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ORIGINAL RESEARCH

Comparable Clinical Outcomes with Tiotropium/Olodaterol or Fluticasone Furoate/Umeclidinium/Vilanterol in Patients with COPD and Blood Eosinophil Count ≤300 Cells/μL

Sanjay Sethi[1], Brendan Clark[2], Erin K Buysman[3], Andrew Sargent[3], Lindsay GS Bengtson[3]

[1]Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, USA; [2]HEOR Value Demonstration, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; [3]Health Economics and Outcomes Research, Optum Life Sciences, Eden Prairie, MN, USA

Correspondence: Brendan Clark, HEOR Value Demonstration, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Ridgefield, CT, 06877, USA, Email brendan.clark@boehringer-ingelheim.com

Introduction: Assessment of blood eosinophil count (BEC) is recommended to guide the use of inhaled corticosteroids in chronic obstructive pulmonary disease (COPD), with BEC ≥300 cells/μL predictive of patients most likely to benefit.

Objective: To compare outcomes between patients initiating dual bronchodilator therapy with tiotropium/olodaterol (TIO/OLO) versus triple therapy with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) in patients with COPD and BEC ≤300 cells/μL.

Methods: A retrospective cohort study using claims data from the Optum Research Database. Patients with COPD initiated on TIO/OLO or FF/UMEC/VI between 01 June 2015 and 30 November 2019, with a baseline BEC were included. TIO/OLO initiators were 1:1 propensity score matched with FF/UMEC/VI initiators. Time to first exacerbation and pneumonia diagnosis were assessed using Kaplan-Meier analysis. COPD exacerbations and COPD and/or pneumonia-related healthcare resource utilization (HRU) and cost outcomes were presented as population annualized averages.

Results: The study population included 3867 individuals with a baseline BEC result. Among these, 3168 (81.9%) had BEC ≤300 cells/μL. After matching, 1098 matched pairs with BEC ≤300 cells/μL were retained. The follow-up annualized count of moderate/severe exacerbations was not significantly different between TIO/OLO and FF/UMEC/VI initiators (1.05 vs 0.99, p=0.535). Annualized counts of COPD and/or pneumonia-related HRU were not significantly different, except for emergency department visits, which were lower for TIO/OLO than FF/UMEC/VI (0.59 vs 0.83, p=0.018). Annualized COPD and/or pneumonia-related emergency department ($370 vs $538, p=0.034) and pharmacy costs ($4692 vs $6573, p<0.001) were lower for TIO/OLO versus FF/UMEC/VI initiators.

Conclusion: Eight in ten patients with COPD who initiated FF/UMEC/VI had BEC ≤300 cells/μL. TIO/OLO and FF/UMEC/VI users with BEC ≤300 cells/μL experienced similar rates of COPD exacerbations. TIO/OLO initiators incurred lower pharmacy costs related to COPD and/or pneumonia than FF/UMEC/VI initiators. These results support treatment recommendations of reserving inhaled corticosteroids for frequent exacerbators and patients with elevated eosinophil counts.

Plain Language Summary: Chronic obstructive pulmonary disease (COPD) is a condition caused by lung damage that makes breathing difficult. Patients with COPD have several inhaler options for treating their symptoms and preventing COPD flareups. Some inhalers include steroids, which can help reduce lung inflammation. However, inhaled steroids can also cause side effects such as pneumonia.

To choose the best inhaler for COPD patients, a blood draw can be used to check the levels of eosinophils, a type of white blood cell. Patients with high blood eosinophil count are most likely to benefit from inhaled steroids. However, most patients with COPD do not have high eosinophil levels.

This study included patients without high eosinophil levels and compared COPD flare-ups and pneumonia outcomes in patients who used an inhaler with two (no steroid) or three medications (including a steroid). It also examined how often these patients needed to be treated for COPD or pneumonia and how expensive it was.

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The study found that for patients without high eosinophil levels, the number of COPD flare-ups and pneumonia events was similar for those who received an inhaler containing a steroid and those who did not. It was also found that medication costs related to COPD treatment were lower in patients using an inhaler without steroids. These findings indicate that COPD patients without high eosinophil counts are less likely to benefit from inhaled steroids and may help encourage healthcare providers to check eosinophil levels when selecting inhaled medications for patients with COPD.

Keywords: dual bronchodilator, triple therapy, eosinophil, claims, exacerbations, costs

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory lung disease characterized by airflow obstruction and symptoms of dyspnea, cough, and sputum production.[1] Airway inflammation in COPD is predominantly neutrophil-mediated; however, an estimated 20–40% of patients also have elevated eosinophilic inflammation.[2–4] Evidence suggests that patients with eosinophilic phenotypes are most likely to respond favorably to treatment with anti-inflammatory inhaled corticosteroids (ICS), presenting an opportunity for personalized medicine.[5,6]

Peripheral blood eosinophil counts (BEC) have been shown to correlate with sputum eosinophil counts and are increasingly used as a more convenient surrogate for eosinophilic lung inflammation.[7] BEC predicts the magnitude of the effect of ICS in the prevention of COPD exacerbations, with BEC ≥300 cells/μL predictive of the greatest likelihood of treatment benefit.[5,8] For patients with BEC in the range of 100–300 cells/μL, treatment response may be variable. In contrast, ICS have little or no effect in patients with BEC <100 cells/μL and may increase the risk of pneumonia.[8,9] Therefore, BEC has emerged as a biomarker for responsiveness to ICS treatment in patients with COPD.[10,11]

The 2025 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report recommends pharmacological management of stable COPD based on assessment of patient symptoms, history of exacerbations, and BEC.[12] Bronchodilator therapy with a long-acting muscarinic antagonist (LAMA), long-acting beta2-agonist (LABA), or a combination of LAMA+LABA is recommended as initial maintenance therapy in patients with zero or one moderate exacerbation (not leading to hospital admission) per year (GOLD group A/B). For patients with two or more moderate exacerbations or at least one exacerbation leading to hospitalization (GOLD group E), dual therapy with LAMA+LABA is recommended. Triple therapy (LAMA +LABA+ICS) may be considered as an initial treatment for GOLD group E patients with BEC ≥300 cells/μL. Follow-up treatment is recommended based on the presence of dyspnea or exacerbations while on current maintenance therapy. Escalation to triple therapy is suggested only for patients with continued exacerbations on bronchodilator monotherapy with BEC ≥300 cells/μL or dual bronchodilator therapy with BEC ≥100 cells/μL.

Although treatment algorithms have changed over time, since 2011, GOLD has consistently recommended reserving triple therapy for patients with frequent exacerbations. Despite these evidence-based recommendations, one in five patients starting triple therapy in clinical practice is maintenance-naive with a low exacerbation history.[13] The benefits of ICS should be balanced against the potential risks of ICS-associated adverse effects, including pneumonia, oral candidiasis, skin bruising, and unfavorable changes in the lung microbiome.[14,15] We hypothesized that the exacerbation reduction benefits of triple therapy versus LAMA/LABA observed in randomized controlled trials (RCTs) would not translate to routine clinical practice in patients with BEC ≤300 cells/μL. Therefore, this study aimed to compare COPD exacerbations, healthcare resource utilization (HRU), and costs in patients initiating dual bronchodilator therapy with tiotropium/olodaterol (TIO/OLO) or triple therapy with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI), with BEC ≤300 cells/μL.

Methods

Study Design and Data Source

This retrospective, non-interventional cohort study used medical and pharmacy claims data from the Optum Research Database (ORD). Medical claims included diagnosis and procedure codes recorded using the International Classification of Diseases, Ninth (ICD-9-CM) and Tenth (ICD-10-CM) Revisions, Clinical Modification codes, Current Procedural Terminology codes, Healthcare Common Procedure Coding System codes, site of service codes, provider specialty

codes, revenue codes (for facilities), paid amounts, and other information. This claims database is fully de-identified and compliant with the Health Insurance Portability and Accountability Act. This study used aggregated, de-identified insurance claims data and, therefore, required no review by an institutional review board or informed consent procedures. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to ensure thorough reporting of the cohort study design, participant selection, variable measurements, and statistical analysis. This study was registered at ClinicalTrials.gov (identifier: NCT05127304). The results for the overall study population have been reported elsewhere.[16]

Study Population

Patients with COPD were identified based on the presence of at least one facility claim with a diagnosis of COPD in the primary position or at least two professional claims with a diagnosis code of COPD in any position on separate dates of service from 01 June 2014 through 31 December 2019 (study period). The study population included patients with at least 30 consecutive days supply of TIO/OLO or FF/UMEC/VI initiated during the identification period of 01 June 2015 to 30 November 2019, allowing for a minimum of 12 months of data prior to and 30 days after treatment initiation. The index date was defined as the fill date of the first TIO/OLO or FF/UMEC/VI pharmacy claim with a minimum of 30 days of consecutive treatment during the identification period. Continuous health plan enrollment with medical and pharmacy coverage for 12 months prior to and including the index date (baseline period) and for at least 30 days following the index date was required. Included patients were at least 40 years of age on the index date. Individuals with pharmacy claims for both TIO/OLO and FF/UMEC/VI on the index date, and those who switched to another maintenance therapy (any non-index LAMA, LABA, or ICS) within 30-days following the index date were excluded. Patients with two or more baseline medical claims on separate dates of service with a diagnosis of asthma, cystic fibrosis, lung cancer, or interstitial lung disease, or any medical claim for lung volume reduction procedure were also excluded. Patients with 7 or more days of overlapping supply of LAMA and LABA, with or without ICS, in the six months prior to the index date were excluded to ensure that the included patients were new users at the class level. Individuals were also excluded due to unknown age, gender, business line, or unknown/other geographic region.

The subgroup of patients with at least one blood eosinophil laboratory result during the 6 months prior to the index date through 15 days after the index date was retained for this analysis.

Measures

The 12-month period prior to and including the index date (index date – 364 days through index date) was used to assess baseline patient characteristics. Baseline measures included patient demographics, clinical characteristics, exacerbation history, respiratory medication use, HRU, and costs. Baseline respiratory medication use excluded claims on the index date. Patients without any baseline claims for LAMA, LABA, or ICS were considered maintenance-naive.

BEC results from 6 months prior to the index date through 15 days after the index date were assessed and categorized as ≤300 cells/μL or >300 cells/μL, utilizing the result closest to the index date. The highest value was retained for multiple eosinophil laboratory results on the same service date.

Moderate COPD exacerbation was defined as an ambulatory (office or outpatient) visit with a diagnosis code for COPD plus a pharmacy claim for an oral corticosteroid and/or COPD-guideline-recommended antibiotic within seven days of the visit. Severe exacerbation was defined as an inpatient or emergency department (ED) visit with 1) a primary diagnosis of COPD, 2) a primary diagnosis of acute respiratory failure plus a COPD diagnosis, or 3) a primary diagnosis of acute respiratory failure plus an inpatient or ED visit with a COPD diagnosis in any position within ± seven days. Exacerbations occurring within 14 days of each other were considered a single exacerbation episode and were classified according to the highest severity contributing event. Patients were categorized into GOLD group A/B (zero or one baseline moderate exacerbation [not leading to hospital admission]) or GOLD group E (two or more baseline moderate exacerbations or at least one exacerbation leading to hospitalization).

HRU measures included ambulatory (physician office and hospital outpatient), ED, inpatient, other medical visits, and pharmacy claims. Other medical visits included services provided at independent laboratories, assisted living facilities, and by home health providers. COPD and/or pneumonia-related HRU measures were restricted to medical claims with

a diagnosis of COPD, pneumonia, or acute bronchitis/bronchiolitis and pharmacy claims for COPD-related treatment, including guideline-recommended antibiotics.

HRU costs were computed as the sum of health plan and patient-paid (copay and/or coinsurance) costs. Total costs were presented as combined medical and pharmacy costs. Costs were adjusted to 2020 US dollars using the medical care component of the Consumer Price Index.[17]

Outcomes were assessed over a variable follow-up period, with a minimum of 30 days and maximum of 12 months. Patients were followed up until the earliest of treatment switch, discontinuation, health plan disenrollment, end of the study period (31 December 2019), or 1 year of follow-up. Discontinuation was defined as a gap in therapy of ≥60 days following the runout of days' supply, and the discontinuation date was defined as the runout prior to the gap in therapy. Patients with <60 days of observation time following the runout of their last index prescription claim were flagged as censored because the discontinuation status of patients was unobservable, and their observation period ended on the runout date. An index therapy switch was defined as a pharmacy fill for ≥30 consecutive days of non-index ICS-, LABA-, or LAMA-containing medication (switch date = the first date of the new treatment regimen). The outcomes assessed during the follow-up period included COPD exacerbations, HRU, and costs.

Statistical Analysis

Patients were matched in a 1:1 ratio of TIO/OLO to FF/UMEC/VI initiators without replacement, using nearest-neighbor matching with a caliper of ±0.01. Covariates in the logistic regression model used to compute propensity scores included patient demographics (age, sex, geographic region, insurance type), proxies for COPD severity (baseline moderate and severe exacerbation counts, GOLD group), baseline COPD medication use (maintenance-naive status, count of controller and rescue medications, nebulized respiratory medication, and oxygen therapy), baseline HRU, and costs (all-cause, COPD-related, and pneumonia-related total costs). Patients not matched were excluded from the post-match analysis.

Baseline characteristics before and after propensity score matching were compared between TIO/OLO and FF/UMEC/VI initiators using standardized differences. A standardized difference of ≤10% for a measure was considered an acceptable threshold for balance between the treatment cohorts.

Kaplan-Meier analyses were conducted to examine the time to the first COPD exacerbation (any or severe) and pneumonia diagnosis. Cumulative incidence was estimated as the complement of the Kaplan-Meier survival function. Follow-up counts of COPD exacerbations, HRU, and costs were compared between cohorts and presented as annualized population averages with Wald 95% confidence intervals, using Taylor expansion to estimate the standard error. Annualized population averages were computed as the [(sum of outcome events or costs for each cohort)/(sum of follow-up time in years for each cohort)].

COPD and/or pneumonia-related total, medical, and pharmacy costs were also modeled using generalized linear modeling with a gamma distribution and log link to adjust for residual imbalance after propensity score matching. Statistical tests between cohorts included variance adjustments for clustering due to matching.

Results

From the overall population of TIO/OLO (n=6681) and FF/UMEC/VI (n=9657) initiators who met the study inclusion criteria, 1649 (24.7%) and 2218 (23.0%) had a baseline blood eosinophil laboratory result, respectively (Figure 1). Among these, 1372 (83.2%) TIO/OLO initiators and 1796 (81.0%) FF/UMEC/VI initiators had BEC ≤300 cells/μL. Prior to matching, baseline characteristics between TIO/OLO initiators and FF/UMEC/VI initiators were imbalanced for age, insurance coverage, anxiety, allergic rhinitis, sleep apnea, exacerbation history, prior COPD medication use, and costs (Table 1). After matching, 1098 patients from each cohort were retained. TIO/OLO and FF/UMEC/VI initiators were well balanced on baseline characteristics, except for index year, prior respiratory medication use, allergic rhinitis, and anxiety. Proxies of disease severity, including baseline COPD exacerbations, pneumonia-related events, as well as all-cause and disease-related HRU and cost measures, were well balanced between the study cohorts. Approximately 55% of the patients in each cohort were naive to maintenance therapy and 68% had a GOLD A/B exacerbation history. The mean follow-up durations (days) were similar between cohorts (mean [SD]: 122.6 [112.7] and 129.3 [106.4] for TIO/OLO and FF/UMEC/VI, respectively). However, the reason for the end of follow-up differed between cohorts, with 6.9% of TIO/OLO initiators and

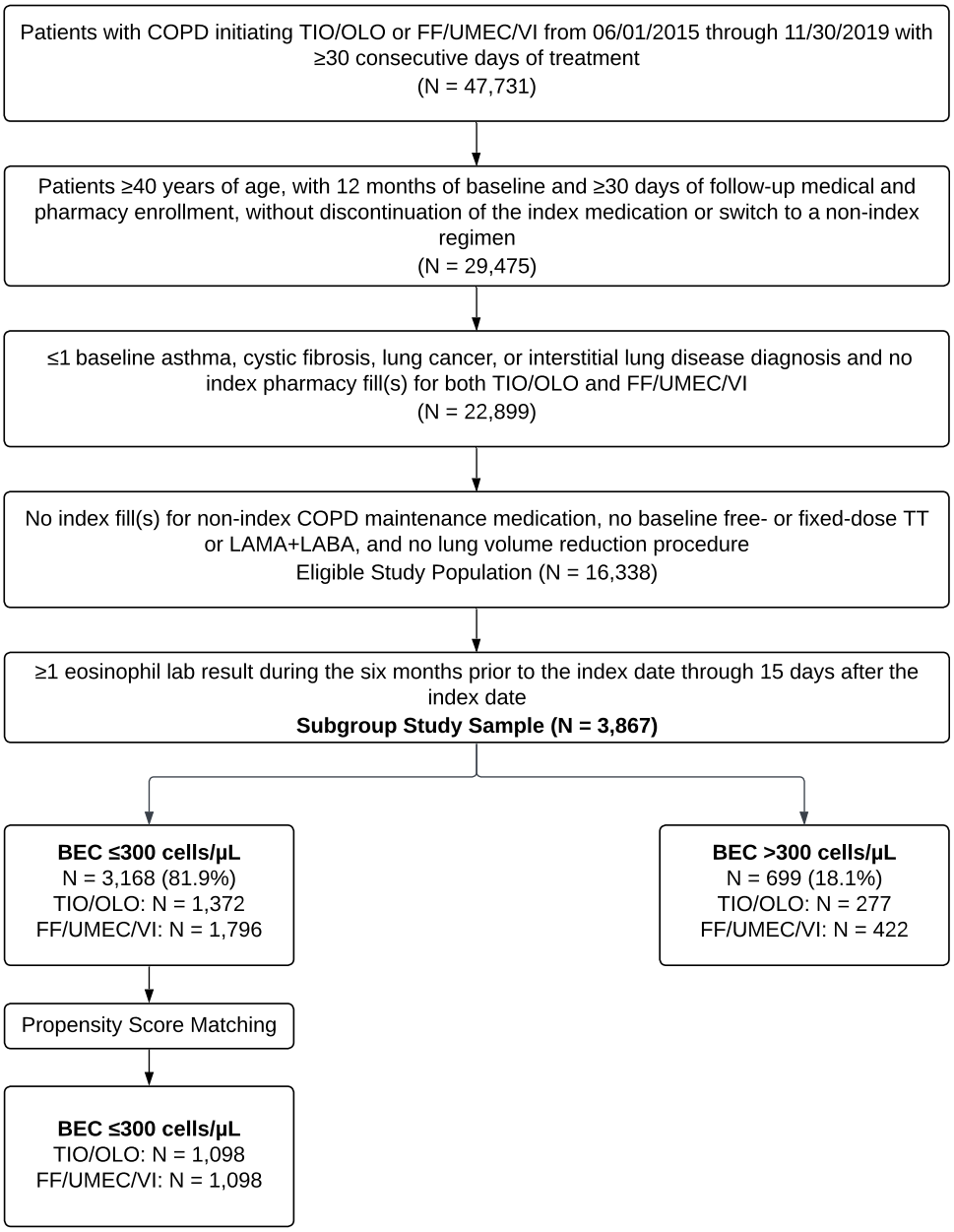


Figure 1 Patient Disposition.
Notes: Bold text indicates study sample and blood eosinophil count cohorts, before and after propensity score matching.
Abbreviations: COPD, chronic obstructive pulmonary disease; TIO/OLO, tiotropium/olodaterol; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; BEC, blood eosinophil count; TT, triple therapy; LAMA, long-acting muscarinic antagonist; LABA, long-acting beta2-agonist.

23.6% of FF/UMEC/VI initiators censored due to end of the study period (31 December 2019). Approximately, 9.4% of the TIO/OLO cohort and 5.7% of the FF/UMEC/VI cohort had a complete 12-months of follow-up.

COPD Exacerbations and Pneumonia

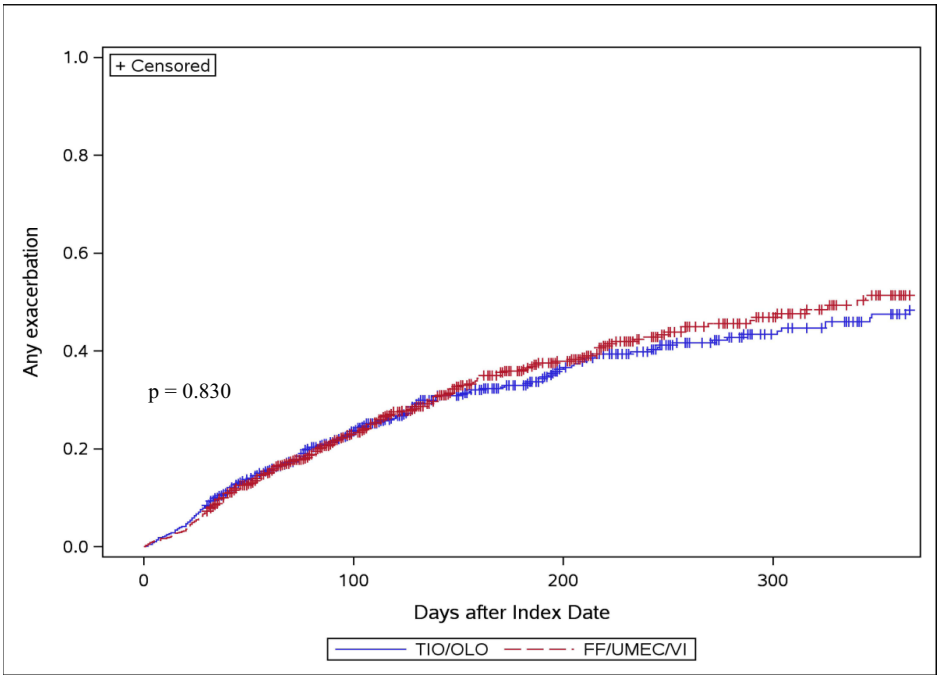
Kaplan-Meier analysis censor-adjusted proportions of patients experiencing moderate or severe exacerbation at one year were 48.4% for TIO/OLO initiators and 51.4% for FF/UMEC/VI initiators. The incidence of severe exacerbation at one year was 18.0% for TIO/OLO initiators and 18.6% for FF/UMEC/VI initiators. The time to the first moderate or severe exacerbation (p=0.830) and severe exacerbation (p=0.988) was not significantly different between the TIO/OLO

Table 1 Baseline Characteristics of TIO/OLO and FF/UMEC/VI Cohorts with BEC ≤300 Cells/μL Before and After Propensity Score Matching

Characteristic	Pre-Matching			Post-Matching		
	TIO/OLO (N=1372)	FF/UMEC/VI (N=1796)	Standardized Difference[a] (%)	TIO/OLO (N=1098)	FF/UMEC/VI (N=1098)	Standardized Difference[a] (%)
Age, years (mean, SD)	71.6 (8.8)	70.4 (9.3)	**13.3**	71.6 (8.8)	71.5 (8.9)	1.1
Female (n, %)	721 (52.6)	959 (53.4)	1.7	580 (52.8)	580 (52.8)	0.0
Insurance coverage (n, %)						
MAPD	1323 (96.4)	1525 (84.9)	**40.4**	1049 (95.5)	1048 (95.5)	0.4
Commercial	49 (3.6)	271 (15.1)	**40.4**	49 (4.5)	50 (4.6)	0.4
CCI score excluding COPD (mean, SD)	2.1 (2.0)	2.0 (2.0)	1.9	2.1 (2.0)	2.1 (2.0)	1.0
Baseline comorbidities (n, %)						
Heart failure	341 (24.9)	499 (27.8)	6.7	282 (25.7)	300 (27.3)	3.7
Allergic rhinitis	180 (13.1)	330 (18.4)	**14.5**	156 (14.2)	199 (18.1)	**10.7**
Anxiety	319 (23.3)	515 (28.7)	**12.4**	256 (23.3)	306 (27.9)	**10.5**
Pneumonia	242 (17.6)	370 (20.6)	7.5	214 (19.5)	195 (17.8)	4.5
Sleep apnea	348 (25.4)	565 (31.5)	**13.5**	292 (26.6)	337 (30.7)	9.1
Baseline respiratory medication use (n, %)						
Naive to maintenance therapy[b]	857 (62.5)	786 (43.8)	**38.2**	602 (54.8)	613 (55.8)	2.0
LAMA	279 (20.3)	343 (19.1)	3.1	270 (24.6)	152 (13.8)	**27.5**
LABA/ICS	237 (17.3)	737 (41.0)	**54.2**	228 (20.8)	354 (32.2)	**26.2**
Baseline COPD exacerbations						
Count of baseline COPD exacerbations (mean, SD)	0.9 (1.3)	1.3 (1.5)	**29.1**	1.0 (1.4)	1.0 (1.3)	0.2
≥ 1 moderate or severe exacerbation (n, %)	677 (49.3)	1135 (63.2)	**28.2**	601 (54.7)	605 (55.1)	0.7
≥ 1 severe exacerbation (n, %)	259 (18.9)	509 (28.3)	**22.4**	236 (21.5)	248 (22.6)	2.6
GOLD A/B[c] (n, %)	994 (72.5)	1063 (59.2)	**28.2**	750 (68.3)	746 (67.9)	0.8
COPD and/or pneumonia-related costs, $ (mean, SD)						
Total	$8965 ($20,483)	$12,558 ($24,172)	**16.0**	$9761 ($21,278)	$9567 ($16,699)	1.0
Medical	$7930 ($20,239)	$10,924 ($23,968)	**13.5**	$8570 ($21,019)	$8286 ($16,541)	1.5
Pharmacy	$1036 ($1660)	$1634 ($2134)	**31.3**	$1191 ($1749)	$1281 ($1879)	5.0

Notes: [a]Bold values indicate a standardized difference >10%; [b]Naive to ICS, LAMA, and LABA during the baseline period; [c]No baseline exacerbation or one baseline exacerbation not leading to hospitalization.

Abbreviations: MAPD, Medicare Advantage with Part D; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; LAMA, long-acting muscarinic antagonist; LABA, long-acting beta2-agonist; ICS, inhaled corticosteroid; GOLD, Global Initiative for Chronic Obstructive Lung Disease.



		0	1	30	60	90	120	150	180	210	240	270	300	330	360	365
TIO/OLO	proportion	0.000	0.001	0.085	0.157	0.214	0.265	0.308	0.330	0.382	0.398	0.417	0.434	0.460	0.475	0.484
	at risk	1,098	1,098	1,008	552	431	290	237	200	158	134	109	89	79	65	61
FF/UMEC/VI	proportion	0.000	0.003	0.073	0.151	0.213	0.275	0.328	0.359	0.387	0.429	0.456	0.469	0.493	0.514	0.514
	at risk	1,098	1,098	1,022	622	481	329	253	205	161	118	92	74	52	34	30

Figure 2 Time to First Moderate or Severe Exacerbation in the Matched Population with Eosinophil Count ≤300 cells/μL.
Abbreviations: TIO/OLO, tiotropium/olodaterol; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol.

and FF/UMEC/VI initiators (Figures 2 and 3). The follow-up counts (95% CI) of annualized COPD exacerbations were also not significantly different between TIO/OLO and FF/UMEC/VI initiators for moderate or severe exacerbations (1.05 [0.92–1.18] vs 0.99 [0.88–1.11], p=0.535) and severe exacerbations (0.29 [0.23–0.36] vs 0.28 [0.22–0.34], p=0.821).

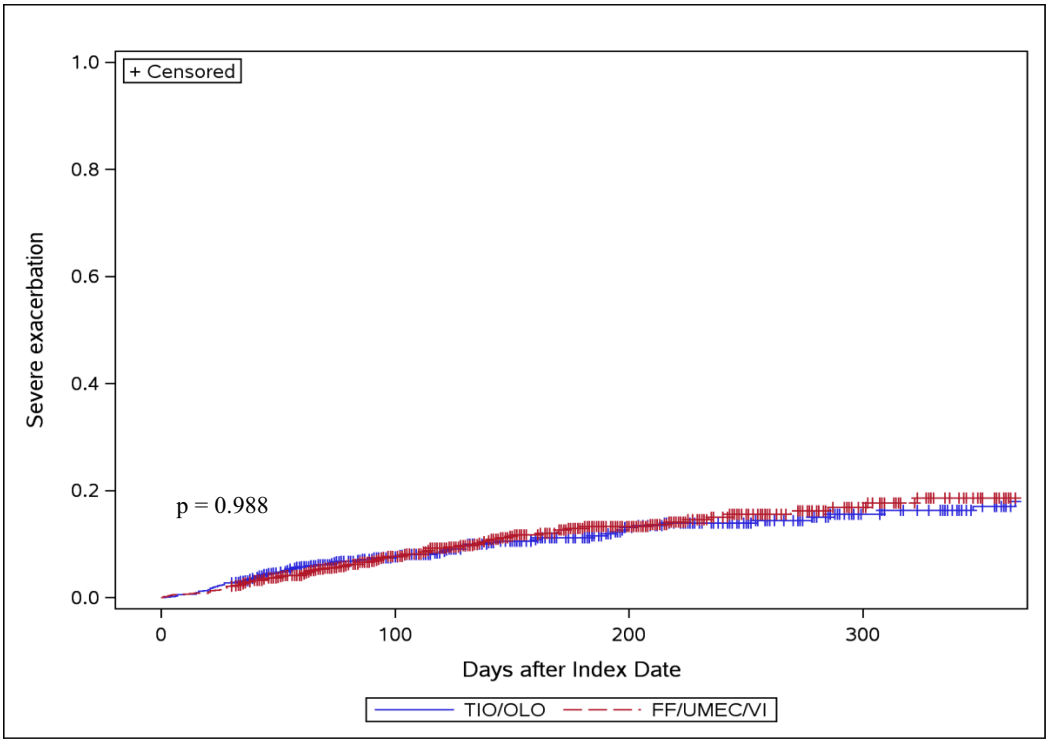
The censor-adjusted findings from the Kaplan-Meier analysis indicated the proportions of patients with a pneumonia diagnosis at one year were 15.6% of TIO/OLO initiators and 17.8% of FF/UMEC/VI initiators, with no significant difference in time to first pneumonia diagnosis (p= 0.772) (Supplementary Figure 1).

Healthcare Resource Utilization

Follow-up annualized COPD and/or pneumonia-related HRU measures were not significantly different between cohorts, except for fewer ED visits among TIO/OLO initiators versus FF/UMEC/VI (0.59 [0.46–0.71] vs 0.83 [0.67–0.98], p=0.018) (Table 2).

Costs

The follow-up population annualized average COPD and/or pneumonia-related total (medical and pharmacy) and medical costs were not significantly different between the TIO/OLO and FF/UMEC/VI initiators (Table 3). The total COPD and/or pneumonia-related costs for the TIO/OLO and FF/UMEC/VI initiators were $18,097 and $20,130, respectively (p=0.326). Pharmacy costs were 28.6% lower for TIO/OLO initiators than for FF/UMEC/VI initiators



		0	1	30	60	90	120	150	180	210	240	270	300	330	360	365
TIO/OLO	proportion	0.000	0.000	0.027	0.058	0.072	0.086	0.105	0.112	0.135	0.139	0.144	0.156	0.163	0.171	0.180
	at risk	1,098	1,098	1,068	624	507	357	297	254	210	179	152	127	117	97	92
FF/UMEC/VI	proportion	0.000	0.002	0.021	0.042	0.068	0.092	0.115	0.129	0.137	0.150	0.162	0.169	0.186	0.186	0.186
	at risk	1,098	1,098	1,075	698	560	408	328	274	214	168	133	107	79	55	49

Figure 3 Time to First Severe Exacerbation in the Matched Population with Eosinophil Count ≤300 cells/μL.
Abbreviations: TIO/OLO, tiotropium/olodaterol; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol.

($4692 vs $6573, p<0.001). The ED visit costs were also lower for TIO/OLO than for FF/UMEC/VI initiators ($370 vs $538, p=0.034). Costs adjusted for baseline characteristics with residual imbalance after propensity score matching using a generalized linear model were consistent with the population annualized costs (Supplementary Table 1).

Table 2 Population Annualized Average Counts of Follow-up COPD and/or Pneumonia-Related Healthcare Resource Utilization in Matched TIO/OLO and FF/UMEC/VI Cohorts with BEC ≤300 Cells/μL

	TIO/OLO (N=1098)	FF/UMEC/VI (N=1098)	p-value[a]
COPD and/or pneumonia-related utilization counts – Population annualized averages (95% CI)			
Ambulatory visits[b]	9.58 (8.31–10.86)	9.88 (8.85–10.90)	0.723
ED visits	0.59 (0.46–0.71)	0.83 (0.67–0.98)	**0.018**
Inpatient visits	0.46 (0.37–0.54)	0.50 (0.41–0.58)	0.519
Inpatient days	5.53 (3.98–7.09)	5.35 (3.89–6.81)	0.866
Other medical visits	4.76 (4.15–5.36)	5.23 (4.61–5.84)	0.282
Pharmacy fills	15.62 (14.95–16.29)	15.34 (14.73–15.95)	0.552

Notes: [a]Bold values indicated p<0.05; [b]Sum of physician office and outpatient visits.
Abbreviations: COPD, chronic obstructive pulmonary disease; CI, confidence interval; ED, emergency department.

Table 3 Population Annualized Average Costs of Follow-up COPD and/or Pneumonia-Related Healthcare Resource Utilization in Matched TIO/OLO and FF/UMEC/VI Cohorts with BEC ≤300 Cells/μL

	TIO/OLO (N=1098)	FF/UMEC/VI (N=1098)	p-value[a]
COPD and/or pneumonia-related costs – Population annualized averages (95% CI)			
Medical visits	$13,405 ($10,592-$16,219)	$13,557 ($10,592-$16,522)	0.941
Ambulatory visits	$2529 ($1865-$3194)	$2480 ($2048-$2911)	0.902
ED visits	$370 ($278-$462)	$538 ($412-$665)	**0.034**
Inpatient visits	$10,011 ($7376-$12,646)	$10,126 ($7255-$12,996)	0.954
Other medical visits	$495 ($383-$607)	$413 ($352-$475)	0.210
Pharmacy	$4692 ($4562-$4821)	$6573 ($6425-$6721)	**<0.001**
Total[c]	$18,097 ($15,284-$20,910)	$20,130 ($17,153-$23,108)	0.326

Notes: [a]Bold values indicate p<0.05; [b]Sum of physician office and outpatient visits; [c]Total costs are the sum of pharmacy and medical costs.
Abbreviations: COPD, chronic obstructive pulmonary disease; CI, confidence interval; ED, emergency department.

Discussion

This retrospective, non-interventional cohort study assessed clinical and economic outcomes following the initiation of dual bronchodilator therapy with TIO/OLO compared to triple therapy with FF/UMEC/VI in patients with COPD and BEC ≤300 cells/μL. In accordance with GOLD treatment recommendations, the findings suggest that triple therapy did not reduce the risk of COPD exacerbation compared with LAMA/LABA therapy. This result is consistent with that of another real-world study comparing single-inhaler triple therapy with LAMA/LABA, which found no significant difference in the incidence of moderate or severe COPD exacerbations in patients with BEC ≤300 cells/μL, even among a subset of GOLD E patients.[18,19]

Evidence from RCTs of triple therapy supports the role of BEC in the identification of patients who are most likely to benefit from the addition of ICS to LAMA/LABA. AIRWISE was a pragmatic clinical trial that randomized patients not controlled on LABA, LAMA, or LABA/ICS to either TIO/OLO or triple therapy. A post-hoc subgroup analysis found that the risk of a first moderate or severe COPD exacerbation was similar between TIO/OLO and triple therapy for patients with BEC <300 cells/μL (hazard ratio [95% CI]: 1.02 [0.68–1.53]).[20] The IMPACT and ETHOS trials, which randomized patients to single-inhaler triple therapy or LAMA/LABA, found that the magnitude of the benefit of triple therapy on exacerbation reduction was greater with increased BEC. Data modeling from the IMPACT trial revealed a continuous relationship between BEC and exacerbation risk reduction above BEC of 100 cells/μL.[21] Post-hoc analysis of the ETHOS trial found that the benefit of triple therapy in reducing the rate of moderate/severe exacerbations compared to LAMA/LABA was greatest in patients with BEC >300 cells/μL.[22] However, the generalizability of RCT findings of TT to routine clinical practice may be limited by the study design and selected patient population. The IMPACT and ETHOS trials primarily enrolled patients with a history of exacerbation in the previous year and use of maintenance medications at screening.[23,24] Notably, most patients included in our study (approximately 68%) had GOLD A/B exacerbation history, and over half had no evidence of maintenance inhaler therapy in the 12 months prior to the initiation of TIO/OLO or FF/UMEC/VI. A study that examined the eligibility of patients with COPD seen in routine

clinical practice in England (n=79,810) for inclusion in RCTs estimated that only 8.9% and 2.0% of the patients would have been eligible for the IMPACT and ETHOS trials, respectively.[25] The inclusion criteria for COPD exacerbations and the use of prior maintenance medication led to the exclusion of the greatest proportion of patients, highlighting the lack of generalizability of these trials.

In this study, HRU and costs were generally similar among initiators of TIO/OLO and FF/UMEC/VI. However, ED visits and pharmacy costs related to COPD (including maintenance medications, short-acting bronchodilators, oral corticosteroids, and antibiotics) were significantly lower among TIO/OLO users.

Approximately 17% and 19% of patients initiating TIO/OLO and FF/UMEC/VI, respectively, had a baseline BEC >300 cells/μL. This finding suggests that most patients with COPD who initiate dual bronchodilator or triple therapy do not have high eosinophil counts. Furthermore, less than half (47.2%) of the FF/UMEC/VI initiators with BEC >300 cells/μL also had GOLD E exacerbation history, which is the population most likely to benefit from TT.

The limitations of this study include those inherent to the use of administrative claims data for retrospective observational research. Claims are subject to miscoding, omissions, and lack some clinically important data such as lung function measures, symptom burden, and behavioral characteristics. Propensity score matching was employed to mitigate the risks of confounding by indication, and resulted in well-balanced baseline characteristics of TIO/OLO and FF/UMEC/VI initiators with BEC ≤300 cells/μL. However, several baseline measures remained imbalanced after matching. The proportion of patients with comorbid allergic rhinitis and anxiety differed between cohorts, with standardized differences just above the a priori defined threshold of 10%. Prior maintenance medication use also differed, with a greater number of FF/UMEC/VI initiators with baseline use of LABA/ICS, reflecting expected treatment patterns. Multivariable analyses adjusted for baseline measures that remained imbalanced after matching were conducted for select cost outcomes, with consistent results. Our findings are also limited due to relatively short follow-up duration of approximately 4 months on average, however this reflects real-world treatment patterns (ie, treatment switching and discontinuation), our study design, and data limitations (eg, censoring due to end of data cut).

Additionally, the limited sample size and differences in baseline characteristics between cohorts with BEC >300 cells/μL resulted in inadequate balance after propensity score matching; therefore, we were unable to assess the outcomes in this population. Given the differing dates of market availability, TIO/OLO users who initiated therapy in the years prior to the approval of FF/UMEC/VI were included in this study, resulting in an imbalance in index year. A greater proportion of FF/UMEC/VI patients had index dates in 2019, which resulted in more frequent censoring of follow-up due to the end of the data period. Furthermore, the generalizability of our findings is limited by the study population, which may not represent the broader COPD patient population without commercial or Medicare Advantage insurance coverage. Finally, COPD exacerbations were identified using a claims-based algorithm, which may have resulted in misclassifications. However, the algorithm used in this study was similar to that used in other COPD studies using claims data, including validated algorithms with high performance characteristics.[26]

Conclusion

Among patients with COPD initiating FF/UMEC/VI, eight in ten had BEC ≤300 cells/μL and less than 10% had BEC >300 cells/μL with GOLD E exacerbation history. TIO/OLO and FF/UMEC/VI initiators with BEC ≤300 cells/μL experienced similar rates of COPD exacerbations and COPD and/or pneumonia-related HRU. TIO/OLO initiators incurred lower ED and pharmacy costs related to COPD and/or pneumonia compared with FF/UMEC/VI initiators. These findings support practice recommendations for the assessment of BEC when considering initiating triple therapy and for reserving triple therapy for frequent exacerbators and patients with BEC ≥300 cells/μL.

Data Sharing Statement

The data used were licensed from Optum and are not publicly available.

Ethics Approval and Informed Consent

As this was a retrospective study, informed consent was not required. All data were de-identified, and therefore, the study did not necessitate ethics committee approval and was fully compliant with HIPAA regulations.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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