Four-year trial of tiotropium in chronic obstructive pulmonary disease

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Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;359(15):1543-54. Epub 2008 Oct 5.

Clinical question

Does long-term treatment with tiotropium alter the rate of decline in forced expiratory volume in 1 second (FEV_1), health-related quality of life, exacerbations, related hospitalization, or mortality in patients with chronic obstructive pulmonary disease (COPD)?[1]

Type of article and design

This trial, referred to as the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial, was a 4-year, randomized, double-blind, placebo-controlled, parallel-group trial involving patients with moderate to very severe COPD. The primary end points included the yearly rate of decline in mean FEV_1 before the use of tiotropium and short-acting bronchodilators in the morning (prebronchodilator), and after the use of tiotropium from day 30 until completion of the double-blind treatment. Secondary end points included the rate of decline in the mean forced vital capacity (FVC) and slow vital capacity, health-related quality of life as measured by the total score on St George's Respiratory Questionnaire, rates of COPD exacerbations and related hospitalizations, and the rates of death from any cause and from lower respiratory conditions. Patients were not recruited in Canada, as Canadian approval bodies thought it was unethical to deprive COPD patients of either short- or long-acting anticholinergics in the placebo arm for 4 years.

Relevance to family medicine

It has been well described[2] that as FEV_1 declines in COPD, some patients will experience considerable disability and premature death. Until now only smoking cessation has been shown in prospective fashion to alter the rate of decline of FEV_1 in patients with COPD.[3] It is believed that slowing the rate of decline in FEV_1 might improve relevant clinical outcomes, including mortality. Recently, the Toward a Revolution in COPD Health (TORCH) trial[4] showed a reduction in mortality (that came very close to achieving traditional statistical significance) in COPD patients who received a combination of fluticasone and salmeterol. Given the escalating burden of COPD on a global scale, new therapies are desperately needed to reverse the troubling trend of FEV_1 decline.[5]

Overview of the study and outcomes

The UPLIFT study involved 5993 patients recruited from 490 investigational centres in 37 countries. Patients were 40 years of age or older and had a smoking history of at least 10 pack-years. Postbronchodilator FEV_1 was 70% or less of the predicted value, with an FEV_1-FVC ratio of less than 70% after bronchodilator administration. After a screening period, patients were randomized (in a 1:1 ratio) to receive either tiotropium or a matching placebo daily, delivered through the HandiHaler inhalation device. All respiratory medications except other anticholinergic drugs could be used during the trial. Spirometry tests were performed in accordance with the American Thoracic Society guidelines[6] when patients were randomized, at the 1-month visit, at visits every 6 months throughout the study period, and at a follow-up visit about 30 days after

BOTTOM LINE Tiotropium added to aggressive respiratory therapy in moderate to severe chronic obstructive pulmonary disease resulted in no difference in the rate of decline in forced expiratory volume in 1 second compared with placebo; a significant improvement ($P<.001$) in mean forced expiratory volume in 1 second and forced vital capacity that was maintained throughout the treatment period; a significant improvement in quality of life ($P<.001$), exacerbations ($P<.001$), and cardiovascular morbidity ($P<.05$); and a trend toward reduced all-cause mortality.

POINTS SAILLANTS L'ajout de tiotropium à une thérapie respiratoire puissante pour une maladie pulmonaire obstructive chronique de modérée à grave n'a pas modifié le taux de déclin du volume expiratoire maximal par seconde par rapport au placebo. Il a entraîné une amélioration significative ($P<,001$) du volume expiratoire maximal moyen par seconde et de la capacité vitale forcée, qui a été maintenue durant toute la période du traitement. Il a produit une amélioration significative de la qualité de vie ($P<,001$), des exacerbations ($P<,001$) et de la morbidité cardiovasculaire ($P<,05$) et on a constaté une tendance vers une mortalité réduite toutes causes confondues.

the end of the study. The study sample size provided a power of more than 90% at a significance level of 5%. The primary end points were analyzed with the use of a normal random-effects model in which mean FEV_1 changed linearly after day 30 for each patient.

Results

Differences between study groups in the rate of decline in the mean values for FEV_1 and FVC, before or after bronchodilation from day 30 to the end of the study drug treatment, were not significant. Tiotropium use was associated with significant improvements ($P<.001$) in the mean values for FEV_1 and FVC (compared with placebo) that were maintained at all time points after randomization. While there were significant improvements in total score on St George's Respiratory Questionnaire, favouring tiotropium ($P<.001$), these changes were less than what is considered to be clinically significant. There was a significant delay in the time to first exacerbation with tiotropium compared with placebo (16.7 vs 12.5 months, respectively; $P<.05$). The mean number of exacerbations was reduced by 14% ($P<.001$) in the tiotropium group compared with placebo. During the period of 48 months plus 30 days that was included in the intention-to-treat analysis, 14.9% and 16.5% of patients died in the tiotropium and placebo groups, respectively (hazard ratio 0.89, 95% CI 0.79 to 1.02, $P=.09$). Fewer patients in the tiotropium group experienced myocardial infarction and congestive heart failure ($P<.05$). The proportion of serious adverse events was 51.6% and 50.2% in the tiotropium and placebo groups, respectively. The data reported in this study have prompted the Food and Drug Administration to report[7] that tiotropium use does not increase the risk of stroke, myocardial infarction, or death as they had previously described in 2008.[8]

Analysis and methodology

A comparison of the rate of decline in FEV_1 between tiotropium and placebo treatment is certainly a clinically relevant outcome given the value of FEV_1 as a predictor of morbidity and mortality. This study was unique in that patients were allowed to use respiratory medications, with the exception of anticholinergic drugs, during the treatment phase. In fact, about 60% of the study population in both treatment groups used inhaled corticosteroids and long-acting β_2-agonists. Some patients used these medications in fixed combination. Given the known benefits of inhaled corticosteroid and long-acting β_2-agonist combination therapy in COPD,[4] it is possible that the results of this study were influenced by aggressive background respiratory therapy that was left to the discretion of the study physicians.

Application to clinical practice

Improving the rate of decline in FEV_1 using pharmacotherapy in COPD remains an elusive target. Despite the allowance of aggressive background respiratory therapy, tiotropium use resulted in improvements in mean FEV_1 and FVC and in a reduced risk of exacerbations, improved quality of life, reduced cardiorespiratory morbidity, and numerically fewer deaths from any cause. It is relevant to consider that improvements in these latter outcomes might be more important than changes in FEV_1 decline over time. To date the only intervention to influence the rate of decline in FEV_1 in COPD is smoking cessation.[3] The UPLIFT trial suggests that the addition of tiotropium to other respiratory medications (other than anticholinergic drugs) improves many cardiorespiratory end points despite little change in the natural history of this debilitating disease.

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Competing interests

Dr D'Urzo has received research, consulting, and lecturing fees from GlaxoSmithKline, Sepracor, Schering-Plough, Altana, Methapharm, AstraZeneca, ONO Pharmaceutical, Merck Canada, Forest Laboratories, Novartis, Boehringer Ingelheim Ltd, Pfizer Canada, SkyePharma, and KOS Pharmaceuticals.

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