



Emerging role of long-acting anticholinergics in children with asthma

Christian Vogelberg

Purpose of review

Although the use of inhaled anticholinergics in obstructive airway disease has been established for several years, the clinical experience using these medications in treating patients with asthma is limited. Only few studies so far have included pediatric patients with asthma, but these studies demonstrate relevant therapeutic effects. This review will explore the pharmacological effects of inhaled anticholinergics, provide an overview about current adult and pediatric asthma studies using tiotropium, and describe future research needs.

Recent findings

In a phase II study with tiotropium as add-on to maintenance treatment to inhaled corticosteroids (ICSs) in moderate persistent adolescent with asthma, significant improvement of peak and trough forced expiratory volume in 1 s (FEV₁) with a good safety profile could be demonstrated. A pediatric phase II study in symptomatic patients with asthma aged 6–11 with comparable study design also demonstrated significant improvement of peak FEV₁ with no serious adverse events. However, both studies could not document a significant clinical improvement analyzed by standardized scores.

Summary

Tiotropium might become an add-on treatment option in symptomatic pediatric and adolescent patients with asthma despite adequate therapy with ICS and long-acting β 2-agonist (LABA) or as an alternative to LABA in patients with safety concerns related to LABA. For a better assessment of the clinical effect, long-term studies are needed.

Keywords

asthma, bronchodilator, inhaled anticholinergic agents, tiotropium

INTRODUCTION

The effect of add-on inhaled anticholinergic medications to standard inhaled β 2-agonists in adult and pediatric patients with asthma has been evaluated in several studies within the past 25 years [1–4] and its use in the treatment of acute asthma has systematically been reviewed by Rodrigo and Castro-Rodriguez [5]. All of these 16 studies included in this meta-analysis were performed with ipratropium bromide, and were able to demonstrate a dose-dependent effect on hospital admission rate and pulmonary function parameters. Other effects in some of the pediatric studies within the review concerned improvement of clinical scores. Based on these data, the combination of inhaled anticholinergics and β 2-agonist for treatment of acute asthma attacks is now part of current asthma treatment guidelines [6].

The predominant clinical experience with tiotropium, a long-acting anticholinergic, results from

its use in chronic obstructive pulmonary disease (COPD) [7]. However, based on the pathophysiological changes because of cholinergic effects within the lung in patients with asthma, the pharmacological properties of tiotropium reveal a substantial rationale for its use in asthma including children [8–14,15[■],16]. Only recently, the first studies examining the effects of tiotropium as add-on therapy in adult and pediatric asthma were published.

Department of Pediatric Pulmonology and Allergology, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

Correspondence to Christian Vogelberg, MD, PhD, Department of Pediatric Pulmonology and Allergology, University Hospital Carl Gustav Carus, Technische Universität Dresden, Fetscherstr. 74, 01307 Dresden, Germany. Tel: +49 351 4585699; e-mail: christian.vogelberg@uniklinikum-dresden.de

Curr Opin Pulm Med 2016, 22:74–79

DOI:10.1097/MCP.0000000000000229

KEY POINTS

- Release of acetylcholine results in multiple effects within the airways including contraction and proliferation of airway smooth muscles, mucus production, increase of ciliary beat frequency and release of pro-inflammatory mediators by airway epithelial cells, proliferation of fibroblasts, and vasodilation.
- Inhaled long-acting anticholinergics have been successfully used in chronic obstructive airway disease for many years.
- Few clinical studies in adults with uncontrolled asthma demonstrated beneficial effects of inhaled long-acting anticholinergics as add-on therapy to inhaled corticosteroids comparable to long-acting β_2 -agonists.
- Recent initial studies in pediatric or adolescent patients with moderate persistent asthma who are not controlled by inhaled corticosteroids alone suggest substantial beneficial effects and a good safety profile of add-on treatment with tiotropium.
- Future studies are needed to further characterize the patients who are likely to have a beneficial response to additional treatment with long-acting anticholinergics and investigate the effects of these medications on the course of the disease.

Effect of anticholinergic drugs on the lung

Within the human lung, the dominant innervation is provided by cholinergic parasympathetic nerves, which release acetylcholine as messenger. These parasympathetic nerves are carried by the vagus nerve into the thorax and to the ganglia near the airways [17]. The highest density of postganglionic nerves is located along the bronchi proximal to the terminal bronchioles [18]. Release of acetylcholine results in multiple effects within the airways including contraction and proliferation of airway smooth muscles, mucus production and electrolyte release by goblet cells and submucosal glands, increase of ciliary beat frequency and release of pro-inflammatory mediators by airway epithelial cells, proliferation of fibroblasts, and vasodilation [19,20]. The predominant types of receptors for acetylcholine are the nicotinic and the muscarinic receptors. Five subtypes of the muscarinic receptor (M1–M5) have so far been identified, although only three (M1–M3) receptor types are present within the lung [21]. M1 receptors are predominantly located in the peripheral airways in peribronchial ganglia, whereas M2 and M3 receptors are mainly expressed in the large airways on airway smooth muscle cells [22]. Although M1 and M3 receptors regulate smooth muscle contraction, M2 receptors function as

autoreceptors with inhibitory effect on the release of acetylcholine from cholinergic nerves.

Tiotropium is the only long-acting muscarinic receptor antagonist (LAMA), which has been approved for asthma therapy in some countries. Although it also binds to all three muscarinic receptors, it dissociates faster from M2 than from M1 or M3 [23]. With a maximum effect occurring at 30–60 min, its duration of blocking cholinergic transmission is around 35 h and therefore a once-daily admission is feasible.

Long-acting inhaled anticholinergics in adults with asthma

The first double-blind, triple-dummy study in adults with uncontrolled asthma compared the add-on effect of tiotropium bromide with the add-on effect of 160 μ g salmeterol or doubling of the steroid doses over 14 weeks [24]. With change of the morning peak expiratory flow (PEF) as primary outcome parameter, tiotropium was superior to doubling the inhaled corticosteroid (ICS) dose and noninferior to salmeterol.

The efficacy and safety of two different doses of tiotropium (5 and 10 μ g) were investigated in uncontrolled patients with severe asthma [25]. Peak and trough FEV₁ and daily PEF measured at home were significantly higher in both tiotropium doses compared with placebo.

Another study with adult patients with asthma who have a B16-Arg/Arg genotype compared the effects of tiotropium administered with 5 μ g via Respimat daily with 50 μ g salmeterol twice daily or placebo [26]. Tiotropium was noninferior to salmeterol and both superior to placebo with regard to weekly PEF changes.

The effect of a long-term treatment with 5 μ g tiotropium administered with Respimat inhaler over 48 weeks was reported by Kerstjens *et al.* [27]. Peak FEV₁ and predose FEV₁ improved significantly compared to placebo as did the rate of severe asthma exacerbations and the time to the first severe asthma exacerbation.

Within a large group of patients with moderate symptomatic asthma, two doses of tiotropium (2.5 and 5 μ g) were compared with salmeterol 100 μ g and placebo over a period of 24 weeks [28]. Again peak and trough FEV₁ were significantly improved within both tiotropium groups compared to placebo and noninferior to salmeterol.

A recently published trial demonstrated no differences between a once daily administration of 5 μ g tiotropium compared with 2.5 μ g twice daily on peak or trough FEV₁ or PEF [29]. However, a dose-dependent response to add-on tiotropium could be

demonstrated in patients with moderate symptomatic asthma treated with stable medium-dose ICS [30]. A similar result was reported by Ohta *et al.* [31] who published results of a long-term trial in patients with symptomatic asthma despite treatment with ICS $\pm$ LABA. The safety profile was comparable to placebo in both tiotropium doses.

Based on the above data in adults, the 2015 revision of the Global Initiative for Asthma 2015 strategy document the inclusion of tiotropium as a therapeutic option in addition to ICS and LABA in adult patients [6].

Long-acting anticholinergics in pediatric asthmatics

In pediatric patients, current treatment guidelines recommend the use of ICS as preferred treatment with the option to add a leukotriene receptor antagonist (LTRA) and/or a LABA in patients with moderate–severe disease [6].

The first study to investigate the use of tiotropium in adolescents with asthma was performed in 105 patients with a mean age of 14 years with moderate persistent asthma on medium-dose ICS with or without LTRA [32[■]]. Safety and efficacy of a 4-week add-on treatment with different doses (1.25, 2.5, and 5 μ g) of tiotropium delivered by Respimat Soft Mist Inhaler was tested. As the phase II study was conducted with an incomplete crossover design over a 12-week treatment period, every participant received three different doses or placebo without washout within between (Fig. 1). Lung function was measured before and at the end of each treatment

period and PEF and FEV₁ measurements were performed at home with an electronic device and logged in an electronic diary. Peak FEV₁ response within the first 3 h after inhalation (FEV_{1(0–3h)}) from baseline as primary end point was significantly higher with 5 μ g tiotropium compared to placebo and highest 1 h after inhalation. Both other doses (1.25 and 2.5 μ g) resulted in a nonsignificant increase of FEV_{1(0–3h)} compared to placebo. Trough FEV₁ was also statistically higher with 5 μ g tiotropium compared to placebo, but the magnitude of improvement was less with the other doses. Morning PEF response was significantly higher in all doses compared to placebo, whereas evening PEF response was only significantly elevated in the 5 and 2.5 μ g groups. Clinical symptoms defined by a seven question Asthma Control questionnaire (ACQ-7) [33] improved in all groups without significant differences. The number of adverse events (AEs) did not differ significantly and no drug related severe AEs were documented.

The same study design was used in 101 children aged 6–11 years, who were symptomatic at screening and randomization despite a medium-dose ICS maintenance therapy (200–400 μ g budesonide or equivalent) [34[■]]. Symptoms were defined by ACQ-7, and greater than 12% increase of FEV₁ after 200 μ g salbutamol was part of the inclusion criteria. Prebronchodilator FEV₁ variability between screening and randomization had to be $\pm$ 30%. Whereas LABA therapy had to be interrupted during the study, LTRA was permitted as add-on therapy. The primary and secondary endpoints included the parameters of the adolescent study with maximum

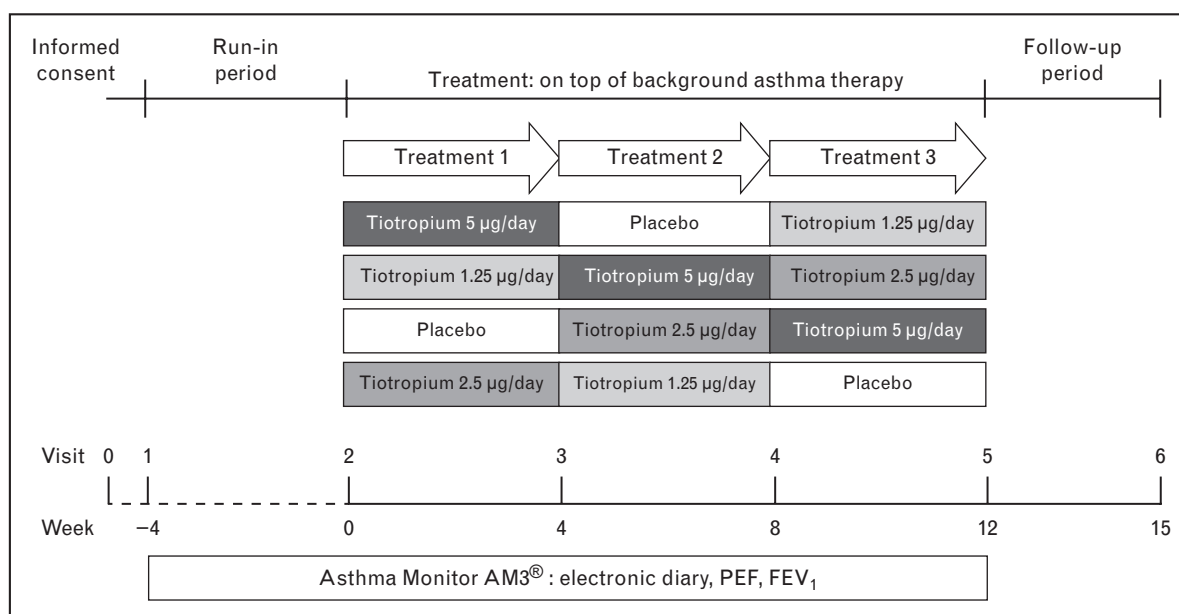


FIGURE 1. Study design [33]. FEV₁, forced expiratory volume in 1 s; PEF, peak expiratory flow.

mid-expiratory flow (MEF_{25–75%}) and Standardised Paediatric Asthma Quality of Life Questionnaire (PAQLQ[S]) [35] as additional endpoints. For FEV_{1(0–3h)} as primary endpoint, all three doses of tiotropium were significantly superior to placebo without a dose-dependent response. The same was observed for trough FEV₁ response, for FEV₁ area under the curve within 3 h postdosing (AUC_(0–3h)), MEF_{25–75%} and morning PEF response again without a dose-dependent effect. Peak forced vital capacity response within the first 3 h after inhalation (FVC_(0–3h)), trough forced vital capacity (FVC) and FVC AUC_(0–3h) responses improved in all dose groups but significantly versus placebo only for FVC AUC_(0–3h) within the 2.5 µg group. Evening PEF response improved significantly versus placebo in the 5 µg group. Asthma symptoms and quality of life improved nonsignificantly in all dosage groups. The incidence of AEs did not differ between the groups and placebo, and no severe AE was reported.

All pediatric asthma studies were performed with the Respimat Soft Mist Inhaler. This hand-held device generates an aerosol with a high, fine-particle fraction, supporting an efficient lung deposition. Both, lung deposition and handling studies were recently published demonstrating the suitability of the inhalation device even in children younger than 5 years of age [36,37]. On the basis of these data, even children less than 2 years may be able to successfully inhale with the device, although the use of a valved holding chamber is still recommended below the age of 5 years.

Long-acting anticholinergics in other pediatric lung diseases

The first placebo-controlled trial that examined the use of tiotropium in pediatric patients was performed in children suffering from postinfectious bronchiolitis obliterans [38]. Different spirometry parameters including plethysmography were analyzed during the first 24 h after inhalation of 18 µg tiotropium compared to placebo. Significant differences were reported for relevant parameters reflecting bronchial obstruction.

A trial in cystic fibrosis patients revealed a benefit of a 12-week treatment with either 2.5 or 5 µg tiotropium delivered by Respimat Soft Mist Inhaler [39]. FEV₁ within the first 4 h after inhalation improved significantly in both dosage groups, whereas trough FEV₁ improved only with 5 µg. These effects were predominantly observed in children less than 12 years of age. Pooled phase II/III and phase III data of randomized trials in pediatric and adult cystic fibrosis patients could not confirm these results [40]. Comparable to pediatric asthma studies,

Table 1. Future research needs in the pediatric population

Long-term safety data
Identification of phenotypes responding better to LAMA
Synergistic effects with ICS
Anti-inflammatory effects of LAMA
Interaction with ICS
Studies comparing the superiority/inferiority to other therapies such as LABA or LTRA

ICS, inhaled corticosteroid; LABA, long-acting β₂-agonist; LAMA, long-acting muscarinic receptor antagonist.

the safety profile in cystic fibrosis children treated with tiotropium is good and tiotropium peak plasma concentration similar to that seen in healthy volunteers or patients with COPD [41].

Future needs

Although the pediatric studies on tiotropium published so far indicate relevant clinical effects, further questions need to be answered (Table 1). All studies consistently document a good safety profile of tiotropium, both in adults and in children. However, there is a lack of long-term safety data which needs to be resolved in future studies. In addition, there is a lack of data concerning the individual response to inhaled anticholinergic bronchodilators compared with long-acting β₂-agonists. Although Peters *et al.* identified an acute response to salbutamol and a higher cholinergic tone as predictor for a positive response to tiotropium in adult patients, no features are so far reported in pediatric patients [42] and therefore this will need to be investigated. Several studies comparing the effect of add on LABA or tiotropium to different dosage of ICS reveal comparable heterogeneous responses in both groups [24,26,28]. Also, studies in asthmatic children comparing the effect of LAMA versus LABA such as performed in adults or LAMA versus LTRA are lacking and need to be initiated. In addition, possible synergistic effects between LAMA and ICS comparable to LABA and ICS need to be investigated [43]. Although certain immunological effects mediated by muscarinic receptors are described, possible anti-inflammatory effects of LAMA in the context of asthmatic disease are insufficiently investigated and therefore need to be studied in the future [22]. In addition, possible pharmacological interactions with ICS need to be identified.

CONCLUSION

Although inhaled tiotropium was recently included in the most recent GINA document as an add-on

therapy in adults with severe asthma, only few studies have so far demonstrated its efficacy and safety in the pediatric population. Most relevant changes are reported in lung function parameters and more frequently with the use of 5 µg dose compared to the lower doses, whereas clinical effects measured by standardized scores reveal only non-significant improvement. One reason might be the relatively short duration of these studies, which might not allow estimating the maximum clinical effect of an add-on therapy.

Although all studies documented a very good safety profile of tiotropium in adults and children, long-term safety data are important aspects for further studies and the identification of predictors for response to tiotropium. Nevertheless, as a step further to a more individualized medicine, the add-on therapy with tiotropium might be an option in the future in those pediatric asthmatics not responding adequately to an additional LABA therapy or in those with safety concerns about the use of LABA therapy.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

The author has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of ALK Abello, Allergopharma, Boehringer Ingelheim, Engelhard Arzneimittel, HAL Allergy, Infectopharm, Merck Sharp & Dohme, and Novartis and as a member of the advisory board for ALK Abello, Boehringer Ingelheim, Engelhard Arzneimittel, Merck Sharp & Dohme, and Novartis. He was an investigator on the pediatric tiotropium studies.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Flynn CA. Ipratropium bromide in acute asthma exacerbation. *J Fam Pract* 1999; 48:745–746.
2. Dotson K, Dallman M, Bowman CM, *et al.* Ipratropium bromide for acute asthma exacerbations in the emergency setting: a literature review of the evidence. *Pediatric Emerg Care* 2009; 25:687–692.
3. Griffiths B, Ducharme FM. Combined inhaled anticholinergics and short-acting beta2-agonists for initial treatment of acute asthma in children. *Cochrane Database Sys Rev* 2013; 8:CD000060.
4. Vézina K, Chauhan BF, Ducharme FM. Inhaled anticholinergics and short-acting beta(2)-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital. *Cochrane Database Syst Rev* 2014; 7: CD010283.
5. Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. *Thorax* 2005; 60:740–746.
6. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Updated 2015. http://www.ginasthma.org/local/uploads/files/GINA_Report_2015.pdf. [Accessed 17 July 2015]
7. Barnes PJ. The role of anticholinergics in chronic obstructive pulmonary disease. *Am J Med* 2004; 20:24S–32S.
8. Scott GD, Fryer AD. Role of parasympathetic nerves and muscarinic receptors in allergy and asthma. *Chem Immunol Allergy* 2012; 98:48–69.
9. Novelli F, Costa F, Latorre M, *et al.* Tiotropium: a new therapeutic option in asthma. *Monaldi Arch Chest Dis* 2013; 79:109–115.
10. Bollmeier SG, Lee SY. The emerging role of tiotropium for patients with asthma. *Ann Pharmacother* 2013; 47:704–713.
11. Antoniu SA, Antohe I. Evaluation of inhaled tiotropium in asthma, uncontrolled with standard combination therapy. *Expert Opin Pharmacother* 2013; 14:967–969.
12. Rashid Q, Klein R. Tiotropium in the treatment of patients with asthma. *South Med J* 2014; 107:330–337.
13. Tian JW, Chen JW, Chen R, *et al.* Tiotropium versus placebo for inadequately controlled asthma: a meta-analysis. *Respir Care* 2014; 59:654–666.
14. Price D, Fromer L, Kaplan A, *et al.* Is there a rationale and role for long-acting anticholinergic bronchodilators in asthma? *NPJ Prim Care Respir Med* 2014; 24:14023.
15. Rodrigo GJ, Castro-Rodriguez JA. Tiotropium for the treatment of adolescents with moderate to severe symptomatic asthma: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol* 2015; 115:211–216.
- A recently published review evaluating the role of tiotropium in asthmatic adolescents.
16. Rodrigo GJ, Castro-Rodriguez JA. What is the role of tiotropium in asthma?: a systematic review with meta-analysis. *Chest* 2015; 147:388–396.
17. Aquino SL, Duncan GR, Hayman LA. Nerves of the thorax: atlas of normal and pathological findings. *Radiographics* 2001; 21:1275–1281.
18. Richardson J. Nerve supply to the lungs. *Am Rev Respir Dis* 1979; 119:785–802.
19. Meurs H, Oenema TA, Kistemaker LE, Gosens R. A new perspective on muscarinic receptor antagonism in obstructive airways diseases. *Curr Opin Pharmacol* 2013; 13:316–323.
20. Quizon A, Colin AA, Pelosi U, Rossi GA. Treatment of disorders characterized by reversible airway obstruction in childhood: are anticholinergic agents the answer? *Curr Pharm Des* 2012; 18:3061–3085.
21. Quirce S, Dominguez Ortega J, Barranco P. Anticholinergics for treatment of asthma. *J Investig Allergol Clin Immunol* 2015; 25:84–93.
22. Buels KS, Fryer AD. Muscarinic receptor antagonists: effects on pulmonary function. *Handbook Exp Pharmacol* 2012; 208:317–341.
23. Barnes PJ. The pharmacological properties of tiotropium. *Chest* 2000; 117:63–66.
24. Peters SP, Kunselman SJ, Icitovic N, *et al.* Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med* 2010; 363:1715–1726.
25. Kerstjens HAM, Disse B, Schröder-Babo W, *et al.* Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. *J Allergy Clin Immunol* 2011; 128:308–314.
26. Bateman ED, Kornmann O, Schmidt P, *et al.* Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma. *J Allergy Clin Immunol* 2011; 128:315–322.
27. Kerstjens HAM, Engel M, Dahl R, *et al.* Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med* 2012; 367:1198–1207.
28. Kerstjens HA, Casale TB, Bleecker ER, *et al.* Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials. *Lancet Respir Med* 2015; 367–376.
29. Timmer W, Moroni-Zentgraf P, Cornelissen P, *et al.* Once-daily tiotropium Respimat[®] 5 µg is an efficacious 24-h bronchodilator in adults with symptomatic asthma. *Respir Med* 2015; 109:329–338.
30. Beeh KM, Moroni-Zentgraf P, Ablinger O, *et al.* Tiotropium Respimat[®] in asthma: a double-blind, randomised, dose-ranging study in adult patients with moderate asthma. *Respir Res* 2014; 15:61.
31. Ohta K, Ichinose M, Tohda Y, *et al.* Long-term once-daily Tiotropium Respimat[®] is well tolerated and maintains efficacy over 52 weeks in patients with symptomatic asthma in Japan: a randomised, placebo-controlled study. *PLoS One* 2015; 10:e0124109.
32. Vogelberg C, Moroni-Zentgraf P, Leonaviciute-Klimantaviciene M, *et al.* A randomised dose-ranging study of tiotropium Respimat[®] in children with symptomatic asthma despite inhaled corticosteroids. *Respir Res* 2015; 16:20.
- The first published study about the effect of tiotropium in asthmatic children.
33. Juniper EF, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med* 2005; 99:553–558.
34. Vogelberg C, Engel M, Moroni-Zentgraf P, *et al.* Tiotropium in asthmatic adolescents symptomatic despite inhaled corticosteroids: a randomised dose-ranging study. *Respir Med* 2014; 108:1268–1276.
- The first published study about the effect of tiotropium in asthmatic adolescents.
35. Juniper EF, Guyatt GH, Cox FM, *et al.* Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J* 1999; 14:32–38.

36. Kamin W, Frank M, Kattenbeck S, *et al.* A handling study to assess use of the Respimat[®] Soft Mist[™] Inhaler in children under 5 years old. *J Aerosol Med Pulm Drug Deliv* 2015; 28:372–381.
 37. Bickmann D, Kamin W, Sharma A, *et al.* In vitro determination of Respimat[®] dose delivery in children: an evaluation based on inhalation flow profiles and mouth-throat-models. *J Aerosol Med Pulm Drug Deliv* 2015. [Epub ahead of print]
 38. Teixeira MF, Rodrigues JC, Leone C, *et al.* Acute bronchodilator responsiveness to tiotropium in postinfectious bronchiolitis obliterans in children. *Chest* 2013; 144:974–980.
 39. Bradley JM, Koker P, Deng Q, *et al.* Testing two different doses of tiotropium Respimat[®] in cystic fibrosis: phase 2 randomised trial results. *PLoS One* 2014; 9:e106195.
 40. Ratjen F, Koker P, Geller DE, *et al.* Tiotropium Respimat[®] in cystic fibrosis: phase 3 and pooled phase 2/3 randomized trials. *J Cyst Fibros* 2015; 14:608–614.
 41. Konstan MW, Sharma A, Moroni-Zentgraf P, *et al.* Safety, tolerability, and plasma exposure to tiotropium Respimat[®] in children and adults with cystic fibrosis. *J Aerosol Med Pulm Drug Deliv* 2015; 28:137–144.
 42. Peters SP, Bleecker ER, Kunselman SJ, *et al.* Predictors of response to tiotropium versus salmeterol in asthmatic adults. *J Allergy Clin Immunol* 2013; 132:1068–1074.
- An analysis of predictors of response to tiotropium versus salmeterol in adult asthmatics.
43. Taylor DR, Hancox RJ. Interactions between corticosteroids and β agonists. *Thorax* 2000; 55:595–602.