Tiotropium in paediatric asthma

Jonathan Grigg

Affiliation: Centre for Genomics and Child Health, Blizard Institute, Barts and The London School of Medicine and Dentistry, London, UK.

Correspondence: Jonathan Grigg, Centre for Child Health, Blizard Institute, Barts and The London School of Medicine and Dentistry, London, E1 2AT, UK. E-mail: j.grigg@qmul.ac.uk

@ERSpublications
No significant benefit of inhaled tiotropium was found in a trial in children and young people with severe asthma http://ow.ly/jmK1306ck1N

Cite this article as: Grigg J. Tiotropium in paediatric asthma. *Eur Respir J* 2017; 49: 1602034 [https://doi.org/10.1183/13993003.02034-2016].

The emerging evidence that there are many types of asthma that may respond differently to treatment suggests a need for novel inhaled therapies beyond the current armamentarium of short-acting β_2-agonists, long-acting β_2-agonists (LABA) and inhaled corticosteroids (ICS). Recent phase III trials suggest that tiotropium, a long-acting muscarinic antagonist, is a promising treatment for adult asthma. In this patient population, two recent Cochrane reviews have evaluated: 1) adding tiotropium to LABA/ICS combinations in patients whose asthma is not well controlled by LABA/ICS alone; and 2) adding tiotropium to ICS compared with adding a LABA to ICS. As an add-on to ICS/LABA, the Cochrane review concluded that patients on tiotropium have fewer exacerbations requiring oral steroids [1]. As a replacement for LABA, tiotropium performs better for some measures of lung function, although LABA appears to be slightly better in improving quality of life, albeit that the differences are small [2]. Thus, phase III trials of tiotropium in children and young people are of particular interest. The first of these studies, published in 2016, sought to assess the efficacy of tiotropium in moderately severe paediatric asthma when added to ICS both without our without a leukotriene antagonist (LTRA) [3]. This 24-week study (with a 24-week blinded extension) recruited children and young people aged 12–17 years. Subjects had to be symptomatic on ICS with or without a LABA or LTRA controller, have a forced expiratory volume in 1 s (FEV_1) of 60–90% predicted and ⩾12% reversibility. At 24 weeks, the trial reached its primary outcome, *i.e.* demonstrating superiority of 5 µg tiotropium once a day for peak FEV_1 within 3 h of dosing. This positive result triggered further statistical analysis, which showed a superior (compared with placebo), but reduced, effect of a 2.5 µg dose. For the secondary outcomes, there was no effect on use of rescue medication or measures of asthma control.

The efficacy of tiotropium in children with more severe asthma has now been addressed by a phase III study reported in this issue of the *European Respiratory Journal* [4]. The trial's design is broadly similar to the previous study in moderately severe asthma, recruiting symptomatic children and young people with a mean Asthma Control Questionnaire (ACQ) score of ⩾1.5. There are, however, important differences. These include study duration of 12 weeks and a requirement for high-dose ICS with at least one additional controller therapy (either LABA or LTRA). Although this trial did not reach its primary FEV_1 outcome for the 5 µg once a day dose and the statistical analysis plan allowed no further analyses, there were descriptive improvements in pre-dose morning and evening peak expiratory flow, and some beneficial trends in ACQ scores.

What can paediatricians learn from these two large paediatric trials? First, the study in children with moderately severe asthma convincingly shows that tiotropium may provide clinically important bronchodilation in this age group. However, it must be noted that no conclusion from this trial should be drawn about its effect relative to LABA. Indeed, 30% of children in the moderately severe asthma trial had

Received: Oct 17 2016 | Accepted: Oct 21 2016

Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com

to stop their LABA both before and during the study, a therapeutic change that is not usually part of standard clinical management. The absence of efficacy of tiotropium in the more severe paediatric asthma serves as a reminder that extrapolating from studies in adults to children is always problematic. Why no bronchodilator effect of tiotropium was found in severe paediatric asthma is puzzling. Perhaps there is a different mix of asthmas in "severe" and "moderate" paediatric asthma? Alternatively, since all children in the severe asthma trial continued to use their controllers, this may be the first indication that tiotropium provides no additional benefit when added on to LABA. Thus, until more studies are done, the place for tiotropium in the paediatric management pathway remains unclear. However, one immediate niche could be where ICS step up is needed but there is a relative contraindication to LABA; for example, in a child receiving prophylactic azithromycin therapy.

References

1 Kew KM, Dahri K. Long-acting muscarinic antagonists (LAMA) added to combination long-acting β2-agonists and inhaled corticosteroids (LABA/ICS) *versus* LABA/ICS for adults with asthma. *Cochrane Database Syst Rev* 2016; CD011721.
2 Kew KM, Evans DJ, Allison DE, *et al.* Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus addition of long-acting β2-agonists (LABA) for adults with asthma. *Cochrane Database Syst Rev* 2015; CD011438.
3 Hamelmann E, Bateman ED, Vogelberg C, *et al.* Tiotropium add-on therapy in adolescents with moderate asthma: a 1-year randomized controlled trial. *J Allergy Clin Immunol* 2016; 138: 441–450.
4 Hamelmann E, Bernstein JA, Vandewalker M, *et al.* A randomised controlled trial of tiotropium in adolescents with severe symptomatic asthma. *Eur Respir J* 2017; 49: 1601100.