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Evaluation of Celli B, Decramer M, Kesten S, et al. Mortality in the 4-year trial of tiotropium (UPLIFT) in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2009;180(10):948-55

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Tiotropium therapy and mortality risk in COPD patients: the most severe, the most protected?

Evaluation of Celli B, Decramer M, Kesten S, et al. Mortality in the 4-year trial of tiotropium (UPLIFT) in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2009;180(10):948-55

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Importance of the field: Tiotropium bromidum is an inhaled long acting anticholinergic used as first line monotherapy in stable COPD due to its beneficial effects on the lung function, respiratory symptoms, quality of life or disease morbidity. However there is limited data on its effects on mortality.
Areas covered in this review: The results of the UPLIFT (Understanding Potential Long-Term Impacts on Function with Tiotropium) study evaluating the effects of 4 year therapy with tiotropium on above mentioned outcomes including mortality.
What the reader will gain: Tiotropium demonstrated an uniform beneficial effect on mortality risk reduction but subset analyses yielded relevant results as well.
Take home message: On long-term basis tiotropium therapy can reduce mortality rate overall and can exert such protective effects in various subsets such as patients with very severe COPD.

Keywords: COPD, mortality, tiotropium, UPLIFT

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is currently defined by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) as a preventable and treatable disease characterized by not full reversible airflow limitation [1]. Airflow limitation is usually both progressive and associated with abnormal inflammatory response of the lungs to noxious particles of gases.

COPD is a major cause of morbidity and mortality worldwide and further increases in its prevalence are expected in the future [2].

Bronchodilators were already considered the first-line therapy for chronic obstructive pulmonary disease and recently, in the TORCH trial [3], they were shown to potentially improve survival when added to inhaled corticosteroids. Before, only several interventions had been evidence to decrease mortality in COPD, including smoking cessation [4,5], oxygen treatment in patients with persistent hypoxemia [6,7] and lung volume reduction surgery in selected patients [8].

Tiotropium, a long-acting anticholinergic bronchodilator has been demonstrated to be clinically effective in COPD, improving airflow, reducing both dynamic and resting hyperinflation and improving symptoms [9]. Like the long-acting β-agonist, tiotropium can improve exercise performance by increasing resting inspiratory capacity and delaying the time to critical mechanical limitation of breathing during exercise. Several studies have, in addition, demonstrated that tiotropium is associated with a

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reduction in exacerbations of COPD and even of those requiring hospitalizations [10] Unsurprisingly, these changes are accompanied by improvements in health-related quality of life.

In the UPLIFT (Understanding Potential Long-Term Impacts on Function with Tiotropium) trial [11], it was demonstrated that tiotropium long-term therapy was able to reduce lung function decline in COPD patients with less advanced disease and overall to improve health-related quality of life and to decrease risk for exacerbations, episodes of respiratory failure, and hospitalizations due to COPD exacerbations compared with patients receiving placebo.

The study discussed below analysed the mortality data in the UPLIFT study [12].

2. Methods and results

The study was a 4-year, randomized, double-blind, placebo-controlled, parallel-group trial in patients with COPD in which all patients were permitted to continue use of all respiratory medications other than inhaled anticholinergics. The treatment arms were tiotropium 18 µg once daily or matching placebo. The primary endpoints were yearly rate of decline of pre and post bronchodilator lung function until completion of the double-blind treatment. Secondary outcome included lung function with spirometry, quality of life measured by the St. George's Respiratory Questionnaire (SGRQ), COPD exacerbations (defined as an increase in or new onset of more than on respiratory symptom with a duration of three or more days requiring treatment with antibiotic and/or systemic steroids) and related hospitalizations and mortality. Mortality was collected on standard adverse report forms as well as through a trial-specific vital status case report form for patients who prematurely discontinued study group. A mortality adjudication committee consisting of three independent physicians, who were not UPLIFT investigators determined a primary cause of death from available information [11,12].

There were 5993 randomized patients (3006 to placebo and 2987 to tiotropium). The mean age was 65 + 8 years, 75% of them were men and at randomization 30% were smokers. Mean baseline prebonchodilator FEV1 was 1.10 + 0.40 l (39% predicted) and baseline postbronchodilator FEV1 was 1.32 + 0.44 l (48% predicted). The total number of reported deaths from any cause during study drug treatment was 792, 411 (13.6%) in the placebo group and 381 (12.8%) in the tiopropium group (hazard ratio HR tiotropium/placebo, 0.84; 95% confidence interval [CI], 0.73 – 0.97; p = 0.016). During per protocol-defined treatment period 921 deaths were reported (HR 0.89, 95% confidence interval [CI], 0.76 – 0.99; p = 0.034. Various subgroup analyses were performed on pre-specified time intervals according to age, sex, baseline smoking status, concomitant medication use or GOLD severity stage and no significant subgroup treatment effects on all cause mortality were constantly found except for (most notably) ex smokers (HR 0.82 compared to 1.09 in current smokers). The most common causes of death irrespective of the period analysed were lower respiratory, cancer, general disorders and cardiac disorders. The hazard ratios for lower respiratory and cardiac mortality during treatment were 0.86 (95% CI, 0,68 – 1.09) and 0.86 895% CI, 0.75 – 0.99), respectively.

3. Discussion

Mortality statistics are still used to explore the epidemiology of COPD as the disease doesn't have a clearly standardized diagnosis. Mortality, as well as hospital admission, rates are based on clinical diagnoses. According to the World Health Organization, COPD is currently the fourth leading cause of death in the world, with 2.75 million deaths worldwide, representing 4.8% of all deaths [13]. Cigarette smoke is the most prominent factor determining the increased prevalence and mortality of COPD worldwide, this is the reason that smoking cessation is mentioned as the mainstay of intervention in several clinical guidelines on COPD [14,15].

There is limited knowledge on the effect of pharmacotherapy on mortality in patients with COPD. The TORCH study which assessed the impact of salmeterol, fluticasone or their combination over placebo on several outcome measures including COPD all cause mortality. In 6112 patients there were 875 deaths reported over 3 years and all-cause mortality rates were 12.6% in the combination-therapy group, compared to 13.5% in the salmeterol group, and 16.0% in the fluticasone group and 15.2% in the placebo group. Salmeterol/fluticasone combination therapy reduced significantly the mortality risk compared to placebo (0.825 (95% confidence interval [CI], 0.681 to 1.002; p = 0.052), whereas each component demonstrated an effect comparable to that of placebo [3].

In a previous meta-analysis including studies lasting at least 3 months it was demonstrated that anticholinergics added to beta agonist bronchodilators were able to reduce COPD morbidity (severe exacerbation rate) and mortality [16]. However, tiotropium in particular although it reduced significantly the exacerbations and hospitalisations for exacerbation rate was not found to exert a similar effect on all cause or respiratory cause mortality rates [17].

4. Expert opinion

In stable COPD the currently available pharmacological therapies are able to exert various beneficial effects on disease morbidity and symptoms, on quality of life and on lung function. An important therapeutic benefit of such therapies would be also represented by mortality reduction, but demonstration of such an effect requires longer-term studies which are fewer compared to the shorter duration trials evaluating mainly other outcomes. Therefore studies such as TORCH or UPLIFT are very useful as they document appropriately the effects of long-term inhaled therapies on mortality and

demonstrate that both tiotropium and salmeterol/fluticasone combination are able to reduce all cause mortality in COPD irrespective of the severity stage.

Furthermore subgroup analyses in the UPLIFT study provide a number of supportive results regarding various subpopulations: for example it reduces significantly mortality rate in ex smoker patients, in advanced age patients (≥ 75 years) and in patients with concomitant inhaled corticosteroids therapy. Irrespective of the observation period analysed and even non-significant, the therapeutic effect of tiotropium on mortality reduction was most substantial in patients with very severe COPD, population in which usually mortality risk is the highest and in which only long-term oxygen therapy (when indicated) can have similar beneficial effects. Therefore such an effect can be considered among the most relevant for clinical practice and deserves further evaluation in subsequent studies.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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