ORIGINAL ARTICLE

Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease

Y. Zhou, N. Zhong, Xiaochen Li, S. Chen, J. Zheng, D. Zhao, W. Yao, R. Zhi, L. Wei, B. He, X. Zhang, C. Yang, Ying Li, F. Li, J. Du, J. Gui, B. Hu, C. Bai, P. Huang, G. Chen, Y. Xu, C. Wang, B. Liang, Yinhuan Li, G. Hu, H. Tan, X. Ye, X. Ma, Y. Chen, X. Hu, J. Tian, X. Zhu, Z. Shi, X. Du, M. Li, S. Liu, R. Yu, J. Zhao, Q. Ma, C. Xie, Xiongbin Li, T. Chen, Y. Lin, Lizhen Zeng, C. Ye, W. Ye, X. Luo, Lingshan Zeng, S. Yu, W. Guan, and P. Ran

ABSTRACT

BACKGROUND

Patients with mild or moderate chronic obstructive pulmonary disease (COPD) rarely receive medications, because they have few symptoms. We hypothesized that long-term use of tiotropium would improve lung function and ameliorate the decline in lung function in patients with mild or moderate COPD.

METHODS

In a multicenter, randomized, double-blind, placebo-controlled trial that was conducted in China, we randomly assigned 841 patients with COPD of Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 1 (mild) or 2 (moderate) severity to receive a once-daily inhaled dose (18 μg) of tiotropium (419 patients) or matching placebo (422) for 2 years. The primary end point was the between-group difference in the change from baseline to 24 months in the forced expiratory volume in 1 second (FEV_1) before bronchodilator use. Secondary end points included the between-group difference in the change from baseline to 24 months in the FEV_1 after bronchodilator use and the between-group difference in the annual decline in the FEV_1 before and after bronchodilator use from day 30 to month 24.

RESULTS

Of 841 patients who underwent randomization, 388 patients in the tiotropium group and 383 in the placebo group were included in the full analysis set. The FEV_1 in patients who received tiotropium was higher than in those who received placebo throughout the trial (ranges of mean differences, 127 to 169 ml before bronchodilator use and 71 to 133 ml after bronchodilator use; P<0.001 for all comparisons). There was no significant amelioration of the mean (±SE) annual decline in the FEV_1 before bronchodilator use: the decline was 38±6 ml per year in the tiotropium group and 53±6 ml per year in the placebo group (difference, 15 ml per year; 95% confidence interval [CI], −1 to 31; P=0.06). In contrast, the annual decline in the FEV_1 after bronchodilator use was significantly less in the tiotropium group than in the placebo group (29±5 ml per year vs. 51±6 ml per year; difference, 22 ml per year [95% CI, 6 to 37]; P=0.006). The incidence of adverse events was generally similar in the two groups.

CONCLUSIONS

Tiotropium resulted in a higher FEV_1 than placebo at 24 months and ameliorated the annual decline in the FEV_1 after bronchodilator use in patients with COPD of GOLD stage 1 or 2. (Funded by Boehringer Ingelheim and others; Tie-COPD ClinicalTrials.gov number, NCT01455129.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Ran at 151 Yanjiang Xi Rd., 510120 Guangzhou City, Guangdong, China, or at pxran@gzhmu.edu.cn.

A complete list of the investigators in the Tiotropium in Early Chronic Obstructive Pulmonary Disease Patients in China (Tie-COPD) trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Zhou and Zhong contributed equally to this article.

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Chronic obstructive pulmonary disease (COPD) is a highly prevalent disease, with a prevalence among people 40 years of age or older of 10.1% worldwide and 8.2% in China.[1,2] COPD has become the third leading cause of death worldwide and is estimated to become the disease with the seventh greatest burden worldwide in 2030.[3-5] More than 70% of patients with COPD have Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 1 (mild) or 2 (moderate) disease, with very mild or no apparent respiratory symptoms such as exercise limitation and dyspnea.[2,6] (Patients with GOLD stage 1 COPD have a forced expiratory volume in 1 second [FEV_1] of ≥80% of the predicted value, and those with GOLD stage 2 disease have an FEV_1 between 50% and 79% of the predicted value.) This situation may account for infrequent physician consultations until their COPD is more advanced.

Tiotropium (Spiriva, Boehringer Ingelheim) is a long-acting anticholinergic bronchodilator that selectively binds to muscarinic receptors on smooth-muscle cells in the airway. Tiotropium ameliorates airflow limitation in patients with moderate-to-severe COPD, reduces air trapping and exertional dyspnea, and improves exercise tolerance and health-related quality of life.[7-9] In contrast, little is known about the treatment of COPD of GOLD stage 1 and early stage 2 (FEV_1 ≥60% of the predicted value). In small trials and in subgroup analyses of trials involving patients with COPD, tiotropium therapy improved lung function (as measured by FEV_1 and forced vital capacity [FVC]) in patients with GOLD stage 1 and early stage 2 disease.[10,11] We conducted a prospective trial to investigate the effect of tiotropium on the FEV_1 in patients with GOLD stage 1 or 2 COPD.

Methods

Trial Design

From October 2011 through September 2015, we conducted a multicenter, randomized, double-blind, placebo-controlled phase 4 trial involving patients with GOLD stage 1 or 2 COPD. Patients were identified from community screening at 24 centers in mainland China[12] and were randomly assigned in a 1:1 ratio to receive either tiotropium (at a dose of 18 μg once daily) or matching placebo, administered by means of an inhaler (HandiHaler) once daily for 2 years. Randomization was centralized and conducted with the use of block sizes of four, stratified according to trial site.

The primary end point was the between-group difference in the change from baseline to 24 months in the FEV_1 before bronchodilator use. Secondary end points included the following: between-group difference in the change from baseline to 24 months in the FEV_1 after bronchodilator use; the FVC before and after bronchodilator use at 24 months from baseline; the annual declines in the FEV_1, the FEV_1 as a percentage of the predicted value before and after bronchodilator use, and the FEV_1:FVC ratio from day 30 through month 24; the changes in the COPD Assessment Test (CAT) score (scores range from 0 to 40, with higher scores indicating more severe disease),[13] the Clinical COPD Questionnaire (CCQ) score (scores range from 0 to 6, with higher scores indicating worse clinical control),[14] and the modified Medical Research Council (mMRC) dyspnea scale score (scores range from 0 to 4, with higher scores indicating more severe breathlessness) from baseline to 24 months; the duration and severity of COPD exacerbations; the time to the first COPD exacerbation; and the use of rescue medications. Further details of the trial design have been published previously.[12] The protocol is available with the full text of this article at NEJM.org.

Patients

The key inclusion criteria were an age of 40 to 85 years and a diagnosis of COPD of GOLD stage 1 or 2, defined as an FEV_1:FVC ratio of less than 0.70 after bronchodilator use plus respiratory symptoms, a history of exposure to risk factors (e.g., smoking, air pollution, biomass combustion), or both and an FEV_1 of 50% or more of the predicted value, measured 20 minutes after the inhalation of 400 μg of albuterol (Ventolin, Glaxo Wellcome).[15] Key exclusion criteria were a COPD exacerbation occurring in the 4 weeks before screening, large-airway disease (e.g., cancer), asthma, and severe systemic disease.[12]

Procedures

Follow-up was scheduled at 1 month and every 3 months thereafter. The data that were collected at each visit included symptom-score assessment, physical examination, adverse events, medication

administration, exacerbation information, and smoking status. Laboratory assessments were conducted at baseline and at month 24.

Spirometric values were measured during individual visits (at screening and at months 1, 6, 12, 18, 24, and 25) at approximately the same time of day (within a 4-hour window) at each visit by the same trained technicians according to international standards.[16] Spirometric values that were obtained before bronchodilator use were measured approximately 24 hours after the previous dose of tiotropium or placebo. Spirometry that was performed after bronchodilator use was conducted 20 minutes after the inhalation of 400 μg of albuterol. Short-acting bronchodilators were withheld for at least 6 hours before the next spirometry. The predicted FEV_1 was derived with the use of reference values from the European Coal and Steel Community 1993[17] and by the application of conversion factors (0.95 in men and 0.93 in women).[18]

An acute exacerbation of COPD was defined as worsening of at least two major symptoms (cough, sputum volume, sputum purulence, wheezing, or dyspnea) that persisted for at least 48 hours, after the presence of cardiac insufficiency, pulmonary embolism, pneumothorax, pleural effusion, or cardiac arrhythmia had been ruled out.[19] Patients immediately contacted investigators in the case of worsening of respiratory symptoms. The duration, interval, severity, and management of acute exacerbations of COPD were recorded on diary cards and were adjudicated by investigators who graded the severity according to the following categories. A mild event was one that resulted in domiciliary management with COPD medications alone. A moderate event was one that resulted in an outpatient or emergency department visit and the modification of regimen, including antibiotic agents, oral glucocorticoids, or both. A severe event was one that resulted in hospitalization. Assessments of the mMRC dyspnea scale and quality of life (including the CAT and CCQ assessments) were completed at each visit.[13,14]

Long-term concomitant use of other maintenance medications for COPD such as bronchodilators was avoided throughout the trial, except for medications that were clinically necessary or that had been initiated before recruitment. Ipratropium was used as rescue medication if needed but was not intended for long-term use (patients were instructed to contact their trial investigator immediately to seek guidance regarding the use of rescue medication, verification of an acute COPD exacerbation, and initiation of treatment associated with the acute exacerbation). Rundo International Pharmaceutical Research and Development was convened to monitor the quality of and check adherence to the trial regimen.

TRIAL OVERSIGHT

The trial protocol was approved by the local institutional review board or independent ethics committee at each site, according to the requirement of the Chinese guidelines for Good Clinical Practice. Participants provided written informed consent before enrollment. Statistical analyses were performed by employees of Rundo International Pharmaceutical Research and Development. The funding sources had no role in the design, data analysis, or interpretation of the results in this trial. The sponsor (Boehringer Ingelheim) was given the opportunity to review the manuscript for medical and scientific accuracy as it related to its product (tiotropium) and intellectual property considerations. Albuterol was purchased at full cost. The first and last authors vouch for the accuracy and completeness of the data and analyses reported and for the fidelity of the trial to the protocol. All the authors approved the submission of the manuscript for publication.

STATISTICAL ANALYSIS

We calculated the sample size to detect a difference in the FEV_1 before bronchodilator use between the tiotropium group and the placebo group, assuming a difference of 100 ml and a standard deviation of 350 ml at month 24, with a two-sided significance level of 5% and a power of 90%, taking into account an anticipated withdrawal rate of 35%.[7,9] We estimated that a total of 400 patients per group would be required for the primary analysis.

Confirmatory hypothesis testing was planned only for the primary end point. All the secondary and subgroup analyses are exploratory in nature and were not adjusted for multiple comparisons. Repeated-measures analysis of variance (ANOVA) was used to compare the FEV_1 before and after bronchodilator use at each visit, with values at each follow-up visit as a dependent variable, with the trial-group assignment, baseline

FEV_1 values, follow-up visits (categorical variable), interactions between trial group and follow-up visit, and hospital as fixed effects and with participants as random effects. Assuming that trial-group effects varied linearly with the duration of the trial, a random coefficient regression model was used to compare the annual declines in FEV_1, FVC, and the FEV_1:FVC ratio, with the annual declines being expressed as regression coefficients. We used likelihood-based methods to handle missing data for the repeated-measures model and the random-coefficient model. No imputation was deemed to be necessary.

The time to the first acute exacerbation of COPD was compared by means of a log-rank test. The Wilcoxon rank-sum test was applied to assess the interval, duration, and severity of acute exacerbations of COPD. Fisher's exact test was used for the comparison of differences in the use of rescue medication. The frequency and number of severe acute exacerbations of COPD were compared with the use of a Poisson regression model, with correction for exposure of trial-regimen doses and overdispersion (i.e., presence of greater variability in the data set than the expected heterogeneity in exacerbation rates). Transfer tables were used for the comparison of changes in the mMRC dyspnea scale scores between baseline and the end of the trial. Differences between the changes from baseline to the end of the trial were compared with the use of repeated-measures ANOVA. Subgroup analyses were performed with the use of stratification of COPD according to CAT score (<10 vs. ≥10) and GOLD stage (1 vs. 2) and category (A vs. B). Patients with A or B category disease are considered to be at low risk for an acute exacerbation of COPD; patients with A category disease have few symptoms, and those with B category disease have more symptoms.

The data from patients who underwent randomization and received at least one dose of tiotropium or placebo and had available data regarding efficacy measurement after baseline (i.e., patients who underwent spirometric assessment after bronchodilator use at any scheduled follow-up visit) were included in the full analysis set. The number of exacerbations in each trial group was reported. All the analyses were conducted with the use of SAS software, version 9.2.2 (SAS Institute), and all reported P values are two-sided.

RESULTS

BASELINE DEMOGRAPHIC CHARACTERISTICS AND ADHERENCE TO TRIAL REGIMEN

We randomly assigned 841 patients with COPD (367 patients with GOLD stage 1 disease and 474 with stage 2) to receive placebo (422 patients) or tiotropium (419) (Fig. 1). Among 771 patients who were included in the full analysis set (383 patients in the placebo group and 388 in the tiotropium group), 585 completed the follow-up visits for 2 years. A total of 256 patients withdrew from the trial (140 patients [33.2%] in the placebo group and 116 [27.7%] in the tiotropium group). There were no significant differences in the demographic characteristics or in the reasons for withdrawal (Fig. 1, and Table S1 in the Supplementary Appendix, available at NEJM.org). The demographic and clinical characteristics were similar between the patients who withdrew and those who did not withdraw, except for the mean (±SD) CCQ score (1.09±0.79 in patients who withdrew vs. 0.94±0.71 in those who completed the trial, P=0.008) and the CAT score (6.9±5.8 vs. 7.8±6.3, P=0.03) (Table S2 in the Supplementary Appendix).

The baseline values of the patients in the full analysis set were similar in the two groups. The mean age of the patients was 63.9 years in the placebo group and 64.2 years in the tiotropium group, and the median smoking index (the number of packs of cigarettes per day, multiplied by the years of smoking) was 55.1 pack-years and 50.6 pack-years, respectively. The mean FEV_1 before bronchodilator use was 1.82 liters (73.4% of the predicted value) in the placebo group and 1.80 liters (72.6% of the predicted value) in the tiotropium group; the mean FEV_1 after bronchodilator use was 1.94 liters (78.1% of the predicted value) and 1.93 liters (77.9% of the predicted value), respectively. No significant between-group differences were observed in the mMRC dyspnea scale, CAT, or CCQ scores and in the use of concomitant respiratory medications (Table 1).

The mean exposure to the trial regimen was 604 days in the placebo group (adherence rate, 90.5%) and 638 days in the tiotropium group (adherence rate, 93.3%) (P=0.009 for the comparison of mean exposure; P=0.004 for the comparison of adherence rate). The number of times of administration and the number of days of

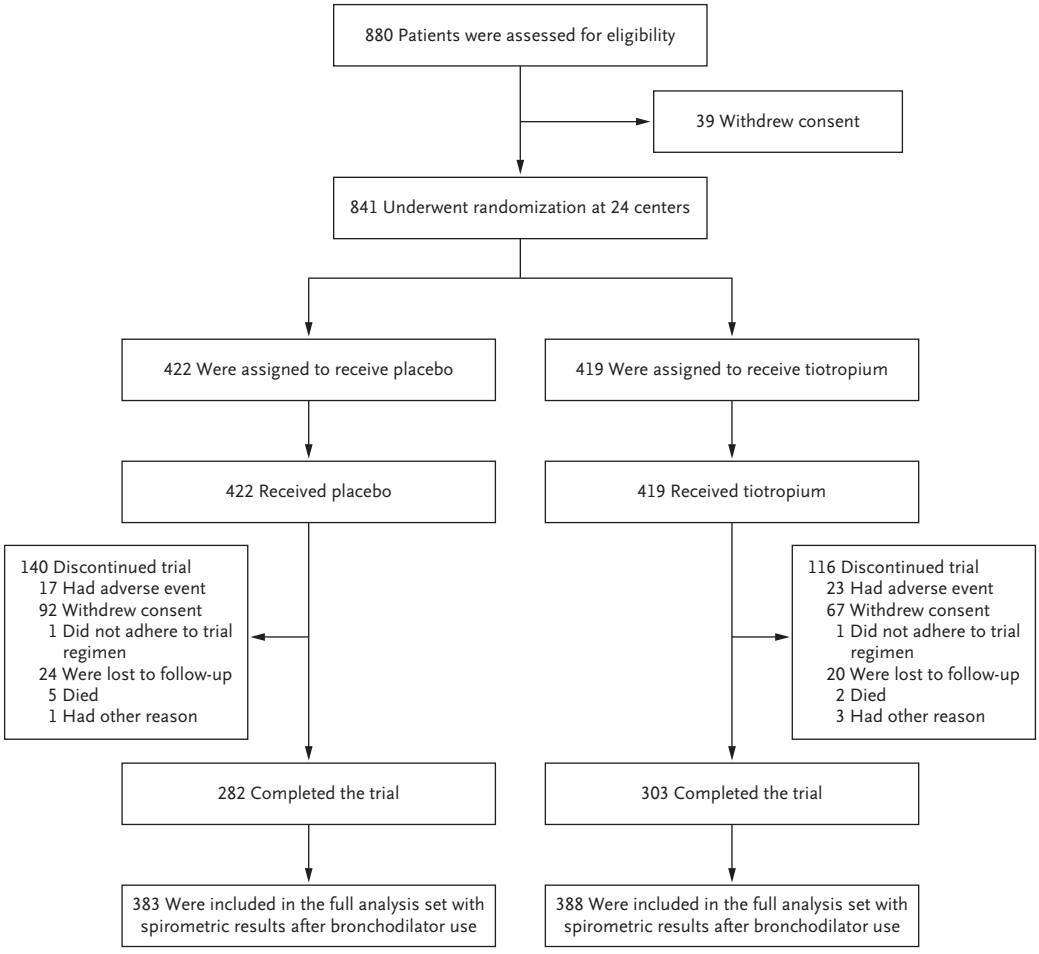

Figure 1. Randomization and Follow-up of Patients with Chronic Obstructive Pulmonary Disease (COPD) of GOLD Stage 1 or 2.

Reasons for discontinuation of the trial did not differ significantly between the two groups. A total of 140 patients (33.2%) in the placebo group withdrew, as did 116 (27.7%) in the tiotropium group (P=0.27). Patients who underwent randomization and received at least one dose of tiotropium or placebo and had available data regarding efficacy measurement after baseline (i.e., patients who underwent spirometric assessment after bronchodilator use at any scheduled follow-up visit) were included in the full analysis set.

rescue-medication use were greater in the placebo group than in the tiotropium group (P=0.002 and P=0.02, respectively). There was no significant between-group difference with regard to smoking status or the use of other respiratory medications (Table S3 in the Supplementary Appendix).

LUNG FUNCTION

Tiotropium resulted in a significantly higher FEV_1 before bronchodilator use than placebo at month 24, with a between-group difference of 157 ml (95% confidence interval [CI], 123 to 192; P<0.001) (Fig. 2, and Table S4 in the Supplementary Appendix). At each visit, both the mean FEV_1 (ranges of mean differences, 127 to 169 ml before bronchodilator use and 71 and 133 ml after bronchodilator use) and the mean FVC (ranges of mean differences, 110 to 164 ml before bronchodilator use and 53 to 96 ml after bronchodilator use) were significantly higher in the tiotropium group than in the placebo group (P<0.001 for all comparisons of FEV_1 and P<0.05 for all comparisons of FVC at follow-up visits to month

24) (Fig. 2, and Table S4 in the Supplementary Appendix).

From day 30 through month 24, the annual decline in the FEV_1 before bronchodilator use was 38 ml per year in the tiotropium group and 53 ml per year in the placebo group (difference, 15 ml per year; 95% CI, −1 to 31; P=0.06), whereas the annual decline in the FEV_1 after bronchodilator use was 29 ml per year in the tiotropium group versus 51 ml per year in the placebo group (difference, 22 ml per year; 95% CI, 6 to 37; P=0.006). Similar findings were observed for the between-group differences in the percent of the predicted FEV_1 value and in the analyses after adjustment for smoking status, the percent of the predicted FEV_1 value at baseline, age, sex, hospitalization, GOLD stage, and body-mass index (the weight in kilograms divided by the square of the height in meters). The groups did not differ significantly in the

Table 1. Characteristics of the Patients at Baseline (Full Analysis Set).*

Characteristic	Placebo Group (N=383)	Tiotropium Group (N=388)	P Value†
Age — yr	63.9±8.6	64.2±8.2	0.57
Male sex — no. (%)	330 (86.2)	328 (84.5)	0.52
Body-mass index‡	22.5±3.2	22.6±3.4	0.57
Smoking status			0.84
Never smoked	77 (20.1)	82 (21.1)	
Current smoking	154 (40.2)	160 (41.2)	
Former smoking	152 (39.7)	146 (37.6)	
Smoking index — pack-yr§	55.1±86.1	50.6±57.8	0.97
Duration of COPD — days¶	208±568	202±654	0.88
Previous respiratory disease other than COPD — no. (%)	17 (4.4)	18 (4.6)	0.89
Previous medication for respiratory disease — no. (%)	69 (18.0)	88 (22.7)	0.11
Traditional Chinese medicine for respiratory disease — no. (%)	21 (5.5)	13 (3.4)	0.15
Spirometric values at baseline			
Before bronchodilator use			
FEV_1 — liters	1.82±0.55	1.80±0.52	0.55
FEV_1 — % of predicted value	73.4±17.9	72.6±16.4	0.53
FVC — liters	3.09±0.77	3.08±0.75	0.80
FEV_1:FVC ratio	58.5±8.3	58.6±7.7	0.83
After bronchodilator use			
FEV_1 — liters	1.94±0.54	1.93±0.52	0.72
FEV_1 — % of predicted value	78.1±17.1	77.9±15.8	0.88
FVC — liters	3.23±0.77	3.21±0.74	0.77
FEV_1:FVC ratio	59.9±7.4	60.2±7.9	0.55
Airflow reversibility — no. (%)‖	56 (14.6)	72 (18.6)	0.14
GOLD stage — no. (%)**			0.67
1	165 (43.1)	173 (44.6)	
2	218 (56.9)	215 (55.4)	
CAT score††			
Mean score	6.8±5.9	7.4±6.2	0.18
Distribution — no. (%)			0.20
<10	288 (75.2)	276 (71.1)	
≥10	95 (24.8)	112 (28.9)	

Table 1. (Continued.)

Characteristic	Placebo Group (N=383)	Tiotropium Group (N=388)	P Value†
mMRC dyspnea scale score‡‡			
Mean score	0.8±0.7	0.7±0.7	0.70
Distribution — no. (%)			0.96
<2	339 (88.5)	343 (88.4)	
≥2	44 (11.5)	45 (11.6)	
CCQ score§§	0.96±0.74	0.99±0.73	0.58

* Plus–minus values are means ±SD. There were no significant between-group differences at baseline. The full analysis set included patients who underwent randomization and received at least one dose of tiotropium or placebo and had available data regarding efficacy measurement after baseline (i.e., patients who underwent spirometric assessment after bronchodilator use at any scheduled follow-up visit). Percentages may not sum to 100 because of rounding. COPD denotes chronic obstructive pulmonary disease, FEV_1 forced expiratory volume in 1 second, and FVC forced vital capacity.

† P values for continuous variables were calculated by Student's t-test or the Wilcoxon rank-sum test, and P values for categorical variables were calculated by the chi-square test.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ The smoking index was defined as the number of packs of cigarettes that were smoked daily, multiplied by the years of smoking. The smoking index was known for 301 patients who were current or former smokers in the placebo group and for 302 in the tiotropium group.

¶ The duration of COPD was unknown for one patient in the placebo group and for two in the tiotropium group.

‖ Airflow reversibility was defined as an FEV_1 value obtained after bronchodilator use that increased by 200 ml or more and by 12% or more from the measurement obtained before bronchodilator use.

** The Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging system is used to assess the severity of lung disease. Stages range from 1 to 4, with higher stages indicating more severe disease. Stage 1 (mild disease) is defined as an FEV_1 of 80% or more of the predicted value, and stage 2 (moderate disease) as an FEV_1 between 50 and 79% of the predicted value.

†† Scores on the COPD Assessment Test (CAT) range from 0 to 40, with higher scores indicating more severe disease.

‡‡ Scores on the modified Medical Research Council (mMRC) dyspnea scale range from 0 to 4, with higher scores indicating more severe breathlessness.

§§ Scores on the Clinical COPD Questionnaire (CCQ) range from 0 to 6, with higher scores indicating worse clinical control.

FVC, the percent of the predicted FVC value, and the FEV_1:FVC ratio as assessed before and after bronchodilator use (Table 2).

ACUTE EXACERBATIONS OF COPD

A total of 112 patients (28.9%) in the tiotropium group and 150 (39.2%) in the placebo group had an acute exacerbation of COPD. The time to the first acute exacerbation of COPD was longer with tiotropium than with placebo (P<0.001). The 25th-percentile value for the time to the first acute exacerbation of COPD was 522 days (95% CI, 341 to 649) in the tiotropium group and 236 days (95% CI, 177 to 331) in the placebo group. The hazard ratio for the first acute exacerbation of COPD in the tiotropium group, as compared with the placebo group, was 0.60 (95% CI, 0.50 to 0.80; P<0.001) (Fig. 2).

The frequency of acute exacerbations of COPD was lower with tiotropium than with placebo (0.27 vs. 0.50 events per patient-year; risk ratio, 0.53; 95% CI, 0.39 to 0.73; P<0.001) (Table 3). Tiotropium also resulted in a lower frequency of hospitalizations per patient per year than placebo (0.03 vs. 0.07 hospitalizations per patient-year, P=0.009) (Table 3).

QUALITY OF LIFE

Tiotropium was more effective than placebo with regard to mMRC dyspnea scale and CAT scores at all time points except for months 1, 3, and 12. Changes in the CCQ scores also favored tiotropium over placebo at all visits except for month 12. Details are provided in Tables S5, S6, and S7 in the Supplementary Appendix.

ADVERSE EVENTS

There were no significant between-group differences in the incidence of adverse events, serious adverse events, and death except for mild adverse events, such as oropharyngeal discomfort. Oropharyngeal discomfort, including dry mouth and pharyngeal discomfort, occurred in 63 patients (15.0%) in the tiotropium group, as compared

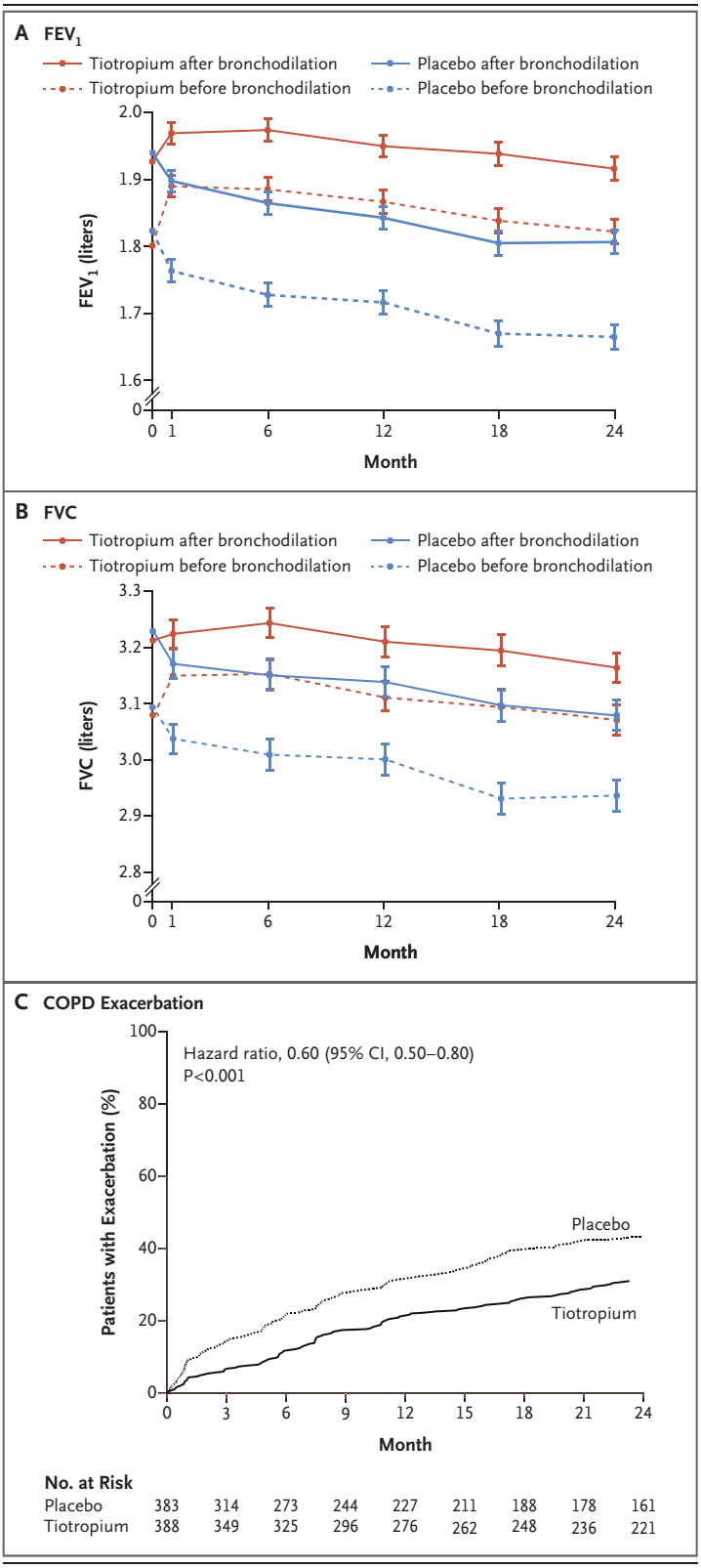

Figure 2. Mean Forced Expiratory Volume in 1 Second (FEV_1) and Forced Vital Capacity (FVC) before and after Bronchodilator Use and the Risk of Acute Exacerbation of COPD over Time.

Tiotropium resulted in a significantly higher FEV_1 before bronchodilator use than placebo at 24 months, with a between-group difference of 157 ml (95% CI, 123 to 192; P<0.001), and at each visit (ranges of mean differences, 127 to 169 ml in the FEV_1 before bronchodilator use and 71 to 133 ml in the FEV_1 after bronchodilator use; P<0.001 for all comparisons) (Panel A). The FVC was significantly higher in the tiotropium group than in the placebo group (ranges of mean differences, 110 to 164 ml in the FVC before bronchodilator use and 53 to 96 ml in the FVC after bronchodilator use; P<0.05 for all comparisons) (Panel B). I bars indicate ±1 SD. The use of tiotropium resulted in a significantly longer time to the first acute exacerbation of COPD (25th percentile, 522 days; 95% CI, 341 to 649) than placebo (25th percentile, 236 days; 95% CI, 177 to 331). The incidence of an acute exacerbation of COPD was lower with tiotropium than with placebo (Panel C).

with 28 (6.6%) in the placebo group (P<0.001) (Table S8 in the Supplementary Appendix).

SUBGROUP ANALYSIS

In this trial, 614 of 841 patients (73.0%) had a CAT score of less than 10, and no significant between-group difference was observed with regard to baseline demographic and clinical characteristics, exposure to the trial regimen, use of other respiratory medication, or smoking status except for the number of times that rescue medication (ipratropium) was administered (Tables S9 and S10 in the Supplementary Appendix). Data on the FEV_1 and FVC values before and after bronchodilator use at individual visits, stratified according to CAT score, are provided in Table S11 in the Supplementary Appendix. In patients with a CAT score of less than 10, the mean decline in the FEV_1 before bronchodilator use was 54 ml per year in the placebo group and 37 ml per year in the tiotropium group, with a difference in the annual decline of 17 ml per year (95% CI, −1 to 35; P=0.07). The mean decline in the FEV_1 after bronchodilator use was 47 ml per year in the placebo group and 28 ml per year in the tiotropium group, with a difference in the annual decline of 20 ml per year (95% CI, 2 to 37; P=0.03) (Table 2). In patients with a CAT score of 10 or more, the between-group difference

in the annual decline in the FEV_1 after bronchodilator use was not significant (P=0.07) (Table 2).

Tiotropium prolonged the time to the first acute exacerbation of COPD and decreased the total numbers of all acute exacerbations of COPD and of acute exacerbations of moderate or worse severity in patients with a CAT score of less than 10. In patients with a CAT score of less than 10, the mMRC dyspnea scale score and quality-of-life assessment scores were lower (indicating clinical improvement) in the tiotropium group than in the placebo group at months 15, 21, and 24. Details are provided in Tables S12 through S16 in the Supplementary Appendix.

Subgroup analyses that were stratified according to GOLD stage and category (1 vs. 2 and A vs. B) showed results that were similar to those in the overall analysis. Details are provided in Tables S17 through S23 in the Supplementary Appendix.

DISCUSSION

We investigated the efficacy and safety of tiotropium in a large cohort of patients who had GOLD stage 1 or stage 2 COPD. Tiotropium resulted in a significantly higher FEV_1 than placebo at 24 months and ameliorated the annual decline in the FEV_1 assessed after bronchodilator use but not the FEV_1 assessed before bronchodilator use. Moreover, tiotropium resulted in a lower frequency of acute exacerbations of COPD than placebo and improved quality of life in patients with GOLD stage 1 or 2 COPD. Similar results were found in patients who had a CAT score of less than 10.

Clinical trials with medication intervention in patients with GOLD stage 1 COPD or a CAT score of less than 10 are scarce, with some data available from post hoc subgroup analyses.[9,11,20] Our multicenter trial involved patients with GOLD stage 1 or 2 COPD and enrolled more than 40% of patients with stage 1 disease and more than 70% of patients with a CAT score of less than 10, mainly from the community by means of a COPD screening program. At baseline, the majority of patients had a low frequency of acute exacerbations of COPD and had received minimal medications.

Attempts to decrease the progression rate of COPD with tiotropium have not been fully successful. In a subgroup analysis of the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial, tiotropium resulted in an annual decline in the FEV_1 after bronchodilator use in patients with GOLD stage 2 COPD that was less than the decline in patients who received placebo. However, the mean between-group differences were small and not clinically significant (6 ml per year).[9] In our trial, we recruited only patients with mild or moderate COPD, which might have contributed to the differences in findings between the two trials. Previous reports have shown that in previously untreated patients with COPD, tiotropium led to an annual decline in the FEV_1 that was slower than that with placebo.[20] In another study involving patients with mild-to-moderate COPD, the FEV_1 after bronchodilator use was significantly greater after 12 weeks of tiotropium than after placebo, which suggests that tiotropium might be effective for mild COPD.[10] However, in a real-world retrospective cohort study involving patients with early-stage COPD (FEV_1 ≥70% of the predicted value), tiotropium did not lead to a significantly slower decline than placebo in the FEV_1 (decline in FEV_1 before bronchodilator use, 30.4 ml per year in the tiotropium group and 21.9 ml per year in the placebo group; decline in FEV_1 after bronchodilator use, 23.9 ml per year and 22.5 ml per year, respectively).[21] This finding could be due to the retrospective study design and the small sample size.

The case definition for COPD that we used was an FEV_1:FVC ratio of less than 0.70 after bronchodilator use plus respiratory symptoms, a history of exposure to risk factors (e.g., smoking, air pollution, biomass combustion), or both.[15,22,23] Patients with early-stage COPD remain asymptomatic but have a rapid decline in lung function.[24-26] In our trial, all the participants met the diagnostic definition of COPD in terms of risk factors and spirometric results, and in patients with a CAT score of less than 10, tiotropium resulted in an annual decline in the FEV_1 after bronchodilator use that was less than the decline observed with placebo. It is not known whether the prevention of COPD-related loss of lung function that was associated with tiotropium has any effect on the underlying disease mechanisms in COPD. If it does not, then the benefit that we

Table 2. Annual Declines in the FEV_1, FVC, Percent of Predicted FEV_1, Percent of Predicted FVC, and FEV_1:FVC Ratio before and after Bronchodilator Use.*

Variable	Decline per Year			P Value	
	Placebo Group (N=383)	Tiotropium Group (N=388)	Difference (95% CI)†	Unadjusted	Adjusted‡
Total					
FEV_1 (ml)					
Before bronchodilator use	53±6	38±6	15 (–1 to 31)	0.06	0.06
After bronchodilator use	51±6	29±5	22 (6 to 37)	0.006	0.006
FVC (ml)					
Before bronchodilator use	59±9	46±9	13 (–13 to 39)	0.32	0.36
After bronchodilator use	50±9	35±9	15 (–10 to 40)	0.23	0.26
FEV_1:FVC ratio					
Before bronchodilator use	0.5±0.2	0.3±0.2	0.2 (–0.2 to 0.6)	0.32	0.27
After bronchodilator use	0.7±0.2	0.3±0.2	0.3 (–0.1 to 0.8)	0.10	0.09
FEV_1 (% of predicted value)					
Before bronchodilator use	2.1±0.2	1.6±0.2	0.5 (–0.1 to 1.2)	0.10	0.10
After bronchodilator use	2.1±0.2	1.2±0.2	0.9 (0.2 to 1.5)	0.008	0.007
FVC (% of predicted value)					
Before bronchodilator use	0.6±0.6	0.5±0.5	0.1 (–1.4 to 1.7)	0.86	0.97
After bronchodilator use	0.4±0.5	0.1±0.5	0.3 (–1.1 to 1.8)	0.65	0.75
CAT score <10					
FEV_1 (ml)					
Before bronchodilator use	54±7	37±7	17 (–1 to 35)	0.07	0.07
After bronchodilator use	47±6	28±6	20 (2 to 37)	0.03	0.03
FVC (ml)					
Before bronchodilator use	62±11	54±11	8 (–22 to 38)	0.59	0.62
After bronchodilator use	52±10	43±10	9 (–19 to 37)	0.53	0.55
FEV_1:FVC ratio					
Before bronchodilator use	0.6±0.2	0.2±0.2	0.4 (–0.1 to 0.9)	0.10	0.09
After bronchodilator use	0.5±0.2	0.2±0.2	0.3 (–0.1 to 0.8)	0.16	0.15
FEV_1 (% of predicted value)					
Before bronchodilator use	2.2±0.3	1.5±0.3	0.7 (0.0 to 1.4)	0.06	0.06
After bronchodilator use	1.9±0.3	1.1±0.3	0.8 (0.1 to 1.5)	0.02	0.02
FVC (% of predicted value)					
Before bronchodilator use	0.9±0.7	0.5±0.7	0.4 (–1.6 to 2.3)	0.71	0.84
After bronchodilator use	0.5±0.6	0.1±0.6	0.3 (–1.4 to 2.1)	0.72	0.84
CAT score ≥10					
FEV_1 (ml)					
Before bronchodilator use	48±13	39±11	9 (–24 to 41)	0.60	0.60
After bronchodilator use	63±13	32±11	31 (–2 to 64)	0.07	0.06
FVC (ml)					
Before bronchodilator use	48±20	26±17	21 (–29 to 72)	0.41	0.51
After bronchodilator use	42±20	14±17	28 (–24 to 80)	0.29	0.30
FEV_1:FVC ratio					
Before bronchodilator use	0.4±0.3	0.7±0.3	–0.3 (–1.1 to 0.6)	0.53	0.63
After bronchodilator use	1.1±0.3	0.7±0.3	0.5 (–0.3 to 1.3)	0.26	0.22

Table 2. (Continued.)

Variable	Decline per Year			P Value	
	Placebo Group (N=383)	Tiotropium Group (N=388)	Difference (95% CI)†	Unadjusted	Adjusted‡
FEV_1 (% of predicted value)					
Before bronchodilator use	2.0±0.6	1.8±0.5	0.1 (–1.3 to 1.6)	0.85	0.79
After bronchodilator use	2.6±0.6	1.4±0.5	1.2 (–0.3 to 2.7)	0.11	0.10
FVC (% of predicted value)					
Before bronchodilator use	0.3±1.0	0.3±0.8	–0.1 (–2.6 to 2.4)	0.96	0.95
After bronchodilator use	0.6±1.0	0.0±0.9	0.5 (–2.1 to 3.2)	0.68	0.63

* Plus–minus values are means ±SE per year. A total of 288 patients in the placebo group and 276 in the tiotropium group had a CAT score of less than 10, and 95 patients in the placebo group and 112 in the tiotropium group had a CAT score of 10 or more. Values were measured from day 30 until the end of the trial (including 30 days after discontinuation of the trial regimen). A random-effects model was adopted, with the annual decline at individual time point as the random-effects variable, group assignment and individual baseline values as fixed-effect variables, and age, sex, baseline smoking status, hospitalization, GOLD stage, body-mass index, and individual baseline values as the fixed-effect covariates. The predicted value of FEV_1 was calculated for men as follows: (–2.49+0.043×body height [in cm]–0.029×age [in years])×0.95; and for women as follows: (–2.60+0.040×body height [in cm]–0.025×age [in years])×0.93.

† The difference was calculated as the value in the placebo group minus the value in the tiotropium group. Values may not sum as expected owing to rounding.

‡ P values were adjusted by the above-mentioned fixed-effect covariates, including age, sex, baseline smoking status, hospitalization, GOLD stage, body-mass index, and individual spirometric values at baseline (FEV_1, FVC, percent of predicted FEV_1, and FEV_1:FVC ratio before and after bronchodilator use).

Table 3. Acute Exacerbations of COPD and Hospitalizations Due to COPD.*

Variable	Placebo Group (N=383)	Tiotropium Group (N=388)	Relative Risk for Tiotropium vs. Placebo (95% CI)	P Value
No. of exacerbations per patient-year†				
Total	0.50±0.05	0.27±0.03	0.53 (0.39–0.73)	<0.001
Of moderate or worse severity	0.38±0.04	0.20±0.03	0.51 (0.37–0.72)	<0.001
No. of hospitalizations per patient-year†‡	0.07±0.01	0.03±0.01	0.38 (0.19–0.78)	0.009
Days of exacerbation per patient-year†	3.60±0.40	2.28±0.31	0.63 (0.45–0.89)	0.009
Days of hospitalization per patient-year†	0.65±0.14	0.27±0.09	0.42 (0.19–0.92)	0.03
No. of patients with exacerbation§				
Total — no. (%)	150 (39.2)	112 (28.9)	0.63 (0.47–0.85)	0.002
Of moderate or worse severity — no. (%)	121 (31.6)	87 (22.4)	0.63 (0.45–0.86)	0.004
Resulting in hospitalization — no./total no. (%)‡	30/370 (8.1)	19/378 (5.0)	0.60 (0.33–1.09)	0.09

* Plus–minus values are means ±SE. The number of exacerbations or hospitalizations per patient-year was the number of times of exacerbation or hospitalization for a single patient per year. The days of exacerbation or hospitalization per patient-year was the number of days since the day of onset to the end of treatment for an acute exacerbation of COPD or hospitalization; if the event occurred multiple times, the durations of all the events were taken into account. We assumed that the duration of the acute exacerbation of COPD or hospitalization was 0 days in patients who did not have any event during the trial. Data on the number of hospitalizations per patient-year, the days of exacerbation per patient-year, and the days of hospitalization per patient-year were missing for 14 patients in the placebo group and for 15 in the tiotropium group.

† The relative risk was calculated with the use of Poisson regression, with correction for exposure to the trial regimen and overdispersion.

‡ Patients with incomplete data were not included in this analysis.

§ The comparisons in this category were calculated with the use of the chi-square test.

observed may simply delay the development of more severe disease rather than prevent it.

The prevention of acute exacerbations of COPD has been listed explicitly as a cardinal goal for patients who have COPD of any grade of severity.[15] Tiotropium resulted in a significantly lower fre-

quency of acute COPD exacerbations than placebo, which reaffirms previous reports.[7,9,20] Finally, our trial showed no remarkable differences with regard to side effects (e.g., cardiovascular effects, urinary tract disease) that have been associated with tiotropium as compared with placebo, except for dry mouth or pharyngeal discomfort.

In conclusion, this trial showed that tiotropium was effective in improving lung function and quality of life and resulted in a lower frequency of acute COPD exacerbations than placebo among patients with GOLD stage 1 or 2 disease. Whether early intervention with tiotropium alters the long-term course of COPD remains an open question.

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APPENDIX

The authors' full names and academic degrees are as follows: Yumin Zhou, M.D., Ph.D., Nan-shan Zhong, Ph.D., Xiaochen Li, M.D., Shuyun Chen, M.D., Jinping Zheng, M.D., Dongxing Zhao, M.D., Weimin Yao, M.D., Rongchang Zhi, M.D., Liping Wei, M.D., Bingwen He, M.D., Xiangyan Zhang, M.D., Changli Yang, M.D., Ying Li, M.D., Fenglei Li, M.D., Juan Du, M.D., Jianping Gui, M.D., Bin Hu, M.D., Chunxue Bai, M.D., Ping Huang, M.D., Gang Chen, M.D., Yongjian Xu, M.D., Changzheng Wang, M.D., Biao Liang, M.D., Yinhuan Li, M.D., Guoping Hu, M.D., Hui Tan, M.D., Xianwei Ye, M.D., Xitao Ma, M.D., Yan Chen, M.D., Xiwei Hu, M.D., Jia Tian, M.D., Xiaodan Zhu, M.D., Zhe Shi, M.D., Xiufang Du, M.D., Minjing Li, M.D., Shengming Liu, M.D., Ronghuan Yu, M.D., Jianping Zhao, M.D., Qianli Ma, M.D., Canmao Xie, M.D., Xiongbin Li, M.D., Tao Chen, M.D., Yingxiang Lin, M.D., Lizhen Zeng, M.D., Changxiu Ye, M.D., Weishu Ye, M.D., Xiangwen Luo, M.D., Lingshan Zeng, M.D., Shuqing Yu, M.D., Wei-jie Guan, Ph.D., and Pixin Ran, Ph.D.

The authors' affiliations are as follows: the National Center for Respiratory Diseases, State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Diseases, the First Affiliated Hospital (Y.Z., N.Z., Xiaochen Li, S.C., J. Zheng, D.Z., W.G., P.R.), the Third Affiliated Hospital (L.W., G.H.), and Liwan Hospital (F.L., Y.C.), Guangzhou Medical University, Guangzhou Panyu Center Hospital (R.Z., Yinhuan Li), the First Affiliated Hospital, Sun Yat-sen University (C.X.), and the First Affiliated Hospital of Jinan University (S.L.), Guangzhou, Chenzhou No. 1 People's Hospital, Chenzhou (B. He, H.T.), Guizhou Provincial People's Hospital, Guizhou (X. Zhang, X.Y.), Wengyuan County People's Hospital (C. Yang, Lizhen Zeng, C. Ye) and Shaoguan Iron and Steel Group Company Limited Hospital (T.C.), Shaoguan, Henan Provincial People's Hospital, Zhengzhou (Ying Li, X.M.), the Affiliated Hospital of GuiYang Medical College, GuiYang (J.D., X.H.), the Second People's Hospital of Hunan Province, Changsha (J.G., J.T.), Huizhou First Hospital, Huizhou (B. Hu, Z.S.), Affiliated Zhongshan Hospital of Fudan University (C.B., X. Zhu) and Shanghai Xuhui Central Hospital (R.Y.), Shanghai, Shenzhen Sixth People's Hospital, Shenzhen (P.H., X.D.), the First People's Hospital of Foshan, Foshan (G.C., M.L.), Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology, Wuhan (Y.X., J. Zhao), Xinqiao Hospital, Chongqing (C.W., Q.M.), the Affiliated Hospital, Guangdong Medical University (W. Yao, B.L.), and the Second People's Hospital of Zhanjiang (Xiongbin Li), Zhanjiang, Beijing Chao-Yang Hospital, Beijing (Y. Lin), and Lianping County People's Hospital, Heyuan (W. Ye, X. Luo, Lingshan Zeng, S.Y.) — all in China.

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