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PrescQIPP Community Interest Company

Tiotropium bromide (Spiriva Respimat® 2.5 microgram, inhalation solution) in asthma

This bulletin reviews the evidence and place in therapy of tiotropium bromide (Spiriva Respimat®), a long acting acting muscarinic antagonist (LAMA) that now has an extended licence for use in asthma (in addition to chronic obstructive airways disease, COPD). The bulletin reviews its usage at step 4 of the British Thoracic Society (BTS) guidelines. This is currently the only LAMA licensed for use in asthma. This bulletin should be used along with the asthma focus bulletin. PrescQIPP Bulletin 83 available via: https://www.prescqipp.info/asthma-focus/viewcategory/316-asthma-focus

Recommendations

- The evidence to support the use of tiotropium (Spiriva Respimat®) in asthma is relatively weak.[1] There is an additional drug acquisition cost associated with the use of tiotropium as an add on treatment.[1]
- Tiotropium (Spiriva Respimat®) may be considered for use only within its licensed indication as add-on therapy at step 4 of the BTS guidelines in adult patients with asthma but where control is still inadequate and have experienced one or more severe exacerbations in the previous year.[2,3]
- Consider referral to a specialist (or practitioner with a specialist interest in asthma) for review before adding tiotropium (Spiriva Respimat®) therapy.[1]
- Expert opinion suggests that tiotropium (Spiriva Respimat®) may be better suited in those patients with more severe disease and fixed airways obstruction where there is a pattern of illness and physiology more similar to COPD.[4]
- When considering step-down in treatment, stop tiotropium (Spiriva Respimat®) before stepping down. Tiotropium (Spiriva Respimat®) is not licensed for use in patients who are not taking high dose ICS in combination with LABA.[2]
- Those patients at step 4, with this level of disease severity or instability should be receiving regular reviews of their treatment. It is imperative that adherence, inhaler technique and discussion of potential trigger factors are assessed before initiating additional agents in patients who remain symptomatic on ICS and LABA therapy.[3]
- Ensure that criteria for starting (as above) and stopping treatment are checked. Review treatment in patients receiving tiotropium (Spiriva Respimat®), one to two months following treatment initiation.
- Ensure regular review of cardiovascular risk factors.[2,5]
- In patients with moderate to severe renal impairment (creatinine clearance, CrCl ≤ 50ml/min), only use tiotropium (Spiriva Respimat®) if the benefits outweigh the risks.[2]

Background

Licensed indications

Tiotropium bromide is a long acting muscarinic antagonist with affinity to the receptor subtypes M1 to M5. In the airways, tiotropium bromide competitively and reversibly binds to the M3 receptors in the bronchial smooth musculature, antagonising the cholinergic (bronchoconstrictive) effects of

acetylcholine (released from the parasympathetic nerve endings) resulting in bronchial smooth muscle relaxation.[2]

Tiotropium (Spiriva Respimat®) 2.5 micrograms is licensed as an add-on maintenance bronchodilator treatment in adult patients with asthma who:

- Are currently treated with the maintenance combination of inhaled corticosteroids (≥ 800 micrograms budesonide/day or equivalent) and long-acting β2 agonists and
- Have experienced one or more severe exacerbations in the previous year.

The delivered dose (the dose after leaving the mouthpiece) is 2.5 microgram tiotropium per puff (2 puffs comprise one medicinal dose) and is equivalent to 3.124 microgram tiotropium bromide monohydrate. The Respimat® Soft Mist inhaler has a long spray duration and generates a slow-moving aerosol cloud which is independent of inspiratory effort.[2]

Summary of evidence

Efficacy: Evidence and limitations

- Two replicate randomised controlled trials (RCTs; total n=912) over 24 weeks of identical design evaluated tiotropium (Spiriva Respimat®) versus placebo in adults with poorly controlled asthma and persistent airflow obstruction who were already treated with an ICS, (median dose 800 microgram/day) and a LABA. Participants were required to have had at least one exacerbation that needed oral corticosteroids in the previous 12 months. People with diagnosed COPD and those who had a smoking history of 10 pack-years or more, or who had smoked in the year before the study, were excluded. However participants were required to have persistent airflow obstruction, defined as a post- bronchodilator FEV1 of 80% or less of the predicted value and 70% or less of forced vital capacity (FVC).[6,7]
- Primary endpoints were met:
  - Pooled results from both trials showed that over 24 weeks, tiotropium (Spiriva Respimat®) improved peak and trough FEV1 (co-primary outcomes) by 0.110 litres (95% CI 0.063 to 0.158, p<0.0001) and 0.093 litres (95% CI 0.050 to 0.137, p<0.0001) respectively.
  - Whilst there is no minimal clinically important difference (MCID) for this degree of asthma severity, the European Medicines Agency (EMA) states that the improvements over placebo were smaller than those normally considered to be clinically meaningful in asthma patients with baseline airways obstruction, i.e. 12% or 200ml.[8]
  - Time to first severe exacerbation in 25% of participants (deterioration needing initiation or doubling of oral corticosteroids for at least three days) measured over 48 weeks was statistically significantly increased by 56 days (p =0.03) compared with placebo (282 days compared with 226 days,; p=0.03).[6,7]
- Fewer participants receiving tiotropium (Spiriva Respimat®) had a severe exacerbation than those receiving placebo (26.9% versus 32.8%, hazard ratio [HR] 0.79, 95% confidence interval [CI] not stated, p<0.05, number needed to treat [NNT] 17 over 48 weeks).[4]
- Both asthma control and asthma-related quality of life were improved in both studies. At week 24, for both asthma control and asthma-related quality of life, there was only a trend towards improvement in trial 1 and a statistically significant improvement in trial 2. The minimal clinically important difference of 0.5 units for both the scores was not achieved in either trial.[7]
- Patients recorded morning and evening Peak Expiratory Flow (PEF), asthma symptoms and medication use twice daily. There were small and non-significant differences in the number of symptom-free days, while the use of rescue medication was similar in the two study groups.[7]

- There are no RCTs comparing tiotropium (Spiriva Respimat®) with other active treatments recommended at step 4 of the asthma guidelines or in people with asthma (in line with its licensed indication) without persistent airflow obstruction.[7]
- Patients with certain cardiovascular conditions were excluded from the clinical trials and these conditions may be affected by the mode of action of tiotropium (Spiriva Respimat®).[6] The MHRA have advised that the treatment of all patients already taking tiotropium delivered via Respimat® or Handihaler® to treat COPD be reviewed as part of the comprehensive management plan to ensure that it remains appropriate for them; and that there should be regular review of treatment of patients at high risk of cardiovascular events.[5]

Adverse effects

- Adverse effects were reported in 73.5% of patients in the tiotropium (Spiriva Respimat®) group and 80.3% of patients in the placebo group.[7]
- Dry mouth was reported in 1.8 % of patients (n=8) in the tiotropium (Spiriva Respimat®) group as compared with 0.7% (n=3) in the placebo group.[2]
- Serious adverse effects were reported in 8.1% of patients (n=37) in the tiotropium (Spiriva Respimat®) group and 8.8% of patients (n=40) in the placebo group.[7]
- The NICE evidence summary reports that in trial 1 there were five serious cardiac adverse events (arrhythmia supraventricular, atrial fibrillation, coronary artery occlusion, coronary artery stenosis and ventricular tachycardia) in the tiotropium (Spiriva Respimat®) group. No serious cardiac adverse events were reported in the placebo group in trial 1, or in either group in trial 2.[7]
- It should be noted that tiotropium (Spiriva Respimat®) should be used with caution in patients with recent myocardial infarction; any unstable or life threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or a change in drug therapy in the past year; hospitalisation for heart failure (NYHA Class III or IV).[2] These patients were excluded from the trials. This trial exclusion and cautionary advice is however also consistent with other licensed LAMAs in COPD.
- Consistent with its anticholinergic activity, tiotropium (Spiriva Respimat®) should be used with caution in people with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction.[2]
- Special precautions are needed in patients with CrCl ≤50ml/min.[2]

Guidelines

The BTS/SIGN asthma guideline, updated in October 2014, recommends a stepwise approach to pharmacological treatment with the aim of abolishing symptoms as soon as possible and maintaining control. Patients should start treatment at the step most appropriate to the initial severity of their asthma, and step up and down based on their response and control achieved. Avoidance of triggers and non pharmacological approaches are needed.

Adherence and inhaler technique should be assessed before adding new therapies.[3]

The licensed indications for tiotropium (Spiriva Respimat®) place it at step 4 of the BTS/SIGN guidelines. Step 4 of the guidelines states for “Poor Control On Moderate Dose Of Inhaled Corticosteroid + Add-On Therapy: addition of fourth drug”:

- Increasing inhaled corticosteroids (ICS) to 2,000 micrograms beclometasone dipropionate (BDP)/day (adults)
- Leukotriene receptor antagonists
- Theophyllines
- Slow release β2 agonist tablets, although caution needs to be used in patients already on long-acting β2 agonists.[3]

Note that BTS step 4 does not stipulate that patient should have had an exacerbation prior to further add on therapy whereas the license for tiotropium Respimat® in asthma is clear that patient should have had a severe exacerbation in the past year.

The guidelines state that "*Long-acting muscarinic antagonists appear to be as effective as salmeterol in the short term and may be superior to doubling the dose of ICS in fixed airways obstruction. Long term studies are required to confirm this evidence. There would also appear to be benefit in adding tiotropium (Spiriva Respimat®) to ICS and salmeterol in patients who remain symptomatic despite these medications. There are no controlled trials indicating which of these is the best option, although the potential for side effects is greater with theophyllines and β2 agonist tablets.*"[3]

Alternative add-on therapy (i.e increasing inhaled corticosteroids to 2,000 micrograms BDP/day, leukotriene receptor antagonists, theophyllines or slow release β2 agonist (if not on LABA)) is also an option at step 4 of the BTS guidelines. They note that there are very few clinical trials to guide management at step 4 and that the recommendations at this step are largely based on extrapolation of trials of add on therapy to ICS alone. In patients who achieve asthma control, the BTS/SIGN guideline promotes a step-down in treatment to the lowest level at which control is maintained.[3] However the key clinical trials do not provide evidence to guide a step down in treatment in patients who initiate tiotropium (Spiriva Respimat®) at step 4 and achieve control. When considering step-down in treatment, it should be noted that tiotropium (Spiriva Respimat®) is not licensed for use in patients who are not taking high dose ICS in combination with LABA. Therefore tiotropium should be reviewed and stopped first before stepping down; it is important that patients are not escalated to and then remain on triple therapy, when in fact stepping down in line with BTS guidance may be appropriate.[3]

The NICE evidence summary states that local decision makers will need to consider the available evidence on efficacy and safety, as well as cost and individual patient factors, when making decisions about using tiotropium (Spiriva Respimat®) for treating asthma in adults.[7] The Midlands Therapeutics Review and Advisory Committee (MTRAC) whilst stating that tiotropium is suitable for prescribing in primary care, also states that it has a lower place and weak evidence. It is not known how the efficacy of tiotropium as add-on therapy compares with other active treatments recommended at step 4 of the British guideline on the management of asthma.[7] According to MTRAC specialist opinion, tiotropium (Spiriva Respimat®) is an option following a trial of leukotriene antagonists and that at this stage of disease severity, referral to specialist for review may be a preferred option rather than an additional inhaled therapy.[1] Specialist opinion from NICE medicines evidence commentary states, that it would seem logical that if LAMAs are going to help anyone with asthma, it is most likely to be those with more severe disease and a pattern of illness and physiology more similar to that seen in COPD.[4]

Costs

The cost of one month's treatment with tiotropium (Spiriva Respimat®) at the recommended dose, 5 micrograms (2 puffs) daily is £33.50. The cost relative to other add on treatments at step 4 is shown below:

Preparation	Cost/30 days[9,10]
Tiotropium 2.5 microgram (Spiriva Respimat®) 2 sprays once in the morning	£33.50
Zafirlukast 20mg twice daily	£19.02
Nuelin SA® (theophylline) 250mg twice daily	£8.92
Slo-phyllin® (theophylline) 250mg twice daily	£4.66
Uniphyllin® (theophylline) continus 200 twice daily	£3.17
Montelukast 10mg one daily	£2.36

The NICE evidence summary states that the manufacturer predicts that 763 per 100,000 people will be eligible for treatment with tiotropium (based on trial data[6]) and that uptake will be 8 per 100,000 in year one rising to 84 per 100,000 in year five.[7] Using this data, there would be an additional annual cost across England (assuming a population of £60 million) of £1.9 million in year one increasing to £20 million in year five.

Summary

- The evidence for tiotropium (Spiriva Respimat®) is considered to be relatively weak.[1] Longer term studies are required to confirm its evidence. The licensed indications place it as an alternative to one of the other strategies advised at step 4 (i.e. increasing steroid dose, addition of leukotriene receptor antagonist, theophyllines or slow release β2 agonist tablets). Expert opinion suggests that consideration should be given to using tiotropium (Spiriva Respimat®) in more severe disease where there is evidence of fixed airways obstruction. Consider referral for specialist review before prescribing.

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Additional PrescQIPP resources

 Briefing

 Data pack

 Presentation

Available here: https://www.prescqipp.info/resources/viewcategory/446-tiotropium-in-asthma

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