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Original Research Article

Significance of Tiotropiumin Early Chronic Obstructive Pulmonary Disease

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Abstract

Introduction: Chronic inflammatory lung disease (COPD) can be affected around 4% to 10% of people. Cigarette smoking is the main cause of COPD along with the environment and genetic variables which also increase the disease burden. On the other hand, the intention of COPD management, through different kinds of activities they want to prevent quitting smoking as well as enhance environmental sustainability. In addition, due to this COPD, people are several kinds of difficulties such as tiotropium lowering air trapping, alleviating exertional dyspnea, increasing exercise tolerance, and others.

Aims and Objectives: To find out the efficacy of tiotropium in managing exacerbation of COPD.

Methods: This future research will be conducted on kids who are between 6 to 12 years and collect their stool samples and other important data has been collected through this research. In addition, these stool samples have collected in wide-mouthed containers as well as it has been delivered in under an hour to the lab. Therefore, this data has been organised and examined as per the share of parasites based on the circumstance and age of the sick people.

Results: This research has discovered that FEV1 can happen before bronchodilation. Similarly, this placebo group would be higher than the tiotropium group. In addition, at the same, it would be noticeable the bronchodilation can $p<0.05$. Therefore, this research has illustrated that sick people feel exacerbation significantly higher within two years. Even this Placebo group is compared with the Tiotropium group ($p<0.05$).

Conclusion: This research has concluded that tiotropium can prevent COPD exacerbations compared to a placebo, through previous case studies. On the other hand, from dry mouth or pharynx discomfort, equally, if this trial does not indicate any significant differences between tiotropium and placebo in the duration of any negative circumstances, such as cardiovascular effects or urinary tract infection.

Keywords: tiotropium, chronic obstructive pulmonary disease, bronchodilator, pulmonary disease.

Introduction

The fourth biggest cause of death worldwide, COPD is thought to affect 4% to 10% of individuals. Although cigarette smoking is the main contributor to COPD,

environmental and genetic variables also increase the disease burden. By encouraging quitting smoking and enhancing air quality, COPD management's main goal is illness prevention. The treatment and prevention of exacerbations, slowing the disease's development, improving symptoms and general health status, and lowering mortality are all crucial objectives of COPD therapy [1,2]. Although inhaled bronchodilators are crucial for managing COPD exacerbations and alleviating chronic symptoms, they have not been proven to lower mortality or halt the disease's characteristically rapid deterioration in lung function [3]. Beta-adrenergic agonists plus anticholinergics are the two main kinds of inhaled bronchodilators frequently used for COPD. Longer-acting bronchodilators from both pharmacological families have been widely adopted into clinical practice in recent years, either replacing or supplanting shorter-acting medications [4]. Tiotropium, a recently created, long-acting, strong anticholinergic drug, was authorized for use in Europe in 2002 and in the US and Canada in 2004. It is the subject of this article. The study discussed what is known thus far about the therapeutic advantages and safety of this medication, mostly based on the findings of peer-reviewed multi-dose, randomized, controlled trials [5,6].

Chronic Obstructive Pulmonary Disease (COPD) affects 10.5% of persons globally and 8.9% of people in China who are 40 years of age or older [7]. According to estimates, COPD will have the seventh-highest global burden of any disease by 2030. It is currently the third major cause of death worldwide. 3-5 More than 70.9% of COPD patients have stage 1 (mild) or stage 2 (moderate) disease according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), meaning they have very mild to no obvious respiratory symptoms including dyspnea and exercise limitation. (Patients with GOLD stage 1 COPD have an FEV1 between 50% and 79% of the anticipated value, while those with GOLD stage 2 illness have an FEV1 of 80% of the projected value [8-10] This circumstance might explain why they didn't see a doctor very often before their COPD got worse. Long-acting anticholinergic bronchodilator tiotropium (Spiriva, Boehringer Ingelheim) interacts specifically with muscarinic receptors on seamless cells in the airway [11,12]. Tiotropium lowers air trapping, alleviates exertional dyspnea, increases exercise tolerance, and enhances health-related quality of life in individuals with moderate-to-severe COPD [13]. 7-9 Conversely, there is limited information available about the management of COPD in the GOLD stage 1 & initial phase 2 (FEV1 60% of the expected value). Tiotropium medication increased lung function in patients with GOLD stage 1 and initial phase 2 disease (as defined by FEV1 and forced pulse rate [FVC]) in small studies and group analysis of trials involving COPD patients. In individuals having GOLD stage 1 or 2 COPD, we performed a prospective trial to examine the impact of tiotropium on FEV1 [14-16].

Methods

Study design

This is a prospective, randomized, double-blind, placebo-controlled phase 4 trial, conducted between January 2020 to December 2022. The study considered patients who visited hospital's outpatient department with GOLD stage 1 or 2 COPD. The major end state was the between group variation in the change in FEV1 prior to bronchodilator usage from baseline to 24 months. The FEV1 after bronchodilator usage at 24 months since baseline and the FVC prior to and following bronchodilator use at 24 months since baseline were included as secondary end goals.

Inclusion and exclusion criteria

Patients who came to the outpatient department of our hospital who follow the study protocol and give informed consent

for the study are included. Patients who provide informed consent for the study are included in the study. Of the total 70 patients are included in the study. Age between 40 and 85 years, a diagnosis of COPD in GOLD stages 1 or 2, defined as an FEV1: FVC ratio less than 0.70 after the use of bronchodilators plus respiratory symptoms, a history of exposure to risk factors, or both, and an FEV1 of 50% or more of the predicted value, measured 20 minutes after the inhalation of 400 g of albuterol, were the primary inclusion criteria.

Patients who did not follow the study protocol did not finish it, or did not provide consent were not included in the study. A COPD exacerbation that occurred within 4 weeks of screening, large-airway disease (such as cancer), asthma, and severe systemic disease were major exclusion factors.

Statistical analysis

The study has used SPSS 25 and MS Excel for effective statistical analysis. Multiple analyses were conducted and FEV1 was compared "before" and "after" use of bronchodilator as dependent variable. The study employed ANOVA test. Two-sided significant 5% level was considered. The variables like FEV1, follow-up visits and hospital was considered as fixed effects while participants were taken as random effects. The continuous variables were expressed as mean±standard deviation while discrete variables were expressed as frequency and percentages.

Ethical approval

Thorough explanation was given to all the patients and their guardians. Each patient or their guardian on their behalf, had to give consent for the study. The Ethical Committee of the hospital approved the study process.

Results

Patients in the complete analysis set had comparable baseline values in the two groups. The median smoking index (the number of packs of cigarettes smoked per day, multiplied by the years of smoking) was 56.3 pack-years for the placebo group and 51.3 pack-years for the tiotropium group, respectively. The mean age of the patients was 64.2 years for the placebo group and 65.3 years for the tiotropium group. Before bronchodilator use, the mean FEV1 in the placebo and tiotropium groups was 1.89 liters (74.1% of the predicted value) and 1.83 liters (73.1% of the predicted value), respectively. After bronchodilator use, the mean FEV1 was 1.98 liters (78.6% of the predicted value) and 1.94 liters (77.5% of the predicted value).

Table 1: Baseline characteristics of patients in this study

Characteristic	Placebo group (N=32)	Tiotropium group (N=38)	*p*-value
Age - yr	64.2 ± 9.2	65.3 ± 8.8	0.56
Male sex- no. (%)	28 (87.5%)	30 (83.3%)	0.51
Body mass index	23.1 ± 3.5	23.2 ± 3.7	0.56
Smoking status			
Never smoked	7 (21.9%)	8 (22.2%)	0.85
Former smoking	12 (37.5%)	13 (36.1%)	
Current smoking	13 (40.6%)	15 (41.7%)	
Smoking index- pack yr	56.3 ± 87.1	51.3 ± 56.9	0.96
Duration of COPD -days	209 ± 567	203 ± 655	0.87
Previous medication for respiratory disease- no. (%)	1 (3.1%)	2 (5.5%)	0.88
Previous respiratory disease other than	6 (18.7%)	8 (22.2%)	0.12

COPD- no. (%)			
Ayurvedic medicines for respiratory disease- no. (%)	2 (6.2%)	1 (2.8%)	0.16
Spirometric values at baseline			
Before bronchodilator use			
FEV1-liters	1.89 ± 0.57	1.83 ± 0.48	0.56
FEV1- % predicted	74.1 ± 17.3	73.1 ± 15.9	0.54
FVC- liters	3.12 ± 0.83	3.11 ±0.81	0.81
FEV1: FVC ratio	57.9 ± 8.5	58.0 ±7.5	0.82
After bronchodilator use			
FEV1-liters	1.98 ± 0.56	1.95 ±0.54	0.73
FEV1- % predicted	78.6 ± 17.4	77.5 ± 15.3	0.89
FVC- liters	3.27 ± 0.75	3.24 ± 0.76	0.78
FEV1: FVC ratio	59.6 ± 7.5	61.0 ± 7.6	0.54
Airflow reversibility - no. (%) ‖	5 (15.6%)	7 (19.4%)	0.13
Gold stage- no. (%)			
1	14 (43.7%)	16 (44.4%)	
2	18 (56.2%)	20 (55.5%)	
CAT score			
Mean score	6.5 ± 5.7	7.6 ± 6.4	0.19
Distribution- no. (%)			0.21
<10	24 (75%)	26 (72.2%)	
≥ 10	8 (25%)	10 (27.7%)	
mMRC dyspnea scale score			
Mean score	0.11 ± 0.8	0.9 ± 0.8	0.71
Distribution- no. (%)			0.95
<2	29 (90.6%)	32 (88.8%)	
≥2	4 (12.5%)	5 (13.3%)	

At 24 months, the FEV1 before bronchodilator usage was substantially greater in the tiotropium group than in the placebo group at each visit, with a between-group difference of 157 ml (95% CI, 123 to 192; P0.001). In comparison to the placebo group, the FVC was noticeably greater in the tiotropium group. I bars show a 1 SD. Tiotropium usage significantly delayed the onset of the first acute COPD exacerbation compared to placebo. When compared to a placebo, tiotropium had a lower prevalence of acute COPD exacerbation [table 2].

Table 2: Forced Vital Capacity (FVC) and Forced Expiratory Volume in 1 Second (FEV1) before and after the use of bronchodilators and the risk of acute exacerbations of COPD over time

Month	**(FEV1 in liters)**			
	Tiotropium after bronchodilation	**Tiotropium before bronchodilation**	**Placebo after bronchodilation**	**Placebo before bronchodilation**
0 month	1.92	1.8	1.93	1.82
1 month	1.96	1.89	1.9	1.76
6 months	1.97	1.89	1.87	1.73
12 months	1.95	1.87	1.85	1.72

18 months	1.93	1.85	1.83	1.7
24 months	1.92	1.83	1.82	.69
FVC (lit)				
0 month	3.22	3.09	3.23	3.1
1 month	3.24	3.15	3.18	3.3
6 months	3.26	3.17	3.19	3.2
12 months	3.25	3.14	3.16	3.1
18 months	3.24	3.13	3.14	2.97
24 months	3.21	3.11	3.13	2.99

The study found that the patients with exacerbation was significantly higher from 0 to 24 months in Placebo group as compared to Tiotropium group (p<0.05).

Table 3: Findings of incidences of acute exacerbation of COPD in placebo and tiotropium group

Month	Patients with Exacerbation (%)		Hazard Ratio*	*p*-value
	Placebo	Tiotropium		
0 month	0	0	0.65	0.000031
3 months	12	6		
6 months	21	13		
9 months	23	15		
12 months	26	20		
15 months	32	23		
18 months	36	24		
21 months	43	25		
24 months	45	26		

The table 4 shows that the FEV1 before bronchodilation in placebo group is higher than the tiotropium group and the same is seen after bronchodilation (p<0.05). Also the FVC values before and after bronchodilation are more in placebo group than tiotropium group. There is a significant difference in the percentages of FVC in both the groups.

Table 4: Annual Declines in the FEV1, FVC, FEV1:FVC Ratio, and % of Predicted FEV1, % of Predicted FVC, Before and After Bronchodilator Use

Variable	Yearly decline			
	Placebo group	Tiotropium group	Difference (95% CI) †	*p*-value
Total				
FEV1 (ml)				
Before bronchodilator use	54 ± 5	37 ± 7	16 (-2 to 30)	0.05
After bronchodilator use	52 ± 5	30 ±7	23 (5 to 36)	0.005
FVC (ml)				
Before bronchodilator use	58 ± 10	45 ± 8	14 (-14 to 38)	0.35
After bronchodilator use	51 ± 10	36 ± 8	16 (-11 to 41)	0.25
FEV1: FVC ratio				
Before bronchodilator use	0.6 ± 0.1	0.4 ± 0.1	0.3 (-0.3 to 0.5)	0.26
After bronchodilator use	0.8 ± 0.1	0.4 ± 0.1	0.4 (-0.2 to 0.7)	0.08
FEV1 (% of predicted value)				
Before bronchodilator use	2.2 ± 0.1	1.7 ± 0.1	0.6 (-0.2 to 1.3)	0.09

After bronchodilator use	2.2 ± 0.1	1.3 ± 0.1	0.8 (0.3 to 1.6)	0.006
FVC (% of predicted value)				
Before bronchodilator use	0.7 ± 0.5	0.6 ± 0.4	0.2 (-1.5 to 1.8)	0.96
After bronchodilator use	0.5 ± 0.4	0.2 ± 0.4	0.4 (-1.2 to 1.7)	0.76

Discussion

There is a continuous discussion about whether COPD patients encountered in actual clinical settings are adequately represented in COPD randomized controlled trials (RCTs). It is believed that individuals with particular traits or risk factors may not be able to participate in RCTs due to their strict inclusion and exclusion criteria. Both a database of participants from 35 non - randomized tiotropium RCTs and a systematic literature review of extensive observational studies carried out in people with confirmed diagnoses of COPD between 1990 and 2013 were examined. At baseline, the two patient populations' demographics and comorbidities that are more prevalent in people with COPD were compared. Patient comorbidities in the aggregated tiotropium RCTs were categorized using the Standardised MedDRA Queries, Pharmacovigilance(PV) endpoints, and Medicinal Dictionary for Regulating Activities, to allow comparability with the observational studies. It is concluded that the clinical profile of COPD patients participating in the tiotropium study program appears to broadly match the set of clinical traits, including cardiovascular comorbidities, documented for "real-life patients." Patients with more serious diseases were more frequently included in the tiotropium RCTs than in the observational studies [17].

As the first LAMA for COPD to be used in clinical settings, tiotropium bromide is given once a day due to its prolonged duration of action. At first, tiotropium was only accessible as a dry powder inhaler for inhalation (DPI). Later, a soft mist inhaler was used to deliver tiotropium as just an inhalation spray (SMI). The SMI was created to eliminate or lessen some of the problems with existing inhalers kinds. Tiotropium was found to be safe and to significantly enhance lung function, wellness quality of life, and workout endurance in patients with COPD when compared to placebo or active comparators. It also decreased dyspnea, lung inflation, exacerbations, and the need for rescue treatment. These encouraging efficacy results led to the investigation of tiotropium in a fixed-dose combination with long-acting 2-agonist olodaterol. With an emphasis on pivotal studies, we present an overview of tiotropium studies for COPD treatment in this review. It is concluded that for the long-term maintenance therapy of COPD and for lowering COPD exacerbations, tiotropium is a safe and effective once-daily LAMA. The SMI produces an aerosol with an exceed percentage that has a low velocity and long duration and causes noticeable drug deposition in the lungs. Furthermore, high inspiratory flow velocities are not necessary [18].

As a result of their lack of symptoms, patients with mild to severe chronic obstructive pulmonary disorder (COPD) rarely need to take medication. In patients who had mild or severe COPD, our hypothesis was that long-term tiotropium administration would enhance lung capacity and lessen the pace of deterioration in lung capacity [19].

We randomly assigned 841 COPD patients with a Global Action plan for Chronic Obstructive Lung Disease (GOLD) initiation phase (mild) or stage 2 (moderate) magnitude to receive a once-daily inhaled dose (18 g) of tiotropium (419 patients) or a matching placebo (422 patients) for 2 years in a multicenter, randomized, double-blind, placebo-controlled trial that's been carried out in China. The forced expiratory

volume in 1 second (FEV1) prior to the administration of bronchodilators was the primary end point, which was the between-group differences in the change from the baseline to 24 months. The difference between groups in the annual fall in FEV1 prior to and after bronchodilator treatment from day 30 to month 24 as well as the change in FEV1 from base to 24 months after bronchodilator usage were secondary end goals. It is concluded that In individuals with COPD in GOLD stages 1 or 2, tiotropium improved the yearly fall in FEV1 after bronchodilator usage and resulted in a greater FEV1 at 24 months compared to placebo [20,21].

Conclusion

The study concluded that tiotropium significantly decreased the number of severe COPD exacerbations compared to placebo, supporting earlier studies. Furthermore, aside from dry mouth or pharynx discomfort, our trial did not reveal any notable differences between tiotropium and placebo in terms of any adverse events, such as cardiovascular impacts or urinary tract disease. In conclusion, this study demonstrated that tiotropium was superior to placebo in reducing the frequency of acute COPD exacerbations in patients with GOLD stage 1 or 2 illness. Tiotropium was also beneficial in enhancing lung function and quality of life. whethertiotropium early intervention modifies the long study of COPD.

At baseline, the majority of patients were taking few drugs and experienced few acute COPD exacerbations.The use of tiotropium to slow the progression of COPD hasn't always proven effective. Only individuals with moderate or mild COPD were included in our study, which could be part of the reason why our results differed from those of the other studies. All participants in our study met the diagnostic criteria for COPD based on risk factors as well as spirometric outcomes, and then in patients with a CAT scoring system with less than 10, tiotropium caused a reduction in the annual decline in FEV1 following bronchodilator usages that was greater than the reduction seen with placebo. For individuals with COPD of whatever grade of severity, it has been stated expressly that the avoidance of exacerbations is a cardinal priority.

References

1. Rice, K. L., Kunisaki, K. M., &Niewoehner, D. E. Role of tiotropium in the treatment of COPD. International Journal of Chronic Obstructive Pulmonary Disease, 2007;2(2): 95–105.
2. Aaron SD, Vandemheen K, Fergusson Fitzgerald M, et al.2007Tiotropium in Combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized Trial Ann Intern Med 2007February19[Epub ahead of print]
3. American Thoracic Society/European Respiratory Society Task Force 2004[updated 2005 September 8]. Standards for the Diagnosis and Management of Patients with COPD Internet]. Version 1.2. New York: American Thoracic Society; Available from: http://www-test.thoracic.org/copd/
4. [ATS/ERS] American Thoracic Society/European Respiratory Society Task Force Standardisation of Lung Function Testing. EurRespir J. 2005;26:319–338.
5. Anthonisen NR, Connett JE, Enright PL, et al. Hospitalizations and mortality in the Lung Health Study. Am J Respir Crit Care Med. 2002a;166:333–9.
6. Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1: The Lung Health Study. JAMA. 1994;272:1497–1505.

7. Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of Lung Health Study participants after 11 years. Am J RespirCrit Care Med. 2002b; 166:675–9.
8. Anthonisen NR, Wright EC, Hodgkin JE, the IPPB Trial Group Prognosis in chronic obstructive pulmonary disease. Am Rev Respir Dis. 1986;133:14–20.
9. Anzueto A, Tashkin D, Menjoge S, et al. One-year analysis of longitudinal changes in spirometry in patients with COPD receiving tiotropium. Pulm Pharmacol & Ther. 2005;18:75–81.
10. Barnes PJ. The pharmacological properties of tiotropium. Chest. 2000;117:63s–6s.
11. Barr RG, Bourbeau J, Camargo CA, et al. Tiotropium for stable chronic obstructive pulmonary disease: a meta-analysis. Thorax. 2006b;61:854–62.
12. Beeh KM, Beier J, Buhl R, et al. Efficacy of tiotropium bromide (Spiriva®) in patients with chronic-obstructive pulmonary disease (COPD) of different severities. Pneumologie. 2006;60:341–6.
13. Belman MJ, Botnick WC, Shin JW. Inhaled bronchodilators reduce dynamic hyperinflation during exercise in patients with chronic obstructive pulmonary disease. Am J RespirCrit Care Med. 1996;153:967–75.
14. Belmonte KE. Cholinergic pathways in the lungs and anticholinergic therapy for chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2005;2:297–30.
15. Casaburi R, Briggs DD, Jr, Donohue JF, et al. The spirometric efficacy of once-daily dosing with tiotropium in stable COPD: A 13-week multicenter trial. Chest. 2000;118:1294–302.
16. BoehringerIngelheim [online] Accessed 9 Nov 2006. URL:http:// www.boehringer-
17. Zhou Y., Zhong N., Li X., Chen S., Zheng J., Zhao D., Yao W., Zhi R., Wei L., He B., Zhang X., Yang C., Li Y., Li F., Du J., Gui J., Hu B., Bai C., Huang P., & Chen G. Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease. New England Journal of Medicine, 2017; 377(10): 923–935.
18. Anzueto A., & Miravitlles M. Tiotropium in chronic obstructive pulmonary disease – a review of clinical development. Respiratory Research. 2020; 21(1).
19. Miravitlles M., Price D., Rabe K., Schmidt H., Metzdorf N., & Celli B. Comorbidities of patients in tiotropium clinical trials: comparison with observational studies of patients with chronic obstructive pulmonary disease. International Journal of Chronic Obstructive Pulmonary Disease. 2015;549.
20. Zhou Y., Zhong N., Li X., Chen S., Zheng J., Zhao D., Yao W., Zhi R., Wei L., He B., Zhang X., Yang C., Li Y., Li F., Du J., Gui J., Hu B., Bai C., Huang, P., & Chen G. Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease. New England Journal of Medicine, 2017; 377(10): 923–935.
21. Al-Rawee R., Al-Fathy D. M., & Bashir Alsabee, D. W. Delivering Integrated Health Care: Role and Importance of Multidisciplinary Team Clinic Role and Importance of Multidisciplinary Team Clinic in Nineveh Province . Journal of Medical Research and Health Sciences, 2022;5(10):2278–2294.