Review

Tiotropium (SPIRIVA®) in mild COPD: Is it worth it?

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Abstract

Purpose: Tiotropium (SPIRIVA®) is used in the treatment of moderate to severe chronic obstructive pulmonary disease (COPD) in patients with persistent dyspnea despite using a short acting bronchodilator (SABD). This paper explores the role of tiotropium in the treatment of mild COPD. Methods: The Cochrane Library, EMBASE, Pubmed, and Clinicaltrials.gov were searched on February 2018. We included randomized controlled trials (RCTs) that evaluated tiotropium in patients with mild COPD. Three authors assessed studies for eligibility. Outcomes included symptoms, quality of life, exercise duration, lung function, COPD exacerbations and hospitalizations, and serious adverse events. Results: Three RCTs were selected as the best available evidence. Based on the results of the main trial, quality of life and symptoms were improved with tiotropium as compared to placebo with a difference between groups at 24 months to be 1.2 (95% CI: 0.5 to 1.9; p=0.0011) using the COPD Assessment test (CAT) score. Frequency of acute exacerbations of COPD (AECOPD) requiring hospitalization was reduced by 10.3% (28.9% with tiotropium vs 39.2% with placebo) in patients receiving tiotropium. One RCT reported no statistically significant difference in exercise duration (27 ± 27 secs) in the tiotropium group vs 50 ± 21 secs in the placebo group; (p=0.4153). Oropharyngeal discomfort was more common with tiotropium (number needed to harm of 12) compared to placebo. Conclusions: Evidence suggests that tiotropium may reduce COPD exacerbations and hospitalizations and improve quality of life in patients with mild COPD. There is an increased risk of oropharyngeal discomfort with tiotropium.

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease with partially reversible airway obstruction that is characterized by shortness of breath, sputum production, and an insignificant increase in FEV1 (forced expiratory volume in 1 second) after bronchodilator administration[1,2]. The 2018 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines classifies the severity of airflow limitation into four stages based on predicted FEV1 values (Table 1).

The prevalence of mild COPD (GOLD stage one) in Canadians aged 35-79 from 2007 to 2009 was 14.8% for women and 18.4% for men[3]. Symptoms of COPD usually manifests after the age of 40, which explains the lack of data in younger individuals[4]. Based on the 2017 Canadian Thoracic Society (CTS) position statement, Modified Medical Research Council (mMRC) and COPD Assessment Test (CAT) symptom scores along with the frequency and severity of acute exacerbations of COPD (AECOPD) are used to classify COPD patients as mild, moderate and severe[5].

Table 1. Classification of airflow limitation severity in COPD from the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[1]

Classification	Predicted FEV_1 values (post-bronchodilator)
GOLD stage one (mild)	≥80%
GOLD stage two (moderate)	50-79%
GOLD stage three (severe)	30-49%
GOLD stage four (very severe)	<30%

The current recommended management of mild COPD is a short acting bronchodilator (SABD) as needed for symptoms such as dyspnea, wheezing and coughing[1]. Commonly used short-acting bronchodilators include beta-agonists such as salbutamol (Ventolin®) and terbutaline (Bricanyl®) as well as short-acting muscarinic antagonist such as ipratropium (Atrovent®). Tiotropium (SPIRIVA®), which is a first line therapy for patients with moderate to severe COPD, is a long-acting muscarinic receptor antagonist that causes airway relaxation[6].

A 2014 Cochrane review evaluated 22 studies that looked at the effect of tiotropium as compared to placebo in patients with all stages of COPD and found a reduction in the number of exacerbations with an odds ratio of 0.78 (95% CI: 0.70 to 0.87) and number needed to treat of 16 to avoid one additional exacerbation7. There was an improvement in quality of life using the Saint George Respiratory Questionnaire (SGRQ) with a mean difference of -2.89 (95% CI -3.35, -2.44). Considering the threshold for a clinically significant mean difference between groups in the SGRQ is four units, this was not clinically significant[8]. There was also a slight reduction in the number of hospitalizations due to COPD exacerbations (OR: 0.85, 95% CI 0.72 to 1) which is unlikely to be clinically significant. There was an improvement in lung function with an FEV1 mean difference of 118.92 ml; 95% CI 113.07 to 124.77 ml in favor of tiotropium. There was no statistically significant difference in non-fatal serious adverse effects (OR: 1.03, 95% CI 0.97 to 1.10)[7]. It should be noted that the results were mainly observed in patients with moderate

to severe COPD due to the fact that only two studies out of the 22 in the Cochrane review included mild to moderate COPD patients with a total of 1945 patients. A subgroup analysis of the UPLIFT randomized control trial (RCT) suggested that using tiotropium in earlier stages of COPD (GOLD stage two) showed a benefit in reducing the number of exacerbations. For example, the mean difference in the number of exacerbations per patient year for patients treated with tiotropium as compared to placebo for GOLD stage two was 0.80 (95% CI: 0.72–0.88; p-value≤0.0001) which was statistically significant[9]. Although the UPLIFT trial focused on patients with moderate to severe COPD, the subgroup analysis suggested that there may be a benefit in starting tiotropium earlier in terms of a reduction in exacerbations and improvement in lung function. Therefore, the objective of this paper is to explore the potential role of tiotropium in patients with mild COPD (GOLD stage 1).

Case (Note: This is a fictional case)

JL, a 62 year old female, 155 cm tall and 66 kg (BMI 27.5 kg/m^2), presented to a primary care clinic and reported generalized fatigue, shortness of breath and cough with sputum. For the last four months, JL had been experiencing occasional shortness of breath from walking up the hill to her one-storey house and had to "take it easy" some days. JL had no history of heart failure or previous lung conditions. She denied fever, recent infectious illnesses or hospitalizations. JL smoked one pack of cigarettes per day and had a 30 pack-year history. Past medical history was also significant for hypertension. JL reported no allergies, and her medications included calcium 1200 mg daily, vitamin D 800 IU daily, and hydrochlorothiazide 12.5 mg daily. She reported being adherent to her medication regimen and had drug coverage through Pharmacare. Immunizations were up to date.

Given her history and symptoms, JL was worked up for a diagnosis of COPD. She underwent spirometry testing which demonstrated the following: Pre-bronchodilator FEV1/FVC (forced expiratory volume in one second/forced vital capacity) ratio of 0.66 and FEV1 of 81% predicted. Post-bronchodilator FEV1/FVC ratio of 0.68 and FEV1 of 85% predicted. Her symptoms were consistent with grade one dyspnea on the mMRC which indicates shortness of breath when hurrying on level ground or walking up a slight hill. She had a CAT score of nine which indicates that JL's COPD mainly affects her when she is exerting herself, with most days being manageable[1].

Clinical Question

In a 62 year old female with mild symptomatic COPD (GOLD Stage one), does tiotropium (Spiriva®) improve symptoms, quality of life, exercise duration, and lung function (FEV1) as compared to a SABD alone or no drug therapy, while minimizing adverse events?

Search strategy

The Cochrane Library, EMBASE, PubMed and Clinicaltrials.gov were searched February 2018 for the best available evidence. Search terms included: "mild COPD", "early stage COPD", "mild chronic obstructive pulmonary disease", "early stage chronic obstructive pulmonary disease" and "tiotropium". MeSH terms included "Pulmonary Disease, Chronic Obstructive" and the EMTREE term used was "chronic obstructive lung disease". Searches were limited to RCTs and interventional/clinical studies. Studies were excluded if they were published in a non-English language and if samples included less than 100 participants. After duplicates were removed, 66 abstracts were assessed for eligibility and of those, 20 articles were reviewed independently by three assessors. Of those, three articles were selected as the best available evidence.

Results

Three RCTs were chosen as the best available evidence based on the quality of methods and applicability to the clinical question (Table 2)[10,13-14]. The three RCTs compared tiotropium (SPIRIVA®) Handihaler to placebo in patients with different COPD severities; however, the focus was on assessing outcomes for mild COPD.

Zhou et al. performed an RCT that compared tiotropium 18 mcg inhaled daily with SABD as needed compared to matching placebo with SABD as needed in 841 patients with mild to moderate COPD (according to the GOLD criteria) over two years[10]. Of those, 338 patients had mild COPD based on an FEV1 > 80% of the predicted value as well as a post-bronchodilator FEV1/FVC ratio of 0.70 with certain respiratory symptoms or a previous exposure to risk factors or both. The primary outcome was the difference in the change in pre-bronchodilator FEV1 from baseline to 24 months between groups. The pre-bronchodilator FEV1 remained significantly higher in the tiotropium group as compared to the placebo group throughout the study with a point estimate difference of 162 ml (95% CI: 115-210ml; p<0.0001). For the CAT score < 10 subgroup: the pre-bronchodilator FEV1 point estimate difference was 165 ml (126 to 205ml) from baseline to 24 months. There was no statistically significant difference in the annual decline in pre-bronchodilator FEV1 between tiotropium and placebo. The average decline was 38ml/year in the tiotropium mild COPD group and 53ml/year in the placebo group with a

difference of 15ml per year (95% CI: -1,31; p=0.06)[10]. The difference in decline was not clinically significant (less than 100 ml)[10-11].The frequency of AECOPD at 2 years was 28.9% in the tiotropium group and 39.2% in the placebo group which gives an absolute risk reduction (ARR) of 10.3% in favor of tiotropium[10]. This ARR could be considered clinically significant because for every 10 (number needed to treat) people with mild to moderate COPD treated with tiotropium and SABD as needed for 25 months as compared to SABD alone, 1 less patient will experience an AECOPD.

There was a longer time to AECOPD with tiotropium versus placebo ($p \leq 0.001$) in mild to moderate COPD patients. The shortest average time to onset of AECOPD based on the 25th percentile was 522 days in the tiotropium group as compared to 236 days in the placebo group. Similar trends in the time to AECOPD were found for the CAT score <10 subgroup. Number of hospitalizations per patient year due to AECOPD were less with tiotropium as compared to placebo with a mean ± standard error of 0.27±0.03 for the tiotropium group and 0.50±0.05 for the placebo group which was not clinically significant. Quality of life was measured using the CAT score, mMRC, and Clinical COPD Questionnaire (CCQ) for mild to moderate COPD. With the exception of months one, three, and twelve, there was a greater improvement in mMRC and CAT scores with tiotropium as compared to placebo[10]. For example, the mean difference in CAT scores between the two groups at month 12 was 0.3 (95% CI:-0.3 to 0.9; p-value=0.32) and at month 24 was 1.2 (95% CI: 0.5 to 1.9; p-value=0.0011). However, since these improvements were not consistent throughout the duration of the trial, overall, its clinical significance is not fully clear. In addition, since the CAT score did not improve by the minimal clinically important difference of two units over two-three months, the change in the CAT score observed in the tiotropium group was not clinically significant[12]. The most common adverse event reported was oropharyngeal discomfort which included dry mouth and pharyngeal discomfort. Oropharyngeal discomfort occurred in 15.0% in the tiotropium group, as compared to 6.6% in the placebo group[10]. Therefore, for every 12 (number needed to harm) people with mild-moderate COPD using tiotropium with a SABD as needed for 25 months in comparison to SABD alone, 1 additional person will experience oropharyngeal discomfort. Other adverse events were not statistically significant between the groups. The main limitation of the latter results is that aside from the primary outcomes, secondary outcomes are only reported for the mild to moderate COPD group rather than being specific to mild COPD. This would impact how reliable these results are in answering the clinical question. Other limitations of the study included a potential lack of generalizability due to the study being conducted in an industrial country such as China where there could be greater exposure to air pollution and more symptomatic patients with mild COPD. This is supported by the fact that approximately 20% of participants did not have a prior smoking history which suggests an environmental cause of COPD. Another limitation is the results may be impacted by an attrition bias due to a large participant withdrawal rate of 33.2% in the placebo group and 27.7% in the tiotropium group (p=0.27); however, the results were analyzed using an intention-to treat-analysis which included all patients who underwent randomization and received at least one dose of tiotropium or placebo and had available data regarding efficacy measurement at any scheduled follow-up visit. Strengths of this study included a longer study duration compared to previous studies and appropriate methods of randomization and blinding. In addition, a large sample size of patients with mild to moderate COPD were included which provided adequate power (90%) and accounted for a large withdrawal rate. Finally, 73% of the participants had a CAT score of <10 which is consistent with patients that are less symptomatic and would be applicable in patients who have mild COPD (GOLD stage one).

Johansson et al. randomized 224 participants with mild to moderate COPD to either tiotropium or a matching placebo with salbutamol on as needed basis allowed for both groups for a 12 week duration[13]. Mild COPD was classified as FEV1/FVC <70% and FEV1 >60% which corresponds to mild to moderate COPD according to GOLD criteria. It is worth noting that about 28% of the patients had a baseline FEV1 ≥ 80% of predicted value. The primary outcome was the change in AUC0-2h FEV1 from baseline after 12 weeks of treatment. The difference between the tiotropium and the placebo group was 166 ± 26 ml (p<0.0001). There was a decrease in the use of rescue medications for the tiotropium group versus placebo with a difference of 0.17-0.23 doses/day (p<0.05) which was statistically, but likely not clinically significant[13]. There was no significant difference in adverse effects between the two groups. The study used the dyspnea index (BDI focal score) and mMRC to assess the patients' level of dyspnea with no significant differences observed for either groups[13]. The main limitations of this study included a limited study duration of only 12 weeks and inadequate power to detect changes in quality of life. The study could not consider long term effects of tiotropium on the progression of COPD and did not clearly define 'significant diseases' in the exclusion criteria. Strengths included a low rate of attrition (tiotropium 1.9%, placebo 3.4%) and the assessment of patient-centered

Table 2. Summary of clinical trials that evaluated the effects of tiotropium compared to placebo on lung function, quality of life, exercise tolerance, AECOPD, hospitalization, symptom score and adverse events in mild COPD (GOLD stage one). R: randomized DB: double-blind; COPD: chronic obstructive pulmonary disease; GOLD: Global initiative for chronic obstructive lungdisease; CI: confidence interval; SE: standard error; mMRC: Modified Medical Research Council; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; ADR: adverse drug reaction; AUC: area under the curve; CWR: constant work rate.

Study	Study Design	n	Participants	Intervention	Comparator	Results
Zhou[10] (2017)	2 year R(1:1), DB, multi-centered RCT	771	40- 85 years old, GOLD 1-2, exposure to risk factors (eg: smoking)	tiotropium 18 ug/ day ± ipratropium as needed	Placebo ± ipratropium as needed	Annual decline in FEV1 pre-bronchodilator: Tiotropium: (mean ± SE: 38± 6ml/year); Placebo: (mean± SE: 53±6ml/year); difference (95% CI: (-1,31); p=0.06 -Relative risk of tiotropium versus placebo for number of hospitalizations per patient year due to COPD: 0.38 (95% CI 0.19-0.78) - frequency of AECOPD: 28.9% in the tiotropium (SPIRIVA®) group and 39.2% in the placebo group; lowered by 10.3% (ARR) with tiotropium versus placebo
Johansson[13] (2008)	12-week R(1:1) , DB, multi-centered RCT	224	≥ 40 years mild-moderate COPD (GOLD), 10 or more pack years, MRC= 2 or more	Tiotropium 18 ug/ day ± salbutamol as needed	Placebo ± salbutamol as needed	-Change in AUC0-2h FEV1 from baseline to Day 85 compared with placebo, a mean difference of 166 ± 26 ml, p less than 0.0001 -Similar results for MRC score for both groups (tiotropium 0.83 ± 0.01; placebo 0.85 ± 0.01) - There was no significant difference in adverse effects between the two groups
Casaburi[14] (2014)	22 week, multi-centered R(1:1), DB, cross-over RCT	126	40 years or older, 10 or more pack years, GOLD 1-2 COPD, baseline dyspnea index focal score less than or equal to 9	tiotropium 18 ug/ day for 6 weeks, followed by a washout period of 4 weeks and then crossover to placebo for another 6 weeks -salbutamol used as needed	placebo for 6 weeks, followed by a washout period of 4 weeks and then crossover to tiotropium for another 6 weeks -salbutamol used as needed	-Differences in exercise duration in secs (tiotropium vs placebo): GOLD 1: (Mean± SE: -24±29) (95% CI: -81,34) (p=0.4153) GOLD 2: (Mean ± SE: 63± 23) (95% CI: 18,108) (p=0.007) - Adverse events: 28.9% tiotropium 30.1% for placebo group).

outcomes such as dyspnea, exacerbations, and the use of rescue medications.

Casaburi et al. examined the effects of tiotropium with a SABD compared to SABD alone on exertional dyspnea, treadmill exercise duration and safety in 118 patients with mild to moderate COPD[14]. Mild COPD was defined as FEV1/ FVC < 0.7 and FEV1 ≥ 80% of predicted value. Patients received a six-week trial of either tiotropium or placebo, after which, there was a four weeks washout and then, a cross over to the opposite intervention. Spirometric measures were obtained before the administration of either tiotropium or placebo and before exercise testing. Exercise testing was done prior to the administration of tiotropium or placebo as well as at follow up visits after the six-week trials. Patients were also followed up for 30 days after completion of the last six week period of treatment or if discontinuation occurred earlier, the results for the final dose of study medication were included in the study[14].The difference in exercise duration in seconds for the tiotropium versus placebo group was statistically significant for moderate (70±21 seconds in the tiotropium group vs 7±21 seconds in the placebo group; p=0.007) but not mild COPD (27±27 seconds in the tiotropium group vs 50±21 seconds; p=0.4153). In addition, the latter results for moderate COPD would not be considered clinically significant as the mean difference in exercise duration is about one minute longer on a treadmill. Adverse events were reported at similar rates between both groups (28.9% for tiotropium and 30.1% for placebo group)[14]. A strength of this study is that it evaluated the effects of tiotropium on exercise related outcomes such as inspiratory capacity, treadmill exercise, exercise duration and exertional dyspnea in patients with mild COPD. Limitations included a small sample size of only 48 mild COPD patients and an unspecified method of blinding which could lead to performance bias and/or observer bias. In

summary, it appeared that tiotropium did not improve outcomes related to inspiratory capacity at isotime (i.e., at the time the shortest test ended), treadmill exercise duration, or exertional dyspnea in patients with mild COPD.

Conclusion

There is limited literature evaluating the use of tiotropium (SPIRIVA®) in patients with mild COPD. Based on current best available evidence, which consists of mainly one RCT, (Zhou et al.)[10] tiotropium may improve FEV1. Measurements of symptoms and quality of life, such as CAT score, mMRC and CCQ, demonstrated an improvement with the tiotropium group as compared to placebo, however that improvement was not consistent throughout the trial duration and the study did not report these results by stratifying the severity of COPD. The RCT also demonstrated that tiotropium may also reduce the risk of AECOPD as well as reduce the risk of hospitalizations due to AECOPD with a mean ± standard error of 0.27±0.03 for the tiotropium group and 0.50±0.05 for the placebo group in patients with mild to moderate COPD[10]. There was no clinically significant effect observed in one study that evaluated the effect on exercise duration[14]. It is also estimated that one in 12 patients may experience oropharyngeal discomfort while receiving tiotropium[10]. Additional prospective trials of sufficient duration are required to confirm the utility of long-acting bronchodilators in patients with mild COPD.

Through shared decision-making between the patient and health care provider(s), JL could consider whether or not the small possible benefit of tiotropium outweighs the burden of using a daily inhaler and the potential cost. Her options would include a trial of a SABD as needed for symptoms of dyspnea, such as Ipratropium (Atrovent) which would cost ~$33 per month and would be covered by Pharmacare15. Another option would be initiating a trial of tiotropium monotherapy. The estimated cost would be ~$67 per month, not including the dispensing fees, given it is not covered by Pharmacare unless she has a trial of a SABD first[15]. In either situation, efforts to engage and support JL in smoking cessation should be a priority.

References

1. GOLD 2018 Global Strategy for the Diagnosis, Management and Prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease - GOLD. Global Initiative for Chronic Obstructive Lung Disease; 2018 [cited 2018 Feb 13]. Available from: https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf
2. The Lung Association of Nova Scotia. The Nova Scotia Lung Health Strategy; 2010 [cited 2017 Oct 21]. Available from: https://ns.lung.ca/sites/default/files/NS%20Lung%20Health%20Strategy.pdf.
3. Evans J, Chen Y, Camp P, Bowie D, McRae L. Prevalence of airflow obstruction compatible with chronic obstructive pulmonary disease, by definition of airflow obstruction and selected characteristics, household population aged 35-74, Canada, 2007 to 2009. [online] 2012 Statistics Canada. Available at: http://www.statcan.gc.ca/pub/82-003-x/2014003/article/11908/tbl/tbl2-eng.htm [Accessed 13 Feb. 2018].
4. World Health Organization. Chronic Obstructive Pulmonary Disease (COPD); 2016 [cited 2017 Nov 11] Available from: http://www.who.int/mediacentre/factsheets/fs315/en/.
5. Bourbeau J, et al. CTS position statement: Pharmacotherapy in patients with COPD—An update. Canadian Journal of Respiratory, Critical Care, and Sleep Medicine. 2017;1(4):222-241.
6. Boehringer Ingelheim. Spiriva [Internet]. 2017 [updated 2017 Nov 24; cited 2017 Nov 26]. Available from: https://pdf.hres.ca/dpd_pm/00042330.PDF.
7. Chong J, Karner C, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2014 Jul 21;(7):CD009285.
8. Jones P. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. European Respiratory Journal. 2002;19(3);398-404.
9. Decramer M, Celli B, Kesten S, Lystig T, Mehra S, Tashkin D. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomized controlled trial. The Lancet. 2009;374(9696):1171-1178.
10. Zhou Y, et al. Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease. N Engl J Med. 2017 Sep 7;377(10):923-935.
11. Jones P, et al. Minimal clinically important differences in pharmacological trials. American Journal of Respiratory and Critical Care Medicine. 2014;189(3):250-255.
12. Polkey M, Vogelmeier C, Hansel N. COPD Assessment Test: Healthcare professional user guide. [Internet] Catestonline.org. 2016 [cited 27 July 2018]. Available from: http://www.catestonline.org/images/UserGuides/CAT HCP%20User%20Guide.pdf
13. Johansson G, et al. Bronchodilator efficacy of tiotropium in patients with mild to moderate COPD. Prim Care Respir J. 2008;17(3):169-175.
14. Casaburi R, et al. Effects of tiotropium on hyperinflation and treadmill exercise tolerance in mild to moderate chronic obstructive pulmonary disease. Ann Am Thorac Soc. 2014;11(9):1351-61.
15. Crawley A, Jensen B, Regier L. RxFiles [Internet]. Rxfiles.ca. 2018 [cited 9 June 2018]. Available from http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-COPD-Tx.pdf