Add-on tiotropium versus step-up inhaled corticosteroid plus long-acting beta-2–agonist in real-world patients with asthma

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ABSTRACT

Background: *A step-up approach (increasing inhaled corticosteroid [ICS] dose and/or add-on treatment) is recommended for asthma that is uncontrolled despite ICS plus long-acting beta-2–agonist (LABA) combination treatment. Understanding the impact of different treatment options on health outcomes can help guide treatment decision-making.*

Objective: *To compare the effectiveness of add-on tiotropium 1.25 μg (two puffs once daily) versus an increased ICS plus LABA dose in a real-world cohort of patients with asthma initiated on ICS plus LABA.*

Methods: *De-identified data from patients ages ≥12 years and with asthma who were initiated on ICS plus LABA, and then had tiotropium added (Tio group; index date) or an ICS plus LABA dose increased (inc-ICS group; index date) were collected from two medical and pharmacy claims data bases (2014–2018). To account for population/group differences, propensity score matching was performed. The primary end point was the exacerbation risk after the index date. Secondary end points included exacerbation rates 6 and 12 months postindex, health-care resource utilization, costs, and short-acting beta-2–agonist (SABA) refills 12 months postindex.*

Results: *Overall, 7857 patients (Tio group, 2619; inc-ICS group, 5238) were included. The exacerbation risk was 35% lower in the Tio group than in the inc-ICS group (hazard ratio 0.65 [95% confidence interval, 0.43–0.99]; $p = 0.044$). Exacerbation rates in the Tio group also were significantly lower within 6 and 12 months postindex (64% and 73%, respectively). All-cause and asthma-related emergency department (ED) visits were 47% and 74% lower, respectively ($p < 0.0001$ for both), and all-cause and asthma-related hospitalizations were 48% ($p < 0.01$) and 76% ($p < 0.001$) lower, respectively, in the Tio group. Also, significantly fewer patients in the Tio group versus the inc-ICS group required SABA refills (56% versus 67%, $p < 0.0001$).*

Conclusion: *Add-on tiotropium significantly decreased the risk and rate of exacerbations, decreased all-cause and asthma-related ED visits and hospitalizations, and reduced SABA refills compared with increasing the ICS plus LABA dose. The findings supported the use of add-on tiotropium for patients with uncontrolled asthma taking ICS plus LABA.*

(Allergy Asthma Proc 41:1–8, 2020; doi: 10.2500/aap.2020.41.200036)

Asthma is a heterogeneous condition that is usually characterized by chronic airway inflammation.[1] In 2017, >25 million Americans had asthma, >11 million people reported having one or more exacerbations in the past year, and ~1.7 million emergency department (ED) visits were documented.[2] According to the Global Initiative for Asthma (GINA) strategy,[1] a control-based asthma management cycle that involves a stepwise pharmacologic approach should be followed to achieve good symptom control and to minimize future risk (of

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B. Chipps reports personal fees from AstraZeneca, Boehringer Ingelheim, Circassia, Genentech, Novartis, Regeneron, and Sanofi, outside the submitted work. G. Mosnaim reports having received research grants from AstraZeneca and GlaxoSmithKline, and a current research grant from Propeller Health; owned stock in Electrocore; and served as a consultant and/or member of a scientific advisory board for GlaxoSmithKline, Sanofi-Regeneron, Teva, Novartis, AstraZeneca, Boehringer Ingelheim and Propeller Health. S. Mathur reports personal fees from Boehringer Ingelheim, during the conduct of the study and personal fees from AstraZeneca outside the submitted work. A. Shaikh, S. Khoury, G. Gopalan, and S.R. Palli are employees of Boehringer Ingelheim Pharmaceuticals, Inc. L. Lamerato is an employee of Henry Ford Health System, with research funding from eMAX Health. J. Casciano is a major shareholder of eMAX Health, which reports fees from AstraZeneca, Boehringer Ingelheim, Regeneron, Sanofi, and Teva, outside the submitted work. R. Settipane reports personal fees from Boehringer Ingelheim during the conduct of the study; grants and personal fees from AstraZeneca, Genentech, Regeneron, Sanofi, and Teva; and grants from Chiesi and GlaxoSmithKline, outside the submitted work. Z. Dotiwala has no conflicts of interest to declare pertaining to this article.

This work was supported by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI). BIPI provided funding and was involved in the analysis and interpretation of data, in the writing of the report, and in the decision to submit the article for publication.

Supplemental data available at www.IngentaConnect.com

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exacerbations and medication adverse effects). For patients who remain uncontrolled while on low-dose inhaled corticosteroid (ICS) plus long-acting beta-2–agonist (LABA) combination treatment, other controller options outlined in the GINA treatment strategy[1] include medium-dose ICS or low-dose ICS plus leukotriene receptor antagonist (GINA step 3[1]). For patients uncontrolled on medium- or high-dose ICS plus LABA, one of the treatment options includes tiotropium, a long-acting muscarinic antagonist (GINA steps 4 and 5).[1] Despite recommendations and effective treatments, many patients with asthma remain uncontrolled. According to a web-based survey from the United States (U.S.) of patients with asthma diagnoses for ≥1 year and on multiple controller medications, 55% had uncontrolled asthma.[3] Comparable results were also observed in the European National Health and Wellness Survey.[4]

Uncontrolled asthma is an important risk factor for exacerbations[1,5] and may lead to oral corticosteroid use, ED visits, and/or hospitalizations.[6] Further, 20-year (2019 to 2038) direct and indirect costs associated with uncontrolled asthma are projected to be $963.5 billion (in 2018 dollars), with adults and adolescents losing ~15.5 million quality-adjusted life years.[7] When considering this substantial socioeconomic burden,[7] achieving and maintaining asthma control represent important treatment goals.[1] Tiotropium (Spiriva Respimat (Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, Connecticut, U.S.), 1.25 μg [two puffs once daily]), a long-acting muscarinic antagonist delivered *via* the Respimat soft-mist inhaler, is approved in the U.S. for long-term, once-daily maintenance treatment of asthma in patients ≥6 years of age.[8]

Add-on tiotropium improves lung function and reduces exacerbations and asthma worsening.[9–11] The efficacy and safety of add-on tiotropium have been demonstrated across age groups (children, adolescents, and adults) and asthma severities (mild, moderate, and severe).[9–17] To better understand the impact of different treatment options on health outcomes and, ultimately, to help guide treatment decisions, we compared the effectiveness of add-on tiotropium versus an increased ICS plus LABA dose in a real-world cohort of U.S. patients with asthma who were newly initiated on ICS plus LABA.

METHODS

Data Sources

De-identified data for patients with asthma were collected from the IMS LifeLink PharMetrics Plus (IQVIA, Durham, North Carolina, U.S.) and the EMRClaims+ (eMAX Health Systems, New York, U.S.) data bases between January 2014 and December 2018. IMS LifeLink PharMetrics Plus is one of the largest U.S. health plan claims data bases. In addition to covering 90% of the U.S. hospitals, this data base contains administrative insurance data of medical and pharmacy claims, and enrollment information derived from ~150 million commercially insured and Medicare lives.[18] The EMRClaims+ data base includes medical and pharmacy claims of >2 million lives and contains >20 million electronic records from nine states in the U.S.[19]

Study Design

In this retrospective cohort study, all the patients with asthma were required to have received ICS plus LABA therapy, and the ICS plus LABA initiation date was defined as the date of the first ICS plus LABA prescription (Fig. 1). This cohort was followed up to identify two arms of the study. One group received tiotropium Respimat 1.25 μg (two puffs once daily) (Tio group), and the other group had their ICS plus LABA dose increased (inc-ICS group). The index dates were defined as the date on which add-on tiotropium Respimat (1.25 μg, two puffs once daily) was prescribed or the date on which the ICS plus LABA dose was escalated (baseline low- to medium-/high-dose ICS plus LABA, baseline medium- to high-dose ICS plus LABA, or an additional prescription or refill of high-dose ICS plus LABA after the first prescription of baseline high-dose ICS plus LABA [evidenced by ≥90 days of prescription use]). Because further dose escalation in the group of patients on high-dose ICS plus LABA was not possible, they were compared with patients who had tiotropium added to a high dose of ICS plus LABA. The time between the ICS plus LABA initiation date and the index dates was defined as the preindex period, and the follow-up period was a minimum of 1 month postindex. The follow-up time was weighted based on the number of months available for each patient, which eliminated the effect of any aggregate differences in the follow-up time.

Because de-identified retrospective claims data were used for analyses, the study was considered as "not human subjects research" according to the National Institutes of Health guidance,[20] and the analysis was exempted by our institutional review board. However, institutional review board approval was obtained for the EMRClaims+ source by the Henry Ford Health System. Author contributions were the following. B. Chipps, G. Mosnaim, S.K. Mathur, L. Lamerato, and R. Settipane contributed to the study design and the implementation, data analysis and interpretation, and were involved in the preparation of the manuscript. A. Shaikh, S. Khoury, G. Gopalan, and S.R. Palli are employees of Boehringer Ingelheim Pharmaceuticals, Inc., and contributed to study concept, design, implementation and management, data analysis and interpretation, and preparation of the manuscript. J. Casciano

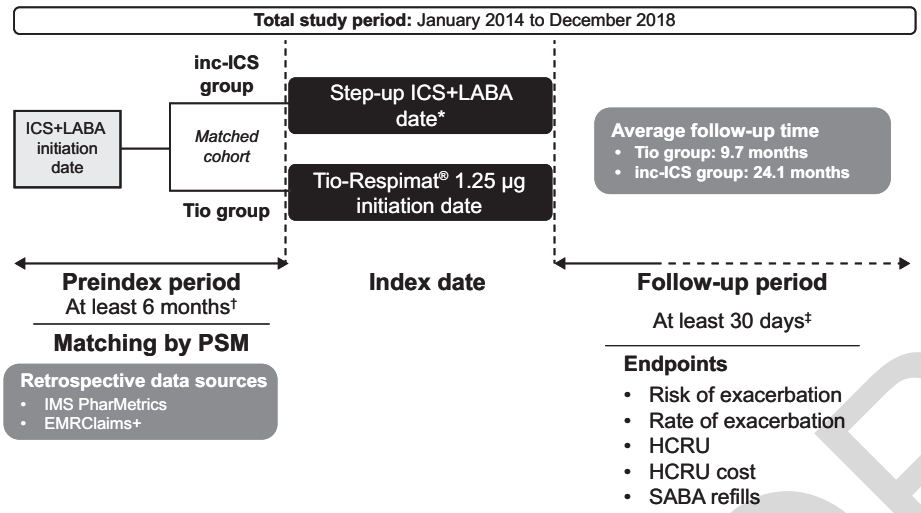

Figure 1. *Study design *"Step-up" from low-dose ICS+LABA to medium-/high-dose ICS+LABA or from medium-dose ICS+LABA to high-dose ICS+LABA or an additional prescription/refill of high-dose ICS+LABA after the first prescription of high-dose ICS+LABA (evidenced by ≥90 days of prescription utilization) within the study period; †Patients could not have used tiotropium during the preindex period or biologics for 12 months before the index date; ‡Could be as long as until the last day of enrollment, treatment, or data extraction. HCRU = Health-care resource utilization; ICS = inhaled corticosteroid; inc-ICS = increased dose of ICS; LABA = long-acting beta-2–agonist; PSM = propensity score matching; SABA = short-acting beta-2–agonist; Tio = tiotropium.*

and Z. Dotiwala are employees of eMAX Health and contributed to the overall design of the study, study management, data analysis and interpretation, and manuscript development. All the authors were involved in the writing of the manuscript and the decision to submit the manuscript for publication.

Study Population

Patients ages ≥12 years with an asthma diagnosis who were initiated on ICS plus LABA and then started on the add-on tiotropium Respimat 1.25 µg (two puffs once daily) (Tio group) or had their ICS plus LABA dose increased (inc-ICS group) were included. Patients were required to have continuous enrollment for 6 months before (baseline period) and ≥1 month after (follow-up period) the index date, with no limit on the maximum allowed follow-up. Data from the patients in the inc-ICS group were excluded if they used add-on tiotropium during the study period.

Patients with a diagnosis of chronic obstructive pulmonary disease at any time during the study period, patients who received tiotropium Respimat during the preindex period or one or more biologics for asthma management 12 months before the index dates, and patients who were unmatched after propensity score matching (PSM) were excluded. By matching the patients in the case and control groups, PSM was used to estimate the average effect of treatment and reduce bias due to confounding variables, such as population and group differences.[21] Each patient in the case (Tio) group was matched to two similar patients in the control (inc-ICS) group to create a balanced dataset for the comparison of the groups (Supplemental Table 1).

Data Collection

Patients' sex and age were recorded on the ICS plus LABA initiation date. Comorbidities included in the Charlson Comorbidity Index (CCI) were identified, and a composite CCI score was calculated. Other specific comorbidities identified were hypertension, gastroesophageal reflux disease, anxiety and depression, and endocrine and metabolic disorders. Polypharmacy was calculated as the total number of drug claims identified at baseline. To better qualify the patients before PSM, a binary measure was used to classify baseline asthma control status as either "well controlled" (if patients had no prescriptions for an oral corticosteroid and no asthma-related ED visits or hospitalizations other than the first diagnosis) or "poorly controlled" (if any of the events occurred).

End Points

The primary end point was the risk of exacerbation (ED visit or hospitalization with a primary diagnosis of asthma or an asthma exacerbation diagnosis) after the index date. Secondary end points included the rates of exacerbation within 6 and 12 months postindex, health-care resource utilization (frequency of all-cause and asthma-related ED visits, hospitalizations, and outpatient visits during follow-up, and associated medical and pharmacy costs), and short-acting beta-2–agonist (SABA) refills (proportion of users and the number of medications among users) within 12 months postindex.

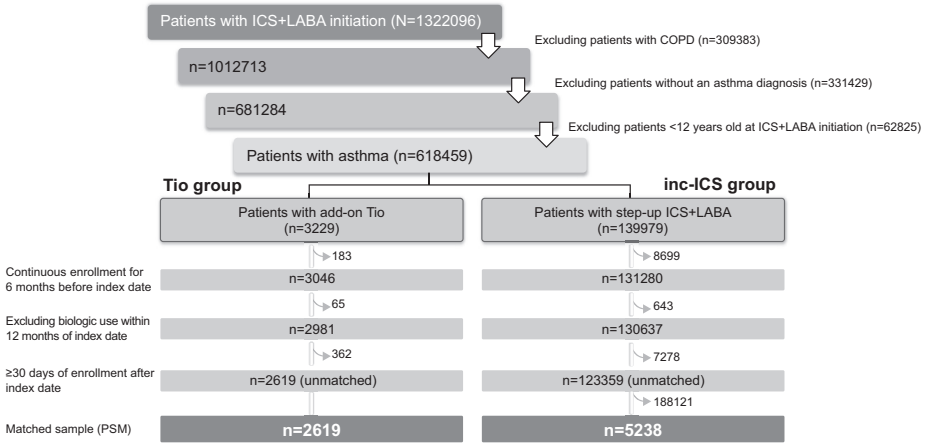

Figure 2. *Patient disposition. COPD = Chronic obstructive pulmonary disease; inc-ICS = increased dose of inhaled corticosteroid; LABA = long-acting beta-2–agonist; PSM = propensity score matching; Tio = tiotropium.*

Data Analysis

To ensure that the study was sufficiently powered, 6300 evaluable patients were required to show significance based on the effect size for the primary end point. More than 7800 patients were included in these analyses; therefore, the power was estimated to be >80%. The primary end point (exacerbation risk) was analyzed by using the Cox proportional hazards model, which considers both the occurrence and time to occurrence of the first event. For the secondary end points, exacerbation rates (per 100 patient-years) within 6 and 12 months postindex were determined; rates (per 100 patient-years) of all-cause and asthma-related ED visits, hospitalizations, and outpatient visits postindex were calculated to determine health-care resource utilization within 12 months postindex; and the proportion of patients with SABA refills and the mean ± standard deviation number of SABA medications refilled within 12 months postindex were determined.

RESULTS

Study Population and PSM Distribution

In total, 1,322,096 patients who initiated treatment with ICS plus LABA during the preindex period were screened (Fig. 2). Of these, 7857 patients were included in the analyses, with 2619 patients in the Tio group and 5238 patients in the inc-ICS group. Significant differences in each baseline parameter were observed before PSM. However, PSM eliminated confounding parameters and balanced all covariates, except for age distribution and CCI score, which were significantly higher in the Tio group ($p < 0.05$) (Supplemental Table 2). The follow-up time was shorter for the Tio group than for the inc-ICS group (9.7 versus 24.1 months, respectively) (Fig. 1). Because the study included patients from 2014 through 2018 and tiotropium was approved for asthma management in the U.S. in September 2015, patients in the inc-ICS group who started before September 2015 had a longer available follow-up time.

Exacerbations

The risk of exacerbation was 35% lower in the Tio group versus the inc-ICS group (hazard ratio 0.65 [95% confidence interval, 0.43–0.99]; $p < 0.05$). Compared with the patients in the inc-ICS group, those in the Tio group had significantly lower exacerbation rates within 6 months (64% lower; 41.4 versus 116.1 cases per 100 person-years, $p < 0.0001$) and 12 months (73% lower; 15.7 versus 57.2 cases per 100 person-years; $p < 0.0001$) postindex (Fig. 3).

Health-Care Resource Utilization

Within 12 months postindex, all-cause and asthma-related ED visit rates were 47% and 74% lower ($p < 0.0001$ for both) in the Tio group than in the inc-ICS group, respectively. Similarly, all-cause and asthma-related hospitalization rates were 48% ($p < 0.01$) and 76% ($p < 0.001$) lower in the Tio group than in the inc-ICS group, respectively, within 12 months postindex. All-cause and asthma-related outpatient visits were not significantly different between the two groups (Fig. 4).

SABA Refills

The proportion of patients with SABA refills was significantly lower in the Tio group (56%) than in the inc-ICS group (67%) ($p < 0.0001$) (Fig. 5*a*). Further, among patients with SABA refills, those in the Tio group refilled significantly fewer SABA prescriptions versus those in the inc-ICS group (mean ± standard deviation, 3.0 ± 3.0 versus 3.6 ± 4.4; $p < 0.05$) (Fig. 5*b*).

DISCUSSION

The results of this study provided real-world evidence on treatment effectiveness, in the U.S., in patients with asthma uncontrolled on ICS plus LABA, and highlighted the impact of making appropriate

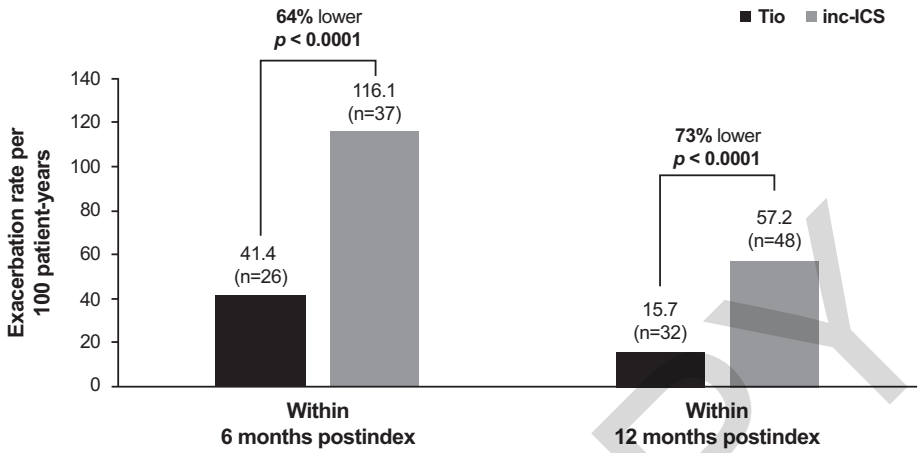

Figure 3. Rate of exacerbations (per 100 patient-years) within 6 and 12 months post-index. inc-ICS = Increased dose of inhaled corticosteroid; n = number of patients who had one or more exacerbations within the time frame; Tio = tiotropium.

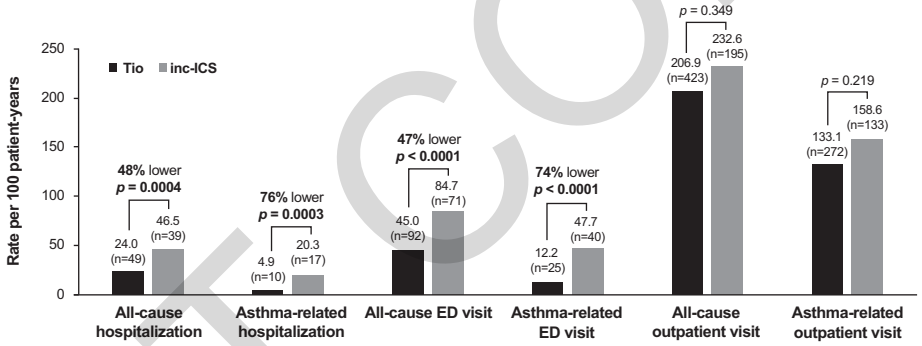

Figure 4. Rate of HCRU within 12 months postindex. ED = Emergency department; HCRU = health-care resource utilization; inc-ICS = increased dose of inhaled corticosteroid; n = number of patients who used the respective health-care resources; Tio = tiotropium.

treatment choices to optimize patient care. Specifically, these findings supported maximizing bronchodilation compared with increasing the dose of ICS plus LABA (at GINA step 4[1])—adding tiotropium Respimat 1.25 μg (two puffs once daily) to ICS plus LABA significantly impacted health outcomes (*i.e.*, reduced the risk and rate of exacerbations) in a real-world cohort of patients with uncontrolled asthma despite ICS plus LABA therapy. When considering that the 12-month exacerbation rate included the 6-month data, the results indicated that patients with uncontrolled asthma benefited as early as 6 months after initiating tiotropium add-on therapy. Reductions in the rates of exacerbation were accompanied by reductions in all-cause and asthma-related ED visits and hospital admissions as well as SABA refills. Analysis and interpretation of cost data are ongoing.

The results observed in this real-world study complement the evidence from the tiotropium development program in asthma, in which add-on tiotropium Respimat had beneficial effects on exacerbations and asthma worsening.[9,10] In real-world studies conducted in other countries, tiotropium add-on therapy also was effective in reducing asthma exacerbations and ED visits.[22,23]

Use of biologic therapy as a controller treatment option for managing asthma is expensive,[24] and is limited by the need for phenotype assessment (*e.g.*, for anti-immunoglobulin E, anti–interleukin (IL) 5, anti–IL-5 receptor, anti–IL-4/IL-13 receptor)[1] and the challenges associated with identifying predictors of response (*e.g.*, blood eosinophil counts ≥260 cells/μL, exhaled nitric oxide ≥20 ppb, childhood-onset asthma, and a clinical history that suggests allergen-driven symptoms as potential predictors of good asthma response to omalizumab),[25] a focus of current research.[26] In an exploratory subgroup analysis of four randomized controlled trials (RCTs), tiotropium added to ICS with or without LABA in patients with symptomatic asthma led to improvements in lung function, exacerbation risk, and symptom control, independent of the patients' T2 phenotype.[27]

Moreover, tiotropium added to ICS plus LABA was a cost-effective alternative to add-on omalizumab or continued standard therapy for uncontrolled allergic asthma in a U.S. cost-effectiveness analysis.[28] Real-world studies in several European countries also show that tiotropium added to the standard of care is cost effective.[29–33] Collectively, results of the present and other real-world studies suggest that treatment with

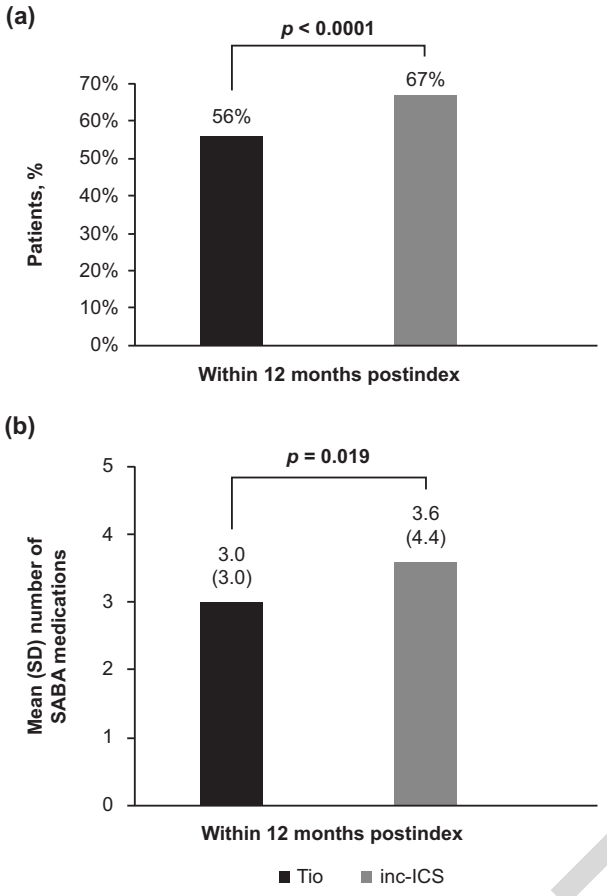

Figure 5. *(a) Proportion of patients with SABA refills within 12 months postindex (b) and mean ± SD number of SABA medications refilled within 12 months postindex. inc-ICS = Increased dose of inhaled corticosteroid; SABA = short-acting beta-2–agonist; SD = standard deviation; Tio = tiotropium.*

add-on tiotropium should be considered before prescribing biologics at GINA step 5.[1]

Finally and importantly, results of the present study and other real-world studies are also consistent with clinical trials that demonstrated the impact of add-on tiotropium on exacerbations and ED visits, and provided reassurance and much needed evidence that treatment with add-on tiotropium is effective not only in a highly selective cohort of patients typical of RCTs[9,10] but also in real-world settings.[22,23] Moreover, in a subgroup analysis of two replicate RCTs, asthma control was improved, and the risk of severe exacerbations was reduced in patients with asthma who remained symptomatic despite medium-dose ICS, largely independent of baseline characteristics.[34]

An important strength of this study included generation of clinically relevant findings by using a large, real-world cohort in the U.S. of patients with asthma by using two large health services and claims data bases (IMS LifeLink PharMetrics Plus and EMRClaims+). These patients are presumed nationally representative of patients with asthma. PSM was performed to precisely estimate the treatment effect and to eliminate bias by accounting for population and group differences. Although residual confounding (*e.g.,* significantly higher CCI scores in the Tio group after PSM) may slightly reduce internal validity, use of two large data bases provides a comprehensive geographic representation of patients in a real-world setting, which enabled high external validation and generalization of the results to a wider population across the U.S. Moreover, results of RCTs of tiotropium in adolescents (RubaTinA-asthma)[17] corroborate in adults (MezzoTinA-asthma)[10] with comparable asthma severity, which suggested that findings across the tiotropium development program are consistent in both adolescents and adults with asthma.

Limitations included those inherent to the design of a retrospective real-world study[35] and the lack of information about events and rate of events that did not result in a paid claim, actual SABA use, inhaler technique, medication adherence, and influence of comorbidities on uncontrolled symptoms. Time to biologic use could not be assessed in the study population because an insufficient sample size precluded reliable comparisons between the treatment groups. In addition, SABA refills were used as a surrogate of asthma control; however, this approach does not necessarily accurately reflect patient's symptoms, activity limitation, and actual SABA use.

Although minimizing SABA use represents an important goal for asthma management,[36] refilling more than one SABA inhaler within a 12-month time frame in a real-world setting may suggest inadequate control in both treatment groups.

Further, bias may have been introduced because of remnant confounding after PSM and the different follow-up durations between the two treatment groups. Whether factors besides the type of treatment (add-on tiotropium or increasing dose of ICS plus LABA) influenced the difference in follow-up duration was unknown.

CONCLUSION

Maximizing bronchodilation by adding tiotropium Respimat 1.25 μg (two puffs once daily) added to ICS plus LABA significantly reduced the risk and rate of exacerbations compared with increasing the ICS plus LABA dose in a real-world cohort in the U.S. of patients with asthma. These significant clinical improvements translated to fewer ED visits and hospitalizations. The findings of this real-world study supported the use of tiotropium Respimat as add-on therapy for patients with uncontrolled asthma who were taking ICS plus LABA at a low dose.

ACKNOWLEDGMENTS

Writing, editorial support, and formatting assistance was provided by Praveen Kaul, Ph.D., and Maribeth Bogush, Ph.D., Cactus Life Sciences (part of Cactus Communications), which was contracted and compensated by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) for these services. The authors meet the criteria for authorship as recommended by the International Committee of Medical Journal Editors. The authors received no direct compensation related to the development of the manuscript. BIPI was given the opportunity to review the manuscript for medical and scientific accuracy as well as for intellectual property considerations.

REFERENCES

1. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. 2020 [cited 2020 May 4]. Available from http://ginasthma.org/.
2. Centers for Disease Control and Prevention (CDC). Most recent national asthma data. 2019 [cited 2020 May 4]. Available from: https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm.
3. Peters SP, Jones CA, Haselkorn T, Mink DR, Valacer DJ, Weiss ST. Real-World Evaluation of Asthma Control and Treatment (REACT): findings from a national web-based survey. J Allergy Clin Immunol. 2007; 119:1454–1461.
4. Demoly P, Paggiaro P, Plaza V, Bolge SC, Kannan H, Sohier B, et al. Prevalence of asthma control among adults in France, Germany, Italy, Spain and the UK. Eur Respir Rev. 2009; 18:105–112.
5. Haselkorn T, Fish JE, Zeiger RS, Szefler SJ, Miller DP, Chipps BE, et al. Consistently very poorly controlled asthma, as defined by the impairment domain of the Expert Panel Report 3 guidelines, increases risk for future severe asthma exacerbations in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. J Allergy Clin Immunol. 2009; 124:895–902.e1-e4.
6. Fuhlbrigge A, Reed ML, Stempel DA, Ortega HO, Fanning K, Stanford RH. The status of asthma control in the U.S. adult population. Allergy Asthma Proc. 2009; 30:529–533.
7. Yaghoubi M, Adibi A, Safari A, FitzGerald JM, Sadatsafavi M. The projected economic and health burden of uncontrolled asthma in the United States. Am J Respir Crit Care Med. 2019; 200:1102–1112.
8. Spiriva Respimat (tiotropium bromide) inhalation spray, for oral inhalation. Prescribing information. 2019 [cited 2020 May 4]. Boehringer Ingelheim Pharmaceuticals, Inc. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021936s012lbl.pdf.
9. Szefler SJ, Murphy K, Harper T III, Boner A, Laki I, Engel M, 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.
10. Kerstjens HAM, Casale TB, Bleecker ER, Meltzer EO, Pizzichini E, Schmidt O, et al. 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.
11. Kerstjens HAM, Disse B, Schröder-Babo W, Bantje TA, Gahlemann M, Sigmund R, et al. Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. J Allergy Clin Immunol. 2011; 128:308–314.
12. Hamelmann E, Bernstein JA, Vandewalker M, Moroni-Zentgraf P, Verri D, Unseld A, et al. A randomised controlled trial of tiotropium in adolescents with severe symptomatic asthma. Eur Respir J. 2017; 49. pii: 1601100.
13. Paggiaro P, Halpin DM, Buhl R, Engel M, Zubek VB, Blahova Z, et al. 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.
14. Ohta K, Ichinose M, Tohda Y, Engel M, Moroni-Zentgraf P, Kunimitsu S, et al. Long-term once-daily tiotropium Respimat® is well tolerated and maintains efficacy over 52 weeks in patients with symptomatic asthma in Japan: a randomised, placebo-controlled study. PLoS One. 2015; 10: e0124109.
15. Vogelberg C, Engel M, Laki I, Bernstein JA, Schmidt O, El Azzi G, et al. Tiotropium add-on therapy improves lung function in children with symptomatic moderate asthma. J Allergy Clin Immunol Pract. 2018; 6:2160–2162.e9.
16. Vrijlandt EJLE, El Azzi G, Vandewalker M, Rupp N, Harper T, Graham L, 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 Respir Med. 2018; 6:127–137.
17. Hamelmann E, Bateman ED, Vogelberg C, Szefler SJ, Vandewalker M, Moroni-Zentgraf P, et al. Tiotropium add-on therapy in adolescents with moderate asthma: a 1-year randomized controlled trial. J Allergy Clin Immunol. 2016; 138:441–450.e8.
18. IMS LifeLink PharMetrics Plus [cited 2020 May 4]. Available from: https://tri.uams.edu/ims-lifelink/.
19. EMR-linked Claims and Advanced Analytics [cited 2020 May 4]. Available from: http://www.emaxhealth.net/downloads/eMAX_EMRClaimsPlus.pdf.
20. National Institutes of Health (NIH). Definition of Human Subjects Research [cited 2020 May 4]. Available from: https://grants.nih.gov/grants/policy/hs/private-information-biospecimens-flowchart.pdf.
21. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 2011; 46:399–424.
22. Abadoglu O, Berk S. Tiotropium may improve asthma symptoms and lung function in asthmatic patients with irreversible airway obstruction: the real-life data. Clin Respir J. 2016; 10:421–427.
23. Price D, Kaplan A, Jones R, Freeman D, Burden A, Gould S, et al. Long-acting muscarinic antagonist use in adults with asthma: real-life prescribing and outcomes of add-on therapy with tiotropium bromide. J Asthma Allergy. 2015; 8:1–13.
24. Bousquet J, Brusselle G, Buhl R, Busse WW, Cruz AA, Djukanovic R, et al. Care pathways for the selection of a biologic in severe asthma. Eur Respir J. 2017; 50. pii: 1701782.
25. Anderson WC III, Szefler SJ. Cost-effectiveness and comparative effectiveness of biologic therapy for asthma: to biologic or not to biologic? Ann Allergy Asthma Immunol. 2019; 122:367–372.
26. Darveaux J, Busse WW. Biologics in asthma–the next step toward personalized treatment. J Allergy Clin Immunol Pract. 2015; 3:152–160; quiz 161.
27. Casale TB, Bateman ED, Vandewalker M, Virchow JC, Schmidt H, Engel M, et al. Tiotropium Respimat add-on is efficacious in symptomatic asthma, independent of T2 phenotype. J Allergy Clin Immunol Pract. 2018; 6:923–935.e9.
28. Zafari Z, Sadatsafavi M, FitzGerald JM; Canadian Respiratory Research Network. Cost-effectiveness of tiotropium versus omalizumab for uncontrolled allergic asthma in US. Cost Eff Resour Alloc. 2018; 16:3.
29. Echave M, Ojanguren ME, Elías I, de Andrés-Nogales F, Oyagüez I, Casado MÁ, et al. Cost-effectiveness of tiotropium in the treatment of patients with asthma. Value Health. 2015; 18: PRS47.PA501–PA502.

30. Silva Miguel L, Manaças M, Pinheiro B. Economic evaluation of tiotropium for severe persistent asthma in Portugal. Value Health. 2015; 18: PRS52.PA502.
31. Pawlik M, Walczak J, Pieniazek I. Economic evaluation of tiotropium administrated through the Respimat inhaler as add-on therapy in patients with uncontrolled severe asthma in Poland. Value Health. 2015; 18:PRS51.PA502.
32. Willson J, Bateman ED, Pavord I, Lloyd A, Krivasi T, Esser D. Cost effectiveness of tiotropium in patients with asthma poorly controlled on inhaled glucocorticosteroids and long-acting β-agonists. Appl Health Econ Health Policy. 2014; 12:447–459.
33. Willson J, Bateman ED, Pavord I, Lloyd A, Krivasi T, Esser D, et al. Erratum to: cost effectiveness of tiotropium in patients with asthma poorly controlled on inhaled glucocorticosteroids and long-acting β-agonists. Appl Health Econ Health Policy. 2016; 14:119–125.
34. Casale TB, Aalbers R, Bleecker ER, Meltzer EO, Zaremba-Pechmann L, de la Hoz A, et al. Tiotropium Respimat® add-on therapy to inhaled corticosteroids in patients with symptomatic asthma improves clinical outcomes regardless of baseline characteristics. Respir Med. 2019; 158:97–109.
35. Blonde L, Khunti K, Harris SB, Meizinger C, Skolnik NS. Interpretation and impact of real-world clinical data for the practicing clinician. Adv Ther. 2018; 35:1763–1774.
36. Papaioannou AI, Kostikas K, Zervas E, Kolilekas L, Papiris S, Gaga M. Control of asthma in real life: still a valuable goal? Eur Respir Rev. 2015; 24:361–369. □