Comparative Responses in Lung Function Measurements with Tiotropium in Adolescents and Adults, and Across Asthma Severities: A Post Hoc Analysis

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Received: January 28, 2020 / Published online: March 16, 2020 © The Author(s) 2020

ABSTRACT

Introduction: Airway obstruction is usually assessed by measuring forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC) and peak expiratory flow (PEF). This post hoc study investigated comparative responses of lung function measurements in adults and adolescents (full analysis set, N = 3873) following treatment with tiotropium Respimat.

Methods: Lung function outcomes were analysed from five phase III trials in adults (> 18 years) with symptomatic severe, moderate and mild asthma (PrimoTinA-asthma®, MezzoTinA-asthma® and GraziaTinA-asthma®, respectively), and one phase III trial in adolescents (12–17 years) with symptomatic moderate asthma (RubaTinA-asthma®). Changes from baseline versus placebo in FEV₁, FVC, PEF and FEV₁/FVC ratio with tiotropium 5 μg or 2.5 μg added to at least stable inhaled corticosteroids at week 24 (week 12 in GraziaTinA-asthma) were analysed.

Results: All lung function measures improved in all studies with tiotropium 5 μg (mean change from baseline versus placebo), including peak FEV₁ (110–185 mL), peak FVC (57–95 mL) and morning PEF (15.8–25.6 L/min). Changes

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in adolescents were smaller than those in adults, and were statistically significant primarily for FEV\textsubscript{1} and PEF, but not for FVC.

**Conclusion:** Consistent improvements were seen across all lung function measures with the addition of tiotropium to other asthma treatments in adults across all severities, whereas the improvements with tiotropium in adolescents primarily impacted measures of flow rather than lung volume. This may reflect less pronounced airway remodelling and air trapping in adolescents with asthma versus adults.

**PLAIN LANGUAGE SUMMARY**

Asthma is characterised by problems with the way that the lungs work, particularly narrowing of the airways. Doctors can measure the effect of asthma on someone’s breathing in different ways. We looked to see whether these different methods work for different people with asthma, and whether treatment affects all measurements in a similar way. Lung function was measured after treatment with a drug that opens the airways (tiotropium), and comparisons were made between adults and adolescents with asthma. We also looked at people with severe asthma and those whose asthma was less severe. Tiotropium improved all the measures of lung function in both age groups and across severities. One measure improved more in adults than in adolescents. This may be because adolescents had better lung function at the start and thus less room for improvement, or because the adolescents had not had asthma for as long, and so may have had less long-term damage to their airways than adults.

**Trial Registration Numbers:** NCT00772538, NCT00776984, NCT01172808, NCT01172821, NCT01316380, NCT01257230.

**Keywords:** Airway obstruction; Asthma; Muscarinic antagonist; Respiratory function tests; Tiotropium bromide

**INTRODUCTION**

Variable expiratory airflow limitation is a key diagnostic feature of asthma. It is confirmed using various tests that measure different aspects of lung function, including expiratory air volume, such as forced vital capacity (FVC).
and forced expiratory volume in 1 s (FEV₁), or flow, such as peak expiratory flow (PEF) [1, 2]. However, such measures have limitations, including relative insensitivity and variability of results, with FVC being more sensitive to small airway obstruction than FEV₁ and PEF, which are more reflective of large airway function [2, 3]. Spirometry outcomes in patients with asthma are further influenced by severity of disease and lung function, and also by age, technical ability to perform the test and measurement frequency [4].

Once-daily tiotropium Respimat®, a long-acting muscarinic antagonist, is a well-tolerated and efficacious treatment for children (6–11 years) [5, 6], adolescents (12–17 years) [7, 8] and adults (≥ 18 years) [9–11] who have symptomatic asthma despite maintenance treatment with inhaled corticosteroids (ICS) with or without additional controllers across a range of asthma severities. Given the differential changes between different lung function parameters according to age and severity of disease, we investigated the comparative responses of several measures of lung function following treatment with tiotropium Respimat.

METHODS

This was a post hoc analysis of data from six randomised, double-blind, placebo-controlled, parallel-group phase III trials, which have been previously described: the replicate PrimoTinA-asthma® [10] and MezzoTinA-asthma® trials [9] and the GraziaTinA-asthma® trial [11], all in adults (aged ≥ 18 years) with symptomatic severe, moderate and mild asthma; and the RubaTinA-asthma® trial [7] in adolescents aged 12–17 years with symptomatic moderate asthma, allowing comparison of data from the adult and adolescent studies at the same time point (week 24) (Table 1). Data from participants aged < 12 years were excluded due to potential confounding factors such as physiological or anatomical differences, and a child’s ability to perform effective spirometry procedures [4]. Data from a trial lasting only 12 weeks in adolescents with symptomatic severe asthma were excluded, as direct comparisons could not be drawn with the corresponding trial in symptomatic severe adult patients lasting 24 weeks [8]. All studies were conducted in full conformance with the Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. Approval was obtained from all ethics committees/independent review boards at each study site. All patients provided written informed consent.

Participants received at least stable-dose ICS for a minimum of 4 weeks prior to screening: PrimoTinA-asthma: ≥ 800 μg budesonide/ equivalent + a long-acting β₂-agonist ± additional controller medications; MezzoTinA-asthma and RubaTinA-asthma: 400–800 μg budesonide/equivalent in participants aged ≥ 15 years, 200–800 μg budesonide/equivalent in those aged < 15 years ± additional leukotriene receptor antagonist; GraziaTinA-asthma: 200–400 μg budesonide/equivalent without additional controller. All participants received tiotropium 5 μg or 2.5 μg, administered as two puffs once daily via the Respimat inhaler, apart from participants in PrimoTinA-asthma, who received only tiotropium 5 μg once daily via the Respimat inhaler.

FEV₁, FVC and PEF were analysed at week 24 in all trials except GraziaTinA-asthma, in which pulmonary function endpoints were analysed at week 12. FEV₁/FVC ratio was analysed at week 24 in MezzoTinA-asthma and RubaTinA-asthma.

RESULTS

Participant baseline demographics and disease characteristics were generally similar, although there were differences in baseline lung function and medication use according to asthma severity (Table 1).

In adults with asthma, treatment with tiotropium (5 μg and 2.5 μg) significantly increased FEV₁ (peak and trough, absolute and percent predicted) and PEF (morning and evening) across all severities versus placebo. FVC (peak and trough) was significantly increased following treatment with tiotropium (5 μg and 2.5 μg) versus placebo in adults with symptomatic severe and moderate asthma. However, in adults
with symptomatic mild asthma, tiotropium 5 \( \mu g \) provided a non-significant numerical improvement versus placebo (Table 2).

In adolescents with symptomatic moderate asthma, treatment with tiotropium 5 \( \mu g \) resulted in significant increases in FEV\(_1\) (peak and trough, absolute and percent predicted) and PEF (morning and evening). However, unlike in adults with symptomatic moderate asthma, the improvements in FEV\(_1\) for adolescents receiving tiotropium 2.5 \( \mu g \) were only significant for peak FEV\(_1\) (absolute and percent predicted), and the

**Table 1 Baseline demographics and disease characteristics**

| Baseline characteristics | Adults | Adolescents |
|--------------------------|--------|-------------|
| Total participants, N    | 912    | 2100        |
| Age, years \( \pm \)     | 53.0 ± 12.4 | 43.1 ± 12.9 |
| Sex, female, n (%)       | 551 (60.4) | 1239 (59.0) |
| Height, cm \( \pm \)     | 167.0 ± 10.1 | 165.4 ± 9.8 |
| BMI, kg/m\(^2\) \( \pm \) | 28.2 ± 6.0  | 26.8 ± 6.2  |
| Never smoked, n (%)      | 692 (75.9)  | 1756 (83.6) |
| Duration of asthma, years \( \pm \) | 30.3 ± 13.9 | 21.8 ± 14.3 |
| ICS dose of stable maintenance treatment, \( \mu g \) budesonide equivalent at baseline | 1198.1 ± 538.9 | 659.6 ± 212.9 |
| LABA use at baseline, %  | 97.9    | 0.1         |
| LTRA use at baseline, %  | 21.9    | 8.7         |
| Disease characteristics at randomisation (visit 2) |        |             |
| FEV\(_1\), mL \( \pm \) | 1603 ± 540 | 2267 ± 654 |
| FVC, mL \( \pm \)       | 2774 ± 900 | 3458 ± 945 |
| FEV\(_1\), percent predicted \( \pm \) | 56.0 ± 13.1 | 75.1 ± 11.5 |
| FVC, percent predicted \( \pm \) | 80.2 ± 17.01 | 96.7 ± 13.8 |
| FEV\(_1\)/FVC ratio, % \( \pm \) | 58.4 ± 10.1 | 66.1 ± 10.5 |
| PEF\(_{\text{am}}\), L/min \( \pm \) | 270.7 ± 111.1 | 333.6 ± 115.2 |
| PEF\(_{\text{pm}}\), L/min \( \pm \) | 279.8 ± 114.2 | 349.6 ± 117.2 |

\( BMI \) body mass index, \( FEV_1 \) forced expiratory volume in 1 s, \( FVC \) forced vital capacity, \( ICS \) inhaled corticosteroids, \( LABA \) long-acting \( \beta_2 \)-agonist, \( LTRA \) leukotriene receptor antagonist, \( PEF_{\text{am}} \) morning peak expiratory flow, \( PEF_{\text{pm}} \) evening peak expiratory flow

\( a \) All data are pooled from the two replicate trials unless otherwise stated

\( b \) Includes 541 participants within the salmeterol arm of the trial, results of which are not included in this post hoc analysis

\( c \) Values are mean ± standard deviation

\( d \) Pre-bronchodilator

\( \triangle \) Adis
| Response measure | Adults | | | Adolescents | | |
|------------------|--------|---|---|--------|---|---|
| Symptomatic severe asthma<sup>a</sup> | Response measure | N<sup>c</sup> Active vs placebo. Adjusted mean difference ± SE (95% CI); P value | N<sup>c</sup> Active vs placebo. Adjusted mean difference ± SE (95% CI); P value | N<sup>c</sup> Active vs placebo. Adjusted mean difference ± SE (95% CI); P value | N<sup>c</sup> Active vs placebo. Adjusted mean difference ± SE (95% CI); P value |
| Peak FEV<sub>1</sub> (mL) | Tiotropium 5 µg | 422 | 110 ± 24 (63, 158); < 0.0001 | 481 | 185 ± 20 (146, 223); < 0.0001 | 152 | 128 ± 36 (57, 199); 0.0005 | 131 | 174 ± 50 (76, 272); 0.0005 |
| | Tiotropium 2.5 µg | NR | NR | 492 | 223 ± 20 (185, 262); < 0.0001 | 151 | 159 ± 36 (88, 230); < 0.0001 | 120 | 134 ± 51 (34, 234); 0.0085 |
| Peak FEV<sub>1</sub> (pp) | Tiotropium 5 µg | 422 | 3.63 ± 0.77 (2.12, 5.15); < 0.0001 | 481 | 5.80 ± 0.60 (4.61, 7.00); < 0.0001 | 152 | 4.68 ± 1.10 (2.51, 6.85); < 0.0001 | 131 | 4.49 ± 1.42 (1.70, 7.29); 0.0017 |
| | Tiotropium 2.5 µg | NR | NR | 492 | 7.48 ± 0.60 (6.31, 8.66); < 0.0001 | 151 | 4.21 ± 1.11 (2.04, 6.38); 0.0002 | 120 | 4.07 ± 1.46 (1.21, 6.92); 0.0054 |
| Trough FEV<sub>1</sub> (mL) | Tiotropium 5 µg | 421 | 93 ± 22 (50, 137); < 0.0001 | 481 | 146 ± 21 (105, 188); < 0.0001 | 152 | 122 ± 37 (49, 194); 0.0010 | 131 | 117 ± 54 (10, 223); 0.0320 |
| | Tiotropium 2.5 µg | NR | NR | 492 | 180 ± 21 (138, 221); < 0.0001 | 151 | 110 ± 37 (38, 182); 0.0028 | 119 | 84 ± 56 (−25, 194); 0.1307 |
| Trough FEV<sub>1</sub> (pp) | Tiotropium 5 µg | 421 | 3.01 ± 0.75 (1.55, 4.48); < 0.0001 | 481 | 4.63 ± 0.66 (3.33, 5.92); < 0.0001 | 152 | 4.41 ± 1.16 (2.14, 6.68); 0.0001 | 131 | 3.21 ± 1.53 (0.21, 6.20); 0.0361 |
| | Tiotropium 2.5 µg | NR | NR | 492 | 6.03 ± 0.66 (4.74, 7.32); < 0.0001 | 151 | 2.60 ± 1.16 (0.33, 4.87); 0.0249 | 119 | 2.85 ± 1.57 (−0.23, 5.93); 0.0695 |
Table 2 continued

| Response measure | Adults | | Adolescents | |
|------------------|--------|------------------|------------------|------------------|
|                  | Symptomatic severe asthma<sup>a</sup> | Symptomatic moderate asthma<sup>a</sup> | Symptomatic mild asthma<sup>b</sup> | Symptomatic moderate asthma <sup>b</sup> |
|                  | N<sup>c</sup> | Active vs placebo. Adjusted mean difference ± SE (95% CI); P value | N<sup>c</sup> | Active vs placebo. Adjusted mean difference ± SE (95% CI); P value | N<sup>c</sup> | Active vs placebo. Adjusted mean difference ± SE (95% CI); P value | N<sup>c</sup> | Active vs placebo. Adjusted mean difference ± SE (95% CI); P value |
| Peak FVC (mL)    |        |                  |                  |                  |
| Tiotropium 5 µg  | 422    | 87 ± 31 (26, 148); 0.0050 | 481 | 95 ± 22 (53, 138); < 0.0001 | 152 | 57 ± 42 (−25, 140); 0.1714 | 131 | 72 ± 56 (−37, 182); 0.1950 |
| Tiotropium 2.5 µg| NR NR  | 118 ± 29 (62, 175); < 0.0001 | 492 | 141 ± 22 (98, 183); < 0.0001 | 151 | 106 ± 42 (23, 188); 0.0119 | 120 | 88 ± 57 (−24, 200); 0.1231 |
| Trough FVC (mL)  |        |                  |                  |                  |
| Tiotropium 5 µg  | 421    | 118 ± 29 (62, 175); < 0.0001 | 481 | 80 ± 23 (35, 125); 0.0005 | 152 | 66 ± 43 (−19, 151); 0.1290 | 131 | 35 ± 59 (−80, 150); 0.5495 |
| Tiotropium 2.5 µg| NR NR  | 107 ± 23 (62, 152); < 0.0001 | 492 | 107 ± 23 (62, 152); < 0.0001 | 151 | 98 ± 43 (13, 183); 0.0236 | 119 | 63 ± 60 (−55, 181); 0.2921 |
| PEF<sub>am</sub> (L/min) |        |                  |                  |                  |
| Tiotropium 5 µg  | 411    | 22.6 ± 3.2 (16.3, 28.8); < 0.0001 | 472 | 24.3 ± 3.3 (17.9, 30.7); < 0.0001 | 152 | 25.6 ± 5.4 (14.9, 36.2); < 0.0001 | 124 | 15.8 ± 6.9 (2.3, 29.3); 0.0214 |
| Tiotropium 2.5 µg| NR NR  | 25.4 ± 3.3 (19.0, 31.7); < 0.0001 | 485 | 25.4 ± 3.3 (19.0, 31.7); < 0.0001 | 150 | 26.3 ± 5.4 (15.7, 36.9); < 0.0001 | 110 | 9.7 ± 7.0 (−4.1, 23.5); 0.1676 |
| PEF<sub>pm</sub> (L/min)   |        |                  |                  |                  |
| Tiotropium 5 µg  | 408    | 26.4 ± 3.2 (20.1, 32.7); < 0.0001 | 472 | 23.2 ± 3.2 (16.9, 29.5); < 0.0001 | 152 | 27.6 ± 5.3 (17.2, 38.0); < 0.0001 | 131 | 16.7 ± 6.8 (3.4, 30.0); 0.0137 |
| Response measure | Adults | Adolescents |
|------------------|--------|-------------|
|                  | Symptomatic severe asthma | Symptomatic moderate asthma | Symptomatic mild asthma | Symptomatic moderate asthma |
|                  | N<sup>c</sup> | Active vs placebo. Adjusted mean difference ± SE (95% CI); P value | N<sup>c</sup> | Active vs placebo. Adjusted mean difference ± SE (95% CI); P value | N<sup>c</sup> | Active vs placebo. Adjusted mean difference ± SE (95% CI); P value |
| Tiotropium 2.5 μg | NR NR | 483 22.1 ± 3.2 (15.8, 28.4); < 0.0001 | 149 22.4 ± 5.3 (11.9, 32.8); < 0.0001 | 119 12.2 ± 6.9 (−1.3, 25.8); 0.0763 |

All pulmonary function endpoints were analysed using a restricted maximum likelihood-based mixed-effects model with repeated measures (MMRM). The fixed categorical effects of ‘treatment’, ‘centre’ (the term ‘country’ was used for RubaTinA-asthma, and ‘study’ was used for pooled analyses of PrimoTinA-asthma and MezzoTinA-asthma), ‘visit’ and ‘treatment-by-visit interaction’, in addition to the continuous, fixed covariates of ‘baseline value’ and ‘baseline value-by-visit’ interaction, were included in the model. ‘Patient’ was included as a random effect. As this was a post hoc analysis, P values are considered nominal CI confidence interval, FAS full analysis set, FEV<sub>1</sub> forced expiratory volume in 1 s, FVC forced vital capacity, MMRM mixed-effects model with repeated measures, NR not reported, PEF<sub>am</sub> morning peak expiratory flow, PEF<sub>pm</sub> evening peak expiratory flow, pp percent predicted, SE standard error

<sup>a</sup> MMRM adjusted for treatment, study, visit, treatment by visit, baseline and baseline by visit
<sup>b</sup> MMRM adjusted for treatment, centre, visit, treatment by visit, baseline and baseline by visit
<sup>c</sup> Number of patients with observations at respective week
improvements in PEF (morning and evening) for adolescents receiving tiotropium 2.5 μg were non-significant (Table 2).

In contrast to the adult studies, the improvements in FVC (peak and trough) provided by tiotropium (both 5 μg and 2.5 μg) versus placebo in the adolescent study were not statistically significant. The spread of values for FVC in the adolescent group was much larger than that seen for the adults following treatment with tiotropium 5 μg, as demonstrated by the standard errors (SEs) and width of confidence intervals (CIs) (peak FVC adjusted mean difference versus placebo: adults 95 mL; SE ± 22; 95% CI 53, 138; adolescents 72 mL; SE ± 56; 95% CI –37, 182) (Table 2).

In adults across all severities receiving tiotropium 5 μg and 2.5 μg, the mean change in pre-bronchodilator FEV1/FVC ratio improved by 2.8% and 2.3%, respectively, but decreased by 0.2% in adults receiving placebo at week 24.

In adolescents, the FEV1/FVC ratio improved in all three treatment groups (3.0%, 1.6% and 2.0% in tiotropium 5 μg, 2.5 μg and placebo, respectively) at week 24. The improvements in FEV1/FVC ratio with tiotropium 5 μg versus placebo were statistically significant in both adults and adolescents.

**Discussion**

In this post hoc analysis, greater improvements in all lung function measures were seen in studies of tiotropium versus placebo in adults compared with those in adolescents. The variability in response assessed using the different measures should be considered when selecting lung function endpoints in clinical trials or when assessing response to treatment.

Tiotropium significantly improved measures of large airway obstruction, namely FEV1 and PEF, in both adults and adolescents versus placebo. Measures of small airway obstruction, namely FVC, also significantly improved in adults with symptomatic asthma receiving tiotropium. However, the improvements in adolescents were smaller and did not reach statistical significance. This may reflect that the baseline FVC for adolescents was in the normal range, possibly reflecting the shorter mean duration of asthma and less pronounced airway remodelling and air trapping than in the adult patients, allowing less room for improvement [12, 13].

Despite the Global Initiative for Asthma combining adolescents aged > 12 years with adults (≥ 18 years) in their treatment recommendations, the results here suggest that the two age groups may not be similar.

A potential limitation of the study is that, for the comparison across severities, there were fewer adults with mild and severe asthma than with moderate asthma. Furthermore, for the comparison across ages, there were fewer adolescents than adults.

A strength of this analysis is that it included data from a large clinical trial programme (full analysis set, N = 3873) with a wide age range (12–75 years), and comprised placebo-controlled trials with comparable design, offering a high degree of consistency.

Previous reviews of tiotropium efficacy as add-on treatment have looked at differences across asthma severities in adults [14, 15], or at differences between measures of lung function in adolescents [16]. This is the first post hoc analysis that compares the effect of tiotropium add-on therapy on pulmonary function in adults with asthma across a wide range of severities, and differences in measures of lung function between adults and adolescents with symptomatic moderate asthma. The results could assist clinical decision-making and designing of future clinical trials by providing further information on the most appropriate measures of lung function for specific patient subgroups when assessing response to treatment.

**Conclusion**

Consistent improvements were seen across all lung function measures with the addition of tiotropium to other asthma treatments in adults. In contrast, the improvements with tiotropium in adolescents primarily impacted measures of flow rather than lung volume, which may reflect less pronounced airway
remodelling and air trapping in adolescents with asthma versus adults. When assessing lung function changes in asthma trials in adults, and especially in adolescents, a spectrum of measures should be used to gain a comprehensive picture of the effects of interventions.

ACKNOWLEDGEMENTS

The authors would like to thank the patients, family members and participating staff at all study sites.

Funding. This manuscript and the journal’s Rapid Service fee were sponsored by Boehringer Ingelheim.

Medical Writing and/or Editorial Assistance. Support for third-party writing assistance for this manuscript, furnished by Rosie Robson of MediTech Media, under the authors’ conceptual direction and based on feedback from the authors, was provided by Boehringer Ingelheim.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions. DMGH, EHH, PAF, PMM-Z, BvH, AU, HAMK and SJS contributed to the conception and design of the original studies, as well as acquisition and interpretation of the data. The manuscript was critically reviewed and approved by all authors.

Disclosures. David M. G. Halpin reports personal fees from AstraZeneca, Chiesi and Pfizer, and grants and personal fees from Boehringer Ingelheim, GlaxoSmithKline and Novartis, outside the submitted work. Eckard H. Hamelmann and Peter A. Frith have nothing to disclose. Petra M. Moroni-Zentgraf, Benjamin van Hecke and Anna Unseld are employees of Boehringer Ingelheim. Huib A.M. Kerstjens reports fees for advisory boards from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Pfizer and Teva, unconditional research grants from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis and Teva, and patient fees for participation in trials, outside the submitted work. Stanley J. Szefler reports funds to his institution for consulting from Aerocrine, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, GlaxoSmithKline, Genentech, Novartis, Regeneron, Roche, Sanofi and Teva, and has received research support from the National Institutes of Health, the National Heart, Lung and Blood Institute, GlaxoSmithKline and the Colorado Cancer, Cardiovascular and Pulmonary Disease Program, outside the submitted work.

Compliance with Ethics Guidelines. All studies were conducted in full conformance with the Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. Approval was obtained from all ethics committees/independent review boards at each study site. All patients provided written informed consent.

Data Availability. The datasets analysed during the current study are available from the corresponding author on reasonable request.

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REFERENCES

1. Global Initiative for Asthma. Global strategy for asthma management and prevention (2019 report). 2019 [cited October 29, 2019]. https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf.

2. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319–38.

3. Francisco B, Ner Z, Ge B, Hewett J, Konig P. Sensitivity of different spirometric tests for detecting airway obstruction in childhood asthma. J Asthma. 2015;52(5):505–11.

4. Quanjer PH, Stanojevic S, Stocks J, Hall GL, Prasad KV, Cole TJ, et al. Changes in the FEV(1)/FVC ratio during childhood and adolescence: an intercontinental study. Eur Respir J. 2010;36(6):1391–9.

5. Szefler SJ, Murphy K, Harper T, Boner A, Laki I, Engel M, et al. A phase III randomized controlled trial of tiotropium add-on therapy in children with severe symptomatic asthma. J Allergy Clin Immunol. 2017;140:1277–87.

6. Vogelberg C, Engel M, Laki I, Bernstein JA, Schmidt O, El Azzi G, et al. Tiotropium add-on therapy improves lung function in children with symptomatic moderate asthma. J Allergy Clin Immunol. 2018;6(6):2160–2162.e9.

7. Hamelmann E, Bateman ED, Vogelberg C, Szefler SJ, Vandewalker M, Moroni-Zentgraf P, et al. Tiotropium add-on therapy in adolescents with moderate asthma: a 1-year randomized controlled trial. J Allergy Clin Immunol. 2016;138(2):441–450.e8.

8. Hamelmann E, Bernstein JA, Vandewalker M, Moroni-Zentgraf P, Verdi D, Unseld A, et al. A randomised controlled trial of tiotropium in adolescents with severe symptomatic asthma. Eur Respir J. 2017;49:1601100.

9. Kerstjens HA, Casale TB, Bleecker ER, Meltzer EO, Pizzichini E, Schmidt O, 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;3(5):367–76.

10. Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, et al. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med. 2012;367(13):1198–207.

11. Paggiaro P, Halpin DM, Buhl R, Engel M, Zubek VB, Blahova Z, et al. The effect of tiotropium in symptomatic asthma despite low- to medium-dose inhaled corticosteroids: a randomized controlled trial. J Allergy Clin Immunol Pract. 2016;4(1):104–113.e2.

12. Chanez P, Bourdin A. Histopathology and natural history of asthma. In: Castro M, Kraft M, editors. Clinical asthma. 1st ed. Mosby: Elsevier; 2008. p. 23–4.

13. Witt CA, Sheshadri A, Carlstrom L, Tarsi J, Kozlowski J, Wilson B, et al. Longitudinal changes in airway remodeling and air trapping in severe asthma. Acad Radiol. 2014;21(8):986–93.

14. Kew KM, Dahri K. Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta2-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma. Cochrane Database Syst Rev. 2016;(1):CD011721.

15. Chari VM, McIvor RA. Tiotropium for the treatment of asthma: patient selection and perspectives. Can Respir J. 2018;2018:3464960.

16. Meltzer EO, Berger WE. A review of the efficacy and safety of once-daily tiotropium Respimat 2.5 micrograms in adults and adolescents with asthma. Allergy Asthma Proc. 2018;39(1):14–26.