Efficacy of tiotropium in adults with moderate asthma, by leukotriene receptor antagonist use at baseline
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Dear Editor,

In Japan and the United States, leukotriene receptor antagonists (LTRAs) are commonly prescribed for controlling asthma.1,2 The Japanese guidelines for adult asthma recommend LTRAs for adult patients with persistent asthma as an add-on controller option to ICs or a combination of ICs and LABAs.3 Moreover, the co-administration of ICs and LTRAs creates an additional bronchodilating effect in asthma patients.4

Tiotropium, a long-acting muscarinic antagonist (LAMA), has been newly included in the 2016 Global Initiative for Asthma (GINA) guidelines as a bronchodilator treatment for asthma.5 In phase 3 trials replicating the MezzoTinA trial, tiotropium had similar efficacy and tolerability to salmeterol when given as add-on treatment to medium-dose ICS, with or without LTRAs, in adults with persistent asthma.6 Around 9% of patients in the MezzoTinA trials were symptomatic at baseline despite treatment with both ICs and LTRAs. Here, we examine whether LTRA use at baseline impacts the efficacy of tiotropium as add-on treatment to medium-dose ICS in a post hoc analysis of data from the MezzoTinA trials.

Detailed methods have been reported previously.6 Briefly, eligible patients were between 18 and 75 years of age, with symptomatic asthma (mean Asthma Control Questionnaire [ACQ-7] score of ≥1.5), a pre-bronchodilator FEV1 60–90% of predicted normal, were under treatment with medium-dose ICS (400–800 µg budesonide or equivalent) and had never smoked or had a smoking history of <10 pack-years, with no smoking 1 year before enrolment. Patients with COPD or who used concomitant LAMAs or LABAs within 4 weeks prior to randomisation were excluded. Patients could continue use of LTRAs if taking them within 3 months before screening.

Table 1
Demographics and baseline patient characteristics.

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<tr>
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<th>No (n = 1917)</th>
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<th>Yes (n = 183)</th>
<th></th>
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<tr>
<td><strong>ICS maintenance dose, 5 µg QD (n = 472)</strong></td>
<td></td>
<td></td>
<td><strong>ICS maintenance dose, 5 µg QD (n = 45)</strong></td>
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<tr>
<td>Age, years</td>
<td>444 ± 12.8</td>
<td>275 (58.3)</td>
<td>36 ± 11.0</td>
<td>25 (55.6)</td>
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<td>Female, n (%)</td>
<td>432 ± 12.7</td>
<td>280 (59.4)</td>
<td>44.9 ± 14.1</td>
<td>36 (75.0)</td>
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<tr>
<td>Smoker, n (%)</td>
<td>279 (56.5)</td>
<td>283 (59.0)</td>
<td>30.3 ± 14.4</td>
<td>33 (70.2)</td>
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<td>Race, n (%)</td>
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<td></td>
<td><strong>Race, n (%)</strong></td>
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<tr>
<td>American/Indian/Akaka Native</td>
<td>27 (5.7)</td>
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<td>3 (6.7)</td>
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<td>Asian</td>
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<td>1 (2.1)</td>
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<tr>
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<td>28 (5.8)</td>
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<td>Hawaiian/Pacific Islander</td>
<td>19 (4.0)</td>
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<td>20 (44.4)</td>
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<td>White</td>
<td>232 (49.3)</td>
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<td>21 (43.8)</td>
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<td>Body mass index, kg/m²</td>
<td>26.6 ± 6.2</td>
<td>26.6 ± 6.2</td>
<td>26.7 ± 5.6</td>
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<td>Smoking status, n (%)</td>
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<tr>
<td>Ex-smoker</td>
<td>71 (15.1)</td>
<td>77 (15.6)</td>
<td>66 (13.8)</td>
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<td>Never smoked</td>
<td>385 (81.6)</td>
<td>417 (84.4)</td>
<td>414 (86.3)</td>
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<tr>
<td>Smoking history, pack-years</td>
<td>400 ± 84.9</td>
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<td>Duration of asthma, years</td>
<td>402 ± 89.4</td>
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<td>77 (71.1)</td>
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<tr>
<td>ICS maintenance dose, µg</td>
<td>654 ± 216.8</td>
<td>665.9 ± 216.5</td>
<td>672 ± 177.6</td>
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<tr>
<td>FEV1, mL at randomisation</td>
<td>2269 ± 654</td>
<td>2275 ± 666</td>
<td>2227 ± 670</td>
<td>2429 ± 678</td>
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<tr>
<td>FEV1, % predicted normal</td>
<td>75.7 ± 11.7</td>
<td>75.2 ± 11.4</td>
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<td>77.5 ± 11.0</td>
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<tr>
<td>ACQ-7 score</td>
<td>2.2 ± 0.5</td>
<td>2.2 ± 0.5</td>
<td>2.2 ± 0.5</td>
<td>2.2 ± 0.5</td>
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<tr>
<td>AQQ score</td>
<td>4.8 ± 1.0</td>
<td>4.8 ± 0.9</td>
<td>4.8 ± 0.9</td>
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</tr>
</tbody>
</table>

Treated set. All values are mean ± SD unless otherwise stated.

ACQ-7, Asthma Control Questionnaire; AQQ, Asthma Quality of Life Questionnaire; BID, twice daily; LTRA, leukotriene receptor antagonist; QD, once daily.

1 Placebo Regumata® once daily plus placebo hydrofluoralkane metered-dose inhaler twice daily.

1 Budesonide 400–800 µg or equivalent dose.

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After screening and a 4-week run-in period, patients were randomised (1:1:1:1) to self-administer once-daily tiotropium 5 μg via Respimat® inhaler; once-daily tiotropium 2.5 μg (same device); twice-daily salmeterol 50 μg via hydrofluoroalkane metered-dose inhaler (HFA-MDI); or placebo (double-dummy design). The study drug was administered as an add-on to maintenance treatment with ICS (400–800 μg budesonide or equivalent). Rescue treatment (salmeterol HFA-MDI) was permitted throughout the study. For acute asthma exacerbations, temporary ICS dose increases and temporary addition of systemic corticosteroids or theophylline preparations were allowed.

Spirometric lung function tests were conducted to determine peak and trough FEV₁ values at randomisation and throughout the treatment period. Peak FEV₁ response, measured within 3 h after dosing (FEV₁₀⁻³), and trough FEV₁ response, measured at the end of the dosing interval (24 h after previous dose and 10 min before next dose), at the end of the 24-week treatment period were stratified by baseline LTRA use (yes/no).

Patients participated from 233 sites in 14 countries (Latvia, Poland, Romania, Russia, Brazil, China, Colombia, Germany, Guatemala, India, Japan, Mexico, Peru, and the United States). Of 2100 randomised patients (Japanese, 240), 183 were using an LTRA at baseline (of these, tiotropium 5 μg was administered to 45 patients; tiotropium 2.5 μg, 48; salmeterol 50 μg, 47; placebo, 43). Overall, 1975 patients completed the study. Demographics and baseline patient characteristics were comparable regardless of LTRA use at baseline (Table 1). While only a slightly higher proportion of Japanese patients with asthma had comorbid allergic rhinitis compared to the overall population (81/240 [33.8%] vs. 608/2100 [29.0%], respectively), the proportion of Japanese patients taking LTRAs was 3-fold higher than the overall population (60/240 [25.0%] vs. 183/2100 [8.7%], respectively).

Peak FEV₁₀⁻³ and trough FEV₁ improvements were independent of LTRA use at baseline (interaction p values = 0.9057 and 0.9083, respectively) (Fig. 1). Compared with the placebo group, adjusted mean differences for peak FEV₁₀⁻³ increased

![Fig. 1. Differences in lung function at week 24 by LTRA use at baseline compared with placebo; (A) Peak FEV₁₀⁻³, (B) Trough FEV₁. Full analysis set adjusted for treatment, study, visit, baseline, treatment-by-visit and baseline-by-visit. The interaction term ‘treatment-by-subgroup’ and the term ‘subgroup’ were added to the linear model to evaluate the treatment effect across the subgroups. Common baseline mean ± SD = 2265 ± 653 mL. Subgroup baseline values: No — 2267 mL; Yes — 2244 mL. Number of patients receiving placebo overall, n = 492; LTRA use at baseline: No, n = 454; LTRA use at baseline: Yes, n = 38. *Placebo Respimat® once daily plus placebo HFA-MDI twice daily. FEV₁₀⁻³, FEV₁ measured within 3 h of dosing; LTRA, leukotriene receptor antagonist.](image-url)
significant in both patients taking an LTRA at baseline (p < 0.05) and in patients not taking an LTRA at baseline (p < 0.0001). Adjusted mean differences for trough FEV1 also increased; a significant (p < 0.0001) difference was observed among patients not taking an LTRA at baseline, and a similar, though not significant, difference was seen in patients taking an LTRA, probably due to lower patient numbers. It must be noted that <10% of the study population used LTRAs at baseline.

As the proportion of Japanese patients taking an LTRA was 3-fold higher than the overall population, we reported peak FEV1(t=0–3 h) and trough FEV1 in both populations. We did not observe any difference in the improvement of respiratory function regardless of whether patients were Japanese or non-Japanese (interaction p values; peak FEV1, p = 0.7352 and trough FEV1, p = 0.5234; Supplementary Table 1). In addition, the proportion of ACQ-7 responders was recorded in patients with and without LTRA use at baseline. There were more ACQ-7 responders in the tiotropium 5 µg (with LTRA, OR [95% CI], 2.48 [1.00, 6.18], p = 0.0834; without LTRA, 1.25 [0.96, 1.63], p = 0.0162) and 2.5 µg (with LTRA, 1.38 [0.59, 3.22], p = 0.5226; without LTRA, 1.32 [1.01, 1.72], p = 0.0456) groups and the salmeterol group (with LTRA, 1.68 [0.71, 3.97], p = 0.3262; without LTRA, 1.44 [1.11, 1.87], p = 0.0080) than in the placebo group, regardless of LTRA use at baseline. It must be noted that the OR of ACQ-7 responders between the active drug groups and the placebo group exceeded 1 regardless of LTRA use at baseline.

Different mechanisms of action between LTRAs and tiotropium may explain these observations. While LTRAs block leukotriene D4 which induces bronchoconstriction and inflammation associated with asthma,7 tiotropium binds to muscarinic M3 receptors, blocking the effects of acetylcholine on airway smooth muscle and providing 24-h bronchodilation as it slowly dissociates.8 Co-administration of LTRAs and ICS confers complementary effects on inflammatory markers9 and yields an augmented bronchodilator effect.10 In addition to blocking M3 muscarinic receptors on airway smooth muscle, tiotropium in combination with corticosteroids has synergistically modulated airway inflammation in an animal model of chronic asthma.10 These findings suggest that both LTRAs and tiotropium possess bronchodilator effects that are distinct and might be additive.

In conclusion, once-daily tiotropium added to ICS improves lung function in patients with moderate symptomatic asthma, independent of LTRA use at baseline. Future clinical studies with larger populations evaluating impact of LTRAs on other markers should be considered.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jaill.2017.12.002.

Conflict of interest

SH received honoraria from Boehringer Ingelheim, TBC received research grants from Boehringer Ingelheim. HANK received research grants from Boehringer Ingelheim and Novartis; fees for patient recruitment in clinical trials from several pharma companies; and served on the advisory boards for Boehringer Ingelheim, AstraZeneca, Chiesi, GlaxoSmithKline, and Novartis. ME, PMZ, and LJB are employees of Boehringer Ingelheim.

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References