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UPLIFT Study: the effects of long-term therapy with inhaled tiotropium in chronic obstructive pulmonary disease

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Background: In chronic obstructive pulmonary disease (COPD), inhaled tiotropium bromide, a long-acting anticholinergic, has been shown to exert a sustained bronchodilator effect and to be superior to ipratropium bromide, a short-acting formulation of the same pharmacological class. *Objective*: To discuss the effects of long-term therapy with tiotropium in COPD. *Methods/results*: Analysis of efficacy and safety data on tiotropium from a 4-year randomized placebo controlled study performed in moderate to very severe COPD patients. Tiotropium was found to reduce significantly COPD-related morbidity, to improve health-related quality of life (HRQoL) irrespective of disease severity and to slow significantly lung function decline in patients not using inhaled corticosteroids or other long-acting bronchodilators. The safety profile – and in particular cardiovascular safety – of tiotropium was good. *Conclusions*: Tiotropium bromide, alone or in combination with other inhaled therapies, can maintain an adequate control of COPD on a long-term basis.

Keywords: COPD, long-term efficacy, long-term safety, tiotropium

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease in which inflammation, which is usually related to smoking but also, to a lesser extent, to other noxious agents, results in irreversible airways obstruction and, in its more advanced stages, leads to abnormalities in gaseous exchange and to chronic respiratory failure. COPD is currently classified in four degrees of severity – mild, moderate, severe, and very severe – according to the degree of lung-function impairment and to the presence of chronic respiratory failure.

In stable (in terms of respiratory symptoms) COPD, a step-up therapeutic approach according to disease severity is recommended and aims to relieve symptoms, reducing exacerbations and mortality rates and improving HRQoL [1]. Inhaled bronchodilators (short- and long-acting beta-2 agonists or anticholinergics) are used in stable COPD to relieve 'acute' symptoms (short-acting formulations) or to reduce them 'chronically' and improve lung function, exercise capacity or HRQoL [1].

Tiotropium bromide (Spiriva®) is a long-acting anticholinergic drug approved to be used as once-daily maintenance inhalatory therapy in stable COPD. Previous clinical studies have demonstrated its sustained bronchodilator effect and its clinical superiority to placebo and to short-acting ipratropium bromide in terms

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of lung-function and HRQoL improvement, and the rate of reduction of symptoms and exacerbations [2,3].

The Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) Trial was a 4-year, randomized, double-blind, placebo-controlled parallel-group trial aimed at evaluating the effects of long-term therapeutic intervention with tiotropium bromide on lung-function decline, morbidity and mortality in patients with moderate-to-very severe stable COPD [4].

2. Methods and results

The primary endpoint was the effect of inhaled tiotropium on forced expiratory volume in 1 sec (FEV_1) decline rate. Secondary endpoints included, among others, the decline rate of forced vital capacity (FVC), health-related quality of life (HRQoL) measured with the Saint George Respiratory Questionnaire (SGRQ), COPD exacerbations and related hospitalizations. Adverse events, all-cause mortality and respiratory mortality were also recorded throughout the study.

Patients were randomized to receive 18 µg of inhaled tiotropium or matching placebo once daily and were allowed to use other COPD medications except for short-acting anticholinergics (ipratropium bromide). Included in the study were patients with COPD who were aged at least 40, had a smoking history of at least 10 pack-years, a postbronchodilator FEV_1%pred of 70% or less, and a FEV_1/FVC ratio of 70% or less. Exclusion criteria were COPD exacerbation or respiratory infection within 4 weeks before the eligibility check, a history of asthma or of pulmonary surgery, supplemental oxygen use > 12 h/day, and comorbid diseases interfering with participation to the study.

A total of 5993 patients was randomized: 3006 to placebo (P) and 2987 to tiotropium (T). At baseline there were no significant between-group differences in terms of age, nutritional status, lung function or disease severity stages. Overall at baseline, the mean age was 65 ± 8 years, 75% were men, 30% were current smokers, the mean post-bronchodilator FEV_1%pred was 48%. In the T group, the mean postbronchodilator FEV_1 increased significantly compared with the P group (therapeutic effect ranging from 47 to 65 ml, $p < 0.001$). *Post-hoc* analysis of the rate of decline of postbronchodilator FEV_1 demonstrated a significant therapeutic effect of tiotropium in the subgroup of patients not taking inhaled corticosteroids or long-acting beta agonists at baseline (40 ± 3 ml per year in the T group versus 47 ± 3 ml per year in the P group, $p = 0.046$). For FVC, the annual decline rate was higher in P than in T (43 ± 3 ml versus 39 ± 3 ml) for prebrochodilator measurement, whereas for postbronchodilator FVC the rate was similar, 61 ± 3 ml. T improved HRQoL significantly throughout the study, the overall mean difference between the groups being 2.7 ($p < 0.001$), and produced clinically significant HRQoL improvements in significantly higher proportions of patients than P. T was associated with a significantly lower risk of COPD exacerbation or hospitalization [hazard ratio (HR) for both events being 0.86; $p < 0.001$ for exacerbations] and significantly reduced the duration of exacerbation (12.11 days versus 13.64 days, $p = 0.001$). A total of 941 deaths of any cause was reported over the period included in intention-to-treat analysis, 14.9% in T and 16.5% in P (HR 0.89, $p = 0.09$).

The most commonly reported adverse events were related to lower respiratory tract disorders such as COPD exacerbations, pneumonia and dyspnoea, and the proportion of serious adverse events was 51.6% in the T group and 50.2% in the P group. T was associated with a significantly lower relative risk of developing serious adverse events, such as all-type cardiac events (0.84), congestive heart failure (0.59) and myocardial infarction (0.71) as well as COPD exacerbations (0.84), dyspnoea (0.61) and respiratory failure (0.69) ($p < 0.05$).

3. Discussion

The UPLIFT Study demonstrated that, in stable patients with moderate-to-very-severe COPD, long-term therapy with T alone or in combination with other medications was significantly beneficial in terms of COPD-related morbidity reduction and HRQoL improvement, and that T had a good cardiovascular safety profile. Furthermore, in COPD patients with less severe COPD not requiring concomitant therapy with inhaled corticosteroids or with other long-acting $beta_2$ agonists, the therapeutic effect of T on lung-function decline was significant. The effect of T on all-cause mortality was neither significantly beneficial nor, more importantly if safety is considered, significantly deleterious, but further analysis on respiratory cause mortality, and on mortality rates according to COPD disease severity, are certainly required.

In another study performed in patients with severe and very severe COPD, with similar outcome measures, T was evaluated in comparison with an inhaled fluticasone/salmeterol (F/S) combination over a 2-year period. The primary endpoint was represented as the rate of exacerbations requiring healthcare utilization. Both T and F/S had comparable effects on this measure [1.28 with the F/S group and 1.32 in the T group (rate ratio, 0.967, $p = 0.656$)] [5]. However, in this study T was given alone in patients with severe and very severe COPD, whereas current guidelines recommend the addition of inhaled corticosteroids to the bronchodilator maintenance treatment [1].

Cardiovascular safety related to inhaled anticholinergics has been of concern since the ages of the Lung Health Study [6]. A recent meta-analysis on the pooled safety on both short- and long-acting inhaled anticholinergics data detected a significantly higher risk of cardiovascular death, stroke, and myocardial infarction associated with both and with inhaled tiotropium in particular [7]. However, these data have to be interpreted with precaution as far as tiotropium

bromide safety is concerned for several reasons one being the unclear definition of short- and long-term safety.

4. Expert opinion

The UPLIFT Study showed that inhaled tiotropium to be an efficacious therapy irrespective of the stage of severity of COPD. However, the most significant effects seem to be in less severe patients. For more advanced disease, the addition of tiotropium to long-acting beta$_2$ agonists (LABA) such as salmeterol, formoterol or indacaterol, to inhaled corticosteroids, or to both, could also be beneficial. Combined long-acting bronchodilator therapy is recommended in COPD provided that one component is not able to maintain an adequate disease control. If a LABA is added to tiotropium, it is assumed that the combination augments the bronchodilator efficacy of each component. Studies assessing the effects of combining tiotropium with formoterol have generally demonstrated this 'acute', enhancing effect but, given that these studies lasted not more than 6 months, the long-term efficacy could not be documented.

In severe and very severe COPD, inhaled corticosteroids should be added to the maintenance, long-acting bronchodilator regimen. The existing data suggest that this approach could result in a lower COPD hospitalization rate and in better lung function and HRQoL.

The UPLIFT Study was done on smoking-related COPD and showed that, in terms of lung-function decline, the maximum therapeutic benefit was in patients with moderate COPD. This means that, as a therapeutic intervention, the effects of inhaled tiotropium therapy on lung-function preservation were comparable to sustained smoking cessation. Based on such results, it can be expected that, in smokers with COPD, a combination of these two interventions should have a superior effect, whereas in non-smokers with COPD, in whom smoking cessation cannot be used as a therapeutic intervention, tiotropium might be able to slow lung function decline. However, such a plausible hypothesis needs to be supported by data.

Tiotropium might be also effective at the other extreme of severity. For example, in severe and very severe COPD it would be interesting to see if this therapy would be able to reduce gas exchange impairment and to delay chronic respiratory failure.

5. Conclusions

In stable COPD, long-term inhaled therapy is aimed at reducing lung-function impairment, disease morbidity and mortality, and at improving HRQoL. In particular, tiotropium bromide – a potent long-acting inhaled anticholinergic – has been demonstrated as having the potential to fulfil these requirements, on both a short- and a long-term basis and either as a single therapy or combined with other pharmacological classes.

The long-term efficacy of tiotropium is demonstrated by the results of the UPLIFT Study, which also documents its safety profile associated with prolonged use, providing valuable information, especially on potentially fatal cardiovascular events. Sustained therapy with inhaled tiotropium has been shown to be beneficial irrespective of disease severity; however, the maximum therapeutic effect as a stand-alone therapy seems to be in less severe COPD.

Combination with other inhaled compounds, according to disease severity, is recommended and should be further documented for its efficacy and safety, as should the potential of tiotropium to interfere with COPD-related mortality and the development of chronic respiratory failure.

Given the uniformity of beneficial effects irrespective of disease severity, as highlighted by the initial analysis of data from the UPLIFT Study, tiotropium remains a therapeutic mainstay for maintenance therapy in stable COPD.

Declaration of interest

I attended a meeting funded by an unrestricted grant Boehringer and Pfizer but not organized by them (organiser Association for interdisciplinary Study of Respiratory Diseases in Italy). I did not received in person any grant from Boehringer or pfizer in the last three years.

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