Asthma: add-on tiotropium produces small changes in lung function and time to severe exacerbation but no change in quality of life.

Two replicate randomised controlled trials (RCTs), analysed together, found that tiotropium produced small changes in lung function and increased time to first severe exacerbation in people with poorly controlled asthma, compared with placebo. However, it did not produce clinically important improvements in asthma control or quality of life. Unlike many people with asthma, participants in these studies had persistent airflow limitation. Use of tiotropium in asthma would be off-label: it is not recommended in the SIGN/BTS British Asthma Guideline. In addition, these studies used the Respimat device, about which the MHRA has previously highlighted safety concerns.

Overview and current advice

The SIGN/BTS British Asthma Guideline (NICE accredited) is based on a stepwise approach using inhaled short-acting beta-agonists, corticosteroids and long-acting beta-agonists (LABAs), with leukotriene receptor antagonists and theophylline in selected patients. It does not include the use of tiotropium, a muscarinic antagonist licensed for use in chronic obstructive pulmonary disease (COPD) but not for use in asthma. Some small, short-term studies have suggested that tiotropium may have a beneficial effect in people with asthma, but these were focussed on spirometry measures rather than patient-oriented outcomes.

New evidence

Two replicate RCTs, analysed together, compared tiotropium with placebo in people with poorly controlled asthma, including at least one exacerbation requiring systemic corticosteroids in the previous year. The studies included a total of 912 people aged between 18 and 75 years (mean, 53 years) who had impaired asthma control despite daily therapy with inhaled corticosteroid (ICS, at least 800 micrograms of budesonide or the equivalent) and LABA. 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, but participants had to show persistent airflow limitation. This was defined as a post-
bronchodilator FEV₁/FVC ratio of 0.7 or less and FEV₁ 80% predicted or less (mean 62.2% predicted). Thus, although trial participants had asthma, they had the same spirometry characteristics as people with moderate (stage 2) COPD.6

Participants were randomised to receive 5 micrograms of tiotropium via the Respimat device each morning, or placebo, for 48 weeks. Continued use of stable doses of other anti-asthma drugs such as theophylline was permitted. There were three coprimary endpoints: peak and trough FEV₁ at 24 weeks (reported for each trial separately) and time to first severe exacerbation (deterioration necessitating initiation or at least a doubling of systemic corticosteroids for at least 3 days), based on pooled data from both trials obtained over 48 weeks.

Results were analysed from the 907 people who underwent randomisation and received at least one dose of a study drug and had at least one on-treatment efficacy measurement. At 24 weeks, the mean (±Standard Error [SE]) difference from baseline in adjusted peak FEV₁ was greater in the tiotropium groups than in the placebo groups; by 86±34 ml in trial 1 (p=0.01) and by 154±32 ml in trial 2 (p<0.001). The mean (±SE) difference from baseline in trough FEV₁ at 24 weeks was also significantly greater among those receiving tiotropium: by 88±31 ml in trial 1 (p=0.01) and by 111±30 ml in trial 2 (p<0.001).

Fewer participants receiving tiotropium 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). The time to first severe exacerbation was increased by 56 days with tiotropium compared with placebo (282 days versus 226 days, representing the time until at least 25% of the participants had a first severe exacerbation, HR 0.79, 95% CI 0.62 to 1.00, p=0.03). Asthma control and quality of life was assessed on two recognised scales (ACQ–7 and AQLQ respectively). However, between-group differences were small and statistically significant only in Trial 2. Differences were less than the recognised minimum clinically important differences for these scales.

In 2010 the MHRA previously highlighted concerns specifically about tiotropium administered via the Respimat device used in these studies (in contrast to the Handihaler device).7 This advice and a more recent systematic review suggesting a risk were discussed in a National Prescribing Centre Rapid Review (July 2011).

See the NHS Evidence topic page on asthma for a general overview of the condition.

Commentary

Commentary provided by Prof Mike Thomas, Professor of Primary Care Research, University of Southampton and Chief Medical Advisor, Asthma UK

The reasons for persistent poor control of asthma are various, and include co-morbidities, behavioral factors such as poor adherence and smoking, and therapy-resistant disease. Therapeutic options are limited. Long acting anti-muscarinic antagonists (LAMAs) such as tiotropium have clear benefits in COPD, but have traditionally had little role in asthma. However, there is a growing recognition that asthma is a heterogeneous disease, with different sub-groups having different underlying pathological drivers and responding differently to therapies. There is also recognition of an overlap between asthma and COPD: longstanding severe, uncontrolled asthma (even in non-smokers) may result in airways remodeling and fixed airflow obstruction.

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. It is not possible to say whether the persisting airflow obstruction of participants in the studies summarised here was due to ongoing bronchoconstriction despite therapy (i.e. therapy-resistant disease) or to fixed airflow obstruction from remodeling, or to a mixture of both, but the lack of a significant smoking history rules out mis-diagnosis of smoking-related COPD.
Considering the difficult-to-control group studied, the findings of reduced exacerbations and a modest but sustained improvement in lung function are important and potentially clinically relevant, offering a new option to a distinct and defined group.

Currently use of tiotropium in people with asthma would be off label. It seems likely that tiotropium will be considered in future iterations of asthma guidelines, and that new licensed indications will be sought. However, we should be careful not to extrapolate these benefits to patients without airflow obstruction, and the requirement to carefully and accurately assess those with persisting poor asthma control is paramount. Despite the lack of major adverse events in this study, we should be mindful of the cardiovascular safety concerns associated with tiotropium administered through the Respimat device, particularly in those with cardiac rhythm disorders. The role of LAMAs in those with milder asthma awaits investigation.

References
1. SIGN/BTS. British guideline on management of asthma. May 2008, last revised January 2012

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