



Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto Respimat			
Name of active ingredient: Tiotropium + Olodaterol {R03AL06}			
Report date: 14 NOV 2023	Study number: 1237-0110	Version/Revision: 1.0	Version/Revision date: 14 NOV 2023
Title of study:	Effectiveness of Maintenance Treatment with Tiotropium + Olodaterol in Comparison to Inhaled Corticosteroids + Long-acting β2 agonists in COPD patients in Taiwan: a non-interventional study based on the Taiwan National Health Insurance (NHI) data.		
Keywords:	Chronic Obstructive Pulmonary Disease, tiotropium, olodaterol, effectiveness, health insurance claims		
Rationale and background:	<p>Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality throughout the world. Long-acting bronchodilator medications, which include long acting β2-agonists (LABAs) and the long-acting muscarinic antagonists (LAMAs) such as tiotropium, are major maintenance therapies in the management of COPD, with inhaled corticosteroids (ICSs) added for patients with increasing COPD severity. GOLD 2021 recommends initiation of ICS/LABA in patients with high blood eosinophils level and frequent exacerbation history. However, ICS containing therapy has been widely used inappropriately in real world practice.</p> <p>The role of ICS in COPD has been debated for decades and studies have been conducted to investigate the effect of ICS-containing therapy in patients with COPD. Results of the INSPIRE study indicated that ICS/LABA and tiotropium showed similar effects on the reduction of exacerbations, while the risk of pneumonia was higher in the ICS/LABA group. Results of the FLAME study showed that LAMA/LABA was superior to ICS/LABA in terms of exacerbation prevention, while recently published data focusing on fixed dose combination triple therapy showing reversed results.</p> <p>With more and more fixed dose combination medications, i.e. LAMA/LABA, ICS/LABA/LAMA, approved and prescribed in recent years, it is of clinical interest to evaluate the effectiveness and safety profiles of these therapies in real world settings.</p>		

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	The aim of this real-world study was to assess effectiveness and safety profiles between tiotropium/olodaterol (Tio/Olo) and ICS/LABA. The primary outcome of interest was time to first moderate or severe COPD exacerbations. Other outcomes included time to ICS/LABA/LAMA escalation, rate of escalation to triple therapy, pneumonia and rescue medication use.		
Research question and objectives:	<p>Primary objective:</p> <ul style="list-style-type: none"> To compare time to the first moderate or severe COPD exacerbations between initiators of Tiotropium / Olodaterol (Tio/Olo) and inhaled corticosteroids / long-acting β2-agonists (ICS/LABA) after initiation of the drugs between 1st January 2014 and 31st December 2019 <p>Secondary objectives:</p> <ul style="list-style-type: none"> To compare time to escalation to triple therapy between initiators of Tio/Olo and ICS/LABA; To compare the rate of escalation to triple therapy between initiators of Tio/Olo and ICS/LABA; To compare the time to first hospitalization for community-acquired pneumonia between initiators of Tio/Olo and ICS/LABA; To compare the number of prescriptions of rescue medications between initiators of Tio/Olo and ICS/LABA To compare the annualized rate of moderate or severe COPD exacerbation between initiators of Tio/Olo and ICS/LABA <p>The study period of between 1st January 2014 and 31st December 2019 was the same as that for the primary objective.</p>		
Study design:	This study was a non-interventional cohort study based on existing data (NISed).		
Setting:	Data used in this study came from the Taiwan National Health Insurance (NHI) claims data between 2014 and 2019.		

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<p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. At least one prescription for Tio/Olo combined inhaler or a ICS/LABA combined inhaler between 1st January 2014 and 31st December 2019. <ol style="list-style-type: none"> a) The first dispensing of either Tio/Olo or ICS/LABA combined inhaler was defined as the index date; b) For the main analyses, only patients who received fixed dose combination (FDC) inhalers were included. 2. Aged ≥ 40 years on the index date (in a sensitivity analysis we only included patients aged ≥ 55 years on the index date); 3. At least one diagnosis of COPD (ICD9: 491.x, 492.x, 496; ICD10: J41.x, J42, J43.x, J44.x) at any time prior to or on the index date; 4. At least one year of continuous medical and health insurance plan prior to the index date was required to allow for a look-back period to evaluate covariates and operationally define new use of study drugs; 5. At least one record in the health insurance claims database during the look-back period. <p>Exclusion criteria:</p> <ol style="list-style-type: none"> 1. Any use of LAMA/LABA, ICS/LABA, or ICS/LAMA/LABA in free or fixed form during the one year look-back period prior to the index date (free form combination was defined as prescriptions of the individual products within 30 days of each other); 2. Individuals with diagnosis codes for asthma, allergic rhinitis, lung cancer, interstitial lung disease, or lung transplant identified at any time prior to the index date (in a sensitivity analysis we included patients with diagnosis of asthma); 			

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Subjects and study size, including dropouts:	First use of Tio/Olo combination was in 2016. A total of 3,815 Tio/Olo users and 13,203 ICS/LABA users who initiated a drug of interest from 2016 through 2019 fulfilled the selection criteria. Through 1:1 propensity score matching, 3,752 Tio/Olo initiators were matched to 3,752 ICS/LABA initiators. The matched cohorts served as the basis for primary analysis.		
Variables and data sources:	<p>Exposures:</p> <p>Exposure of this study was defined as new initiation of Tio/Olo, or ICS/LABA during the study period.</p> <p>Outcomes:</p> <p>Primary outcome:</p> <ul style="list-style-type: none"> Time to the first moderate or severe COPD exacerbations <p>Secondary outcomes:</p> <ul style="list-style-type: none"> Time to triple therapy escalation Incidence rate of triple therapy initiation; Time to the first hospitalization for community-acquired pneumonia; Annualized rate of prescriptions of rescue medications (calculated as: annualized rate=number of prescriptions/total patient years at risk=number of prescriptions per patient year); Annualized rate of moderate or severe COPD exacerbation (calculated as: annualized rate=number of moderate or severe COPD exacerbations/total patient years at risk=number of exacerbations per patient year) <p>Covariates:</p> <p>Including sex, age, calendar year of cohort entry, season of index date (winter, spring, summer, fall)</p> <p>Additional characteristics were defined during the 1 year pre-index baseline period:</p>		

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		<p>specific previous COPD treatments, use of other respiratory drugs, previous acute COPD exacerbation, hospitalizations caused by exacerbation of COPD, all-cause hospitalizations, comorbidities, Charlson Comorbidity Index (CCI), history of medications dispensed.</p> <p>Data sources:</p> <p>Data sources included Taiwan National Health Insurance (NHI), Taiwan Cancer Registry (TCR) and Taiwan Mortality Data. Taiwan Department of Statistics, Ministry of Health and Welfare is the unit designated by the government to manage health and social welfare statistical databases, and to develop data platform for academic research. Through the services provided by the Health and Welfare Data Science Center of the Department of Statistics, researchers may access a wide range of health and welfare data, including health insurance claims, mortality (with cause of death) and Taiwan Cancer Registry. The Health and Welfare Data Science Center (HWDSC) staff encrypt the unique ID for all individuals according to a secure encryption algorithm that is not made known to the public. The encrypted ID is unique for all individuals and is used for linkage between databases.</p>	
Statistical Analysis	<p>Propensity score method was used to generate two study groups (Tio/Olo users and ICS/LABA users). Time-to-event analysis was used to estimate the hazard ratio for the primary outcome of interest between the two groups. Time-to-event analysis and negative binomial model were used to evaluate the secondary outcomes of interest between the two groups.</p> <p>In addition, four sensitivity analyses were carried out.</p>		
Results:	<p>A total of 17,018 individuals fulfilled the selection criteria, median age was 71 years (interquartile range was 61 years – 81 years) and 13,149 (77.3%) were men. For the 3,815 patients who were in the Tio/Olo group, median age was 72 years (interquartile range was 63 years – 82 years) and 3,364 (88.2%) were men. For the 13,203 patients who were in the ICS/LABA group, median age was 71 years (interquartile range was 61 years – 81 years) and 9,785 (74.1%) were men. The propensity score matching generated two comparable groups of patients</p>		

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		<p>with regards to demographic information and baseline covariates, with 3,752 patients in each group. Median age of the matched cohorts was 72 years (inter-quartile range, 63-82 years). About 30% of them were 80 or older, and 88% were men.</p> <p>For the primary outcome of interest, 424 patients in the Tio/Olo group and 375 patients in the ICS/LABA group had moderate or severe COPD exacerbation during follow up. Hazard ratio (95% confidence interval) for time to moderate or severe COPD exacerbation was 1.00 (0.87, 1.15) when comparing the Tio/Olo users and ICS/LABA users.</p> <p>For secondary outcomes of interest, 122 patients in the Tio/Olo group and 153 patients in the ICS/LABA group initiated ICS/LABA/LAMA triple therapy during follow up. Hazard ratios for time to initiation of ICS/LABA/LAMA triple therapy was 0.67 (0.53, 0.85) when comparing the Tio/Olo users and ICS/LABA users. Incidence rate ratio for the same comparison was 0.66 (0.51, 0.85).</p> <p>As for community-acquired pneumonia, there were 11 cases among the Tio/Olo group and 11 cases among the ICS/LABA group during follow-up. Comparing the Tio/Olo users and ICS/LABA users, hazard ratios of time to first hospitalization of community-acquired pneumonia was 0.84 (0.36, 1.93).</p> <p>736 patients among the Tio/Olo group and 695 patients used rescue medications during follow-up. Rate ratio for use of rescue medications during follow-up was 0.92 (0.81, 1.03) when the two groups were compared.</p> <p>Rate ratio for moderate or severe exacerbations (424 patients in the Tio/Olo group and 375 patients in the ICS/LABA group) was 1.01 (0.87, 1.18).</p>	

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		Results from the sensitivity analyses were broadly consistent with that from the main analysis.	
Discussion:	In this large population-based retrospective cohort study, use of Tio/Olo was not associated with reduction in risk of moderate or severe COPD exacerbations (as defined with health insurance claims) when the use of ICS/LABA was the comparator. A number of factors could contribute to the similar effectiveness in reducing COPD exacerbations associated with the use of Tio/Olo vs. ICS/LABA, including heterogeneity of the study population (for factors not available to be included in the propensity scores, such as spirometry results), timing of initiation of treatment, and relatively short follow-up time. On the other hand, using of Tio/Olo was associated with lower need for escalation to ICS/LABA/LAMA triple therapy (33% less likely) when compared with the use of ICS/LABA.		
Conclusions:	In this large population-based study of COPD treatment in Taiwan, use of Tio/Olo was not found to be associated with lower rate of COPD exacerbations when use of ICS/LABA was the comparator. Use of Tio/Olo was associated with approximately 30% lower need of escalation to ICS/LABA/LAMA triple therapy. No safety concerns were identified for Tio/Olo in this study.		
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