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Evaluation of withdrawal of maintenance tiotropium in COPD

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Summary
Introduction: In chronic diseases such as chronic obstructive pulmonary disease (COPD), patients may not perceive all of the benefits of drug therapy until withdrawal. Thus, we evaluated the effect of tiotropium withdrawal on clinical variables.
Methods: COPD subjects who participated in two identical 1-year, prospective, double-blind, placebo-controlled studies of tiotropium 18 μg once daily who completed a 3-week visit following discontinuation of therapy were included in this analysis. Outcomes measured included dyspnea (transition dyspnea index [TDI]), Peak Expiratory Flow Rate (PEFR), health status (St George's Respiratory Questionnaire [SGRQ]), and rescue β_2-agonist use.
Results: Overall, the tiotropium group exhibited significant improvements in clinical parameters at the end of therapy. Of the entire cohort of 921 patients, 713 patients (77%) completed 3-weeks post-withdrawal evaluation. Patients in the tiotropium group had 1.1 unit worsening in TDI, decreased in PEFR, health status and reduced β_2-agonist medication following treatment discontinuation, while the placebo group remained relatively stable.
Conclusions: The withdrawal of tiotropium results in worsening of COPD over a three-week interval. There was no evidence of a rebound effect in response to tiotropium withdrawal.
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Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease in which patients experience a progressive decline in lung function, worsening exercise capacity with increasing dyspnea and

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frequent exacerbations.[1,2] COPD is a worldwide cause of morbidity and mortality which can be treated. Bronchodilator medications are considered central to the management of airway obstruction. Current treatment guidelines recommend the use of long-acting bronchodilators, either long-acting β_2-agonist or anticholinergic, in symptomatic patients with moderate air-flow obstruction.[1,2]

Due to the long-term nature of the disease, it is important to consider clinical trials with prolonged durations of exposure to evaluate the impact of therapeutic interventions. Such long-term trials need to incorporate multiple measurements of efficacy in COPD including questionnaires such as the transition dyspnea index (TDI)[3] and the St George's Respiratory Questionnaire (SGRQ),[4] which are often used to measure dyspnea and health-related quality of life (HRQL). Similarly, the patient's use of rescue β_2-agonist medication is often used as a surrogate for the degree to which patients are symptomatic due to air-flow limitation.

Tiotropium is an inhaled anticholinergic for the treatment of COPD that leads to bronchodilation for at least 24 hours with once-daily dosing. This sustained bronchodilation is due to the prolonged dissociation half life from the muscarinic M_3 receptor (approximately 35 h).[5] Two long-term, 1-year, placebo-controlled studies in the United States demonstrated that once-daily inhaled tiotropium consistently improved lung function, dyspnea, HRQL and rescue β_2-agonist use compared with placebo over the course of the study.[6] In these studies, patients were invited to be evaluated one additional time 3 weeks after completing study medication. This follow-up visit provided a valuable opportunity to prospectively assess the extent to which patients were able to perceive the effects of treatment withdrawal and to evaluate the effects of tiotropium. In addition, this protocol provided outcome information regarding treatment withdrawal as a measure of treatment efficacy. Therefore, the purpose of this post-hoc analysis is to assess the effect of tiotropium withdrawal on dyspnea (TDI), health status (SGRQ), rescue β_2-agonist use, and Peak Expiratory Flow Rate (PEFR).

Methods

Study patients

Two identical clinical trials designed to evaluate the efficacy and safety of tiotropium were combined and evaluated. The trials used a prospective, randomized, double-blind and parallel-group design. Tiotropium was administered at 18 mcg once daily via the HandiHaler® device (Boehringer Ingelheim GmbH & Co. KG, Ingelheim, Germany). Fifty clinical centers participated in these trials and each center's institutional review board approved the protocol. All patients provided written informed consent prior to participation.

Inclusion and exclusion criteria have been fully described previously.[6] Briefly, the study groups consisted of outpatients of either gender who were at least 40 years of age with a clinical diagnosis of COPD, as defined by the American Thoracic Society.[7] Participants were required to have at least a 10-pack-year history of smoking, clinically stable airway obstruction, an FEV_1 less than 70% of the forced vital capacity (FVC) and a post-bronchodilator FEV_1 of less than 65% of the predicted normal value. Concomitant use of as-needed albuterol (by metered dose inhaler), theophylline (excluding 24-hour preparations), and inhaled steroids were allowed throughout the study period. The use of short-acting anticholinergics, oral β_2-agonists, and long-acting inhaled β_2-agonists were not permitted during active treatment, but were allowed after study medication was withdrawn. Patients were excluded if they had a history of asthma, allergic rhinitis, atopy, or a total blood eosinophil count of more than 600/mm, 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), hospitalization for heart failure (3 years or less), cardiac arrhythmias requiring drug therapy, symptomatic prostatic hypertrophy, or narrow angle glaucoma.

Study protocol

Following a two-week baseline period, patients were randomly assigned in a 3:2 ratio to receive either tiotropium (18 μg) or placebo.[6] Patients were administered active medication (tiotropium in lactose) or placebo (lactose) by inhalation, one dose each morning in identical-appearing capsules via a dry powder inhaler device (HandiHaler®). Three weeks after completion of study medication, patients returned for a follow-up clinical assessment. During this follow-up period, there were no medication exclusions and tiotropium was not available at the time of the study. Dyspnea was assessed using the TDI,[3] health-related quality of life was measured using the SGRQ,[4] morning and evening Peak Expiratory Flow Rate

Table 1 Patient characteristics at baseline of patients who had a valid baseline measurement, and 3-week post-treatment data (mean (SD) unless otherwise specified).

	Tiotropium	Placebo
Total	445	268
Female/Male (%)	34/66	37/63
Age (years)	65 (9)	65 (9)
Body mass index (kg/m^2)	27 (5)	27 (5)
Duration of COPD (years)	8.4 (7.1)	8.0 (6.8)
Smoker/Ex-smoker (%)	34/66	33/66
Smoking history: packs/year	61(29)	60 (32)
FEV_1 (L)	1.02 (0.40)	1.02 (0.43)
FEV_1 (% predicted)[a]	37 (13)	37 (14)
Morning PEFR (L/min)	193 (92)	199 (106)
Evening PEFR (L/min)	206 (97)	213 (104)
BDI	6.1 (1.9)	6.4 (2.2)
SGRQ total score	46 (16)	45 (16)
SGRQ impact score	32 (17)	31 (17)

BDI: baseline dyspnea index; FEV_1: forced expiratory volume in 1 s; FVC: forced volume capacity; PEFR: peak expiratory flow rate; SGRQ; St. George's Respiratory Questionnaire.
[a] ECCS criteria.