

Tiotropium – what role in asthma?

Tiotropium solution for inhalation (Spiriva Respimat – Boehringer Ingelheim) is the first long-acting muscarinic antagonist to be marketed in the UK for the management of asthma.¹ It is licensed as add-on maintenance bronchodilator treatment in adults with asthma who are using an inhaled corticosteroid ($\geq 800\mu\text{g}$ budesonide/day or equivalent) and a long-acting β_2 agonist, and who have had one or more severe exacerbations in the previous year.² This corresponds to use at step 4 of both the British asthma guideline and the Global Initiative for Asthma (GINA) strategy for the treatment of asthma in adults.^{3,4} Here we consider the evidence for tiotropium in the management of asthma and whether it offers any advantages over existing therapeutic options at step 4.

Background

It is thought that the proportion of people affected by asthma in the UK is amongst the highest in the world with over five million people receiving treatment for asthma.⁵ In 2011/2012 there were more than 65,000 admissions to hospital for asthma of which 40,000 were in people over the age of 15 years.⁵ There were more than 1,100 registered deaths with a primary cause of asthma in England and Wales in 2013.⁶

A national investigation into deaths caused by asthma identified issues relating to prescribing and the use of medicines.⁵ Such problems included excessive prescribing of reliever medication, under-prescribing of preventer medication and inappropriate prescribing of long-acting β_2 agonist (LABA) bronchodilator inhalers. The investigation report's authors recommended a series of actions for healthcare professionals who manage people with asthma:

- review patients who have been prescribed >12 short-acting reliever inhalers in the previous 12 months;
- routinely assess inhaler technique;
- check for non-adherence with inhaled corticosteroids (ICS);
- LABA bronchodilators should be prescribed with an inhaled corticosteroid in a single combination inhaler.

In addition, it is recommended that patients with asthma should be referred to a specialist asthma service if they have required more than two courses of systemic corticosteroids in the previous 12 months or require treatment at step 4 or 5 of the British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) guideline to achieve control.⁵

Asthma management

The long-term goals of asthma management are to achieve good control of symptoms and maintain normal activity levels, and to minimise the risk of exacerbations, fixed airflow limitation and adverse effects of treatment.⁴

Pharmacological therapy should be stepped up in response to symptoms and stepped down when good control has been achieved.³ Adherence to

long-term asthma treatment should be routinely and regularly addressed by all healthcare professionals. Poor adherence should be considered when there is a failure to control asthma symptoms.³

The BTS/SIGN guideline for the treatment of asthma states that at step 4 there are few clinical trials to guide management, and recommendations are largely based on extrapolation from trials of add-on therapy to ICS alone.³ At step 4, prescribers are advised to consider increasing the dose of ICS up to beclomethasone dipropionate $2,000\mu\text{g}$ per day (or equivalent) or adding a fourth drug. Options include a leukotriene receptor antagonist (LTRA), a slow-release theophylline or a slow-release β_2 agonist.³

What is tiotropium?

Tiotropium bromide is a long-acting muscarinic antagonist (LAMA) delivered by inhalation. In the airways, tiotropium competitively and reversibly binds to the M3 receptors in the bronchial smooth musculature, antagonising the cholinergic (bronchoconstrictive) effects of acetylcholine and resulting in bronchial smooth muscle relaxation.² It originally received marketing authorisation in 2002 as a maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD). In September 2014, tiotropium $2.5\mu\text{g}$ solution for inhalation (Spiriva Respimat) received a licence extension for use in adults with asthma.¹

The recommended dose for adults is $5\mu\text{g}$ tiotropium (given as two puffs) once daily, at the same time of the day.²

(Tiotropium $18\mu\text{g}$ inhalation powder does not have marketing authorisation for the treatment of asthma.)

Clinical Efficacy

Assessment of outcomes in trials

The European Medicines Agency (EMA) recommends that assessment of drugs used to treat asthma should be based on measures of lung function and clinical endpoints such as exacerbations.⁷ The American Thoracic Society and the European Respiratory Society have also issued guidance on suitable endpoints for clinical trials (see Box).⁸

The EMA guidance suggests that for a new bronchodilator drug administered as concomitant medication with inhaled corticosteroids, an effect on both lung function and exacerbations should be demonstrated. Pre-bronchodilator FEV_1 and exacerbations should be considered as co-primary endpoints.⁷

* DTB CME/CPD

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Box: Endpoints for asthma trials^{3,4,7–9}

Lung function: forced expiratory volume in 1 second (FEV₁). Minimum important difference (MID) is about 10%, but this is not well established. Minimum patient perceivable improvement is 230mL.

Exacerbations: number of exacerbations or exacerbation rate. Clinically relevant endpoint to assess controller treatment in asthma patients.

Symptom scores: there are no validated scores but symptom-free days and number of night-time awakenings are relevant clinical variables for measurement.

Composite scores: provide information about control from the patient's perspective. For example, Asthma Control Questionnaire (ACQ-7 [range 0–6, higher score worse]). MID is 0.5.

Health related quality of life (HRQoL): questionnaire-based assessment. For example, Asthma Quality of Life Questionnaire (AQLQ [range 1–7, higher score better]). MID is 0.5.

Efficacy data

Three studies have assessed the efficacy of tiotropium in patients with severe symptomatic asthma despite treatment with ICS and LABA.^{10,11} In all three studies participants had post-bronchodilator FEV₁ ≤80% predicted.

Tiotropium 5µg and 10µg versus placebo

In a double-blind crossover study with three 8-week treatment blocks, 107 people were randomised to receive tiotropium 5µg or 10µg or matching placebo via the Respimat device.¹⁰ Patients were aged 18–75 years (mean age 55 years) with a ≥5-year history of asthma and a current diagnosis of severe persistent asthma. At baseline all patients were using a LABA and ICS (mean daily dose 1,235µg budesonide equivalent). A short-acting beta₂ agonist was used by 77% of participants (mean daily puffs=4).

The primary endpoint of change from baseline in peak FEV₁ at the end of the treatment period (difference from placebo) was statistically significant for both doses (5µg: 139mL, 95% CI 96 to 181, p<0.001; 10µg: 170mL, 95% CI 128 to 213, p<0.001). The difference between doses was not statistically significant. There were no significant differences in asthma-related health status or symptoms between active and placebo treatments.

The most common adverse effects reported more often with tiotropium treatment than placebo included dry mouth, cough and headache.

Tiotropium 5µg versus placebo

Two replicate randomised controlled studies involving a total of 912 people compared the effect of tiotropium 5µg daily with placebo for 48 weeks as add-on treatment to maintenance asthma therapy of high-dose ICS (median daily dose 800µg budesonide equivalent) and LABA.¹¹ Patients were aged between 18 and 75 years (mean age 53 years) and had a ≥5-year history of asthma that was diagnosed before the age of 40 years. In addition, patients had to have had an exacerbation treated with systemic corticosteroids in the previous year. The two primary lung-function endpoints for each trial were the change from baseline in the peak post-bronchodilator FEV₁ and trough FEV₁ at week 24. The third primary endpoint was the time to a first severe exacerbation that required initiation or doubling of systemic corticosteroid for ≥3 days, assessed at week 48.

The mean baseline pre-bronchodilator FEV₁ for all patients in both trials was 1,603mL. At week 24, the mean change in FEV₁ from baseline was greater with tiotropium than placebo. Compared with placebo the differences in peak FEV₁ in each trial were 86mL (95% CI 20 to 152, p<0.05) and 154mL

(95% CI 91 to 217, p<0.001); changes in trough FEV₁ were 88mL (95% CI 27 to 149, p<0.01) and 111mL (95% CI 53 to 169, p<0.001). The time to first severe exacerbation was 282 days with tiotropium vs. 226 days with placebo (hazard ratio 0.79, 95% CI 0.62 to 1.00, p=0.03), based on the time taken until at least 25% of patients had a severe exacerbation. For tiotropium 122/453 patients (26.9%) had at least 1 severe exacerbation vs. 149/454 patients (32.8%) taking placebo.

Allergic rhinitis was reported at a significantly higher rate among patients taking tiotropium. Drug-related cardiac events were reported in two patients in the tiotropium group and one in the placebo group.

Safety study

A 52-week study in Japan assessed the safety profile of tiotropium in patients with symptomatic asthma who were receiving maintenance treatment with medium-dose ICS (400–800µg budesonide or equivalent) alone or in a fixed combination with a LABA.¹² In this randomised double-blind placebo-controlled parallel-group study, 285 patients received add-on tiotropium (2.5µg or 5µg) or placebo. Drug-related adverse effects were reported by 8.8% (5µg), 5.3% (2.5µg) and 5.3% (placebo) of patients, and included worsening asthma, thirst, dysphonia and headache. No serious drug-related adverse effects were reported in the tiotropium group.

Systematic reviews

A meta-analysis identified six randomised controlled trials (1,635 participants) that used inhaled tiotropium in adults with poorly controlled asthma despite treatment with ICS or ICS plus LABA.¹³ Five studies compared tiotropium with placebo (including three of the studies discussed above) and one trial compared tiotropium with a double dose of ICS. The addition of tiotropium increased mean trough FEV₁ by 97mL (95% CI 71 to 122, p<0.001) and mean peak FEV₁ by 103mL (95% CI 42 to 163, p<0.001). Tiotropium also reduced the risk of severe acute exacerbations (odds ratio [OR] 0.73, 95% CI 0.56 to 0.96, p=0.02) and improved the AQLQ score by 0.10 (95% CI 0.04 to 0.16, p=0.001).

A second meta-analysis (6 trials, 1,648 participants) assessed add-on tiotropium 5µg daily (administered using the Respimat inhaler) with placebo, and was more representative of the UK licensed use.¹⁴ It included two of the trials discussed above. Compared with placebo, tiotropium significantly improved all measures of air flow, including morning and evening peak expiratory flow (weighted mean difference [WMD] 20.6L/min, 95% CI 15.4 to 25.8, p<0.001; and 25.0L/min, 95% CI 19.2 to 30.7, p<0.001 respectively), and peak and trough FEV₁ (WMD 130mL, 95% CI 90 to 180, p<0.001; and 100mL, 95% CI 60 to 140, p<0.001 respectively) without a significant increase in adverse effects. Differences in symptom scores and quality of life indices were not significantly affected, and studies were not generally long enough to show effects on exacerbations or mortality.

Limitations of the data

The evidence for using tiotropium at step 4 of the BTS/SIGN guidance largely relies on two studies that compared add-on treatment with tiotropium against placebo.^{1,2} Overall, the improvement in FEV₁ compared with placebo was relatively small and less than the recommended minimum important difference of 10% or patient perceivable difference of 230mL. In addition, the differences between tiotropium and placebo in patient-assessed asthma control and QoL were small and did not meet the threshold for the minimum important difference.¹ It has been noted that although people with COPD were excluded from these studies, some of the participants had the same degree of persistent airflow obstruction as people with moderate COPD, and so the benefit of tiotropium in patients without persistent airflow obstruction has not been demonstrated.¹

More robust clinical trials will be required to assess whether improvements in pulmonary function and a decrease in exacerbations translate into improved quality of life.¹⁵

Unwanted effects

Most of the experience with tiotropium comes from its use in COPD and many of the undesirable effects can be attributed to its antimuscarinic action.² The most common adverse effect ($\geq 1/100$ to $< 1/10$) is dry mouth. Serious undesirable effects include glaucoma, constipation and urinary retention, all of which are uncommon or rare.

Cautions or contraindications

Tiotropium should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction.²

The Medicines and Healthcare products Regulatory Agency (MHRA) has recently advised that prescribers should consider the risk of antimuscarinic effects when prescribing tiotropium for patients with COPD and a history of cardiovascular disorders.^{16,17} While there is little data from people with asthma, tiotropium should be used with caution in patients with recent myocardial infarction, or cardiac arrhythmia or heart failure (NYHA Class III or IV) within the past year.²

Cost

The estimated annual cost of treatment with tiotropium is £408 per person. This is higher than the annual cost of other drugs used as add-on treatment at step 4: LTRA (montelukast £28, zafirlukast £231); modified-release theophylline (including aminophylline) £63–£217; oral slow-release β_2 agonists £126–£206.

National decisions on the use of tiotropium for asthma

The National Institute for Health and Care Excellence has issued a new medicine evidence summary for tiotropium for asthma but has not issued guidance on its use.¹

The Scottish Medicines Consortium has accepted tiotropium (Spiriva Respimat) for use within NHS Scotland¹⁸ in line with its licensed indication. The All Wales Medicines Strategy Group is developing guidance on the use of tiotropium for asthma.¹⁹

Conclusion

Tiotropium solution for inhalation (Spiriva Respimat) is a long-acting muscarinic antagonist that has recently been licensed as an add-on maintenance bronchodilator treatment in adults with asthma receiving maintenance treatment with the combination of inhaled corticosteroid ($\geq 800\mu\text{g}$ budesonide/day or equivalent) and long acting β_2 agonist, and who have experienced one or more severe exacerbations in the previous year. This is in line with step 4 of the British guidelines for the treatment of asthma. Studies have shown that tiotropium produced statistically significant but small improvements in lung function and reduced exacerbations compared with placebo. However, evidence for the licensed use largely relies on two studies and improvements in lung function, patient-assessed asthma control and quality-of-life indicators have generally been small and have failed to reach minimally important differences. Longer-term studies and comparisons with other add-on medication are needed. Tiotropium is more expensive than other add-on treatments and, while it may provide another option at step 4 of the British asthma guidance, we are unable to recommend it at this time.

[R=randomised controlled trial, M=meta-analysis]

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