



## Early View

Research letter

### **Tiotropium add-on therapy reduces seasonal peaks of asthma worsening in adults with symptomatic severe asthma**

J. Mark FitzGerald, Roland Buhl, Thomas B. Casale, Branko Jugovic, Liliana Zaremba-Pechmann, David M. G. Halpin

Please cite this article as: FitzGerald JM, Buhl R, Casale TB, *et al.* Tiotropium add-on therapy reduces seasonal peaks of asthma worsening in adults with symptomatic severe asthma. *Eur Respir J* 2019; in press (<https://doi.org/10.1183/13993003.00964-2019>).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

## **Tiotropium add-on therapy reduces seasonal peaks of asthma worsening in adults with symptomatic severe asthma**

J. Mark FitzGerald,<sup>1</sup> Roland Buhl,<sup>2</sup> Thomas B. Casale,<sup>3</sup> Branko Jugovic,<sup>4</sup> Liliana Zaremba-Pechmann,<sup>5</sup> David M.G. Halpin<sup>6</sup>

<sup>1</sup>Centre for Heart and Lung Health, Vancouver, British Columbia, Canada; <sup>2</sup>Johannes Gutenberg University Mainz, Mainz, Germany; <sup>3</sup>Division of Allergy and Immunology, University of South Florida Morsani College of Medicine, Tampa, Florida, USA; <sup>4</sup>Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; <sup>5</sup>Elderbrook Solutions GmbH, Bietigheim-Bissingen, Germany; <sup>6</sup>Royal Devon and Exeter Hospital, Exeter, United Kingdom

**Corresponding author contact details:** J. Mark FitzGerald, Institute for Heart and Lung Health, 7th Floor, 2775 Laurel Street, Vancouver, V5Z 1M9, Canada. E-mail: [Mark.Fitzgerald@vch.ca](mailto:Mark.Fitzgerald@vch.ca)

**Target journal:** European Respiratory Journal

**Take-home message:** In adults with symptomatic severe asthma despite inhaled corticosteroid/long-acting  $\beta_2$ -agonist therapy, tiotropium add-on therapy reduces seasonal peaks of asthma worsening, providing a year-round benefit.

**Plain language summary:** In people with asthma, the risk of asthma worsening may be greater in some seasons than others. Tiotropium, an inhaled medicine for treating asthma, has been shown to reduce asthma worsening when it is added on to other prescribed medicines. This study looked at the effects of tiotropium by season in a large trial of adults with severe asthma. It found that tiotropium reduces the risk of asthma worsening, irrespective of the season, and could be of benefit to people with asthma all-year round.

### **To the Editor:**

Despite the use of preferred controller therapies (including inhaled corticosteroids [ICS] with or without additional long-acting  $\beta_2$ -agonists [LABAs]), a large proportion of patients with asthma have poor disease control, leaving them at risk of recurring symptoms and episodes of asthma exacerbations and worsening [1, 2]. Such problems can be triggered by many different environmental factors including pollutants, respiratory infections or allergens [3]. They may occur sporadically, but are often determined by seasons, mirroring seasonal patterns of allergen exposure and prevalence of respiratory viral infection [3, 4]. They can cause reduced quality of life, increase asthma burden [2, 3], and have economic and societal impacts, such as increased absenteeism in school-age children, reduced work productivity and missed workdays in adults [5]. It is therefore important to choose an appropriate asthma treatment to achieve good symptom control and minimise the risk of exacerbations and worsening [2].

Tiotropium has been shown to be an efficacious add-on therapy to ICS in adult patients with symptomatic asthma across all severities [6–8]. In adults with symptomatic severe asthma, the

PrimoTinA-asthma® study consisted of two replicate Phase III, randomised, double-blind, placebo-controlled, parallel-group, 48-week trials (NCT00772538/NCT00776984) [6]. Tiotropium 5 µg add-on therapy prolonged the time to first asthma exacerbation (defined as an episode of progressive increase in  $\geq 1$  asthma symptom(s) [compared with usual day-to-day asthma symptoms], or a decline of  $\geq 30\%$  in morning peak expiratory flow [PEF<sub>am</sub>] for  $\geq 2$  consecutive days as judged by the investigator, requiring systemic corticosteroids [SCS] for  $\geq 3$  days) during the 48-week treatment period by 56 days compared with placebo. This corresponded to a reduction in risk of 21% (hazard ratio [HR] 0.79; 95% confidence interval [CI] 0.62–1.00; adjusted P=0.0343).

In the same trials, data on asthma worsenings, a more moderate and common counterpart to exacerbations, were also collected (defined as an episode of progressive increase in  $\geq 1$  asthma symptom(s) [compared with usual day-to-day asthma symptoms] or a decline of  $\geq 30\%$  in PEF<sub>am</sub> for  $\geq 2$  consecutive days as judged by the investigator). Asthma worsenings include acute deteriorations not requiring SCS, in addition to those requiring SCS for  $\geq 3$  days. Tiotropium add-on therapy was shown to increase the median time to first asthma worsening event by 134 days, corresponding to a reduction in risk of 31% (HR 0.69; 95% CI 0.58–0.82; P<0.0001) compared with placebo [6].

Here, we build on these results to explore whether the effects of tiotropium Respimat® add-on therapy on episodes of asthma worsening in the PrimoTinA-asthma® trials demonstrated any seasonality. The PrimoTinA-asthma trials were selected for this post hoc analysis as patients were recruited and commenced the 48-week treatment period across all months of the year. Episodes of asthma worsening were analysed as they were reported more frequently, capturing the full effect of tiotropium and reducing the likelihood of chance findings in rarer exacerbation events.

This was a *post hoc* analysis of pooled data (full analysis set N=907) from the two PrimoTinA-asthma® trials, details of which have been reported previously [6]. The trials involved adults (aged 18–75 years) with symptomatic severe asthma despite at least daily high-dose ICS ( $\geq 800\mu\text{g}$  budesonide/equivalent) and LABA who were randomised to receive tiotropium 5µg or placebo via the Respimat®. The number of episodes of asthma worsening per month was analysed to determine any seasonality effect, with data from the Southern hemisphere shifted by 6 months (July=Month 1; January=Month 7) to align the seasonal time periods based on meteorological definitions [9].

The ratio of number of episodes of asthma worsening per patient was lower in patients receiving tiotropium versus placebo (rate ratio 0.76; 95% CI 0.63–0.91; P=0.0031). Moreover, when plotted by month, the number of episodes of asthma worsening in the placebo group showed a seasonal pattern, with peaks in autumn and winter months, and troughs in spring and summer months (Figure 1). Tiotropium add-on treatment was shown to reduce the number of episodes of asthma worsening compared with placebo across all seasons, particularly during the autumn peak (Figure 1). The seasonal pattern of episodes of asthma worsening in adults was similar to those reported in previous studies, with peaks in the autumn and winter months [10–12]. It has been suggested that seasonal patterns of asthma exacerbations and worsenings have an age-related difference in response to cyclic triggers [3], with adults more likely to experience peaks in autumn and winter months, and children more likely to experience exacerbations or worsenings in spring and autumn months [11, 12].

Casale *et al.* have previously reported that patients in the PrimoTinA-asthma trials were balanced between treatment groups at baseline in regard to potential allergic asthma (defined as serum

immunoglobulin E [IgE] levels >430 mg/L, blood eosinophils >0.6 x 10<sup>9</sup>/L and clinician judgement of asthma) (tiotropium vs. placebo: serum IgE [>430 µg/L] 45.4 vs. 40.4%; blood eosinophils [>0.6 x 10<sup>9</sup>/L] 22.4 vs. 19.1%; clinician judgement of allergic asthma [yes] 60.5 vs. 62.1%; concomitant diagnosis of allergic rhinitis 22.6 vs. 20.0%). When categorical subgroup analyses were undertaken, it was demonstrated that tiotropium reduced the risk of both asthma exacerbations and worsening compared with placebo, independent of serum IgE levels, blood eosinophil counts and clinician judgement of allergic asthma [13].

The effect of tiotropium add-on to ICS and LABA on seasonal peaks is similar to that observed with other interventions, including ICS/LABA combinations and biologicals. Spahn *et al.* reported that dispensing of ICS/LABA during summer months was associated with a reduction in asthma-related emergency department visits or hospitalisations in the subsequent autumn compared with patients who did not receive ICS/LABA in patients aged 4–55 years with asthma [10]. Busse *et al.* reported that omalizumab almost eliminated spring and autumn exacerbation peaks in patients aged 6–20 years with persistent allergic asthma compared with placebo as add-on to ICS [14]. A study of benralizumab provided further evidence of the beneficial effects of biologicals on seasonal peaks, with the authors reporting that benralizumab as add-on treatment to ICS/LABA in patients aged 12–75 years with severe, uncontrolled, eosinophilic asthma reduced, but did not eliminate, seasonal exacerbation peaks compared with placebo [11]. Furthermore, results from five tiotropium trials in paediatric patients with asthma and persistent asthmatic symptoms also demonstrate the efficacy of tiotropium add-on therapy in reducing seasonal peaks in adverse events (AEs) related to asthma worsening and symptoms in children and adolescents (aged 1–17 years) [15]. AEs related to asthma worsening and symptoms were used as an alternative endpoint because paediatric trials are often not sufficiently powered to assess asthma exacerbations and worsening.

The strengths of this study include its duration, which was long enough to capture seasonal peaks, and the large population of patients with symptomatic severe asthma, details of which have been previously described [6]. Moreover, both trials were placebo-controlled and therefore provided the most valid comparison for assessing episodes of asthma worsening. However, one limitation of the study may include not capturing the cause of worsening within the trials. The narrow patient population (i.e. symptomatic severe asthma patients) may also be considered a limitation, but as this group is particularly prone to exacerbations and worsenings, it represents the optimal population to assess. Furthermore, despite proposals by groups including the Global Initiative for Asthma and the American Thoracic Society/European Respiratory Society, there is no common consensus definition for asthma exacerbations or worsenings. It is suggested that there are rarely two studies that utilise the same definition, making comparisons across multiple clinical trials and studies complex [16].

This assessment of the effects of tiotropium in PrimoTinA-asthma® broadens the evidence supporting the use of tiotropium as add-on therapy in patients with symptomatic asthma despite ICS/LABA therapy to reduce the risk of asthma exacerbations and worsening. This study enhances the literature showing that the peaks of episodes of asthma worsening follow a seasonal pattern. We have shown that tiotropium add-on treatment provides a year-round benefit to patients, which leads to reducing seasonal peaks of worsening.

## **Acknowledgements**

The authors take full responsibility for the scope, direction, content and editorial decisions relating to the manuscript, were involved at all stages of development and have approved the submitted manuscript. Medical writing assistance, in the form of the preparation and revision of the draft manuscript, was supported financially by Boehringer Ingelheim and provided by Rosie Robson of MediTech Media, under the authors' conceptual direction and based on feedback from the authors.

## References

1. Peters SP, Ferguson G, Deniz Y, Reisner C. Uncontrolled asthma: a review of the prevalence, disease burden and options for treatment. *Respir Med* 2006; 100: 1139-1151.
2. Global Initiative for Asthma. GINA report: global strategy for asthma management and prevention. <http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/>. 2018. Date last accessed: October 22 2018.
3. Johnston NW, Sears MR. Asthma exacerbations. 1: epidemiology. *Thorax* 2006; 61: 722-728.
4. Staton TL, Arron JR, Olsson J, Holweg CTJ, Matthews JG, Choy DF. Seasonal variability of severe asthma exacerbations and clinical benefit from lebrikizumab. *J Allergy Clin Immunol* 2017; 139: 1682-1684.e3.
5. Bahadori K, Doyle-Waters MM, Marra C, Lynd L, Alasaly K, Swiston J, FitzGerald JM. Economic burden of asthma: a systematic review. *BMC Pulm Med* 2009; 9: 24.
6. Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, Sigmund R, Seibold W, Moroni-Zentgraf P, Bateman ED. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med* 2012; 367: 1198-1207.
7. Kerstjens HA, Casale TB, Bleecker ER, Meltzer EO, Pizzichini E, Schmidt O, Engel M, Bour L, Verkleij CB, Moroni-Zentgraf P, Bateman ED. 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: 367-376.

8. Paggiaro P, Halpin DM, Buhl R, Engel M, Zubek VB, Blahova Z, Moroni-Zentgraf P, Pizzichini E. 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: 104-113.e2.
9. Trenberth KE. What are the seasons? *Bull Amer Meteor Soc* 1983; 64: 1276-1282.
10. Spahn J, Sheth K, Yeh WS, Stempel DA, Stanford RH. Dispensing of fluticasone propionate/salmeterol combination in the summer and asthma-related outcomes in the fall. *J Allergy Clin Immunol* 2009; 124: 1197-1203.
11. DuBuske L, Newbold P, Wu Y, Trudo F. Seasonal variability of exacerbations of severe, uncontrolled eosinophilic asthma and clinical benefits of benralizumab. *Allergy Asthma Proc* 2018; 39: 345-349.
12. Sears MR. Epidemiology of asthma exacerbations. *J Allergy Clin Immunol* 2008; 122: 662-668.
13. Casale TB, Tashkin DP, Luhmann R, Engel M, Moroni-Zentgraf P, Kerstjens HA. Tiotropium Respimat<sup>®</sup> add-on to at least ICS therapy demonstrates reduced risk of severe asthma exacerbation and asthma worsening in symptomatic asthma, independent of IgE or blood eosinophil levels. *J Allergy Clin Immunol* 2016; 137: AB214.
14. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, Gruchalla RS, Kattan M, Teach SJ, Pongracic JA, Chmiel JF, Steinbach SF, Calatroni A, Togias A, Thompson KM, Szeffler SJ, Sorkness CA. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011; 364: 1005-1015.
15. Vogelberg C, Szeffler SJ, Vrijlandt EJLE, Boner AL, Engel M, El Azzi G, Dan Vulcu S, Moroni-Zentgraf PM, Eickmeier O, Hamelmann EH. Tiotropium add-on therapy is safe and reduces seasonal worsenings in paediatric asthma patients. *Eur Respir J* [submitted].

16. Fuhlbrigge A, Peden D, Apter AJ, Boushey HA, Camargo CA, Jr, Gern J, Heymann PW, Martinez FD, Mauger D, Teague WG, Blaisdell C. Asthma outcomes: exacerbations. *J Allergy Clin Immunol* 2012; 129: S34-S48.



***Figure 1. Number of episodes of asthma worsening by season***

Patients were recruited and commenced the 48-week treatment period across all months of the year.

