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One-year analysis of longitudinal changes in spirometry in patients with COPD receiving tiotropium

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Abstract

Background: Airway medications have not been shown to reduce the loss of lung function in patients with COPD. We explored whether tiotropium 18 μg once daily could slow the rate of decline of lung function over a 1-year period.
Methods: We performed a post-hoc analysis of data from 921 ambulatory COPD patients participating in two, 1-year, double-blind, tiotropium vs. placebo-controlled trials. Serial spirometry was obtained at baseline (before first dose of study drug), on day 8, at 6 weeks, and at 3, 6, 9 and 12 months after start of the study.
Results: Baseline demographics and lung function were comparable. Baseline FEV_1 was 1.01 ± 0.41 (SD) L ($39 \pm 14\%$ predicted). Mean decline in trough FEV_1 (i.e. FEV_1 23–24 h after prior use of medication) between days 8 and 344 was 58 ml/year in the placebo group and 12 ml/year in the tiotropium group ($p = 0.005$ vs. placebo); and between days 50 and 344 was 59 ml/year in the placebo group and 19 ml/year in the tiotropium group ($p = 0.036$ vs. placebo).
Conclusions: Based on a retrospective analysis of 1-year, placebo-controlled clinical trials, tiotropium was associated with a reduced rate of loss of FEV_1. Longer-term trials specifically designed to study this effect are required to confirm this observation.

Keywords: Chronic obstructive pulmonary disease; Tiotropium; Spirometry; Lung function; FEV_1

1. Introduction

Chronic obstructive pulmonary disease (COPD) affects approximately 16 million people in the United States where it is the fourth leading cause of death [1,2]. Airflow obstruction in COPD is generally progressive over a period of years and is only partially reversible [3–5]. Among people who have never smoked, the rate of decline in FEV_1 ranges from 17 to 52 ml per year [3,5–9]. Among smokers, the rate of decline increases to 34–79 ml/year [5–8]. In the Lung Health Study, a large cohort of patients with mild to moderate COPD, the average rate of decline in FEV_1 in continuing smokers was 62 ml/year [3]. Both cross-sectional and longitudinal studies suggest that the rate of decline in lung function after smoking cessation is similar to that in people who have never smoked [3,6–9].

The reversibility of airflow obstruction in COPD is variable and controversial. Tashkin et al. [10] reported that in smokers with mild to moderate airflow limitation over 30% had a decrease of 20% or more in FEV_1 after inhalation of ≤ 5 mg/ml methacholine. Recent studies have suggested that the percentage of COPD patients with reversible airway obstruction exceeds 50% [11,12]. Although airway responsiveness in COPD is variable, there are no studies that have shown that bronchodilators can alter the accelerated rate of decline in lung function over time. The Lung Health study failed to show that inhaled ipratropium can reduce this rate of decline [3]. The only intervention today that has been shown to be effective is smoking cessation [3].

Tiotropium is a new, once-daily, anticholinergic bronchodilator with a long duration of action attributed to slow

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dissociation from airway M_3 muscarinic receptors [13–15]. Two large, long-term, 1-year, placebo-controlled studies conducted in the United States, have shown that once daily inhalation with tiotropium 18 μg significantly improves airflow and forced vital capacity over 24 h in patients with COPD. Furthermore, these benefits were consistently maintained over the year [16]. Since these two trials used an identical protocol, data were pooled to analyze if chronic dosing with tiotropium 18 μg once daily could slow the rate of decline of lung function over the 1-year period of these studies.

2. Methods

2.1. Study subjects

A retrospective analysis of two identical, 1-year, randomized, double-blind, placebo-controlled, parallel-group studies of inhaled tiotropium 18 μg once daily in patients with COPD was performed [16]. Fifty clinical centers participated in these trials. These studies were approved by each center's institutional review board. All patients provided written informed consent prior to participation.

The study groups consisted of outpatients of either gender who were more than 40 years of age and had a clinical diagnosis of COPD, as defined by the American Thoracic Society [4]. Participants were required to have at least a 10-pack-year history of smoking, clinically stable airway obstruction, a forced expiratory volume in 1 s (FEV_1) less than 70% of the forced vital capacity (FVC) and an FEV_1 of less than 65% of the predicted normal value. Patients were excluded if they had a history of asthma, allergic rhinitis, atopy, or a total blood eosinophil count of more than 600/mm^3. Bronchodilator response was not an entry criterion. Patients were excluded if they required regular daytime supplemental oxygen, were on corticosteroid doses exceeding the equivalent of 10 mg of prednisone daily during the month prior to entering the study, had a recent history of myocardial infarction (1 year or less), heart failure (3 years or less), cardiac arrhythmias requiring drug therapy, symptomatic prostatic hypertrophy, or narrow angle glaucoma.

2.2. Study protocol

Following a 2-week baseline period, patients were randomly assigned to receive either tiotropium (18 μg) or placebo. Patients were randomized in 3:2 ratios. Subjects administered, by inhalation, active medication (tiotropium in lactose) or placebo (lactose), one dose each morning in identical-appearing capsules via a dry powder inhaler device (HandiHaler® Boehringer Ingelheim, Ingelheim am Rhein, Germany) [17]. Patients were permitted an albuterol metered dose inhaler, as needed, stable doses of theophylline, inhaled glucocorticoids and an equivalent of 10 mg/day or less of oral prednisone throughout the study. Inhaled anticholinergics (other than study drug) and long-acting inhaled (and oral) beta-agonists were excluded. To treat acute exacerbations during the trial, investigators were permitted to administer what was medically necessary including antibiotics and systemic steroids.

Spirometric testing was conducted on treatment day 1 (baseline), on day 8, at 6 weeks, and at 3, 6, 9 and 12 months of treatment. Drugs were administered at the same time each day (between 7 and 9 am). On test days, FEV_1 and FVC were measured and recorded at 1 h and at 5 min prior to study medication, and at 0.5, 1, 2 and 3 h after dosing. Trough values of FEV_1 and FVC were calculated as the mean of the two pre-dose measurements, i.e. approximately 23 and 24 h after the previous dose of study medication. These were the lowest FEV_1 and FVC values that were obtained between doses of study medication. Spirometric maneuvers were conducted in triplicate and the greatest FEV_1 and FVC were used in subsequent analysis. Predictive values of FEV_1 and FVC were derived from standard reference equations [18]. Spirometers were used as required by ATS standards [19].

To ensure a standardized condition on spirometry testing days, subjects discontinued theophylline 24 h prior to spirometric testing (compliance was ascertained by measuring theophylline levels prior to testing and levels exceeding 5 μg/ml were considered protocol violations). Albuterol and inhaled corticosteroids were stopped at least 12 h prior to spirometric testing.

To determine the change in lung function over time, trough and 3-h post-dose FEV_1 and FVC values from day 8 were compared with those from day 344. Day 8 was chosen as the first trough measurement since several days of therapy are required to reach pharmacodynamic steady-state [20]. An additional analysis comparing spirometric values on day 50 with those measured on day 344 was performed to ensure that analysis at steady state had been achieved.

2.3. Analysis

Data were analyzed using two models. For one model, random coefficient regression (RCR) was used to compare the rate of decline over the year across treatment groups [21]. All randomized patients except those who had less than 2 weeks of data were included in this analysis. Missing data were not imputed for this analysis. For the second model, analysis of covariance (ANCOVA) was used to compare the change in response over the year in the two treatments groups. For this analysis when patients were discontinued due to worsening of their disease (5% of patients), missing data were imputed using the least favorable data observed prior to discontinuation. In all other cases, missing data following patient withdrawal were imputed by carrying the last observation forward. Statistical significance was considered at $p < 0.05$.

3. Results

Of 921 patients enrolled, 550 were randomized to tiotropium and 371 to placebo. There were no differences in the patients' demographic characteristics between studies. The study population had a mean age of 65 years, were predominantly male, smoked an average of 61 pack-years, and had a mean FEV_1 of 1.04 L (Table 1). The groups were similar in all the baseline characteristics.

The acute and chronic bronchodilator improvements with tiotropium have been previously described [16]. There was minimal variability between measures at testing times. The FEV_1 and FVC obtained at 23–24 h were stable over the study period. The mean rate of decline in trough FEV_1 between days 8 and 344 was 58 ml/year in the placebo group and 12 ml/year in the tiotropium group ($p=0.005$; comparison of slopes) (Fig. 1A). The mean rate of decline in trough FEV_1 between days 50 and 344 was 59 ml/year in the placebo group and 19 ml/year in the tiotropium group ($p=0.036$; comparison of slopes) (Fig. 1B). The ANCOVA showed that the pre-dose FEV_1 values (i.e. trough values) (mean ± SE) were elevated in the tiotropium group by 110 ± 10 ml (11 ± 1%) at day 8 and 130 ± 10 ml (13 ± 1%) at day 50 over baseline. These values were superior to placebo by 120 ± 10 and 150 ± 10 ml ($p<0.01$) at days 8 and 50, respectively. Whether using the ANCOVA ($p<0.05$) or RCR model ($p<0.01$), the differences between tiotropium and placebo in rate of decline in pre-dose FEV_1 from days 8 and 50 to 344 were significant (Table 2). While trends were present in favor of tiotropium, there were no significant differences in the mean decline in FEV_1 at 3 h after dosing between the tiotropium and placebo groups (from days 8 to 344 or from days 50 to 344) whether using the RCR or ANCOVA model (Table 2). The analyses for FVC followed a similar pattern. For additional sensitivity, a simple repeated measures analysis of variance of trough FEV_1 was conducted and showed a 7 ml mean decline (days 8 to 344) for the tiotropium group and a 45 ml mean decline for the placebo group ($p=0.012$).

Table 1
Baseline patient characteristics in the tiotropium ($n=550$) and placebo ($n=371$) groups [16]

	Tiotropium	Placebo
Age (years)[a]	65.1 ± 8.6	65.4 ± 8.9
Males (%)	67	63
Duration of COPD (years)[a]	8.6 ± 7.4	8.1 ± 6.8
Smoking history (pack-years)[a]	62.6 ± 30.6	59.0 ± 30.3
Current smokers (%)	34	34
Screening spirometry[a]		
FEV_1 (L)	1.04 ± 0.41	1.00 ± 0.44
FEV_1 (% predicted)	39.1 ± 12.7	38.1 ± 14.1
FVC (L)	2.31 ± 0.79	2.23 ± 0.78
FEV_1/FVC (%)	45.8 ± 11.6	45.5 ± 11.6

Adapted from Casaburi et al. Eur Respir J 2002;19:217–24.
[a] Mean ± SD.

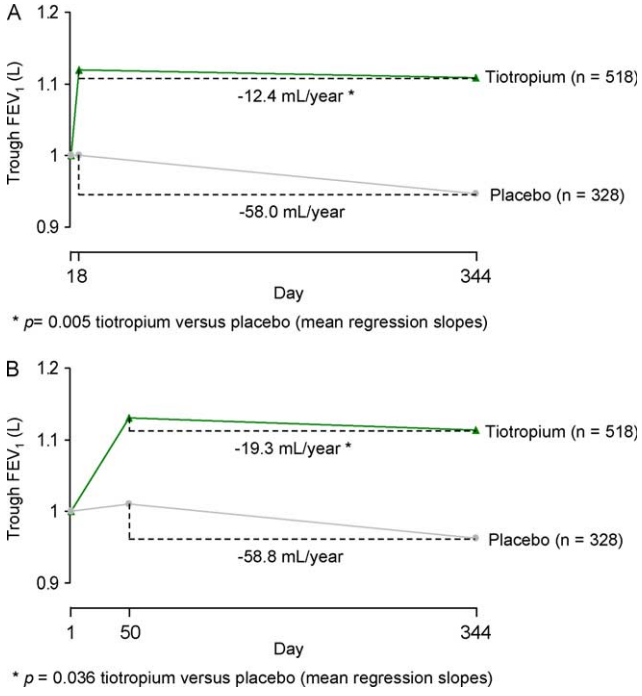

Fig. 1. Mean change in trough FEV_1 (ml/year) in the tiotropium and placebo groups from days 8 to 344 (A) and from days 50 to 344 (B).

An analysis based on smoking status showed that the ex-smokers were older than current smokers (67 vs. 61 years) and had a lower mean FEV_1 at baseline (0.97 vs. 1.08 L, respectively). A change in smoking status during the study period was assumed to be similar between treatment groups. In both ex-smokers and smokers, the rate of decline in trough FEV_1 was numerically lower in the tiotropium group as compared with the placebo group (Table 3). For FEV_1, statistically significant differences in the rate of decline in trough FEV_1 were observed only for ex-smokers from day 8. For FVC, significant (or near-significant) differences were observed only for smokers. It is likely that the failure to show statistically significant differences for FEV_1 in smokers from either day 8 or 50 may be due to the smaller numbers (and hence reduced statistical power) when the analysis is stratified by smoking status.

Additional subgroup analyses on trough FEV_1 were conducted according to baseline use of inhaled corticosteroids and baseline FEV_1. The mean ± SE difference (tiotropium-placebo) in the rate of decline in FEV_1 for the subgroup using inhaled corticosteroids ($n=347$) was 49.2 ± 22.8 ml ($p=0.031$) and was 30.6 ± 18.8 ml ($p=0.103$) for those not using inhaled corticosteroids ($n=499$). The mean ± SE difference (tiotropium-placebo) in the rate of decline in FEV_1 for the subgroup with a baseline $FEV_1<50\%$ predicted ($n=666$) was 51.7 ± 16.3 ml ($p=0.002$) but was −12.4 ± 30.8 ml ($p=0.688$) for those with a baseline $FEV_1>50\%$ predicted ($n=180$), the latter analysis being limited by the significantly smaller sample size.

Table 2
Mean ± SE change in spirometry (ml/year) in the tiotropium ($n=518$) and placebo ($n=328$) groups

		Days 8–344		Days 50–344	
		Tiotropium	Placebo	Tiotropium	Placebo
FEV_1 trough	RCR	−12 ± 10**	−58 ± 13	−19 ± 12*	−59 ± 15
	ANCOVA	−10 ± 10*	−40 ± 10	−20 ± 10*	−50 ± 10
FEV_1 3-h post-dose	RCR	−42 ± 11	−50 ± 14	−41 ± 12	−49 ± 16
	ANCOVA	−40 ± 10	−40 ± 10	−30 ± 10	−40 ± 10
FVC trough	RCR	0 ± 20	−50 ± 26	−16 ± 24	−45 ± 31
	ANCOVA	−10 ± 20	−50 ± 20	−40 ± 20	−50 ± 20
FVC 3-h post-dose	RCR	−79 ± 21	−71 ± 27	−74 ± 25	−54 ± 32
	ANCOVA	−90 ± 10	−90 ± 20	−80 ± 20	−80 ± 20

*$p<0.05$ tiotropium vs placebo; **$p<0.01$ tiotropium vs placebo; RCR, random coefficient regression; ANCOVA, analysis of covariance.

4. Discussion

Recently published 1-year studies of tiotropium 18 μg once-daily in COPD have demonstrated that tiotropium provides 24-h bronchodilation, improvements in dyspnea, decreases in exacerbations, and improvements in health-related quality of life [16,22]. The present post-hoc analysis of two 1-year, placebo-controlled trials suggests that patients continuously using tiotropium have a significant reduction in the rate of decline of their trough (i.e. morning pre-dose) FEV_1 over time as compared with placebo. There were also changes in FVC decline but these changes were more variable.

Bronchodilators are considered first-line therapy in the management of symptomatic COPD [1,4,5]. Although, the Lung Health Study showed that prescribed regular use of ipratropium did not alter the annual decline in FEV_1 in patients with mild COPD [3], several studies have shown that bronchodilators have other effects that may be clinically important such as reduction of dynamic hyperinflation, increased inspiratory capacity, decreased work of breathing, improved ventilatory capacity, and less dyspnea during activity and formal exercise testing [16,23]. The present analysis suggests that patients receiving long-term tiotropium once daily have a lower rate of decline in spirometric indices. The specific mechanism for these changes is unclear; possible hypotheses include a long-term unrecognized benefit of continuous (i.e. 24 h) bronchodilation, an association with a reduction in exacerbations or a pharmacologic effect related to anticholinergic mechanisms.

The decline in lung function with age occurs along a slowly accelerated curvilinear path [6]. Several factors are known to influence the rate of decline in lung function over time. The rate of decline of FEV_1 is known to be steeper for patients who are active smokers than for non-smokers. It has been reported that those who quit smoking completely experience a rate of decline in lung function less than those patients who continue to smoke [3,4,6]. After smoking cessation, only a small amount of lung function is regained but the slope of subsequent decline is substantially reduced [3,6,9]. In the Lung Health Study, among the subjects not receiving ipratropium who stopped smoking at the first annual visit, mean post-bronchodilator FEV_1 increased 47 ml, while the participants who did not stop smoking showed a mean decline in post-bronchodilator FEV_1 of 49 ml [9]. Subsequently, the rate of decline in FEV_1 was only 31 ml/year among the sustained quitters, in contrast to 62 ml/year in the continuing smokers [9]. In the post-hoc analysis of the two 1-year studies comparing tiotropium with placebo, a less decline in FEV_1 was observed in the current smokers vs. the ex-smokers. This seems counterintuitive and we can only speculate on the basis for this observation. The differences may simply represent variability. However, it is possible that those who stopped smoking were those with more rapidly progressing disease such that continued smoking was no longer tolerable (note that mean baseline FEV_1 was lower in the ex-smokers); whereas, if the current smokers were those with more gradual disease progression, they could indeed tolerate continued smoking.

In most individuals, the change in FEV_1 is relatively steep later in life [6]. There is a direct relationship between initial FEV_1 and the slope of FEV_1 decline [24]. There is also a stronger association between a low FEV_1/FVC

Table 3
Mean ± SE rate of decline (ml/year) in trough FEV_1 and FVC in patients treated with tiotropium (current smokers ($n=175$) and ex-smokers ($n=342$)) or placebo (current smokers ($n=115$) and ex-smokers ($n=212$))

	Tiotropium	Placebo	Difference between groups	p-value
FEV_1 change				
Days 8–344				
Ex-smokers	−17 ± 12	−68 ± 16	51 ± 20	0.01
Current smokers	−4 ± 18	−41 ± 22	37 ± 28	0.19
Days 50–344				
Ex-smokers	−29 ± 14	−64 ± 18	35 ± 23	0.13
Current smokers	−1 ± 20	−51 ± 25	50 ± 32	0.12
FVC change				
Days 8–344				
Ex-smokers	−35 ± 25	−62 ± 32	27 ± 40	0.50
Current smokers	72 ± 35	−40 ± 43	111 ± 56	0.05
Days 50–344				
Ex-smokers	−56 ± 29	−48 ± 40	−9 ± 48	0.85
Current smokers	67 ± 42	−58 ± 52	125 + 66	0.06

and subsequent decline in FEV_1 in men, but not in women [25]. Age, which cannot be separated from the number of years of cigarette smoking, is clearly a risk factor for a more rapid decline of lung function [26]. The difference in decline in FEV_1 between tiotropium and placebo was not statistically significant for smokers, nor was it significant for ex-smokers when the slope was calculated from day 50. However, the lack of statistical significance likely reflects the smaller sample sizes (and associated inadequate statistical power) when evaluating the subgroups based on smoking status. In addition, smoking status was only ascertained at the beginning of the tiotropium clinical trials but not at subsequent visits. Thus, we cannot be certain of conclusions regarding smoking status.

There are several limitations to our analysis. Tiotropium is known to have a mean plasma half-life of about 1 week. The trough lung function value between 23 and 24 h after the prior dose is optimal to assess the 24-h effect of the drug. We chose to analyze the rate of decline from trough at days 8 and 50 to trough at day 344, because it represents a comparison at relatively stable and comparable levels. There is a slight bias in that patients treated with tiotropium are assessed in a state of submaximal bronchodilation that is still present at trough, whereas placebo patients are in a completely non-bronchodilated state. The alternatives for demonstrating an alteration in the expected decline in lung function are not possible with this retrospective analysis. The patients would either need to be studied after the drug was discontinued for at least 3 weeks (wash-out period) to eliminate residual bronchodilator effects of tiotropium, or the rate of decline in lung function could have been assessed from peak post-bronchodilator measurements to eliminate the influence of variable bronchomotor tone. Published studies have, in general, used post-bronchodilator values for the analysis of rate of decline in lung function [3]. However, this strategy would have required administering short-acting bronchodilators to both groups of subjects at each spirometry test session and obtaining measurements at the expected time of peak action of the bronchodilator. Comparison of the changes in 3-h post-dosing FEV_1 values from days 8 and 50 to 344 between the tiotropium and placebo groups revealed only small and non-significant differences in the 1-year decline between the two groups. However, while this analytic strategy may have captured peak or near-peak bronchodilator values in the tiotropium group, FEV_1 values in the placebo group could still have been influenced by variable bronchomotor tone.

Another potential limitation is the duration of the study. Prior long term studies in COPD have shown different variations in lung function over time. The Euroscop and Lung Health Study trials showed markedly different results for the first 6 months, which were not present during the remainder of the study period. The changes in morning pre-dose FEV_1 seen with tiotropium were measured after pharmacodynamic steady state was obtained at day 8 and remained similar for up to 1-year. To more fully characterize our observations, clinical studies will have to be conducted over a longer period of time.

The retrospective nature of the data analysis needs to be acknowledged. While the data reported in this manuscript were collected in double-blinded, placebo-controlled studies conducted in a rigorous fashion, the studies were not specifically designed to assess the rate of decline in pulmonary function, thus other variables such as plethysmographic lung volumes were not obtained. Furthermore, there was a differential discontinuation rate with more placebo treated patients discontinuing participation during the trial; however, due to the type of analysis performed it is unlikely that this had a significant influence on the results. One could argue that the more severely ill patients were not able to complete the study period and as a consequence the results may underestimate the tiotropium effect.

A question may arise as to why, in the present study, tiotropium demonstrated long-term changes in rate of loss of FEV_1 compared to placebo, whereas, in the Lung Health Study, ipratropium (another inhaled anticholinergic) did not [3]. Although the Lung Health Study failed to reveal any changes in the annual rate of lung function decline, the group prescribed ipratropium bromide used an average of only two doses per day according to canister weights indicating that there were only limited periods of anticholinergic treatment throughout the day [27]. Inhaler compliance in the Lung Health Study was fair to poor (approximately 50%) when assessed by microelectronic monitoring while compliance with tiotropium was excellent [27,28]. It is possible that full 24-h sustained bronchodilation is the factor that distinguishes these discordant results. In addition, the bronchodilation seen with 18 μg once daily of tiotropium is superior to that of 40 μg four times daily of ipratropium [22].

Tiotropium has recently been demonstrated to lead to reductions in COPD exacerbations [16]. Exacerbations may have an adverse influence on lung function and patients' overall well-being beyond short-term fluctuations. In addition, frequent exacerbations have been shown to reduce health status as measured by the Saint George's Respiratory Questionnaire [29]. In 1-year studies, tiotropium led to sustained improvements in health status [16,22]. The positive influence on exacerbations and health status is supportive of the findings from the present analysis of long-term benefits in the course of lung function change; however, the 1-year study period is inadequate to draw definitive conclusions regarding possible disease modification. Only a long term study of tiotropium 18 μg once-daily in patients with COPD will provide evidence to confirm or refute the 1-year observations regarding the rate of decline in FEV_1.

It is interesting to note the inconsistencies between the statistically significant decrease in the rate of decline in trough FEV_1 with tiotropium compared with placebo

(approximately 45 ml) and the smaller decrease in the rate of decline in peak FEV_1 with tiotropium compared with placebo (approximately 9 ml). In the Lung Health Study, variability in FEV_1 measurements was reduced by administration of inhaled beta-agonists at the time of spirometry [3]. Comparatively, in the 1-year tiotropium trials, spirometry was performed in the morning at approximately the same time of day with scrupulous attention to appropriate washout of other bronchodilators. Possible reasons for the discrepancy of trough FEV_1 and peak FEV_1 rates of decline with tiotropium compared with placebo include an altered response to inhaled tiotropium over 1-year, enhanced circadian variability over time, or an influence of undefined mediators or pathogenic processes, although these possible explanations seem unlikely.

In summary, the present retrospective analysis documents a potential long-term benefit of an airway medication on the natural history of COPD. However, future studies are required to confirm this preliminary observation and need to pre-specify a primary outcome of the rate of decline based on continuing evaluation of trough effects, as well as an assessment of peak post-bronchodilator effects that eliminates bronchomotor tone to the greatest extent possible through the use of a combination of an inhaled short-acting beta-agonist and an inhaled short-acting anticholinergic in all participants prior to spirometry testing.

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References

[1] Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. NHLBI/WHO workshop report. Bethesda, National Heart, Lung and Blood Institute, April 2001; Update of the Management Sections, GOLD website (www.goldcopd.com). Date updated: 1 July 2003.

[2] Hoyert DL, Kochanek KD, Murphy SL. Deaths: final data for 1997. Natl Vital Stat Rep 1999;47:1–104.

[3] Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, Conway Jr WA K, anner P, O'Hara P. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV_1. The Lung Health Study. JAMA 1994; 272:1497–505.

[4] American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995;152:S77–121.

[5] Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, Yernault JC, Decramer M, Higenbottam T, Postma DS, Rees J. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur Respir J 1995;8:1398–420.

[6] Fletcher CM, Peto R, Tinker CM. The natural history of chronic lung disease in working men in London. New York: Oxford University Press; 1976.

[7] Ferguson GT, Enright PL, Buist AS, Higgins MW. Office spirometry for lung health assessment in adults: A consensus statement from the National Lung Health Education Program. Chest 2000;117:1146–61.

[8] Peat JK, Woolcock AJ, Cullen K. Decline of lung function and development of chronic airflow limitation: a longitudinal study of non-smokers and smokers in Busselton, Western Australia. Thorax 1990;45:32–7.

[9] Scanlon PD, Connett JE, Waller LA, Altose MD, Bailey CW, Buist AS, Tashkin for the Lung Health Study Research Group DP. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The Lung Health Study. Am J Respir Crit Care Med 2000;161:381–90.

[10] Tashkin DP, Altose MD, Bleecker for the Lung Health Study Research Group ER. The lung health study: airway responsiveness to inhaled methacholine in smokers with mild to moderate airflow limitation. Am Rev Respir Dis 1992;145:301–10.

[11] Mahler DA, Donohue JF, Barbee RA, Goldman MD, Gross NJ, Wisniewski ME, Yancey SW, Zakes BA, Rickard KA, Anderson WH. Efficacy of salmeterol xinafoate in the treatment of COPD. Chest 1999;115:957–65.

[12] Dorinsky PM, Reisner C, Ferguson GT, Menjoge SS, Serby CW, Witek Jr TJ. The combination of ipratropium and albuterol optimizes pulmonary function reversibility testing in patients with COPD. Chest 1999;115:966–71.

[13] Littner MR, Ilowite JS, Tashkin DP, Friedman M, Serby CW, Menjoge SS, Witek TJ. Long-acting bronchodilation with once-daily dosing of tiotropium (Spiriva) in stable chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000;161:1136–42.

[14] Disse B, Speck GA, Rominger KL, Witek Jr TJ, Hammer R. Tiotropium (Spiriva): mechanistical considerations and clinical profile in obstructive lung disease. Life Sci 1999;64:457–64.

[15] Witek Jr T, Souhrada JF, Serby CW, Disse B. Tiotropium (Ba679). Pharmacology and early clinical observations. Anticholinergics in the upper and lower airways. New York: Marcel Dekker; 1999 p. 137–52.

[16] Casaburi R, Mahler DA, Jones PA, Wanner A, San Pedro G, ZuWallack RL, Menjoge SS, Serby CW, Witek Jr T. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. Eur Respir J 2002;19:217–24.

[17] Chodosh S, Flanders JS, Kesten S, Serby CW, Hochrainer D, Witek Jr TJ. Effective delivery of particles with the HandiHaler dry powder inhalation system over a range of chronic obstructive pulmonary disease severity. J Aerosol Med 2001;14:309–15.

[18] Morris JF, Koski A, Temple WP, Claremont A, Thomas DR. Fifteen-year interval spirometric evaluation of the Oregon predictive equations. Chest 1988;93:123–7.

[19] American Thoracic Society. Standardization of spirometry: 1994 update. Am J Respir Crit Care Med 1995;152:1107–36.

[20] Van Noord JA, Smeets JJ, Custers FLJ, Korducki L, Cornelissen PJ. Pharmacodynamic steady state of tiotropium in patients with chronic obstructive pulmonary disease. Eur Respir J 2002;19:639–44.

[21] Laird NM, Ware JH. Random-effects models for longitudinal data. Biometrics 1982;38:963–74.

[22] Vincken W, Van Noord JA, Greefhorst APM, Bantje ThA, Kesten S, Kordicki L, Cornelissen PJG. Improved health outcomes in patients with COPD during one year treatment with tiotropium. Eur Respir J 2002;19:209–16.

[23] O'Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;160:542–9.

[24] Burrows B, Knudson RJ, Camilli AE, Lyle SK, Lebowitz MD. The "horse-racing effect" and predicting decline in forced expiratory volume in one second from screening spirometry. Am Rev Respir Dis 1987;134:788–93.
[25] Burrows B. Airways obstructive diseases: pathogenetic mechanisms and natural histories of the disorders. Med Clin North Am 1990;74: 547–59.
[26] Ebi-Kryston KL. Predicting 15 year chronic bronchitis mortality in the Whitehall Study. J Epidemiol Community Health 1989;43: 168–72.
[27] Rand CS, Nides M, Cowles MK, Wise RA, Connett J. Long-term metered-dose inhaler adherence in a clinical trial. The Lung Health Study Research Group. Am J Respir Crit Care Med 1995;152:580–8.
[28] Kesten S, Flanders J, Serby CW, Witek TJ. Compliance with tiotropium, a once daily dry powder inhaled bronchodilator, in one year COPD trials. Chest 2000;118:191S.
[29] Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157:1418–22.