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Tiotropium for the treatment of adolescents with moderate to severe symptomatic asthma: a systematic review with meta-analysis

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ABSTRACT

Background: The role of tiotropium for the treatment of adolescents with asthma has not yet been clearly defined.
Objective: To assess the efficacy and safety of inhaled tiotropium in adolescents with moderate to severe symptomatic asthma.
Methods: Randomized, placebo-controlled trials were included in this systematic review. Primary outcomes were peak and trough forced expiratory volume in 1 second (FEV_1).
Results: Three studies (approximately 1,000 patients) were included. Tiotropium was associated with significant improvements in FEV_1 peak (mean change from baseline) by 120 mL ($P < .001$) and trough by 100 mL ($P < .001$) compared with placebo. Tiotropium significantly reduced the percentage of patients who experienced an Asthma Control Questionnaire 7 worsening episode defined as a change from trial baseline of 0.5 points or more compared with placebo (2.1% vs 4.8%, number needed to treat = 38) and also was associated with a significantly decreased in the number of patients with at least one exacerbation compared with placebo (17.6 vs 23.8%, number needed to treat = 16). Finally, no significant differences were found in rescue medication use, withdrawals, withdrawals due to adverse events (AEs), AEs (27.3% vs 27.1%), and serious AEs (6.5% vs 7.1%). Tiotropium in doses of 2.5 μg once daily or 5.0 μg once daily resulted in equivalent effects.
Conclusions: Tiotropium was well tolerated and efficacious as an addition to maintenance treatment with an inhaled corticosteroid or an inhaled corticosteroid plus a long-acting β-agonist in adolescents with moderate to severe asthma. Available data do not suggest an advantage of the 5-μg once-daily dose (used in adults) compared with the 2.5-μg once-daily dose of tiotropium.
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Introduction

Since 1970s there has been a renewed interest in the use of anticholinergics for treatment of obstructive airway diseases, given the need to develop alternatives to therapy with β_2-agonist agents. However, their role in patients with asthma has remained restricted to the use of short-acting anticholinergics (ipratropium bromide) in combination with a short-acting β_2-agonist to treat episodes of acute asthma.[1,2] However, in the last few years, several studies, mainly in adults, have assessed for first time the potential benefits and safety of the use of tiotropium bromide for the treatment of uncontrolled symptomatic moderate to severe asthma.[3–5] A systematic review of published and unpublished randomized clinical trials (RCTs) suggests that tiotropium is noninferior to salmeterol and superior to placebo in patients with moderate to severe asthma not adequately controlled by low to moderate inhaled corticosteroids (ICSs) or high doses of ICSs plus long-acting β_2-agonists (LABAs).[6] Major benefits were concentrated in lung function and, in patients with severe asthma, in an increase of asthma control and a decrease of exacerbations. In addition, tiotropium was safe and well tolerated. On the basis of these studies, the indication for tiotropium administered via inhaler (Respimat) in asthma has been accepted by the regulatory authorities of the European Union and other countries. Currently, tiotropium is indicated as an add-on maintenance bronchodilator treatment in adult patients with asthma who are treated with the maintenance combination of high doses of ICS and LABA.

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Considering that approximately 10% of children aged 12 to 18 years have asthma,[7] there is much interest regarding to the use of tiotropium in this subgroup of asthmatic patients not included in the current indication. Therefore, recently the first clinical trial on tiotropium in adolescents with symptomatic asthma has been published, revealing that tiotropium is well tolerated and efficacious in adolescents as an addition to maintenance treatment with ICSs.[8] Thus, to expand our understanding of a potentially new indication of tiotropium, the aim of this systematic review was to assess the efficacy and safety of tiotropium in adolescents with symptomatic asthma. Two specific questions were identified: (1) Is inhaled tiotropium equally effective and safe in adolescents as in adults with asthma? and (2) Is the 5-mcg once-daily dose appropriate for adolescents?

Methods

Search and Selection Criteria

This study was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (http://www.crd.york.ac.uk/PROSPERO) as CRD42015020649. We adopted Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to perform this review.[9] The authors identified published studies from MEDLINE, Embase, CINAHL, SCOPUS, and the Cochrane Controlled Trials Register (until May 2015) databases and ClinicalTrials.gov using the terms *tiotropium* OR *Ba 679 BR* OR *Spiriva* AND *asthma*. In addition, we performed a search of relevant files from the drug manufacturer's database (published and unpublished). Language restrictions were not applied.

To be included, studies had to meet all the following criteria: (1) adolescents aged 12 to 18 years with symptomatic stable asthma of any severity and receiving ICS or ICS plus LABAs; (2) RCTs (parallel group or crossover) of 4 weeks or longer; (3) comparison of inhaled tiotropium (2.5 or 5 μg once-daily via tiotropium inhaler [Respimat]) vs any treatment; (4) report at least one of the following outcomes: pulmonary function (peak or trough forced expiratory volume in 1 second [FEV_1], morning or evening peak expiratory flow rate as a primary outcome, and rescue medication use [puffs per day]), asthma control (Asthma Control Questionnaire 7 [ACQ-7] total score,[10] ACQ-7 responder rate determined by the percentage of patients with a change from trial baseline $\geq$0.5, or ACQ-7 worsening rate determined by the percentage of patients with a change from trial baseline $\geq$ 0.5), asthma exacerbations (number of patients with one or more episode who required the use of systemic corticosteroids) and withdrawals (total and those due to adverse events [AEs]), and safety (AEs and serious AEs [SAEs]) as secondary outcomes. An SAE was defined as any untoward medical occurrence that sometimes results in death, is life-threatening, requires inpatient hospitalization, or results in persistent or significant disability/incapacity.[11]

Data Extraction and Assessment of Risk of Bias

Titles, abstracts, and citations were independently analyzed by the 2 authors (G.J.R. and J.C.R.). From the full text, they independently assessed all studies for inclusion based on the criteria for population intervention, study design, and outcomes. After obtaining full reports about potentially relevant trials, they assessed eligibility. Both authors were independently involved in all stages of study selection, data extraction, and risk of bias assessment. The latter was assessed according to recommendations outlined in the Cochrane Handbook[12] for the following items: (1) adequacy of sequence generation, (2) allocation concealment, (3) masking of participants and investigators, (4) masking of outcome assessment, (5) incomplete outcome data, and (6) selective outcome reporting and other bias. Disagreements were discussed and resolved by consensus.

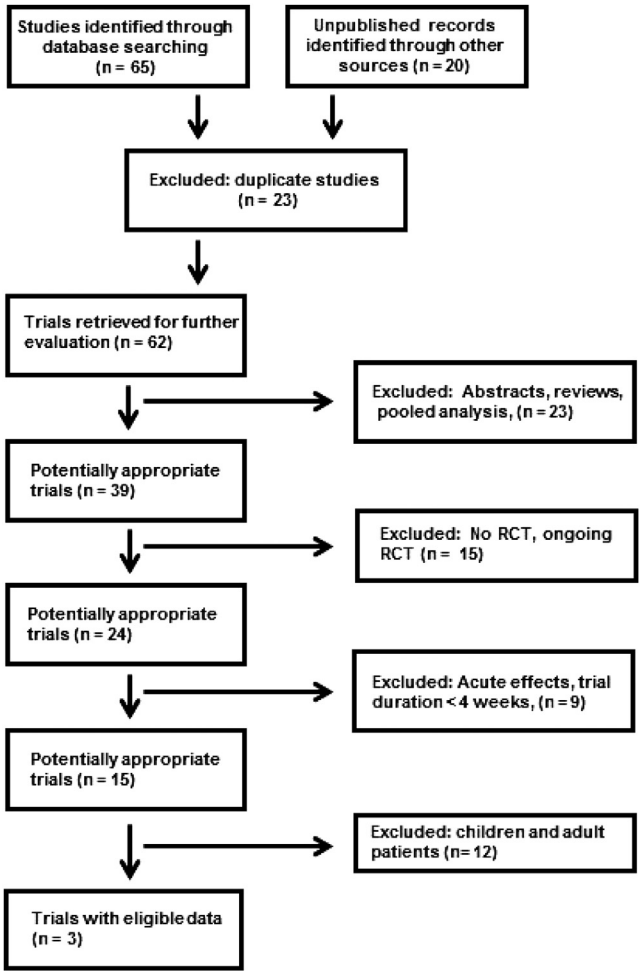

Figure 1. Flowchart for identification of studies selected. RCT indicates randomized clinical trial.

Statistical Analysis

Analysis was by intent to treat and included all participants to minimize bias. Outcomes were pooled using mean differences (inverse variance method) or Mantel-Haenszel risk ratios. The risk difference was used when there were no events in either group. The precision of the estimates was quantified by the 95% CIs. When effect estimates were significantly different between groups, the number needed to treat (NNT) was obtained. Heterogeneity was measured by the I^2 test[13] ($\leq$25% absence, 26%–39% unimportant, 40%–60% moderate, and 60%–100% substantial). A fixed-effects model was used when there was no evidence of significant heterogeneity in the analysis; if significant heterogeneity was found, a random-effects model was used.[14] To be able to include the multiple intervention groups of each study (tiotropium, 2.5 μg and 5 μg once daily) and avoid double-counts of participants in the shared intervention groups, we performed the systematic review combining both tiotropium groups (2.5 and 5 μg) in only one (tiotropium group).[15] As a priori subgroup analysis, we explored the influence of the dose of tiotropium (2.5 vs 5 μg once daily). Subgroups were compared using the residual χ^2 test from the Peto odds ratios.[16] Otherwise, $P < .05$ (2-tailed test) was considered significant. Meta-analysis was performed with Review Manager version 5.3.5 software (Cochrane IMS).

Table 1
Characteristics of included studies

Study	Design	Duration, wk	Randomized patients, n (% female)	Age, mean (range), y	Mean baseline FEV_1, % predicted	Asthma severity	Primary outcome	Comparisons of interest
Vogelber et al[8]	R, DB, PC, CO	4	105 (36)	14 (12–17)	78	Moderate	FEV_1 peak	ICS medium dose + PL vs ICS medium dose + 1.25 μg once daily of tiotropium vs ICS medium dose daily + 2.5 μg of tiotropium daily vs ICS medium dose + 5 μg once daily of tiotropium
NCT01277523[17]	R, DB, PC, PG	12	392 (38)	14 (12–17)	76	Severe	FEV_1 peak	ICS medium/high dose + controller + PL vs ICS medium/high dose + controller + 1.25 μg once daily of tiotropium vs ICS medium/high dose + controller + 2.5 μg once daily of tiotropium vs ICS medium/high dose + controller + 5 μg once daily of tiotropium
NCT01257230[18]	R, DB, PC, PG	48	398 (35)	14 (12–17)	83	Moderate	FEV_1 peak	ICS medium dose + PL vs ICS medium dose + 2.5 μg once daily of tiotropium vs ICS medium dose + 5 μg once daily of tiotropium

Abbreviations: CO, crossover; ICS, inhaled corticosteroid; DB, double-blind; FEV_1, forced volume in 1 second; PC, placebo-controlled; PG, parallel-group; PL, placebo; R, randomized.

Results

The process of study selection is outlined in Figure 1. Three RCTs, including approximately 1,000 patients with asthma, met the entry criteria.[8,17,18] All RCTs had at least two doses or arms of trial medication (tiotropium, 2.5 and 5 μg once daily) compared with placebo and were therefore included in the treated set for pooled efficacy and safety analysis. Trials characteristics are given in Table 1. Two studies included patients with moderate asthma receiving tiotropium once daily added to an ICS (medium dose) vs placebo added to an ICS (medium dose),[8,18] and one study included adolescents with severe symptomatic asthma receiving tiotropium once daily added to an ICS (medium or high dose) plus one or more controller medications (LABAs or leukotriene receptor antagonists) vs placebo added to an ICS (medium or high dose) plus one or more controller medications.[17] Severity was determined according Global Initiative for Asthma (GINA) criteria.[19] The main inclusion criteria were as follows: (1) all patients symptomatic as defined by an ACQ-7 mean score of 1.5 or higher before randomization; (2) a prebronchodilator FEV_1 greater than 60% and less than 90% of the predicted normal; (3) a reversible airways obstruction (improvement in FEV_1 of at least 12% and 200 mL); (4) no current smokers; (5) no asthma exacerbation or acute respiratory tract infection in the past 4 weeks before screening; and (6) treatment adherence greater than 80%. Two trials were unpublished,[17,18] and duration of studies ranged from 4 to 48 weeks. The trials varied from 105 to 398 individuals. The 3 studies were sponsored by the same pharmaceutical company. All studies used an inhaler (Respimat) to administer tiotropium in 2.5- or 5-μg doses. All studies had a low risk of bias in the 6 items of the Cochrane instrument.[12]

Main Outcomes

The analysis of data indicated that tiotropium was associated with significant improvements in FEV_1 peak (mean change from baseline) by 120 mL ($P < .001$) and FEV_1 trough by 100 mL

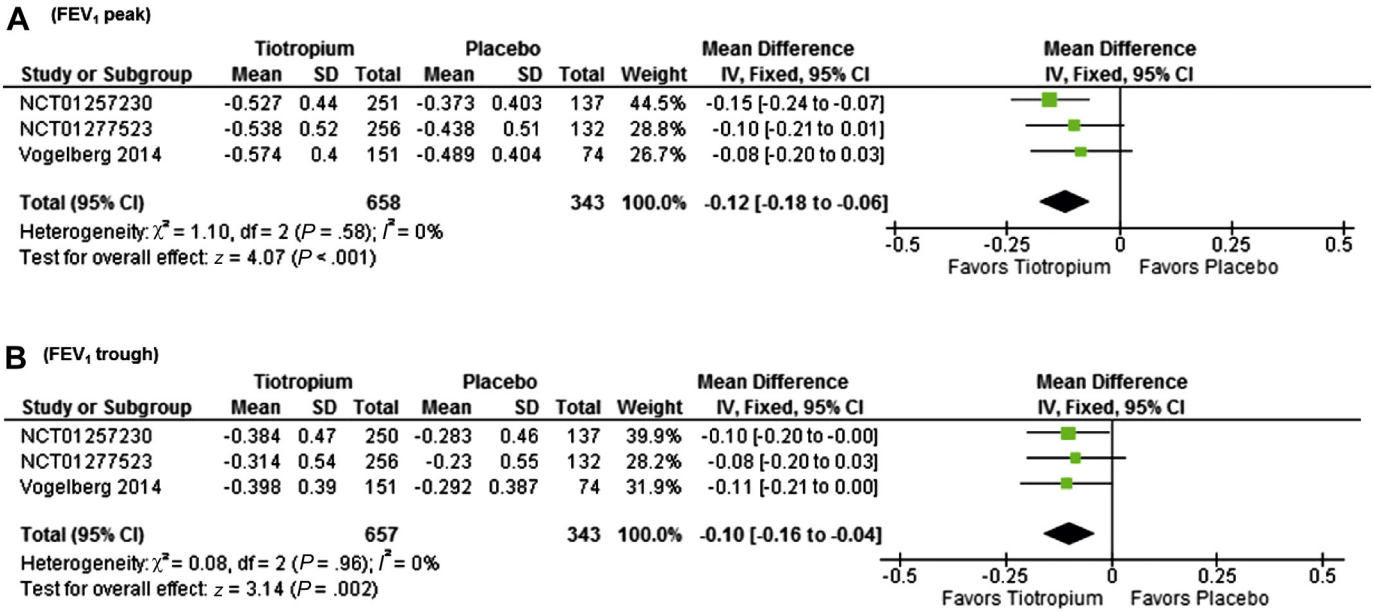

Figure 2. Pooled mean difference for peak (A) and trough (B) forced expiratory volume in 1 second (FEV_1) at the end of treatment (change from baseline) with 95% Cis of elegible studies comparing tiotropium And placebo (patients with moderate to severe asthma).

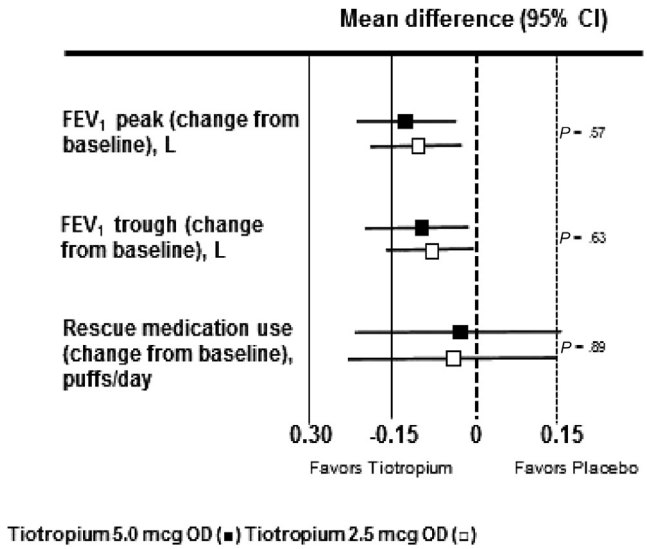

Figure 3. Pooled mean difference for peak and trough forced expiratory volume in 1 second (FEV_1) and rescue medication use at the end of treatment (change from baseline) with 95% Cis of eligible studies comparing 5.0 μg once daily of tiotropium (■) and 2.5 μg once daily of tiotropium (□) vs placebo.

($P < .0001$) compared with placebo. Both comparisons were statistically homogeneous (Fig 2). The predefined post hoc subgroup analysis revealed that both doses of tiotropium (2.5 and 5.0 μg once daily) resulted in equivalent size effects (Fig 3).

Secondary Outcomes

Although there was no significant difference in the rate of ACQ-7 responders between tiotropium and placebo (74.6% vs 69.9%, $P = .17$), tiotropium significantly reduced the percentage of patients who experienced an ACQ-7 worsening episode defined as a change from trial baseline of 0.5 points or more compared with placebo (2.1% vs 4.8%; NNT = 38; 95% CI, 19–139; $P = .05$) (Fig 4). In addition, tiotropium treatment was associated with a significantly decreased risk of exacerbation (number of patients with at least one episode of asthma exacerbation) compared with placebo (17.6% vs 23.8%; NNT = 16; $P = .04$). Finally, no significant differences were found in rescue medication use (mean difference = −0.03; 95% CI, −0.19 to 0.13; $P = .74$), withdrawals, withdrawals due to AEs, AEs (27.3% vs 27.1%), and SAEs (6.5% vs 7.1%) (Table 2). Again, both doses of tiotropium resulted in equivalent effects on different outcomes (Figs 3 and 5).

Discussion

The role of tiotropium has received significant attention over the years and has been summarized in a systematic review recently published.[6] On the basis of the inclusion of 13 studies (all except one involving adults with asthma), it suggests that tiotropium might be an alternative to LABAs in adults with mild to moderate asthma whose symptoms are not well controlled by an ICS alone or as an add-on therapy in patients with severe asthma not controlled with available medications, including an ICS plus a LABA. Major benefits were concentrated in lung function and, in patients with severe asthma, in an increase of control and a decrease of exacerbations. Finally, tiotropium was well tolerated, and no potential safety signals were observed. Aware to the possibility of expanding the use of tiotropium in adolescents, the aim of our systematic review was to assess the efficacy and safety of tiotropium in this subgroup of patients with symptomatic asthma. To our knowledge, this is the first systematic review performed exclusively in adolescents with moderate to severe symptomatic asthma despite adequate treatment.

With regard to efficacy and safety (first question), this review confirms the long-term lung function benefits of adding tiotropium to an ICS with or without a LABA in adolescents with moderate to severe symptomatic asthma. Mean peak and trough FEV_1 responses with tiotropium were significantly greater than placebo (120 and 100 mL, respectively) and were in line with results observed in adults with asthma (80–150 mL).[6] Of note, all increases achieved the minimal clinically important difference (MCID) (100 mL for

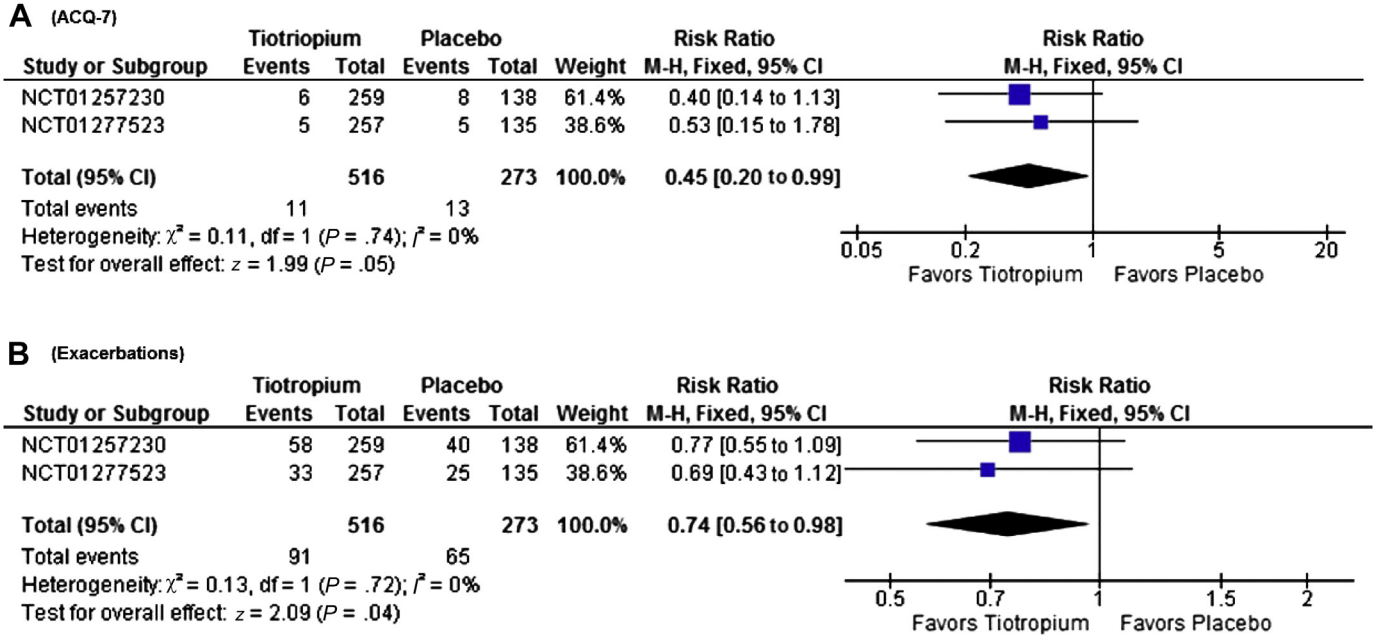

Figure 4. Pooled risk ratio for percentage of patients who experienced an episode of Asthma Control Questionnaire 7 (ACQ-7) worsening (defined as a change from trial baseline of 0.5 points or more) (A) and for the number of patients with at least one significant asthma exacerbation (B) for eligible studies comparing tiotropium with placebo at the end of treatment.

Table 2
Tiotropium vs placebo (secondary outcomes)

Outcome	References	Sample size	Estimate	Effect (95% CI)	I^2, % (*P* value)
Rescue medication use (puffs per day)	8,17,18	993	MD	−0.03 (−0.19 to 0.13)	0 (.74)
ACQ-7 (responder rate)	17,18	576	RR	1.07 (0.97 to 1.17)	21 (.17)
Total withdrawals	8,17,18	1,016	RR	1.10 (0.53 to 2.31)	30 (.79)
Withdrawals due to AEs	8,17,18	1,016	RR	0.29 (0.06 to 1.36)	0 (.12)
Any AE	8,17,18	1,016	RR	1.01 (0.83 to 1.24)	0 (.89)
Serious AEs	8,16,17	1,016	RD	−0.01 (−0.04 to 0.03)	0 (.74)

Abbreviations: ACQ-7 Asthma Control Questionnaire 7; AE, adverse event; MD, mean difference; RD, risk difference; RR, risk ratio.

FEV_1).[19,20] Interestingly, data suggest that the bronchodilator effect correlates with the time of tiotropium exposure (ΔFEV_1 peak = 80 mL at 4 weeks,[8] 100 mL at 12 weeks,[17] and 150 mL at 48 weeks,[18] all vs placebo). These effects were paralleled by significant improvements in other outcomes as asthma control and exacerbations. The ACQ-7 responder or worsening rates are reported as an indicator of asthma control; however, the ACQ-7 results presented here should also be interpreted with caution because they come from the analysis of 2 studies.[17,18] Whereas there was no difference between groups in the ACQ-7 response rate (defined as percentage of patients with a change from trial baseline ≤0.5), on the other hand, tiotropium significantly reduced the percentage of patients who experienced episodes of asthma control worsening (defined as a change from trial baseline ≥0.5 points in ACQ-7) compared with placebo, with an NNT of 38. In addition, tiotropium significantly reduced the number of patients with at least one asthma exacerbations (NNT = 16). Only the 2 longer-term studies (12 and 48 weeks, respectively) were included in the analysis of ACQ-7 and asthma exacerbations. Finally, this systematic review suggests that tiotropium is well tolerated across all doses, and no life-threatening or fatal AEs were reported. These findings were consistent with those found in RCTs involving adults with asthma.[6]

On the basis of efficacy and safety evaluations from this systematic review, including 2 dose-ranging RCTs (second question), the answer is that there is no clear difference between the administration of 2.5 or 5 μg tiotropium once daily via an inhaler (Respimat) device in the treatment of adolescents with moderate to severe symptomatic asthma. However, included studies were rather limited with regard to sample size and duration, so long-term safety and tolerability could not be well investigated. Further investigation of the 2.5- or 5-μg dose added on to ICS maintenance therapy is justified in a larger adolescent population.

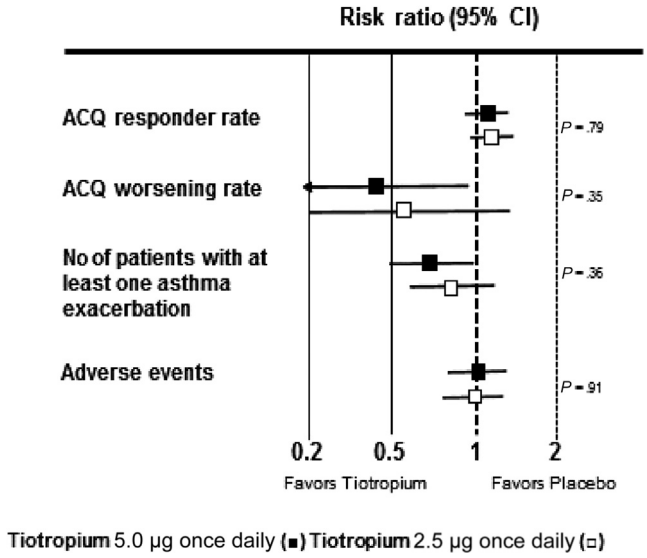

Figure 5. Pooled risk ratio for Asthma Control Questionnaire 7 (ACQ-7) responder rate and worsening rate, number of patients with at least one exacerbation, and adverse events at the end of treatment with 95% Cis of eligible studies comparing 5.0 μg once daily of tiotropium (■) or 2.5 μg once daily of tiotropium (□) vs placebo.

The following are considered strengths of this review: (1) it was performed according to scientific guidelines[9]; (2) different relevant databases were searched in any language; (3) risk of bias was formally assessed and potentially avoided with the inclusion of unpublished studies and the use of trial registries; in fact, meta-analyses excluding unpublished data are likely to overestimate intervention effects[14]; (4) the studies were very homogeneous and had a high methodologic quality; (5) the meta-analysis measures other outcomes than pulmonary function alone (changes in asthma control); and (6) the effect sizes were consistent and homogeneous. However, several potential limitations should be considered: (1) although the use of data from unpublished studies allows the analysis of the latest information and reducing publication bias, these studies are not peer reviewed and data may be incomplete; thus, the online access to one of the long-term studies[17] does not detail how many patients were following each of those baseline treatment regimens; (2) in some cases, it is difficult to evaluate the clinical significance of changes; (3) MCID differences were derived on the basis of differences vs placebo or changes from baseline rather than differences between 2 active treatments,[20,21] and the improvement of different end points occurred in patients with high levels of medication (leukotriene modifiers, oral corticosteroids, ICSs, and LABAs); (4) 1 of the 3 selected studies[6] had a too short duration of treatment (4 weeks) to allow a complete assessment of efficacy and safety; and (5) the inclusion criteria requiring suboptimal spirometry (FEV_1 <90%) and a bronchodilator response may exclude some asthmatic patients with uncontrolled asthma.

In conclusion, this systematic review of tiotropium for adolescents with symptomatic moderate to severe asthma suggests that tiotropium administered via an inhaler (Respimat) is well tolerated and efficacious as an addition to maintenance treatment with ICSs or ICSs plus LABAs. Major benefits are concentrated in lung function. Available data do not suggest an advantage of the 5-μg once-daily dose (used in adults) compared with the 2.5-μg once-daily dose.

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