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BRIEF REPORT

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

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ABSTRACT

Introduction: Airway obstruction is usually assessed by measuring forced expiratory volume in 1 s (FEV_1), 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 FEV_1, FVC, PEF and FEV_1/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 FEV_1 (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_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

Key Summary Points

Spirometry outcomes in patients with asthma are influenced by severity of disease and lung function, and also by age, technical ability to perform the test and measurement frequency.

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 [forced expiratory volume in 1 s (FEV_1); forced vital capacity (FVC); peak expiratory flow (PEF)] following treatment with tiotropium Respimat®.

All lung function measures improved in all studies with tiotropium 5 μg (mean change from baseline versus placebo), including peak FEV_1, peak FVC and morning PEF, although changes in adolescents were smaller than those in adults, and were statistically significant primarily for FEV_1 and PEF, but not for FVC.

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.

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 (FEV_1), 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 FEV_1 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 β_2-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.

FEV_1, FVC and PEF were analysed at week 24 in all trials except GraziaTinA-asthma, in which pulmonary function endpoints were analysed at week 12. FEV_1/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 FEV_1 (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

Table 1 Baseline demographics and disease characteristics

	Adults			Adolescents
	PrimoTinA-asthma[a] (severe asthma)	MezzoTinA-asthma[a,b] (moderate asthma)	GraziaTinA-asthma (mild asthma)	RubaTinA-asthma (moderate asthma)
Baseline characteristics				
Total participants, *N*	912	2100	464	397
Age, years[c]	53.0 ± 12.4	43.1 ± 12.9	42.9 ± 13.0	14.3 ± 1.7
Sex, female, *n* (%)	551 (60.4)	1239 (59.0)	281 (60.6)	139 (35.0)
Height, cm[c]	167.0 ± 10.1	165.4 ± 9.8	167.4 ± 10.2	166.1 ± 11.0
BMI, kg/m^2[c]	28.2 ± 6.0	26.8 ± 6.2	26.4 ± 5.2	21.3 ± 4.3
Never smoked, *n* (%)	692 (75.9)	1756 (83.6)	382 (82.3)	396 (99.7)
Duration of asthma, years[c]	30.3 ± 13.9	21.8 ± 14.3	16.2 ± 11.9	7.9 ± 4.1
ICS dose of stable maintenance treatment, μg[c] budesonide equivalent at baseline	1198.1 ± 538.9	659.6 ± 212.9	381.4 ± 77.8	539.4 ± 292.7
LABA use at baseline, %	97.9	0.1	0.0	0.3
LTRA use at baseline, %	21.9	8.7	0.2	8.3
Disease characteristics at randomisation (visit 2)				
FEV_1, mL[c,d]	1603 ± 540	2267 ± 654	2420 ± 711	2747 ± 662
FVC, mL[c,d]	2774 ± 900	3458 ± 945	3542 ± 929	3559 ± 863
FEV_1, percent predicted[c,d]	56.0 ± 13.1	75.1 ± 11.5	77.7 ± 11.9	82.8 ± 10.6
FVC, percent predicted[c,d]	80.2 ± 17.01	96.7 ± 13.8	96.6 ± 14.5	93.7 ± 13.3
FEV_1/FVC ratio, %[c,d]	58.4 ± 10.1	66.1 ± 10.5	68.5 ± 10.5	77.9 ± 10.4
PEF_{am}, L/min[c]	270.7 ± 111.1	333.6 ± 115.2	355.8 ± 114.5	339.7 ± 91.5
PEF_{pm}, L/min[c]	279.8 ± 114.2	349.6 ± 117.2	369.8 ± 114.9	360.0 ± 91.1

BMI body mass index, *FEV_1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *ICS* inhaled corticosteroids, *LABA* long-acting β_2-agonist, *LTRA* leukotriene receptor antagonist, *PEF_{am}* morning peak expiratory flow, *PEF_{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

with symptomatic mild asthma, tiotropium 5 μg provided a non-significant numerical improvement versus placebo (Table 2).

In adolescents with symptomatic moderate asthma, treatment with tiotropium 5 μg 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 μg were only significant for peak FEV_1 (absolute and percent predicted), and the

Table 2 Key efficacy endpoints (FAS)

Response measure	Adults						Adolescents	
	Symptomatic severe asthma[a]		Symptomatic moderate asthma[a]		Symptomatic mild asthma[b]		Symptomatic moderate asthma	
	N[c]	Active vs placebo. Adjusted mean difference ± SE (95% CI); *P* value	*N*[c]	Active vs placebo. Adjusted mean difference ± SE (95% CI); *P* value	*N*[c]	Active vs placebo. Adjusted mean difference ± SE (95% CI); *P* value	*N*[c]	Active vs placebo. Adjusted mean difference ± SE (95% CI); *P* value
Peak FEV_1 (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_1 (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_1 (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_1 (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[a]		Symptomatic moderate asthma[a]		Symptomatic mild asthma[b]		Symptomatic moderate asthma	
	N[c]	Active vs placebo.Adjusted mean difference ± SE(95% CI); *P* value	*N*[c]	Active vs placebo.Adjusted mean difference ± SE(95% CI); *P* value	*N*[c]	Active vs placebo.Adjusted mean difference ± SE(95% CI); *P* value	*N*[c]	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	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	492	107 ± 23 (62, 152); < 0.0001	151	98 ± 43 (13, 183); 0.0236	119	63 ± 60 (−55, 181); 0.2921
PEF_{am} (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	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_{pm} (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

Table 2 continued

Response measure	Adults						Adolescents	
	Symptomatic severe asthma[a]		Symptomatic moderate asthma[a]		Symptomatic mild asthma[b]		Symptomatic moderate asthma	
	N[c]	Active vs placebo.Adjusted mean difference ± SE(95% CI); *P* value	*N*[c]	Active vs placebo.Adjusted mean difference ± SE(95% CI); *P* value	*N*[c]	Active vs placebo.Adjusted mean difference ± SE(95% CI); *P* value	*N*[c]	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_1 forced expiratory volume in 1 s, *FVC* forced vital capacity, *MMRM* mixed-effects model with repeated measures, *NR* not reported, PEF_{am} morning peak expiratory flow, PEF_{pm} evening peak expiratory flow, *pp* percent predicted, *SE* standard error

[a] MMRM adjusted for treatment, study, visit, treatment by visit, baseline and baseline by visit

[b] MMRM adjusted for treatment, centre, visit, treatment by visit, baseline and baseline by visit

[c] 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 FEV_1/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 FEV_1/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 FEV_1/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 FEV_1 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.

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

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