EXPERT OPINION

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Evaluation of inhaled tiotropium in asthma, uncontrolled with standard combination therapy

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Introduction: In uncontrolled asthma, the suboptimally inhibited airways inflammation is the main pathogenic event. Addition of other medications to the regular regimen might be able to improve disease control by enhancing bronchodilation and/or by reducing the bronchial inflammation. Tiotropium is currently under evaluation as a potential such therapy.
Areas covered: The long-term efficacy and safety of tiotropium was recently evaluated in two studies in patients with poorly controlled asthma under inhaled corticosteroids + long-acting β2 agonists. Tiotropium was able to improve lung function and the effect was sustained, reduced the exacerbations risk (and in particular severe exacerbations risk), but had a marginal effect on symptoms and on quality of life.
Expert opinion: In asthma, inhaled tiotropium is able to increase the bronchodilation, and might also be able to exert an anti-inflammatory effect.

Keywords: asthma, bronchoconstriction, LABA+CST, tiotropium

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1. Introduction

Asthma is an inflammatory disease of the airways manifesting at all ages and associated with an increasing prevalence related to that of atopy and allergies. In asthma, bronchial hyperreactivity induced by the underlying inflammation triggers episodic bronchospasm manifesting clinically with respiratory symptoms such as dyspnoea, cough or chest constriction and with airflow limitation. Asthma therapy usually has two components: the rescue medications used to relieve on acute basis the bronchospasm, and regular therapies aimed at reducing airways inflammation and at maintaining an appropriate bronchodilation. Inhaled corticosteroids and long-acting β2 agonists are used on regular basis in combination to achieve this goal, but sometimes they are not able to control adequately the disease. In such situations other medications are to be added, but not always they are able to improve significantly the symptoms and/or the lung function.

Tiotropium bromide, an inhaled long-acting anticholinergic which is currently widely used in chronic obstructive pulmonary disease (COPD), was recently demonstrated to be potentially useful in asthma as well [1,2]. However, its long-term effects in asthma are not well known. This paper discusses the results of two studies (PrimoTinAsthma 1 and PrimoTinAsthma 2) evaluating the efficacy and safety of tiotropium in patients with asthma uncontrolled with an inhaled corticosteroids–LABA combination [3].

2. Methods and results

These studies had a similar design (randomised, double-blind, placebo-controlled parallel group) and study period (48 weeks). Eligible were subjects aged 18 – 75,

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Article highlights.

- Inhaled corticosteroids and long-acting β2 agonists in combination are usually able to achieve an optimal disease control in asthma.
- Uncontrolled asthma is uncommon and is usually caused by a suboptimally inhibited airways inflammation and/or insufficient bronchodilation.
- Addition of other medications able to improve bronchodilation or to reduce airways inflammation can improve the disease status.
- Inhaled tiotropium is a long-acting anticholinergic which is currently widely used as a COPD therapy.
- Inhaled tiotropium, when given for longer periods of time, is able to improve lung function and to reduce the risk of exacerbations and in particular of severe exacerbations.
- Tiotropium might be used in uncontrolled asthma not only for its bronchodilating effects but also for its potential anti-inflammatory effects, which were demonstrated preclinically but need to be also detected in clinical settings.

This box summarises key points contained in the article.

with an asthma diagnosis of at least 5 years, an asthma control questionnaire (ACQ-7) score of at least 1.5 and a persistent airflow obstruction [defined as a post-bronchodilator forced volume in 1 s (FEV1) %predicted of 80% or less and a FEV1/FVC ratio of not > 70%] while receiving inhaled corticosteroids at a dosage of at least 800 µg/daily combined with inhaled LABAs. Eligible subjects were required to have had at least one exacerbation during the previous year and to be non-smokers. Excluded were subjects with COPD, serious comorbidities or concomitant inhaled anticholinergic therapy. The study medication was represented by two puffs (2 × 2.5 = 5 µg) of inhaled tiotropium delivered via Respimat or matching placebo. Other medications such as anti-IgE, systemic corticosteroids, leukotriene modifiers or methylxantines were allowed.

There were three primary endpoints: peak (maximal) FEV1 response within the first 3 h after administration and the trough (end of the daily therapeutic effect) FEV1 at week 24 expressed as change from baseline FEV1 and by time to the first severe asthma exacerbation. Among the secondary endpoints included were the peak and trough FEV1 and FVC at each scheduled visit, AUC for 3 h after administration of the study maintenance therapies for both FEV1 and FVC, time to first asthma worsening and quality of life. A total of 912 patients were randomised (459 in study 1, 453 in study 2). Per protocol population included 413 patients in study 1 (202 placebo, 211 tiotropium) and 401 in study 2 (203 placebo, 198 tiotropium). In the pooled data analysis the mean age at baseline was 53, most of the patients enrolled were female (60.4%), median duration of the disease was 28 years and about 19% of the patients experienced at least three exacerbations during the previous year. The mean baseline ACQ-7 score was 2.6, whereas the mean post-bronchodilator FEV1%pred was 62.2%.

Tiotropium reduced significantly the airflow obstruction, increasing the peak FEV1 by 86 ± 34 ml ($p = 0.01$) in study 1 and 154 ± 32 ml ($p < 0.001$) in study 2. The overall tiotropium–placebo groups difference in the trough FEV1 was 88 ± 31 ml ($p = 0.01$) in favour of the treatment group, 111 ± 30 ml ($p < 0.001$). Tiotropium also increased significantly the time to the first severe exacerbation (282 days with tiotropium versus 226 days with placebo) and this corresponded to a 21% reduction of the risk of developing such an exacerbation (hazard ratio 0.79, 95% confidence interval 0.62 – 1.00, $p = 0.03$). Tiotropium also improved at 24 weeks other spirometric values such as FEV1 over a 24 h period, PEF, PEF variability and reduced the percentage of patients with at least one severe exacerbation (26.9 vs 32.8% with placebo) as well as the number of severe exacerbations per patient per year (0.53 vs 0.66 with placebo, $p = 0.046$). Tiotropium also reduced significantly the risk of the first exacerbation (time to first exacerbation 315 days vs 181 days with placebo, risk reduction 31%, $p < 0.001$). The improvements in the quality of life were minimal and not clinically meaningful. A subgroup analysis found that the maximum therapeutic benefit on lung function was obtained in patients with more impaired lung function, who were males, or former smokers. There were adverse events reported in 73.5% of the patients in the tiotropium arms and 80.3% of patients on placebo. Drug-related adverse events were reported in 5.7% patients receiving tiotropium and 4.6% with placebo, and dry mouth in particular was detected in 1.8% of patients receiving tiotropium and 0.7% in patients on placebo. Cardiovascular side effects detected were represented by supraventricular tachyarrhythmia, atrial fibrillation, coronary artery occlusion, coronary artery stenosis, and ventricular tachycardia, each of them being reported in 0.4% of the patients included in the tiotropium arm in the first study. Serious adverse events were reported in 8.1% of patients on tiotropium and 8.8% of patients on placebo.

3. Discussion

This study demonstrates that long-term addition of tiotropium to a maximal bronchodilator-anti-inflammatory therapy is mainly to improve the persistent airflow limitation and to reduce the risk of exacerbations and in particular that of severe exacerbations. Moreover, the maximal therapeutic benefit was found in patients with more severe airways obstruction, in males and in patients who used to be smokers but with a low tobacco exposure. A previous study with a similar design and selecting a similar population evaluated the short-term (8 weeks) safety and efficacy of adding either of two tiotropium dosages (5 and 10 µg respectively) to a similar inhaled therapeutic regimen. A dose-dependent effect of tiotropium on lung function and minimal impact on quality of life and on respiratory symptoms were found [4]. Another

previous study demonstrated similar effects on lung function even when tiotropium was added to the inhaled corticosteroids earlier in the disease course, and these effects were comparable to those achieved if instead tiotropium, a long-acting β2 agonist (LABA, i.e., salmeterol) was used, and were superior to those achieved by doubling the usual dose of inhaled corticosteroids. However, this was a three-way, double-blind cross-over trial of a shorter duration performed in an asthma sample with better lung function and given the methodological limitations (mainly the duration), the impact of using tiotropium as a regular bronchodilator on asthma morbidity could not be ascertained [5].

4. Expert opinion and conclusions

Poor disease control in asthma can manifest with symptoms worsening/asthma attacks (diurnal and/or nocturnal), limitation of daily activities, with an increased use of rescue medication and with a persistent airflow limitation. The underlying pathogenic event is represented by the airways inflammation which is not optimally minimised and which consequently is the main risk factor for frequent or persistent symptoms, or for frequent disease exacerbations. The current evidence suggests that despite not having a significant effect on respiratory symptoms, tiotropium can improve significantly and in a sustained manner the lung function, and can reduce the disease exacerbations. The latter effect came to a certain surprise, given this therapy is used for its bronchodilator potential, and in a patient with asthma already taking an inhaled corticosteroid–LABA combination it allows a more prominent bronchodilation acting via a mechanism of action which is different but synergistic with that achieved with β2 agonists. However, preclinical data suggest that apart from relaxation of the bronchial smooth muscle cells, tiotropium was also able to exert direct anti-inflammatory effects in the airways, which were demonstrated by a significant reduction of the eosinophilic inflammation at this level [6]. In a clinical setting this should be detected using non-invasive markers of airways inflammation already validated in asthma such as FeNO. A reduction of FeNO as a result of adding tiotropium to the existent asthma regular therapy would reveal indirectly the anti-inflammatory effects of this compound or of the other of the same class and would, along with exacerbation reduction support the use of long-acting anticholinergics in asthma with suboptimally controlled airways inflammation.

The safety profile of the existing formulation is also very good, with no significant number of cardiovascular events in patients receiving long-term tiotropium therapy. However, this should be further monitored especially when inhaled LABA are to be used concomitantly.

Overall the studies analysed in this paper demonstrate that in patients with uncontrolled asthma, tiotropium can provide a supplementary bronchodilation and can reduce the disease-related morbidity probably due to an extra anti-inflammatory effect. Such a dual effect might be also used in the future as a corticosteroid-sparing strategy.

Declaration of interest

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

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