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Rates of escalation to triple COPD therapy among incident users of LAMA and LAMA/LABA

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ABSTRACT

Background: Improved outcomes have been reported for patients with chronic obstructive pulmonary disease (COPD) receiving combination long-acting muscarinic antagonist/long-acting β_2-agonist (LAMA/LABA) therapy compared with LAMA monotherapy. However, little is known about the relative characteristics of these patients and their rates of escalation to triple therapy (TT, combining a LAMA, LABA, and inhaled corticosteroid). This study aimed to characterize patients initiating treatment with the LAMA tiotropium (TIO) and the fixed-dose LAMA/LABA combination therapy umeclidinium/vilanterol (UMEC/VI), and to compare rates of escalation to TT between patients receiving these therapies.

Methods: Retrospective study of patients with COPD enrolled in a US health insurance plan during 2013–2015 and newly initiated on TIO or UMEC/VI. Patients were ≥40 years of age at index (date of therapy initiation) with continuous enrollment for 12 months pre-index and ≥30 days post-index. LAMA users were propensity score matched 1:1 to LAMA/LABA users, with TT initiation rates reported by cohort using pharmacy claims.

Results: 35,357 patients initiating on TIO and 2407 patients initiating on UMEC/VI were identified. After propensity score matching, the rate of TT initiation was significantly higher in new TIO users (n = 1320) than in new UMEC/VI users (n = 1320) (0.92 vs 0.49 per 100 months of exposure, respectively; $p < 0.001$). Relative to the UMEC/VI cohort, the TIO cohort had an 87% higher risk of TT initiation (hazard ratio: 1.87; 95% confidence interval: 1.4–2.5; p = 0.001).

Conclusions: Patients receiving UMEC/VI progressed to TT more slowly, and were at lower risk of progressing to TT, than patients receiving TIO.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease [1,2] that represents a leading cause of death worldwide [3] and contributes significantly to healthcare costs [4–7]. In addition, patients with COPD experience substantial quality of life limitations [8]. First-line maintenance therapy for many patients with COPD is treatment with a bronchodilator, most commonly a long-acting muscarinic antagonist (LAMA) or long-acting β_2-agonist (LABA) [9–11]. LAMAs and LABAs have been shown to improve lung function and health-related quality of life, and reduce exacerbations [12–18]; however, some patients may not achieve adequate symptom control on bronchodilator monotherapy [19]. For these patients, combined LAMA/LABA therapy has been proposed to improve lung function and symptom control [20]. For patients experiencing further exacerbations on dual bronchodilator therapy, outcomes may be improved with escalation to triple therapy (combining a LAMA, LABA, and inhaled corticosteroid [ICS]) [21–24]. However, available data on the optimal use of triple therapy and comparative outcomes for patients receiving dual or triple therapy are too limited for clear recommendations to be made [25–27].

Several fixed-dose combination (FDC) LAMA/LABA therapies have

Abbreviations: CDS, Chronic Disease Score; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ER, emergency room; FDC, fixed-dose combination; HR, hazard ratio; ICD-9-CM, International Classification of Disease; Ninth Revision, Clinical Modification; ICS, inhaled corticosteroid; IRR, incidence rate ratio; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MAPD, Medicare Advantage Part D; OLO, olodaterol; PDE-4, phosphodiesterase-4; PDP, Prescription Drug Plan; PSM, propensity score matching; SABA, short-acting β_2-agonist; SD, standard deviation; TIO, tiotropium; TT, triple therapy; UMEC, umeclidinium; VI, vilanterol

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recently been approved for maintenance treatment of COPD [28–31]. There has therefore been considerable interest in comparing outcomes for patients receiving LAMA/LABA FDCs with patients receiving monotherapies. Several clinical trials have reported greater improvements in lung function and patient-reported outcomes with LAMA/LABA FDCs compared with the component monotherapies, with no differences in safety profiles [32–35]. However, further research is required; in particular, limited data are available on the specific patient populations which would benefit the most from these therapies, and the potential benefits of initiating a LAMA/LABA FDC compared with LAMA monotherapy in treatment-naïve patients [36].

In order to understand which patient populations might derive the greatest benefit from these treatments, and to further assess the potential benefits of initiation on a LAMA/LABA FDC compared with a LAMA, it is important to understand real-world practice patterns and outcomes. In particular, one outcome of interest for which limited data are available is escalation to triple therapy. This study first aimed to characterize patients initiating treatment with the LAMA monotherapy tiotropium (TIO, the longest-established LAMA available in the USA [37]), and the LAMA/LABA combination therapy vilanterol (UMEC/VI, the only LAMA/LABA FDC available in the USA until May 2015 [29,30,38]). Subsequently, time to escalation to triple therapy was evaluated among the subset of patients newly initiating therapy with TIO or UMEC/VI. In view of the benefits previously reported in lung function and health-related quality of life when using a LAMA/LABA compared with LAMA monotherapy [32–35], our analysis specifically tested the hypothesis that patients initiating therapy on UMEC/VI escalate to triple therapy more slowly than those initiating on TIO.

2. Materials and methods

2.1. Study design

This was a retrospective cohort study (GSK study: HO-15-15257) of patients with COPD in the USA enrolled in commercial or Medicare (Medicare Advantage Prescription Drug [Part C; MAPD], or Prescription Drug Plan [Part D; PDP]) insurance plans, receiving treatment with UMEC/VI or TIO as monotherapy or in combination with olodaterol (OLO) (data from patients receiving TIO/OLO are not presented due to the small number of patients identified.) Medical and pharmacy data from May 1, 2013 through December 31, 2015 were obtained from the Optum Research Database, a large, geographically diverse US administrative claims database.

Eligible patients included: 1) those in the commercial and MAPD plans with both medical and pharmacy claims; and 2) those in PDP plans with pharmacy claims only. Only patients in the commercial and MAPD plans had International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes available from medical claims. Patients were therefore identified based on pharmacy claims for TIO or UMEC/VI prescriptions filled during the patient identification period, which began on May 1, 2014 and ended on August 31, 2015 for commercial/MAPD enrollees and November 30, 2015 for PDP enrollees.

The index date was defined as the first date during the identification period on which patients received a prescription fill for UMEC/VI or TIO. Patients were assigned to mutually exclusive study cohorts based on the index prescription fill (UMEC/VI or TIO), and patients with a claim for both UMEC/VI and TIO on the index date were excluded. Patients were required to be ≥ 40 years of age at index, with at least 12 months of pre-index continuous health plan enrollment. Patients were followed throughout the 12-month baseline period until the end of the follow-up period (minimum of 30 days' duration) defined as the earliest of: 1) initiation of triple therapy (LAMA + LABA + ICS); 2) disenrollment from the health plan; or 3) the end of the study period (September 30, 2015 for commercial/MAPD enrollees and December 31, 2015 for PDP enrollees).

To characterize patients initiating treatment, the study population was limited to patients with no prescriptions for the index therapy during the 12 months prior to index date (i.e., the baseline period). To evaluate time to triple therapy initiation, patients with ≥1 claim for any ICS, LABA, or LAMA during the baseline period or evidence of triple therapy on the index date were excluded. Patients were further required to have a minimum of 30 days' follow-up continuous enrollment to assess the time to triple therapy. For this analysis, patients in the UMEC/VI cohort were matched 1:1 to patients in the TIO cohort using propensity score matching (PSM) methodology.

2.2. Endpoints and assessments

Patient demographics were captured from enrollment records, and economic and clinical characteristics were assessed during the 12-month baseline period. Characteristics evaluated during the baseline period included: Charlson comorbidity index [39], the pharmacy claim-based Chronic Disease Score (CDS) [40,41], controller and rescue medication use, all-cause and COPD-related healthcare costs and resource utilization, and exacerbation history. Costs and utilization were defined as COPD-related by a diagnosis for COPD on a medical claim in any position, or by a pharmacy claim for a COPD-related medication (Supplementary Table 1). Exacerbations were defined as a COPD- or respiratory failure-related inpatient visit; or COPD/respiratory failure-related ER or ambulatory visit with oral corticosteroid or antibiotic use within ± 5 days (Supplementary Table 1).

To evaluate time to triple therapy initiation, an intention-to-treat approach was used to determine time at risk for triple therapy accrued until the end of the follow-up period as defined above. Patients could receive other therapies prior to initiation of triple therapy. The date of triple therapy initiation was identified as the first day with overlapping days' supply of an ICS, LABA, and LAMA. To account for variations in follow-up time, the incidence of triple therapy initiation is reported per 100 person-months at risk.

2.3. Statistical analyses

All variables, including patient characteristics, baseline measures, and outcomes, were analyzed descriptively. Numbers and percentages are provided for categorical variables, while means and standard deviations (SDs) are provided for continuous variables.

Results are stratified by treatment cohort, and appropriate statistical tests (e.g., *t*-test, chi-squared test) were used based on the distribution of the measure. The incidence rate of triple therapy initiation was calculated by cohort. Time to triple therapy initiation was estimated using Kaplan–Meier survival probabilities, with a time to event curve as output. A Cox proportional hazards analysis was performed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of time to triple therapy among patients in the TIO cohort relative to patients in the UMEC/VI cohort.

For the analysis of time to triple therapy, PSM was employed to appropriately match the patient groups on all observable variables. PSM was employed for the commercial/MAPD and PDP enrollees separately, then the results combined and analyzed. The commercial/MAPD model included variables defined based on both medical and pharmacy claims, and the PDP model included variables defined based on pharmacy claims alone. The final list of variables included in the PSM models were determined following review of the pre-match descriptive analysis of patient demographics and baseline characteristics. Both PSM models included age, gender, geographic region, number of short-acting β_2-agonist (SABA) fills, number of ipratropium fills, phosphodiesterase-4 (PDE-4) use, systemic corticosteroid use, pharmacy costs (in quartiles), and CDS. For patients with commercial or MAPD coverage, who had medical claims available, the following variables were also included: insurance type (commercial or MAPD), Charlson score, number of COPD exacerbations, and medical costs (in quartiles).