Tiotropium add-on therapy is safe and reduces seasonal worsenings in paediatric asthma patients

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Supplementary Material

Supplementary Methods

Definition of an adverse event

An adverse event (AE) was defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition; the event did not necessarily have to have a causal relationship with this treatment. For each AE, the investigator was asked to provide the start and end dates, intensity, treatment required, outcome, seriousness and action taken with the investigational drug, and to determine the relationship of the investigational drug to the AE. All AEs were followed up until resolved or sufficiently characterized. A drug-related AE was defined as an AE for which there was a reasonable causal relationship between the randomized trial medication (tiotropium or placebo) and the AE. The medical judgement of the investigator was used to determine the causal relationship, considering all relevant factors (such as the temporal relationship between treatment administration and the AE) and confounding factors (such as concomitant medication, concomitant diseases and relevant history). A serious AE (SAE) was defined as any AE that resulted in death, was immediately life-threatening, resulted in persistent or significant disability/incapacity, required or prolonged patient hospitalization, was a congenital anomaly/birth defect, or was to be deemed serious for any other reason that might have jeopardized the patient and

might have required medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Supplementary Results

Safety topics of interest

The incidence of patients with dry mouth – a common side effect associated with anticholinergic therapies – was low and comparable between treatment groups, including placebo: dry mouth was reported in one patient receiving tiotropium 5 μg, one patient receiving tiotropium 2.5 μg and two patients receiving placebo. Dry mouth did not lead to treatment discontinuation in any of these cases.

Cough was also reported infrequently, and the number of patients reporting was comparable between the tiotropium and placebo groups (five patients receiving tiotropium 5 μg, ten patients receiving tiotropium 2.5 μg and 13 patients receiving placebo). Cough did not lead to treatment discontinuation in any of the cases in the tiotropium treatment groups.

Urinary retention was not reported in any patients, and constipation, another potential class effect event, was only reported by one patient in the placebo group. Cardiac events (metabolic cardiomyopathy and palpitations) were reported by two patients in the placebo group. Eye disorders (allergic conjunctivitis, eye/eyelid pruritus and myopia), another potential class effect, were infrequent and only reported by three patients receiving tiotropium 5 μg, two patients receiving tiotropium 2.5 μg and four patients receiving placebo. Eye disorders did not lead to treatment discontinuation in any of these cases.

Supplementary tables

Table E1. MedDRA-preferred terms included in composite endpoint analysis for patients reported with adverse events related to asthma exacerbations and asthma symptoms

Allergic bronchitis	Pneumocystis jirovecii pneumonia
Allergic cough	Pneumonia
Allergic respiratory symptom	Pneumonia adenoviral
Asthma	Pneumonia anthrax
Asthma exercise induced	Pneumonia bacterial
Asthma prophylaxis	Pneumonia blastomyces
Asthma−chronic obstructive pulmonary disease overlap syndrome	Pneumonia bordetella
Asthmatic crisis	Pneumonia chlamydial
Atypical mycobacterial pneumonia	Pneumonia cryptococcal
Atypical pneumonia	Pneumonia cytomegaloviral
Breathing-related sleep disorder	Pneumonia escherichia
Bronchitis	Pneumonia fungal
Bronchitis bacterial	Pneumonia haemophilus
Bronchitis chronic	Pneumonia helminthic
Bronchitis fungal	Pneumonia herpes viral
Bronchitis haemophilus	Pneumonia influenzal
Bronchitis moraxella	Pneumonia klebsiella
Bronchitis pneumococcal	Pneumonia legionella
Bronchitis viral	Pneumonia measles
Bronchospasm	Pneumonia moraxella
Bronchospasm paradoxical	Pneumonia mycoplasmal
Chest discomfort	Pneumonia necrotizing
Chest pain	Pneumonia parainfluenzae viral
Congenital pneumonia	Pneumonia pneumococcal
Cough	Pneumonia pseudomonal
Dyspnoea	Pneumonia respiratory syncytial viral
Dyspnoea at rest	Pneumonia salmonella
Dyspnoea exertional	Pneumonia staphylococcal
Dyspnoea paroxysmal nocturnal	Pneumonia streptococcal
Dyssomnia	Pneumonia toxoplasmal
Embolic pneumonia	Pneumonia tularaemia
Enterobacter pneumonia	Pneumonia viral
Fatigue	Poor quality sleep
Fibrinous bronchitis	Post procedural pneumonia
Herpes simplex pneumonia	Productive cough
Hyposomnia	Prolonged expiration
Hypoventilation	Psychogenic respiratory distress

Increased bronchial secretion	Reactive airways dysfunction syndrome
Increased viscosity of bronchial secretion	Respiration abnormal
Infective exacerbation of chronic obstructive airways disease	Respiratory depth increased
Initial insomnia	Respiratory distress
Insomnia	Respiratory fatigue
Lethargy	Respiratory tract infection
Lower respiratory tract infection	Respiratory tract infection viral
Lung hypoinflation	Sinobronchitis
Lung infection	Sluggishness
Lung infection pseudomonal	Sputum discoloured
Middle insomnia	Sputum purulent
Miliary pneumonia	Status asthmaticus
Neonatal pneumonia	Tachypnoea
Nocturnal dyspnoea	Terminal insomnia
Noninfective bronchitis	Tracheobronchitis
Obstructive airways disorder	Upper-airway cough syndrome
Orthopnoea	Varicella zoster pneumonia
Peak expiratory flow rate	Wheezing
Peak expiratory flow rate abnormal	
Peak expiratory flow rate decreased	

AEs were coded using MedDRA version 18.1**.**

Definition of abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.

Table E2. AEs reported by ≥2% patients by preferred term in patients aged 1–17 years

	Tiotropium Respimat® 5 µg	**Tiotropium Respimat® 2.5 µg**	**Placebo Respimat®**
Total with AEs, n (%)	**283 (50.5)**	**286 (51.2)**	**310 (54.2)**
Asthma	110 (19.6)	115 (20.6)	143 (25.0)
Decreased peak expiratory flow rate	55 (9.8)	64 (11.4)	68 (11.9)
Nasopharyngitis/rhinopharyngitis	44 (7.9)	46 (8.2)	49 (8.6)
Viral respiratory tract infection (viral)	27 (4.8)	24 (4.3)	30 (5.2)
Headache	14 (2.5)	18 (3.2)	10 (1.7)
Allergic rhinitis	10 (1.8)	14 (2.5)	16 (2.8)
Pharyngitis	8 (1.4)	14 (2.5)	14 (2.4)
Bronchitis	8 (1.4)	13 (2.3)	8 (1.4)
Cough	5 (0.9)	10 (1.8)	13 (2.3)

Definition of abbreviations: AE = adverse event.

Table E3. Patients reporting SAEs by preferred term in subgroups by age

	Tiotropium Respimat® 5 µg	**Tiotropium Respimat® 2.5 µg**	**Placebo Respimat®**
1–5 years, n (%) [1]	**n = 31**	**n = 36**	**n = 34**
Appendicitis	0	0	1 (2.9)
Upper respiratory tract infection	0	0	1 (2.9)
Bronchopneumonia	0	0	1 (2.9)
6–11 years [2,3]	**n = 265**	**n = 271**	**n = 265**
Appendicitis	1 (0.4)	1	0
Appendicitis and paralytic ileus	1 (0.4)	0	0
Asthma	3 (1.1)	3 (1.1)	3 (1.1)
Asthmatic crisis	0	0	1 (0.4)
Gastroenteritis	0	0	1 (0.4)
Renal abscess	0	0	1 (0.4)
Concussion, fall, haematoma and skull fracture	0	0	1 (0.4)
Anaphylactic reaction	0	0	1 (0.4)
Epilepsy	0	1	0
12–17 years [4,5]	**n = 264**	**n = 252**	**n = 273**
Appendicitis	0	1 (0.4)	0

Asthma	2 (0.8)	0	0
Allergy to plants/anaphylactic reaction	1 (0.4)	0	0
Abdominal pain	1 (0.4)	0	0
Atopic dermatitis and pyoderma	0	1 (0.4)	0
Ligament sprain	1 (0.4)	0	0
Multiple injuries	0	1 (0.4)	0
Gastroenteritis	0	0	1 (0.4)
Teratoma	0	0	1 (0.4)

Treated set. Treatment + 30 days. Percentages are calculated using total number of patients per treatment as the denominator.
Definition of abbreviations: SAE = serious adverse event.

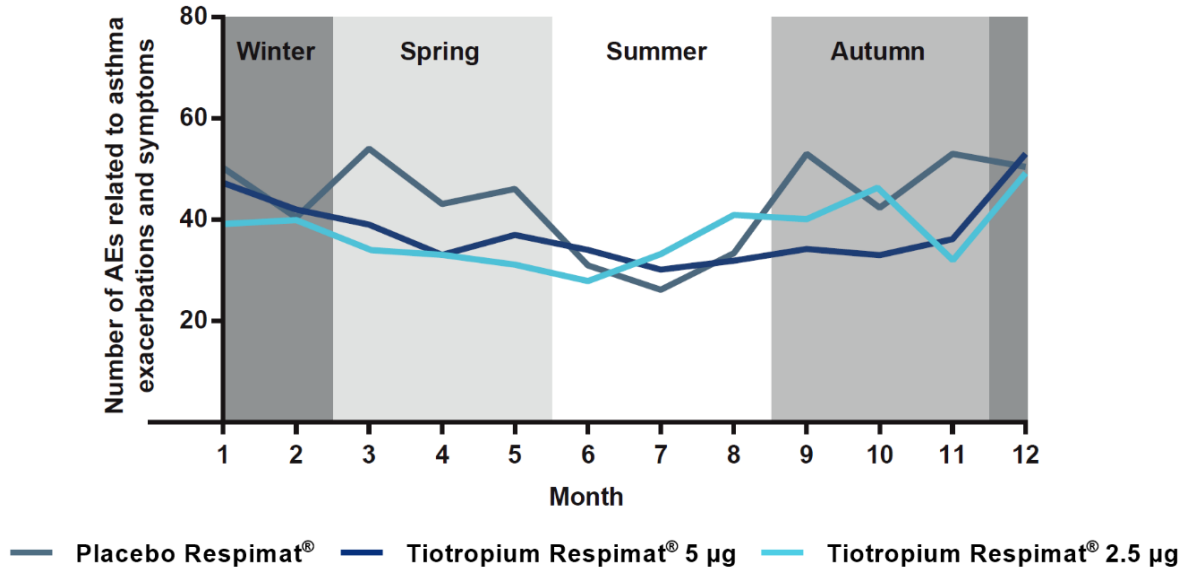
Table E4. Overview of patients reporting AEs by preferred term in the pooled population aged 6–17 years (excluding patients aged 1–5 years)

	Tiotropium Respimat® 5 µg	**Tiotropium Respimat® 2.5 µg**	**Placebo Respimat®**
n (%)	**n = 529**	**n = 523**	**n = 538**
Any AEs	265 (50.1)	266 (50.9)	285 (53.0)
Drug-related AEs	5 (0.9)	1 (0.2)	6 (1.1)
AEs leading to discontinuation	2 (0.4)	0	5 (0.9)
SAEs	10 (1.9)	8 (1.5)	10 (1.9)
AEs reported in ≥5% of patients*			
Asthma exacerbation/worsening	108 (20.4)	110 (21.0)	133 (24.7)
Decreased peak expiratory flow rate	55 (10.4)	64 (12.2)	68 (12.6)
Respiratory tract infection	19 (3.6)	17 (3.3)	28 (5.2)

Treated set. Treatment + 30 days. Percentages are calculated using total number of patients per treatment as the denominator. *In at least one treatment group
Definition of abbreviations: AE = adverse event; SAE = serious AE.

Supplementary Figures

Figure E1. Number of reported AEs related to asthma exacerbations and symptoms over 12 months in the pooled population aged 6–17 years, (excluding patients aged 1–5 years)



Data from the Southern hemisphere shifted by 6 months to align the seasons (Northern hemisphere: June = Month 6; Southern hemisphere: December = Month 6).

Supplementary references

1. Vrijlandt EJLE, El Azzi G, Vandewalker M, et al. Safety and efficacy of tiotropium in children aged 1–5 years with persistent asthmatic symptoms: a randomised, double-blind, placebo-controlled trial. *Lancet Resp Med*. 2018;6(2):127–137.

2. Szefler SJ, Murphy K, Harper T3, et al. A phase III randomized controlled trial of tiotropium add-on therapy in children with severe symptomatic asthma. *J Allergy Clin Immunol*. 2017;140:1277–1287.

3. Vogelberg C, Engel M, Laki I, Bernstein JA, Schmidt O, El Azzi G, Moroni-Zentgraf P, Sigmund R, Hamelmann E. Tiotropium add-on therapy improves lung function in children with symptomatic moderate asthma. *J Allergy Clin Immunol Pract* 2018; [Epub ahead of print].

4. 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):441–450.

4. 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.