Pediatr Drugs (2017) 19:533–538
DOI 10.1007/s40272-017-0258-9

LEADING ARTICLE

Tiotropium Bromide in Children and Adolescents with Asthma

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Published online: 14 August 2017

Abstract Evidence is emerging on the use of long-acting muscarinic antagonists (LAMAs) in the management of asthma. Tiotropium bromide (Spiriva® Respimat®) is the only LAMA approved in children and adolescents. As the use of tiotropium becomes more common in clinical practice, it is necessary to review the existing data to identify patients who may benefit from the addition of this medication to their daily asthma regimen. This review discusses recent evidence on the safety and efficacy of tiotropium bromide in the management of asthma in children and adolescents. Current data support that tiotropium bromide has a bronchodilator effect, as evident by improvements in acute lung function compared with placebo; however, data are not yet available to present a stepwise approach or identify phenotypes that would benefit from the addition of tiotropium bromide. Well-designed studies are needed to compare the different step-up options to tiotropium bromide and provide an evidence-based stepwise approach for the management of asthma in children. Furthermore, study design should include identification of phenotypes that might experience a better clinical response to tiotropium bromide compared with other adjunct medications.

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Key Points

Tiotropium bromide has a bronchodilator effect and improves lung function in children with asthma.

The lung function of children with uncontrolled asthma receiving medium doses of inhaled corticosteroids may improve with the addition of tiotropium bromide.

No data comparing the efficacy of tiotropium bromide with that of other adjunct asthma medications exist.

1 Introduction

Asthma remains the most common chronic condition in children [1]. Over 6 million children and adolescents have asthma in the USA [2], and it is estimated that asthma control is inadequate in more than half of these patients [3]. Inhaled corticosteroids (ICSs) remain the cornerstone of the management of persistent asthma, but variable responses to ICSs and concerns about side effects have spurred the use of adjunctive therapies [4, 5]. Preferred treatment in children and adults includes the addition of long-acting beta$_2$ agonists (LABAs) to ICSs, as recommended by the National Asthma Education and Prevention Program Expert Panel Report 3 (EPR-3) and the Global Initiative for Asthma (GINA) [5, 6]. More recently, long-acting muscarinic antagonists (LAMAs) have been investigated as an adjunctive therapy to ICSs for the management of asthma. In 2015, GINA included tiotropium

bromide as an adjunctive therapy option at steps 4 and 5 for patients aged ≥12 years and as an alternative to LABAs [6]. Four Cochrane reviews [7–10] have evaluated LAMAs as adjunct therapy in adult patients with uncontrolled asthma: (1) in patients with severe asthma, the addition of tiotropium to LABA/ICS combinations reduced the use of oral corticosteroids when compared with the addition of placebo [7]; (2) the addition of LAMAs to ICS monotherapy reduced the likelihood of exacerbations requiring treatment with oral corticosteroids compared with the addition of placebo [8]; (3) differences observed between the addition of LAMAs to any dose of ICS compared with increasing the ICS dose were small and inconclusive [9]; and (4) differences observed when a LAMA was added to ICS versus a LABA added to ICS were also small and inconclusive [10].

1.1 Tiotropium Bromide

Tiotropium bromide (Spiriva® Respimat®) inhalation spray 1.25 μg/puff, two puffs once daily, was approved by the US FDA in 2015 for the once-daily maintenance treatment of asthma in patients aged ≥12 years, and more recently in February 2017 for pediatric patients aged ≥6 years [11]. Tiotropium bromide, a quaternary ammonium compound, reversibly binds to muscarinic receptors on airway smooth muscles (M_3), pulmonary vasculature, mucus glands (M_3), and ganglia (M_1) and postganglionic fibers (M_2), competitively blocking the interaction between the receptor and acetylcholine and resulting in bronchodilation and decreased mucus secretion [12]. Tiotropium bromide exhibits more rapid dissociation from M_2 receptors than from M_1 and M_3 receptors, potentially providing an advantage over more nonselective agents. While it has been suggested that tiotropium bromide may have anti-inflammatory effects, its principal anti-asthmatic effect is long-acting bronchodilation [13].

The aim of this review is to identify and present published data on the efficacy of tiotropium bromide in children and adolescents with asthma. To be consistent with the GINA and EPR-3 recommendations for asthma management, the data are presented for children aged 6–11 or 12–17 years. One phase II trial for each age group, one phase III trial for children aged 6–11 years, and two phase III trials in children aged 12–17 years have been published and presented.

2 Clinical Efficacy and Tolerability in Children and Adolescent Patients with Asthma

2.1 Children (Aged 6–11 Years)

The first phase II study of tiotropium in children aged 6–11 years evaluated the safety and efficacy of tiotropium bromide 5 μg, 2.5 μg, and 1.25 μg and placebo once daily in a randomized, double-blind, placebo-controlled, incomplete-crossover trial [14]. Children with symptomatic asthma receiving maintenance treatment with medium-dose ICS (budesonide 200–400 μg or equivalent dose) as monotherapy or in combination with another controller were eligible. Patients were symptomatic at screening and at the randomization visit as defined by a seven-question Asthma Control Questionnaire (ACQ-7) mean score of ≥1.5. At the screening visit, 36.6% of patients were receiving LABAs and 45.5% of patients were receiving a leukotriene modifier; patients continued their leukotriene modifiers but were asked to stop their LABA for the duration of the trial. Patients were randomized in a 1:1:1:1 ratio to treatment arms for 4-week treatment periods. Each patient was included in three treatment arms during the study, for a total of 12 weeks. The primary efficacy outcome was peak forced expiratory volume in 1 second within 3 h post dosing (peak $FEV_{1(0–3h)}$); spirometry was performed at 30 min, 1, 2, and 3 h after inhalation of study medication at screening, at the end of the 4-week run-in period, and at the end of each 4-week treatment period. Of 101 patients completing the study, 45.5% were receiving a leukotriene modifier. Statistically significant differences were reported for peak $FEV_{1(0–3h)}$ response after 4 weeks of treatment with each tiotropium bromide dose compared with placebo. The adjusted mean improvements were 87 ml ($p = 0.0002$), 104 ml ($p < 0.0001$), and 75 ml ($p = 0.0011$) for tiotropium bromide 5, 2.5, and 1.25 μg, respectively, over placebo. Significant differences in adjusted mean trough FEV_1 (response defined as a change from baseline pre-dose FEV_1 at the end of each of the three 4-week treatment periods, which was measured just prior to the last administration of the randomization treatment), FEV_1 area under the curve over 3 h post-dosing (FEV_1 $AUC_{(0–3h)}$), and forced expiratory flow 25–75% ($FEF_{25–75}$) were also observed for each tiotropium bromide dose group compared with placebo. A statistically significant improvement for AUC peak forced vital capacity within 3 h post-dosing (FVC $AUC_{(0–3h)}$) response was only observed for the 2.5-μg dose. A statistically significant improvement was observed in adjusted mean morning and evening peak expiratory flow (PEF) for the 5-μg dose compared with placebo; the other doses showed a statistically significant difference only in the morning PEF. There were no statistically significant differences in improvement of ACQ-7 and Standardized Pediatric Asthma Quality of Life Questionnaire (PAQLQ[S]). No serious adverse events were reported in the treatment arms, and safety with all doses was comparable to that with placebo. The authors concluded that, in pediatric patients with symptomatic asthma, the addition of tiotropium bromide to medium-dose ICS with or without a leukotriene modifier was

efficacious and safe. However, the dose range of budesonide 200–400 μg daily was in the low-medium dose range for budesonide [5, 6].

The first phase III study evaluated the efficacy and safety of tiotropium bromide once daily in symptomatic children aged 6–11 years as an adjunct therapy to ICS (budesonide >400 μg daily or clinically comparable medication with one or more controller medication [LABA or leukotriene modifier] or budesonide 200–400 μg daily or clinically comparable treatment with two or more controller medications [LABA and/or leukotriene modifier and/or sustained-release theophylline]) [15]. This was a 12-week, double-blind, placebo-controlled, parallel-group trial. Patients were symptomatic at screening and before randomization (defined as an interviewer-administered ACQ [ACQ-AI] mean score of ≥1.5). At the randomization visit, patients were randomized 1:1:1 to tiotropium bromide 5 or 2.5 μg or placebo inhaler once daily over 12 weeks. The primary efficacy endpoint was change from baseline in peak $FEV_{1(0–3h)}$ at the end of the trial. A total of 401 patients were enrolled in the study; 30.2% of participants received ICSs plus one other controller, 69.8% received ICSs plus two other controllers, 78.5% received a LABA, and 84.8% received a leukotriene modifier. All continued use of their controlled medications during the study. A statistically significant improvement in peak $FEV_{1(0–3h)}$ response at week 12 was reported for the 5-μg dose (adjusted mean difference 139 ml; 95% confidence interval [CI] 75–203; $p < 0.001$) but not for the 2.5-μg dose (adjusted mean difference 35 ml; 95% CI 28–99; $p = 0.27$) compared with placebo. Similarly, a significant difference was observed in improvements in trough FEV_1 response versus placebo for the 5-μg dose. No differences in adjusted mean peak $FVC_{(0–3h)}$ or trough FVC responses were observed for either dose. Improvements in adjusted mean peak $FEV_{1(0–3h)}$ percentage of predicted responses were significant for either dose compared with placebo; however, the improvement in adjusted mean trough FEV_1% responses was only significant with tiotropium bromide 5 μg. There was no difference in improvement of ACQ-IA score, with about 75% of participants in each group showing an improvement of at least 0.5. Similarly, there was no difference in improvement in the adjusted mean number of asthma symptom-free days with both doses of tiotropium bromide compared with placebo. The safety and tolerability of tiotropium bromide were comparable to those of placebo. The authors concluded that the addition of tiotropium bromide 5 μg daily improved lung function in children with severe symptomatic asthma receiving ICSs with additional maintenance therapies.

2.2 Adolescents (Aged 12–17 Years)

The first phase II trial in adolescent patients evaluated the safety and efficacy of tiotropium bromide as an adjunctive therapy in symptomatic patients receiving medium-dose ICS with or without leukotriene receptor antagonists [16]. This was a randomized, double-blind, placebo-controlled, incomplete-crossover study. Patients receiving a medium dose of ICS as monotherapy or in combination with LABA or leukotriene modifiers were enrolled. All patients were symptomatic, as defined by an ACQ-7 mean score of ≥1.5 at screening and before randomization. At the screening visit, 22.9% were receiving leukotriene modifiers and continued their medication during the trial, but 43.8% of patients were receiving a LABA and stopped their medication. A total of 105 patients were randomly assigned to receive once-daily placebo or tiotropium bromide 5, 2.5, or 1.25 μg in a 1:1:1:1 ratio during each of the three 4-week treatment periods for a total duration of 12 weeks. The primary efficacy endpoint was peak $FEV_{1(0–3h)}$ as a change from baseline FEV_1 at the end of each of the three 4-week treatment periods. Only peak $FEV_{1(0–3h)}$ response for tiotropium bromide 5 μg was significantly greater versus placebo (113 ml; $p = 0.004$). A statistically significant improvement in trough FEV_1 responses were observed for tiotropium 5 and 1.25 μg compared with placebo; the adjusted mean FEV_1 $AUC_{(0–3h)}$ response was significantly higher for all doses compared with placebo. An improvement in morning PEF response for all three tiotropium doses was observed and was statistically significant compared with placebo; however, evening PEF was only significant for the 5- and 2.5-μg dose groups compared with placebo. All treatment groups had similar improvement in adjusted mean ACQ-7 scores (5 μg, 1.3; 2.5 μg, 1.4; 1.25 μg, 1.2; placebo, 1.4). Tiotropium bromide was well tolerated at all doses; the group receiving 5 μg had a slightly higher incidence of asthma, gastroenteritis, rhinitis, and sinusitis. The authors concluded that tiotropium is an efficacious bronchodilator in adolescent patients with moderate asthma; 5 μg is the preferred dose.

The first phase III trial evaluated the efficacy and safety of two doses of tiotropium bromide (2.5 and 5 μg daily) as an adjunctive therapy to ICS with or without a leukotriene receptor antagonist in adolescents with moderate symptomatic asthma [17]. Permitted doses of ICS maintenance therapy were budesonide 200–800 μg daily or equivalent for patients aged 12–14 years and budesonide 400–800 μg or equivalent for patients aged 15–17 years. About 30% of the patients were receiving ICS/LABA and were asked to discontinue LABAs at the screening visit, whereas 12% of the patients were receiving ICS/leukotriene modifiers and were allowed to continue receiving leukotriene modifiers during the course of the trial. In this randomized, double-

blind, placebo-controlled, parallel-group trial, patients were randomized in a 1:1:1 ratio to receive tiotropium 5 or 2.5 μg or placebo once daily in the evening over 48 weeks. In total, 398 adolescent patients with symptomatic asthma as defined by an ACQ-7 mean score of ≥1.5 were enrolled. A statistically significant improvement in peak $FEV_{1(0–3h)}$ response for both doses of tiotropium bromide compared with placebo was reported after 24 weeks and continued until week 48 of the study. The adjusted mean difference in peak $FEV_{1(0–3h)}$ response was greater with the 5-μg dose (174 ml; 95% CI 76–272) than with the 2.5-μg dose (134 ml; 95% CI 34–234). A post hoc analysis showed no difference in response in the groups aged 12–14 versus 15–17 years. A statistically significant improvement in trough FEV_1 was observed for tiotropium 5 μg compared with placebo. Both doses showed a significant improvement in FEV_1 $AUC_{(0–3h)}$ compared with placebo. There was no difference between treatment arms with regard to peak $FVC_{(0–3h)}$, trough FVC, and FVC $AUC_{(0–3h)}$. There was no difference in improvement of ACQ-7 scores between the treatment groups. The incidence of adverse events was similar among treatment groups. The authors concluded that the addition of tiotropium 5 or 2.5 μg to background treatment with ICS with or without a leukotriene modifier in adolescent patients with moderate symptomatic asthma significantly improves lung function.

In a similar phase III trial, 392 adolescents with severe symptomatic asthma receiving an ICS plus one or more controller therapies were randomly assigned to tiotropium bromide 5 or 2.5 μg or placebo once daily for 12 weeks [18]. All patients were required to have been receiving maintenance treatment with high-dose ICS plus one or more controller therapies or medium-dose ICS plus two or more controllers. High-dose ICS was defined as >400 μg budesonide or equivalent in patients aged 12–14 years and 800–1600 μg budesonide or equivalent in patients aged 15–17 years, and medium-dose ICS was defined as 200–400 μg budesonide or equivalent in patients aged 12–14 years and budesonide 400–800 μg or equivalent in patients aged 15–17 years. It should be noted that these definitions of medium and high doses are not in alignment with those in the EPR-3 and GINA guidelines, which do not differentiate between patients aged 12–14 years and those aged 15–17 years and consider a high dose to be >800 μg (GINA) and >1200 μg (EPR-3) for all patients aged ≥12 years. At screening, all patients were receiving an ICS, 83.2% of patients had been taking a LABA, 80.4% had been taking a leukotriene modifier, and 6.1% had been taking theophylline. During the study, 32 and 68% of patients were receiving two and three controller therapies, respectively. The adjusted mean difference in peak $FEV_{1(0–3h)}$ response with tiotropium 5 μg was not statistically significant (90 ml; 95% CI 19–198; $p = 0.104$); however, a statistically significant improvement in peak $FEV_{1(0–3h)}$ response with the 2.5-μg dose (111 ml; 95% CI 2–220; $p = 0.046$) was reported. Similarly, an improvement in FEV_1 $AUC_{(0–3h)}$ was statistically significant with the 2.5-μg dose compared with placebo. A statistically significant difference was observed in adjusted mean predose morning and evening PEF responses with the 5-μg dose compared with placebo. ACQ-7 scores were comparable for both tiotropium doses and were not significantly different from those for placebo. The authors confirmed the safety and tolerability of tiotropium but could not make conclusions as to the efficacy of once-daily tiotropium add-on to ICS plus at least one controller therapy in adolescent patients aged 12–17 years with severe symptomatic asthma because there was no difference in improvements in peak $FEV_{1(0–3h)}$ and trough FEV_1 responses with tiotropium 5 μg compared with placebo.

3 Discussion

The patient populations and study designs in the presented studies [14–18] have both similarities and differences, which may explain the differing results. Both studies in children [9, 10] enrolled patients with at least a 6-month history of asthma, whereas studies in adolescents included patients with at least a 3-month history of asthma [11–13]. In all trials, patients had to have a pre-bronchodilator FEV_1 of 60–90% predicted at screening visit and bronchodilator reversibility resulting in an FEV_1 increase of ≥12% within 15–30 min after administration of a short-acting β_2-agonist bronchodilator. All the trials defined symptomatic asthma as an ACQ score ≥1.5, which was confirmed at screening and at the randomization visit within 4 weeks of screening. There were a few differences in study designs and patient phenotypes. The different outcomes in the two phase III studies in adolescents may be due to the difference in study duration [17, 18]. When patients were followed-up for 48 weeks [17], tiotropium 5 μg showed more efficacy than the 2.5-μg daily dose; the difference in dose response was not reported when patients were followed-up for only 12 weeks [18]. In all of these trials, lung function was the primary outcome, and peak $FEV_{1(0–3h)}$ was used to assess bronchodilation as it is the most sensitive measurement; however, it only measures acute bronchodilation following administration. In addition, short study durations do not allow for full assessment of asthma control and exacerbations, and all of the studies showed an improved ACQ score in all treatment groups, including placebo. It is important to highlight the noticeable placebo effect in these trials, which can be attributed to improved adherence to baseline maintenance medication in clinical trials.

Table 1 Bronchodilatory effect of tiotropium bromide and long-acting beta agonists in children and adolescents

Study	Patient population	Change in baseline FEV_1 (pre-dose), ml
Tiotropium bromide 2.5 μg/day (US FDA-approved dose for asthma)		
Phase II [14]	Symptomatic asthma, aged 5–11 years, add-on to medium-dose ICS with or without leukotriene modifiers vs. placebo	105[a]
Phase III [15]	Symptomatic asthma, aged 5–11 years, add-on therapy to high-dose ICS with one or more controller medication, or medium-dose ICS with two or more controller medications vs. placebo	18[a]
Phase II [16]	Symptomatic asthma, aged 12–17 years, add-on to medium-dose ICS with or without leukotriene modifiers vs. placebo	62[b]
Phase III [17]	Symptomatic asthma, aged 12–17 years, add-on to medium-dose ICS with or without leukotriene modifiers vs. placebo	84[b]
Phase III [18]	Symptomatic asthma, aged 12–17 years, add-on to ICS plus one or more controller medications vs. placebo	115[b]
LABAs		
Cochrane review [19]	Symptomatic asthma, aged 2–18 years with persistent asthma on ICS therapy: LABA + ICS vs. increased dose of ICS for chronic asthma	100[a]
Cochrane review [19]	Symptomatic asthma, aged 2–18 years with persistent asthma on ICS therapy: LABA + ICS vs. same dose of ICS for chronic asthma	80[a]

FEV_1 forced expiratory volume in 1 second, *ICS* inhaled corticosteroids, *LABAs* long-acting beta-agonists

[a] Statistically significant vs. placebo

[b] Not statistically significant

In both phase II trials [14, 16] and one of the adolescent studies [17], eligible patients could be receiving ICSs plus LABAs or leukotriene modifiers, and about 30–40% of the patients were receiving LABAs at the screening visit. Patients receiving leukotriene modifiers were instructed to continue use during the trial, whereas those receiving LABAs were asked to stop treatment at the screening visit. The only study [18] that allowed patients to continue their previous controller medications did not find a difference between the efficacy of tiotropium bromide or placebo as an adjunctive therapy. It is important that no conclusions be drawn from these trials about the relative effect of LABAs and tiotropium. Interestingly, when the bronchodilatory effect of an approved dose of tiotropium bromide (2.5 μg/day) is compared with those of LABAs [19], the results are numerically similar (Table 1).

4 Conclusions

For now, current data support that tiotropium bromide has a bronchodilator effect, evidenced by improved acute lung function compared with placebo; however, the data are not yet clear enough to enable the creation of a stepwise approach or to identify phenotypes that would benefit from adding tiotropium bromide to treatment. The EPR-3 and GINA both recommend the addition of a LABA to low-dose ICSs in patients with uncontrolled asthma; adding a leukotriene modifier or increasing the ICS dose are also acceptable options [5]. The recent approval of tiotropium bromide for asthma comes with the backdrop of relatively controversial effects of LABAs in children. A large, recently published, safety study found no increased risk of serious asthma events (hospitalizations, intubations, and/or deaths) with salmeterol added to ICS in children aged 4–11 years, but it also found no decreased risk of severe asthma exacerbations (i.e., those requiring oral corticosteroids) [20]. This latter finding is consistent with the latest Cochrane review [19], which found an improvement in lung function and rescue bronchodilator use but no decreased risk of severe exacerbations or improved measures of asthma control. Interestingly, an innovative trial comparing three step-up therapies using a hierarchical endpoint of severe exacerbation → asthma-control days → spirometry reported that the effects of adding an LABA were superior to both a more than doubled ICS dose or the addition of montelukast [21]. Similarly, well-designed studies comparing existing step-up options to tiotropium bromide are needed to identify both an evidence-based stepwise approach to asthma management and phenotypes that might respond better to tiotropium bromide than to other adjunct medications. On that note, use of LAMAs in asthma management in children and adolescents should be investigated. Trials need to clearly describe the background medications and patient populations so clinicians can apply the knowledge to clinical practice.

Until more studies are completed, the place for tiotropium bromide in the management of asthma in children and adolescent remains unclear.

Compliance with Ethical Standards

Funding H. H. Raissy and H. W. Kelly have received no financial assistance for the preparation of this manuscript.

Conflicts of interest H. H. Raissy is the principal investigator of AsthmaNet at the University of New Mexico, which has received drugs from GlaxoSmithKline and Merck for use in clinical trials. H. W. Kelly has received remuneration for work on the steering committees for the FDA-mandated safety trials of ICS/LABA combinations for GlaxoSmithKline, AstraZeneca, Merck, and Novartis and for acting in an advisory capacity for GlaxoSmithKline for their FDA submission of a new ICS/LABA combination. He is a member of AsthmaNet, which has received drugs from GlaxoSmithKline, Merck, Sunovion, Teva, and Boehringer Ingelheim for use in clinical trials.

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