ventilation measured directly over 12 seconds prior to exercise testing). This is a typical finding in COPD patients where there can be other reasons for exercise limitation. In summary, this incremental $\dot{W}$ protocol, specific for patients with COPD, is novel, feasible, and well tolerated by patients with COPD ranging from moderate to very severe by GOLD criteria.[28]

The EXACTT study will evaluate the long-term effect of tiotropium on exercise tolerance in patients with COPD over two years. The rationale for this study is based on the results of several short-term clinical trials in patients with COPD demonstrating improvement with tiotropium 18 µg once daily on exercise duration using different types of exercise protocol.[6,7,14,29] For example, two six-week protocols evaluated constant work cycle ergometry,[6,7] one 12-week study examined the incremental shuttle walk test,[29] and a fourth study examined constant speed treadmill testing as an outcome in patients receiving tiotropium or matching placebo in combination with pulmonary rehabilitation.[14]

Commonly used exercise tests have several limitations. Standard protocols for cardiopulmonary exercise testing, such as the Bruce protocol, are generally too demanding for COPD patients and were designed for other purposes.[30] The six-minute walking test has gained acceptance in a variety of chronic pulmonary diseases, but is subject to preset behaviors and has been shown to be administered inconsistently.[3] This type of functional exercise test exhibits large within-subject variability from day to day, and therefore requires considerable attention to standardization.[2] For example, it has been shown to be nonresponsive to bronchodilator therapy despite improvement in FEV_1, and also in shuttle walking performance.[31] The endurance shuttle walk test may be more responsive than the six-minute walking test,[31] but it could also have limitations given the need to move back and forth on a corridor and to perform sharp turns which might cause instability. Revill et al[8] noted the energy expenditure will likely be higher in the shuttle walk compared with a treadmill test due to the turning of corners. Furthermore, a 20-minute ceiling effect has been recognized with the shuttle test which could pose problems in the evaluation of higher functioning individuals.[32] A potential benefit of constant work treadmill testing is that there may not be a ceiling effect in higher functioning subjects.

Constant work cycle ergometry has an accepted, standardized methodology and has proven to be responsive to pharmacologic interventions.[6,7,33] However, cycling is not usually a habitual activity for COPD patients, and involves different muscle recruitment than walking. Cycle ergometry may mask true treatment effects that improve ventilatory mechanics due to cessation of work from leg fatigue. Pepin et al[11] evaluated changes in endurance time during cycling and walking (endurance shuttle test) in 17 patients with COPD with placebo and ipratropium. Endurance time increased by a mean of 51 seconds with cycling and by a mean of 164 seconds with walking. Quadriceps twitch force was reduced with cycling, but not with walking and, furthermore, there was a shift in the locus of symptom limitation towards dyspnea rather than leg fatigue with the walking test. These observations suggest that walking endurance tests minimize the contribution of leg fatigue to exercise limitation, and should therefore be more sensitive for detecting improvements in dyspnea related to alterations in ventilatory mechanics. These issues highlight the need for an endurance walking test with a standardized protocol that is applicable in COPD patients. Acceptance of a constant work rate endurance test for the evaluation of pharmacologic interventions will certainly require wider experience of such

testing and comparison with functional exercise tests, such as the six-minute walking test.

An optimal test duration of 8–12 minutes is often quoted for maximal incremental exercise testing.[15] According to the power-duration curve, there is a nonlinear relationship between intensity of a task and the duration for which the task can be performed. Thus, a too low intensity results in prolonged exercise duration, masking ventilatory limitation and limiting ability to detect true intervention effects. By contrast, a too high intensity results in insufficient data for interpretation. A recent study of COPD patients (Stages III and IV) performing incremental cycle ergometry suggests an optimal test duration of approximately 5–9 minutes, as compared with 8–12 minutes for normal subjects.[34]

The duration of the second treadmill constant $\dot{W}$ tests at 90% of $\dot{W}$ max on visit 3 of the EXACTT study was 340 seconds. Notably, there were several tests of prolonged duration (one being almost 20 minutes). An obvious reason for such prolonged endurance is that the initial incremental test underestimated true $\dot{W}$max, and thus 90% of this value represented a relatively low intensity. Such prolonged tests need to be avoided in the setting of clinical trials where endurance time is an important clinical endpoint. For this reason, for 21 subjects in EXACTT whose endurance time exceeded 15 minutes, we adjusted the constant $\dot{W}$and repeated the test. For the 470 subjects performing identical constant $\dot{W}$ tests at visits 2 and 3, there was good repeatability of endurance times between the two tests (intraclass correlation 0.85). We considered this degree of variation to be an acceptable baseline for the EXACTT clinical trial.

This study has several limitations. Firstly, it is recognized that the feasibility study included a low number of patients. However, it appeared that patients tolerated the protocol and it was feasible to institute. Secondly, in the EXACTT study, we excluded subjects who were obese, but recognize that a significant proportion of COPD patients do have a body mass index >30. The EXACTT protocol might not be so easily tolerated in heavier subjects, and this will have to be evaluated separately. Thirdly, we deliberately chose to increment the work rate slowly at the beginning of the incremental exercise tests. This was to improve subject comfort during testing. We acknowledge, however, that this might have led to an underestimation of peak power, especially in subjects with lower functional capacity. Had this phenomenon occurred, our selection of 90% of maximum work rate for the endurance tests would be even more appropriate. Another recognized limitation of the study is the exclusion of patients with an $FEV_1 > 65\%$. However, we believe that our subject population is representative of the type of patient seen in clinical practice. Finally, regarding differences in exercise duration between repeated visits, the possibility of a learning effect cannot be excluded.

We have sought to minimize subjective perception of leg fatigue as the factor limiting exercise so as to have a stimulus that would maximize the potential to demonstrate true improvements in ventilatory mechanics. A large international trial involving constant work cycle ergometry suggested that leg fatigue (either alone or in combination with breathlessness) was responsible for 53%–66% of patients reason for stopping exercise.[7] The treadmill protocol we developed resulted in 88% of subjects reporting breathing discomfort alone or in conjunction with leg fatigue as the locus of symptom limitation. This feature renders the EXACTT protocol particularly suitable for eliciting potential improvements in exercise capacity where there is limitation by dyspnea.

Conclusions

In summary, the maximal incremental treadmill exercise test protocols we have developed were well tolerated by patients with moderate to very severe COPD. We believe that treadmill testing is more representative of the physiologic limitations of the COPD patient than cycle ergometry, particularly given that our data show that breathlessness is more likely to be the limiting factor in treadmill exercise tests. Additionally, the test protocols we have developed may be performed easily in a variety of clinical settings. They are being further evaluated as part of a multinational clinical trial.

Disclosure

CC currently holds research contracts with Boehringer Ingelheim Pharmaceuticals and Spiration, and research grants from The Alpha-1 Foundation, Breathe California, and The March of Dimes Research Foundation. He serves on scientific advisory boards for VIASYS Clinical Services, ROX Medical, Boehringer Ingelheim Pharmaceuticals, and Pfizer. He has received honoraria for speaking, along with reimbursement of expenses, from AstraZeneca, Boehringer Ingelheim Pharmaceuticals, and Pfizer. MA is a member of staff of the UCLA Exercise Physiology Research Laboratory and has no conflicts of interest to disclose. DL and SK are full time employees of Boehringer Ingelheim Pharmaceuticals, Inc.

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