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COMMENTARY

Forced Expiratory Flow ($FEF_{25–75\%}$) as a Clinical Endpoint in Children and Adolescents with Symptomatic Asthma Receiving Tiotropium: A Post Hoc Analysis

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ABSTRACT

Introduction: In pediatric patients with asthma, measurements of forced expiratory volume in 1 s (FEV_1) may be normal or may not correlate with symptom severity. Forced expiratory flow at 25–75% of the vital capacity ($FEF_{25–75\%}$) is a potentially more sensitive parameter for assessing peripheral airway function. This post hoc analysis compared $FEF_{25–75\%}$ with FEV_1 as an endpoint to assess bronchodilator responsiveness in children with asthma.

Methods: Change from baseline in trough $FEF_{25–75\%}$ and trough FEV_1 following treatment with either tiotropium (5 μg or 2.5 μg) or placebo Respimat® was analyzed in four phase III trials in children (aged 6–11 years) and adolescents (aged 12–17 years) with symptomatic moderate (VivaTinA-asthma® and PensieTinA-asthma®) and mild (CanoTinA-asthma® and RubaTinA-asthma®) asthma. Data from all treatment arms were pooled and correlations

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between $FEF_{25–75\%}$ and FEV_1 were calculated and analyzed.

Results: A total of 1590 patients were included in the analysis. Tiotropium Respimat® consistently improved $FEF_{25–75\%}$ and FEV_1 versus placebo, although in adolescents with severe asthma, the observed improvements were not statistically significant. Improvements in $FEF_{25–75\%}$ response with tiotropium versus placebo were largely more pronounced than improvements in FEV_1. Statistical assessment of the correlation of FEV_1 and $FEF_{25–75\%}$ showed moderate-to-high correlations (Pearson's correlation coefficients 0.73–0.80).

Conclusions: In pediatric patients, $FEF_{25–75\%}$ may be a more sensitive measure to detect treatment response, certainly to tiotropium, than FEV_1 and should be evaluated as an additional lung function measurement.

Keywords: Airway obstruction; Asthma; Muscarinic antagonist; Tiotropium

Key Summary Points

Interpretation of lung function data from children and adolescents can be challenging because standard measures such as forced expiratory volume in 1 s (FEV_1) do not always correlate with symptom severity.

Forced expiratory flow at 25–75% of the vital capacity ($FEF_{25–75\%}$) could be a more sensitive measure of peripheral airway function than FEV_1 in these patients.

Using pooled data from four phase III trials in patients with asthma aged 6–17 years, we investigated change from baseline in trough $FEF_{25–75\%}$ and FEV_1 following treatment with either tiotropium (5 µg or 2.5 µg) or placebo Respimat®. Trough was defined as the pre-dose $FEF_{25–75\%}$ or FEV_1, respectively, measured 24 h post previous drug administration, 10 min prior to the evening dose of usual asthma medication and daily dose of randomized treatment.

Tiotropium Respimat® consistently improved $FEF_{25–75\%}$ and FEV_1 versus placebo, with improvements in $FEF_{25–75\%}$ largely more pronounced than those seen in FEV_1. Improvements were statistically significant versus placebo except in adolescents with severe asthma.

$FEF_{25–75\%}$ may be a more sensitive measure to detect treatment response, certainly to tiotropium, than FEV_1 and should be evaluated as an additional lung function measurement in pediatric patients.

COMMENTARY

Assessment of standard measures of lung function can be more challenging in children and adolescents compared with adults. Whilst forced expiratory volume in 1 s (FEV_1) is accepted as a standard measure of lung function in adults with asthma, it is often found to be normal in pediatric patients, and measurements may not always correlate with symptom severity [1].

Forced expiratory flow at 25–75% of the vital capacity ($FEF_{25–75\%}$) is potentially a more sensitive parameter than FEV_1 for assessing changes in peripheral airway function in pediatric patients [2, 3]. Indeed, Vilozni et al. reported that $FEF_{25–75\%}$ was a more numerically sensitive index than FEV_1 in detecting airway obstruction and response to bronchodilators [4]. However, current data on the value of $FEF_{25–75\%}$ compared with FEV_1 are limited. $FEF_{25–75\%}$ has been described as less effort-dependent than FEV_1 and is a measurement of small airway dysfunction [2, 3]. In a study comparing children aged 10–18 years with normal FEV_1 (> 80% predicted) and $FEF_{25–75\%}$ (> 60% predicted) with those who had normal FEV_1 (> 80% predicted) and low $FEF_{25–75\%}$, reduced $FEF_{25–75\%}$ in the presence of normal FEV_1 was associated with increased asthma severity and reversible airflow obstruction [2, 3]. However, it was noted that there is no guideline regarding normal values

for $FEF_{25–75\%}$ in children, therefore the authors defined normal $FEF_{25–75\%}$ as > 60% predicted, using a value corresponding to 1 standard deviation from the mean $FEF_{25–75\%}$ obtained from the initial cohort [3]. A separate study supported this finding proposing $FEF_{25–75\%}$- > 65% predicted as normal [5].

Since $FEF_{25–75\%}$ correlates well with bronchodilator responsiveness in children with asthma and may reflect peripheral airway obstruction in the presence of a normal FEV_1 [2, 3], this prompted the evaluation of this parameter in relation to the long-acting muscarinic antagonist bronchodilator tiotropium.

Tiotropium Respimat® (Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany) has been shown to improve different measures of lung function in clinical studies with both children and adolescents, including $FEF_{25–75\%}$ [6–9]. This is a post hoc analysis of four placebo-controlled trials in children and adolescents with symptomatic asthma who remained uncontrolled despite maintenance therapy (inhaled corticosteroids ± long-acting β_2-agonist ± leukotriene receptor antagonist, Table 1). We compare the change in trough $FEF_{25–75\%}$ and trough FEV_1 (defined as the pre-dose $FEF_{25–75\%}$ or FEV_1, respectively, measured 24 h post previous drug administration, 10 min prior to the evening dose of usual asthma medication and daily dose of randomized treatment) following treatment with either tiotropium Respimat (5 μg or 2.5 μg) or placebo Respimat.

We analyzed data from four double-blind, parallel-group, randomized, placebo-controlled phase III trials: VivaTinA-asthma® (NCT01634152; a 12-week trial in 6 to 11-year-old patients with symptomatic severe asthma) [7], PensieTinA-asthma® (NCT01277523; a 12-week trial in 12 to 17-year-old patients with symptomatic severe asthma) [6], CanoTinA-asthma® (NCT01634139; a 48-week trial in 6 to 11-year-old patients with symptomatic moderate asthma) [8] and RubaTinA-asthma® (NCT01257230; a 48-week trial in 12 to 17-year-old patients with symptomatic moderate asthma) [9]. Details for each study have been published previously [6–9]. Each study was conducted in accordance with the amended Declaration of Helsinki. The ethics research boards of the respective institutions approved the protocols, and signed, informed consent was obtained from all patients and/or their parents [6–9].

We compared change from baseline in trough FEV_1 and trough $FEF_{25–75\%}$ at the time of the primary endpoint (PensieTinA- and VivaTinA-asthma at week 12; RubaTinA- and CanoTinA-asthma at week 24), and analyzed correlations between $FEF_{25–75\%}$ response and FEV_1 response at these time points. Pearson's correlation coefficients were calculated between trough FEV_1 and trough $FEF_{25–75\%}$, pooling data from all treatment arms. As measurement of $FEF_{25–75\%}$ relies on accurate measurement of forced vital capacity (FVC), mean $FEF_{25–75\%}$ was calculated from the maneuver (≥ 3 and ≤ 8 maneuvers per time point) with the largest total sum of FEV_1 and FVC. Use and daily calibration of all spirometers used in the four pediatric trials discussed in this analysis met American Thoracic Society/European Respiratory Society criteria [10].

A total of 1590 patients were included in the analysis (Table 1). Across the trials in 6 to 11- and 12 to 17-year-old patients with moderate/severe asthma, tiotropium Respimat consistently improved trough FEV_1 (Fig. 1a) and trough $FEF_{25–75\%}$ (Fig. 1b) versus placebo; although in the PensieTinA-asthma study in adolescents with severe asthma, the observed improvements were not statistically significant, possibly due to a pronounced placebo response, which left little room for differentiation between the treatment groups [6].

Improvements in trough $FEF_{25–75\%}$ response with tiotropium add-on therapy versus placebo were largely more pronounced than improvements in trough FEV_1, as evidenced both by the numerical changes and the percentage difference, suggesting that trough $FEF_{25–75\%}$ may be a more sensitive measure to detect treatment response, certainly to tiotropium, than trough FEV_1. Statistical assessment of the correlation between changes in trough $FEF_{25–75\%}$ and changes in trough FEV_1 showed moderate-to-high correlations (0.73–0.80; Supplementary Fig. 1).

Even though assessment of $FEF_{25–75\%}$ is not currently recommended in asthma guidelines,

Table 1 Baseline patient demographics and disease characteristics (treated set)

Demographic/characteristic	Symptomatic severe asthma		Symptomatic moderate asthma	
	VivaTinA-asthma® (*N* = 400)	PensieTinA-asthma® (*N* = 392)	CanoTinA-asthma® (*N* = 401)	RubaTinA-asthma® (*N* = 397)
Male, *n* (%)	279 (69.8)	242 (61.7)	264 (65.8)	258 (65.0)
Age, years, median (range)	9.0 (6–11)	14.2 (12–17)	8.9 (6–11)	14.3 (11–17)
Race, *n* (%)				
White	358 (89.5)	371 (94.6)	339 (84.5)	368 (92.7)
Asian	2 (0.5)	10 (2.6)	10 (2.5)	13 (3.3)
Black/African American	5 (1.3)	8 (2.0)	7 (1.7)	14 (3.5)
American Indian/Alaska Native	35 (8.8)	3 (0.8)	45 (11.2)	2 (0.5)
Hawaiian/Pacific Islander	0	0	0	0
Ethnicity, *n* (%)				
Hispanic/Latino	72 (18.0)	68 (17.3)	55 (13.7)	42 (10.6)
Never smoked, *n* (%)	–	392 (100)	–	396 (99.7)
No exposure to second-hand smoke, *n* (%)	369 (92.3)	367 (93.6)	372 (92.8)	353 (88.9)
Age at onset of asthma, years, mean ± SD	4.1 ± 2.4	6.5 ± 3.9	4.7 ± 2.4	6.5 ± 4.1
Duration of asthma, years, median (range)	4.9 (0.6–11.0)	7.8 (0.3–16.5)	4.2 (0.5–11.0)	7.9 (0.3–16.3)
Concomitant diagnoses, *n* (%)				
Allergic rhinitis	238 (59.5)	225 (57.4)	230 (57.4)	219 (55.2)
Atopic dermatitis	38 (9.5)	38 (9.7)	55 (13.7)	37 (9.3)
FEV_1, l, mean ± SD[a,b]	1.57 ± 0.35	2.53 ± 0.62	1.63 ± 0.39	2.75 ± 0.66
FEV_1, % predicted, mean ± SD[a,b]	81.64 ± 11.45	79.52 ± 11.49	84.06 ± 10.79	82.79 ± 10.56
FEV_1% reversibility, median (Q1–Q3)[c,d]	24.03 (17.44–34.10)	26.01 (18.31–36.60)	23.19 (16.94–33.60)	23.29 (17.46–33.76)
FVC, l, mean ± SD[a,b]	2.05 ± 0.48	3.32 ± 0.81	2.12 ± 0.56	3.56 ± 0.86
FVC, % predicted, mean ± SD[a,b]	92.34 ± 13.60	91.62 ± 14.69	94.70 ± 14.71	93.70 ± 13.34
FVC, % reversibility, median (Q1–Q4)[c,d]	12.92 (7.00–22.90)	14.15 (7.35–25.62)	13.62 (6.15–26.35)	12.76 (5.03–25.81)
FEV_1/FVC ratio, %, mean ± SD[c]	77.36 ± 10.12	76.87 ± 11.26	77.90 ± 10.08	77.89 ± 10.44
$FEF_{25–75\%}$, l/second, mean ± SD[a,b]	1.39 ± 0.57	2.23 ± 0.96	1.43 ± 0.58	2.48 ± 0.97
$FEF_{25–75\%}$, % predicted, mean ± SD[a,b]	61.30 ± 23.18	61.55 ± 23.06	62.44 ± 22.53	66.09 ± 20.93
$FEF_{25–75\%}$, % reversibility, median (Q1–Q4)[c,d]	51.45 (30.60–79.56)	52.61 (29.38–88.79)	48.00 (28.99–79.78)	46.48 (27.12–71.58)
ACQ score, mean ± SD[b,e]	1.966 ± 0.359	2.13 ± 0.43	1.868 ± 0.309	2.03 ± 0.43
Concomitant therapies at baseline, *n* (%)				
LTRAs	339 (84.8)	315 (80.4)	107 (26.7)	33 (8.3)
LABAs	314 (78.5)	324 (82.7)	1 (0.2)	1 (0.3)
ICS dose of stable maintenance treatment (μg; budesonide or equivalent dose), mean ± SD	457.4 ± 236.0	747.0 ± 357.7	310.0 ± 112.0	539.4 ± 292.7

Data from each study includes from all treatment arms

[a] Pre-bronchodilator

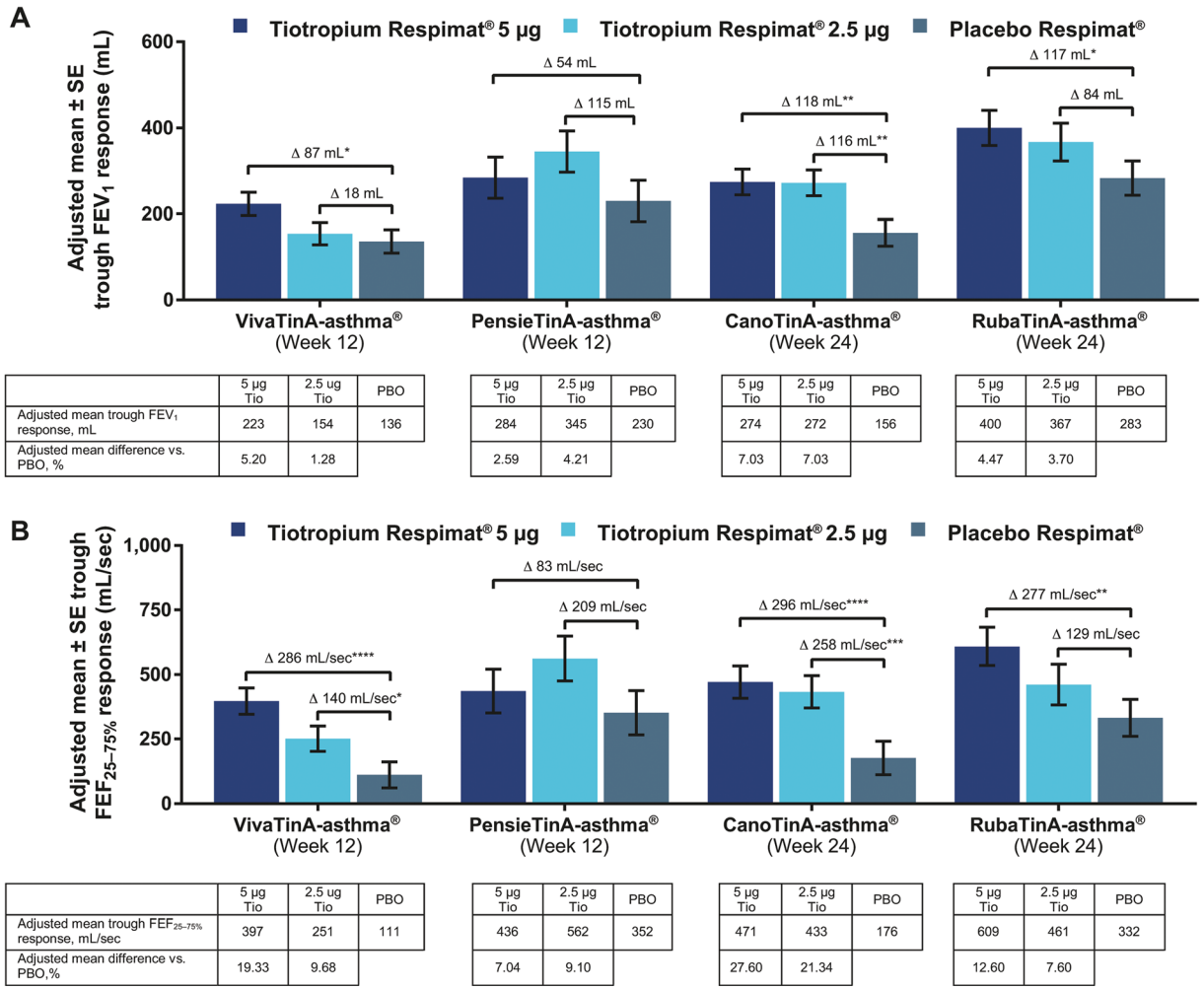
[b] Measured at randomization (Visit 2)

[c] Measured at screening (Visit 1)

[d] Reversibility was calculated using measurements of lung function before and 15–30 min after patients inhaled 400 μg salbutamol

[e] ACQ-IA in CanoTinA-asthma® and VivaTinA-asthma®

ACQ Asthma Control Questionnaire, *ACQ-IA* interviewer-administered ACQ, $FEF_{25–75\%}$ forced expiratory flow at 25–75% of the pulmonary volume, FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity, *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *LTRA* leukotriene receptor antagonist, *SD* standard deviation



	5 µg Tio	2.5 µg Tio	PBO
Adjusted mean trough FEV_1 response, mL	223	154	136
Adjusted mean difference vs. PBO, %	5.20	1.28	

	5 µg Tio	2.5 µg Tio	PBO
	284	345	230
	2.59	4.21	

	5 µg Tio	2.5 µg Tio	PBO
	274	272	156
	7.03	7.03	

	5 µg Tio	2.5 µg Tio	PBO
	400	367	283
	4.47	3.70	

	5 µg Tio	2.5 µg Tio	PBO
Adjusted mean trough $FEF_{25–75\%}$ response, mL/sec	397	251	111
Adjusted mean difference vs. PBO,%	19.33	9.68	

	5 µg Tio	2.5 µg Tio	PBO
	436	562	352
	7.04	9.10	

	5 µg Tio	2.5 µg Tio	PBO
	471	433	176
	27.60	21.34	

	5 µg Tio	2.5 µg Tio	PBO
	609	461	332
	12.60	7.60	

Fig. 1 **a** Trough FEV_1 response; **b** trough $FEF_{25–75\%}$ response. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; $^{****}P < 0.0001$. *$FEF_{25–75\%}$* forced expiratory flow at 25–75% of the pulmonary volume, *FEV_1* forced expiratory volume in 1 s, *PBO* placebo, *SE* standard error, *Tio* tiotropium

there are good arguments for its use to supplement FEV_1 measurements, particularly in children with asthma. During the early stages of asthma, higher, near-normal FEV_1 and FEV_1/FVC values may obscure airway involvement caused by an inflammatory process, whereas $FEF_{25–75\%}$ may signify early functional airway impairment, especially of peripheral airways [11]. $FEF_{25–75\%}$ may also better reflect small airways disease due to peripheral positioning of the airflow choke point in patients with mid-to-low lung volumes [2]. Compared with FEV_1, low $FEF_{25–75\%}$ may be a more sensitive indicator of childhood symptomatic asthma, whereas FEV_1 in children can be normal, even in the presence of symptoms of uncontrolled asthma [3]. Indeed, in our study of children with symptomatic moderate or severe asthma, mean FEV_1 percent predicted at baseline was predominantly in or just under the normal range ($\geq$ 80%). It has been suggested that $FEF_{25–75\%}$ may be a functional marker of asthma severity, whereby low $FEF_{25–75\%}$ alongside normal FEV_1 is associated with increased asthma severity, systemic steroid use, and asthma exacerbations in children [3].

Furthermore, $FEF_{25–75\%}$ has been shown to correlate well with bronchodilator (short-acting

β_2-agonist) responsiveness in children with asthma who have normal FEV_1 [2], and it may therefore be a helpful measure to predict which patients might benefit from further bronchodilation [2]. Certainly, in our study, $FEF_{25–75\%}$ was useful in detecting treatment response to tiotropium. However, it should be noted that tiotropium, as a bronchodilator, may have other mechanisms of action affecting small as well as large airways, although there is currently no evidence of this. A previous study using a different bronchodilator, albuterol, with an alternative delivery device (pressurized metered dose inhaler), provided results in accordance with those reported here, further supporting the utility of $FEF_{25–75\%}$ as a more sensitive measure of airway response to bronchodilators than FEV_1 in children and adolescents with asthma, irrespective of delivery device [4].

$FEF_{25–75\%}$ has certain limitations, including a larger variability than FEV_1, particularly in adults, and its reliance on the valid measurement of FVC [12, 13]. As FVC and total lung capacity can be affected by disease progression or therapeutic interventions, $FEF_{25–75\%}$ pre- and post-interventions may be not be comparable [13]. Ideally, measurements should be standardized for total lung capacity, but this is not usually feasible and the vital capacity is used as a proxy for lung size [13], and was not possible within this post hoc analysis. The potential lack of specificity means that $FEF_{25–75\%}$ by itself may have limited diagnostic value. Quanjer et al. previously challenged both the usefulness of $FEF_{25–75\%}$ as a clinical marker and the hypothesis that reduced mid-expiratory flows are specific for small airways disease [13]. Yet, this analysis provides further support to the literature that suggests the use of $FEF_{25–75\%}$ may help in the identification of children and adolescents who may have a normal FEV_1 but significant asthma symptoms, or who may require further evaluation from a healthcare professional or adjustments to their treatment regimen [14]. In addition, since this analysis of four studies is probably the largest to investigate the effect of a bronchodilator on $FEF_{25–75\%}$ in children and adolescents with asthma, the suggestion that $FEF_{25–75\%}$ should be used as an additional lung function measurement is appropriate.

In conclusion, our results strengthen the evidence that $FEF_{25–75\%}$ should be evaluated as an additional lung function measurement in pediatric patients. Moreover, $FEF_{25–75\%}$ may contribute as a measure to detect response to treatment.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. The data sets analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Spahn JD, Cherniack R, Paull K, Gelfand EW. Is forced expiratory volume in one second the best measure of severity in childhood asthma? Am J Respir Crit Care Med. 2004;169(7):784–6.

2. Simon MR, Chinchilli VM, Phillips BR, et al. Forced expiratory flow between 25% and 75% of vital capacity and FEV1/forced vital capacity ratio in relation to clinical and physiological parameters in asthmatic children with normal FEV1 values. J Allergy Clin Immunol. 2010;126(3):527–34.e1-8.

3. Rao DR, Gaffin JM, Baxi SN, Sheehan WJ, Hoffman EB, Phipatanakul W. The utility of forced expiratory flow between 25% and 75% of vital capacity in predicting childhood asthma morbidity and severity. J Asthma. 2012;49(6):586–92.

4. Vilozni D, Hakim F, Livnat G, Ofek M, Bar-Yoseph R, Bentur L. Assessment of airway bronchodilation by spirometry compared to airway obstruction in young children with asthma. Can Respir J. 2016;2016:6.

5. Ciprandi G, Capasso M, Tosca M, et al. A forced expiratory flow at 25–75% value <65% of predicted should be considered abnormal: a real-world, cross-sectional study. Allergy Asthma Proc. 2012;33(1):e5–e8.

6. Hamelmann E, Bernstein JA, Vandewalker M, et al. A randomised controlled trial of tiotropium in adolescents with severe symptomatic asthma. Eur Respir J. 2017;49:1601100.

7. Szefler SJ, Murphy K, Harper T, 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.

8. Vogelberg C, Engel M, Laki I, et al. Tiotropium add-on therapy improves lung function in children with symptomatic moderate asthma. J Allergy Clin Immunol. 2018;6(6):2160–2.e9.

9. Hamelmann E, Bateman ED, Vogelberg C, et al. Tiotropium add-on therapy in adolescents with moderate asthma: a 1-year randomized controlled trial. J Allergy Clin Immunol. 2016;138(2):441–50.e8.

10. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of spirometry 2019 update: An official American Thoracic Society and European Respiratory Society technical statement. Am J Respir Crit Care Med. 2019;200(8):e70–e88.

11. Sposato B, Scalese M, Migliorini MG, Di Tomassi M, Scala R. Small airway impairment and bronchial hyperresponsiveness in asthma onset. Allergy Asthma Immunol Res. 2014;6(3):242–51.

12. Stanojevic S, Wade A, Stocks J, et al. Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med. 2008;177(3): 253–60.

13. Quanjer PH, Weiner DJ, Pretto JJ, Brazzale DJ, Boros PW. Measurement of $FEF_{25-75\%}$ and $FEF_{75\%}$ does not contribute to clinical decision making. Eur Respir J. 2014;43(4):1051–8.

14. Gibb E, Kaplan D, Thyne SM, Ly NP. Fef 25–75 as a predictor of asthma severity in children. Am J Respir Crit Care Med. 2012;185:A6801.