ORIGINAL RESEARCH

Benefits of Early Roflumilast Treatment After Hospital or Emergency Department Discharge for a COPD Exacerbation

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BACKGROUND: Chronic lower respiratory disease, which includes chronic obstructive pulmonary disease (COPD), is the third leading cause of death in the United States. Roflumilast is an oral, once-daily, selective phosphodiesterase-4 inhibitor approved for reducing the risk for COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

OBJECTIVES: To evaluate the effects of roflumilast treatment timing on COPD exacerbation rates (primary objective) and on resource utilization and healthcare costs (secondary objective) after hospital or emergency department discharge associated with a COPD exacerbation.

METHODS: In this retrospective cohort study, claims data from March 2011 to March 2013 were extracted from Truven Health MarketScan combined commercial healthcare claims and Medicare supplemental claims databases and were analyzed to compare the exacerbation rates and the healthcare resource utilization and costs between the early roflumilast treatment (treatment initiation ≤30 days after hospital or emergency department discharge) and the delayed roflumilast treatment (treatment initiation 31-180 days after discharge) cohorts. Multivariate logistic regression and generalized linear models with log-link function and gamma distribution were adjusted for age, sex, insurance plan type, COPD disease complexity, and comorbidities.

RESULTS: A total of 995 patients (N = 280 early roflumilast treatment, N = 715 delayed roflumilast treatment) were included. Compared with the delayed roflumilast treatment group, patients in the early roflumilast treatment group were 39% less likely to have an exacerbation after hospital discharge (P = .004). The patients receiving early roflumilast treatment also had 42% (P = .003) and 37% (P = .005) lower risks for COPD-related and all-cause rehospitalizations, respectively, than patients in the delayed roflumilast treatment group. Significantly fewer patients receiving early roflumilast treatment had moderate (P = .013) or severe (P = .002) exacerbations. Early roflumilast treatment also was associated with reduced annualized COPD-related (P = .012) and all-cause (P = .009) rehospitalizations, outpatient visits per patient (P <.001 for COPD-related and all-cause), and procedures or therapies (COPD-related, P = .016; all-cause, P = .009). The early treatment group had fewer COPD-related emergency department visits per patient than the delayed roflumilast treatment group (P = .035), and the total mean annualized COPD-related and all-cause costs were reduced by $7273 ($P$ = .014) and $14,111 ($P$ = .002), respectively. Multivariate analyses showed that early treatment was associated with lower COPD-related and all-cause annualized health services costs per patient annually (P <.001 for both).

CONCLUSION: In this real-world study, the patients with COPD who initiated roflumilast treatment ≤30 days after a hospital or emergency department discharge for a COPD-related exacerbation experienced fewer subsequent exacerbations and rehospitalizations, reduced healthcare utilizations, and lower healthcare costs than the patients who delayed their roflumilast treatment.

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KEY WORDS: chronic obstructive pulmonary disease, exacerbations, healthcare costs, healthcare utilization, hospital discharge, rehospitalization, roflumilast

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Chronic obstructive pulmonary disease (COPD) is characterized by persistent, progressive airflow limitation that is not fully reversible.[1] Although COPD treatments can reduce symptoms and can slow disease progression, acute periods of rapid symptom wors-

ening beyond typical day-to-day variations (ie, exacerbations) can lead to hospitalization and a change in medication.[1] Because exacerbations often occur in clusters, with an increased risk for a second exacerbation within 8 weeks of an initial event,[2] treatments that minimize the impact of an active exacerbation and decrease the risk for future exacerbations can improve patient outcomes,[1] which would reduce disease-related costs.

Currently in the United States, chronic lower respiratory disease, which includes COPD, is the third leading cause of death.[3] In addition to the physical and emotional burdens of COPD, the total medical costs of the disease are staggering. In a recent US study, $32.1 billion was attributed to COPD-related medical costs, with a projected increase to $49 billion by 2020.[4] In a large US retrospective claims study, the average cost per COPD-related hospital stay (mean, 4.8 days) was $7500, with acute exacerbations accounting for approximately 63% of all COPD-related hospitalizations (with COPD as the primary diagnosis).[5] In another retrospective claims study, all-cause quarterly incremental US healthcare costs for patients with COPD who experienced an exacerbation were nearly double those of patients without exacerbations.[6]

Roflumilast is an oral, once-daily selective phosphodiesterase (PDE)-4 inhibitor indicated for reducing the risk for COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.[7] Currently, roflumilast is the only PDE-4 inhibitor approved for this indication. The efficacy of roflumilast as adjunctive therapy has been demonstrated in several well-controlled clinical trials, in which patients with severe COPD had fewer exacerbations with roflumilast.[8-10]

This study analyzed the effects of early versus delayed initiation of roflumilast treatment after a hospital or emergency department discharge resulting from COPD exacerbation. Moderate-to-severe exacerbation rates, rehospitalization rates, medication use, health services utilization, and medical costs were calculated for patients with a primary or a secondary diagnosis of COPD, adjusting for COPD disease complexity and comorbidities.

KEY POINTS

- Treatment of COPD can reduce symptoms and slow disease progression, but exacerbations still may occur, which can increase the risk for a subsequent exacerbation.
- This retrospective study of 995 patients with COPD investigated the impact of starting treatment with the PDE-4 inhibitor roflumilast <30 days or 31-180 days after a hospital or an emergency department discharge associated with a COPD exacerbation.
- Early initiation of roflumilast treatment was associated with lower risks for COPD-related (42%) and all-cause rehospitalizations (37%) after ≥6 months of follow-up.
- The early roflumilast treatment group had fewer moderate or severe exacerbations and fewer COPD-related emergency department visits than the delayed treatment group.
- The mean annualized COPD-related total healthcare costs were $7273 lower with early initiation of roflumilast than with the delayed initiation.
- Similarly, the mean annualized all-cause total healthcare costs were $14,111 lower in the early versus delayed roflumilast treatment group.

Methods

Data Source

In this retrospective, observational cohort study, deidentified data from March 2011 through March 2013 were extracted from Truven Health MarketScan combined commercial and Medicare supplemental healthcare claims databases, which contain healthcare costs and utilizations, as well as inpatient, outpatient, and prescription drug services data on almost 230 million patients since 1995.[11] These databases include inpatient and outpatient diagnosis, and drug and procedure codes submitted with each prescription and each professional or facility claim. The coding schemes used in the databases included the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis and procedure codes, *Current Procedural Terminology* procedure codes, Healthcare Common Procedure Coding System codes, and National Drug Codes universal product identifiers.

The index date was defined as the date of the first hospitalization or emergency department visit with a primary or secondary diagnosis of COPD (*ICD-9* codes, 491.xx, 492.xx, 496.xx). Patients with COPD initiating roflumilast treatment ≤30 days after hospital or emergency department discharge were included in the early roflumilast treatment cohort; patients initiating roflumilast 31 to 180 days after discharge were included in the delayed roflumilast treatment cohort. The data were examined for a minimum of 180 days after the index date.

Patient Population

Patients aged ≥40 years at the index date who were continuously enrolled in a health plan during the study period (including 12 months before and ≥6 months after the index date) were included in the analysis if they had ≥1 inpatient hospitalizations with a primary or a second-

ary diagnosis of COPD or 1 emergency department visit with a primary or a secondary diagnosis of COPD and had been dispensed roflumilast within 6 months after the index date. To reduce bias resulting from confounding respiratory diseases, patients were excluded if they had any conditions other than COPD or asthma that can cause chronic airflow limitation, such as cystic fibrosis, congenital cystic lung malformation, allergic alveolitis, respiratory cancer, pneumoconiosis, pulmonary fibrosis, sarcoidosis, or pulmonary tuberculosis.

COPD Classification

The patients were grouped into 1 of 3 COPD complexity categories based on criteria adopted from Pasquale and colleagues and Macaulay and colleagues, which included greater disease complexity (≥1 of the following conditions: nutritional abnormalities; osteoporosis; lung volume reduction surgery; oxygen therapy; COPD-related emergency department visit; or COPD-related outpatient visit), lesser disease complexity (renal failure *ICD-9* codes: 585, 586, v45.1, v42.0, v56), or unclassified.[12,13]

Outcome Measures

The main outcomes measures of this study were the number, rate, and severity of exacerbations, rehospitalization rates, and healthcare resource and utilization costs. Exacerbations were defined as an inpatient hospitalization or emergency department visit with a diagnosis of acute COPD exacerbation (*ICD-9* codes 491.21, 491.22, and 493.22) or emphysema (*ICD-9* code 492.8x); or ≥1 medical claims for primary respiratory failure (*ICD-9* codes 518.81 and 518.84) and a medical claim for a COPD diagnosis with acute exacerbation at secondary diagnosis position or for emphysema (*ICD-9* code 492.8x) at a secondary diagnosis position in an inpatient or an emergency department setting; or ambulatory care of an exacerbation (identified by medical claims for a qualifying diagnosis occurring in a physician office setting or pharmacy claims for qualifying systemic steroids or oral antibiotics frequently used for respiratory infections).

Exacerbation severity was categorized as either moderate (ie, the use of oral corticosteroids and/or oral antibiotics, including those frequently used to treat respiratory infections) or severe (ie, COPD-related rehospitalization or death [discharge status of "died" or *ICD-9-CM* code of 798] that occurred after the index COPD hospitalization and within the study period). This algorithm was chosen based on previous studies in which claims data were used to classify exacerbation severity in the hospital setting.[14,15]

Hospitalization rates were examined at 60 days, 90 days, and 180 days after hospital or emergency department discharge. The use of maintenance drugs and other respiratory medications included long-acting beta-2 agonists, long-acting muscarinic antagonists, theophylline, inhaled corticosteroids, short-acting beta-2 agonists, and short-acting muscarinic antagonists.

Healthcare resource utilization included inpatient care (eg, rehospitalizations) and outpatient care (ie, physician office visits, emergency department procedures, COPD-related services, and other outpatient visits). For the inpatient costs, medications, physician services, procedures and laboratory tests, and general hospital services were evaluated.

The inpatient utilization variables included the length of stay, the number of procedures or laboratory tests performed, the number of medication orders written, and the total dose of COPD medication administered. Comorbidities were defined using the Charlson Comorbidity Index with the Romano adaptation.[16,17]

Statistical Analyses

To evaluate the benefits of early roflumilast treatment after a hospital or an emergency department discharge, univariate and modeling analyses were used. The baseline patient characteristics (including age, sex, and comorbidities) for each cohort were summarized using descriptive statistics, and between-group comparisons were made between those characteristics using *t*-tests for continuous variables and chi-square testing for categorical variables. The comorbidity burden was calculated using the Charlson Comorbidity Index with Romano adaptation[16,17] and was compared between the 2 cohorts. The proportion of patients with exacerbations, COPD-related rehospitalizations, and all-cause hospitalizations were compared between the 2 cohorts using chi-square testing. The annualized exacerbations and the number of exacerbation episodes between the 2 groups were compared using *t*-tests.

Based on previous publications,[1,13] univariate and bivariate analyses were used to select variables with a cutoff for significance of $P < .10$ in the bivariate analysis to be included in the multivariate regression analysis. Factors such as age, sex, comorbidities (ie, asphyxia and respiratory arrest, respiratory infection, nutritional abnormalities, pneumonia, and osteoporosis), COPD complexity, and insurance plan type were used as covariates to examine the effect of early roflumilast treatment in the model development. Logistic regression modeling was used to predict the subsequent exacerbations using the above factors.

The generalized linear models were adjusted for baseline age, sex, COPD complexity, nutritional abnormalities, insurance plan type, and preindex comorbidities, and costs with gamma distribution and log-link function were used to compare the between-group healthcare costs. Utilization and costs were aggregated at the patient level

and were presented by COPD-related and all-cause utilization. The average annual utilization per group for each type of service used was determined. All costs were adjusted to 2013 pricing levels using the medical care component of the Consumer Price Index.

Results

A total of 995 patients were included in the analysis, 280 in the early roflumilast treatment group and 715 in the delayed roflumilast treatment group (**Figure**). Overall, the demographics and baseline clinical characteristics were similar between the cohorts, with the exceptions of COPD complexity, sex, and nutritional abnormalities (**Table 1**).

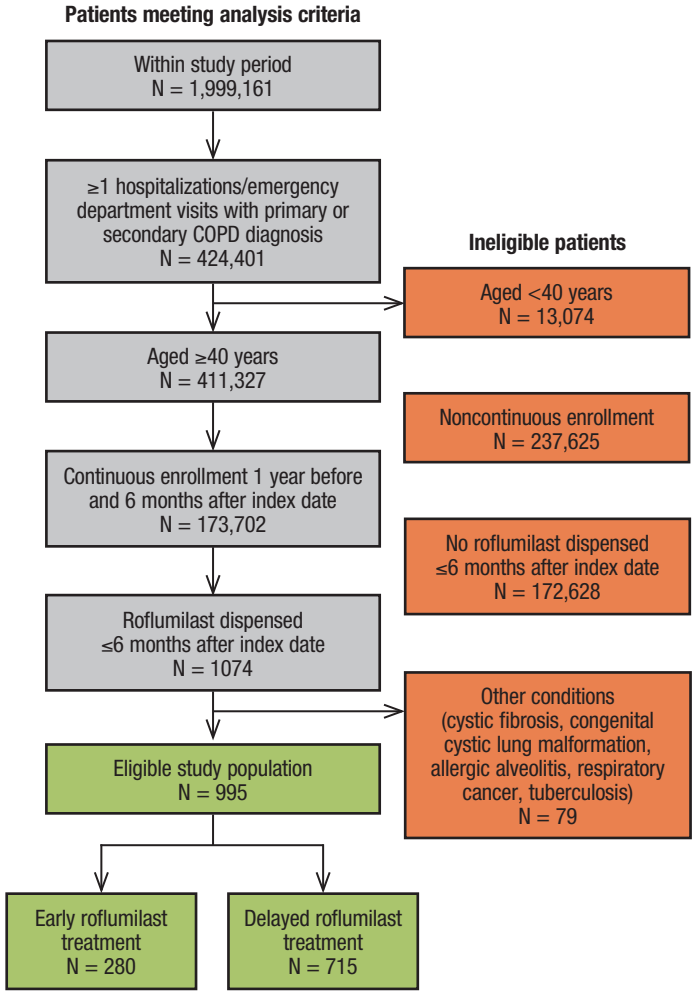
Compared with the delayed roflumilast treatment group, a larger proportion of patients in the early roflumilast treatment group had greater COPD complexity at baseline and a significantly greater proportion were male (P = .05; Table 1). A significantly larger percentage of patients in the early roflumilast treatment group had comorbid nutritional abnormalities compared with the patients in the delayed roflumilast treatment group (P = .01; Table 1). There were no significant between-group differences by preindex medication use, by US region (ie, Northeast, North Central, South, West, or unknown), or by payer status (eg, HMO, preferred provider organization [PPO], point of service [POS], and indemnity health plan).

Clinical Outcomes

Overall, early initiation of roflumilast was associated with significantly fewer and less severe exacerbations. Compared with patients in the delayed roflumilast treatment group, fewer patients in the early roflumilast treatment group had any exacerbation after the index date (73.6% with early roflumilast treatment vs 81.4% with delayed roflumilast treatment; P = .007; **Table 2**). Fewer patients in the early treatment group had moderate (P = .013), severe (P = .002), and moderate and severe (P = .002) exacerbations after the index date compared with the delayed treatment group (Table 2).

During the follow-up period, the patients in the early roflumilast treatment cohort had a lower mean number of exacerbations of any severity (P = .002) and of moderate severity (P = .001) compared with those in the delayed roflumilast treatment cohort (Table 2). There were no significant between-group differences observed in the mean number of severe or of moderate and severe exacerbations or in the time to first exacerbation after the index date (P >.05; Table 2). Similarly, when the exacerbation rates were annualized per patient, no significant differences were observed between the early roflumilast treatment and the delayed roflumilast treatment groups (P >.05; Table 2).

Figure Patient Selection



COPD indicates chronic obstructive pulmonary disease.

Significantly fewer patients in the early roflumilast treatment group were rehospitalized for COPD-related causes at 60, 90, or 180 days after discharge than the patients in the delayed roflumilast treatment group (P = .018, P = .006, and P = .05, respectively; Table 2). Similarly, a smaller percentage of early roflumilast treatment patients were rehospitalized for all causes at 60 or 90 days (P = .025, P = .015), with a similar trend observed at 180 days (P = .068; Table 2). No deaths on discharge were recorded in either cohort.

Overall, the patients in the early roflumilast treatment group had a lower risk for exacerbation than those in the delayed treatment group (**Table 3**). Patients who initiated roflumilast treatment early after hospitalization had a 39% lower risk for an exacerbation than patients who delayed their treatment (odds ratio [OR], 0.608; 95% confidence interval [CI], 0.435-0.851; P = .004; Table 3).

Table 1 Baseline Demographics and Clinical Characteristics

Demographics and clinical characteristics	Early roflumilast treatment (N = 280)	Delayed roflumilast treatment (N = 715)	*P* value[a]
Age, mean, yrs (SD)	68 (10.9)	67 (10.4)	.838
Male, N (%)	147 (52.5)	325 (45.5)	.045
Roflumilast initiation, median, days (minimum-maximum)	14 (12-15)	122 (117-128)	—
COPD complexity, N (%)			
Lesser	11 (3.9)	20 (2.8)	.004
Greater	197 (70.4)	433 (60.6)	
Unclassified	72 (25.7)	262 (36.6)	
Comorbidity score,[b] mean (SD)	3.6 (2.5)	3.3 (2.4)	.153
Comorbidities, N (%)[c]			
Respiratory infections	179 (63.9)	415 (58.0)	.089
Asphyxia and respiratory arrest	89 (31.8)	187 (26.2)	.074
Pneumonia	116 (41.4)	253 (35.4)	.076
Nutritional abnormalities	28 (10.0)	39 (5.5)	.010
Osteoporosis	35 (12.5)	61 (8.5)	.057
Preindex medication use, N (%)[d]			
LABA	103 (36.8)	288 (40.3)	.310
LAMA	156 (55.7)	419 (58.6)	.407
Inhaled corticosteroid	81 (28.9)	212 (29.7)	.822
LABA plus inhaled corticosteroid	169 (60.4)	433 (60.6)	.953
LABA plus LAMA and inhaled corticosteroid	111 (39.6)	310 (43.4)	.286
SABA	29 (10.4)	77 (10.8)	.850
SAMA	80 (28.6)	216 (30.2)	.611
Theophylline	31 (11.1)	77 (10.8)	.890
Oral or intravenous corticosteroid	202 (72.1)	540 (75.5)	.264
Antibiotics	152 (54.3)	414 (57.9)	.763

[a]*t*-tests were used for numerical variables and chi-square for categorical variables.
[b]Charlson Comorbidity Index-Romano adaptation.
[c]For brevity, only comorbidities that reached a significance of $P < .10$ are represented in this table. Comorbidities with $P > .10$ are not represented in the table, including respiratory distress, pulmonary vascular disease, acute respiratory failure, hypertension, heart failure, ischemic heart disease, cerebrovascular accident, angina, diabetes mellitus, skeletal muscle dysfunction, bone fractures, anxiety and depression, anemia, glaucoma, acute renal failure, chronic renal failure, obesity, cholelithiasis (gallstones), osteoarthritis, lower-back pain, gastroesophageal reflux disease, obstructive sleep apnea, and nonalcoholic fatty liver disease.
[d]Six months preindex date.
COPD indicates chronic obstructive pulmonary disease; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta-2 agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation.

Annualized Utilization and Costs

The patients in the early roflumilast treatment group had fewer COPD-related hospitalizations ($P = .012$) and procedures and therapies ($P = .016$), as well as fewer outpatient visits per patient ($P < .001$) and emergency department visits per patient ($P = .035$), than those in the

Table 2 Unadjusted Exacerbations and Rehospitalizations After the Index Date[a]

Exacerbations or rehospitalizations	Early roflumilast treatment (N = 280)	Delayed roflumilast treatment (N = 715)	*P* value[b]
Patients with any exacerbation, N (%)	206 (73.6)	582 (81.4)	.007
Moderate exacerbation	201 (71.8)	566 (79.2)	.013
Severe exacerbation	45 (16.1)	181 (25.3)	.002
Moderate and severe exacerbations	40 (14.3)	165 (23.1)	.002
Exacerbations, mean, N (SD)	3.3 (2.6)	4.3 (3.2)	.002
Moderate exacerbation	3.1 (2.4)	3.9 (2.8)	.001
Severe exacerbation	1.3 (0.7)	1.5 (0.8)	.215
Moderate and severe exacerbations	5.8 (2.8)	6.6 (3.7)	.184
Time to first exacerbation, mean, days (SD)	35.6 (48.3)	42.3 (46.7)	.080
Annualized exacerbations rate per patient, mean, N (SD)			
Any exacerbation	11.6 (9.9)	12.3 (20.2)	.547
Moderate	12.2 (10.1)	13.5 (24.7)	.449
Severe	6.0 (6.9)	5.4 (3.8)	.420
Moderate and severe	15.0 (9.3)	15.9 (8.2)	.544
COPD-related rehospitalization, N (%)	45 (16.1)	181 (25.3)	—
60 days	12 (4.3)	62 (8.7)	.018
90 days	8 (2.9)	54 (7.6)	.006
180 days	30 (10.7)	111 (15.5)	.050
All-cause rehospitalization, N (%)	73 (26.1)	248 (34.7)	—
60 days	21 (7.5)	89 (12.4)	.025
90 days	15 (5.4)	73 (10.2)	.015
180 days	48 (17.1)	160 (22.4)	.068

[a]Index date is the first hospitalization or emergency department visit with a primary or a secondary diagnosis of COPD.
[b]*t*-tests were used for numerical variables and chi-square for categorical variables.
COPD indicates chronic obstructive pulmonary disease; SD, standard deviation.

delayed roflumilast treatment group (**Table 4**). Compared with the patients in the delayed roflumilast treatment group, the patients in the early treatment group had significantly lower total COPD-related costs ($P = .014$) and lower costs for outpatient services ($P = .04$; Table 4).

Early roflumilast treatment was associated with fewer all-cause hospitalizations and emergency department visits, as well as fewer procedures and therapies ($P < .01$; Table 4) and fewer emergency department and outpatient visits per patient ($P < .01$ for all; Table 4). Significantly lower all-cause total and outpatient services costs were observed in the early roflumilast treatment group versus the delayed roflumilast treatment group ($P \leq .01$ for all; Table 4). The mean all-cause total costs in the early roflumilast treatment group also were significantly less than in the delayed treatment group ($41,973 vs $56,084, respectively; $P = .002$; Table 4).

When adjusted for age, sex, insurance plan type, and COPD complexity and comorbidities, the early roflumilast treatment group had a 32% COPD-related annualized cost reduction and a 26% all-cause annualized cost reduction compared with the delayed treatment group ($P < .001$ for both; **Table 5**). The factors that affected the COPD-related costs were a diagnosis of pneumonia in the preindex period ($P = .0001$) and having an HMO versus a PPO health insurance plan ($P = .043$; Table 5). The factors that affected the all-cause costs were age ($P = .023$), a diagnosis of pneumonia in the preindex period ($P = .007$), COPD complexity (lesser vs unclassified; $P = .041$), and having a POS versus a PPO health plan ($P = .029$; Table 5).

Risks for COPD-Related and All-Cause Hospitalizations

Using a logistic regression model and adjusting for demographics, COPD complexity, comorbidities, and insurance plan type, the patients in the early roflumilast treatment group had a 42% lower risk for COPD-related hospitalization (OR, 0.578; 95% CI, 0.403-0.829; *P* = .003) and a 37% lower risk for all-cause hospitalization (OR, 0.633; 95% CI, 0.461-0.869; *P* = .005) than the patients in the delayed roflumilast treatment group.

Discussion

This is the first study to examine the effects of the timing of roflumilast treatment initiation on exacerbation rates and healthcare resource utilization and costs among patients who were discharged from hospitals and emergency department visits as a result of COPD exacerbations. The results from this study demonstrate that the patients receiving roflumilast within 30 days of discharge had significantly fewer future exacerbations, rehospitalizations, and emergency department visits than the patients receiving roflumilast 31 days to 180 days after discharge. The patients who initiated roflumilast treatment early also had a 39% lower risk for a second COPD exacerbation than those who delayed treatment.

Table 3 Adjusted Risk for Exacerbation in Early versus Delayed Roflumilast Treatment[a]

Variable	Odds ratio	95% confidence interval	*P* value
Treatment initiation			
Early vs delayed roflumilast treatment	0.608	0.435-0.851	.004
Age	0.996	0.980-1.012	.618
Sex			
Male vs female	0.964	0.700-1.328	.822
Diagnosed preindex, yes/no			
Asphyxia and respiratory arrest	0.998	0.702-1.418	.990
Respiratory infection	1.217	0.807-1.836	.348
Nutritional abnormalities	1.020	0.542-1.921	.951
Pneumonia	1.122	0.728-1.730	.602
Osteoporosis	1.259	0.702-2.258	.440
COPD complexity			
Lesser vs unclassified	1.310	0.509-3.373	.576
Greater vs unclassified	1.066	0.753-1.508	.720
Insurance plan type			
Indemnity vs PPO	0.808	0.555-1.177	.266
HMO vs PPO	1.118	0.622-2.010	.709
POS vs PPO	0.642	0.366-1.127	.122
Unknown vs PPO	0.672	0.125-3.603	.642
Intercept			.003

[a]Logistic regression model with age, sex, comorbidities (asphyxia and respiratory arrest, respiratory infection, nutritional abnormalities, pneumonia, osteoporosis), COPD disease complexity, and insurance plan as covariates.

COPD indicates chronic obstructive pulmonary disease; HMO, health maintenance organization; PPO, preferred provider organization; POS, point of service.

In a study by Wilkinson and colleagues, the patients who sought earlier treatment for COPD exacerbations (with oral corticosteroids and/or antibiotics) had shorter recovery times (*P* <.001) and a reduced risk for emergency hospitalizations (*P* = .04).[18]

In our study, the early initiation of roflumilast treatment was also associated with a $7273 lower total annualized COPD-related cost and with significantly reduced COPD-related services, resulting in a $14,111 lower annualized all-cause total cost.

Our data were collected during the implementation of the 2010 Affordable Care Act (ACA). The goals of the ACA were to expand the coverage of health insurance, incentivize high-quality healthcare, and make prescription drugs more affordable.[19,20] In 2012, the Centers for Medicare & Medicaid Services (CMS) initiated the Hospital Readmissions Reduction Program, with the aim of penalizing hospitals that have excessive hospital readmissions through the reduction of their Medicare payments.[21] This program was expanded in 2014 to include COPD-related exacerbation readmissions.[21]

Furthermore, although the ACA aimed to reduce costs, prescription drug costs have been increasing. In 2016, a new Covered Outpatient Drugs final rule was issued by the CMS, which aims to ensure that prescription drugs are affordable and accessible to Medicare and Medicaid beneficiaries.[20] As a whole, these systemwide healthcare changes might have had an effect on our results, and future studies evaluating the use of roflumilast after the implementation of the ACA are warranted. Our study could serve as a snapshot of the early ACA implementation landscape and could be compared with more recent claims data that include a similar patient population and study length.

Limitations

Because this study uses claims data that are designed primarily for billing purposes, the severity of COPD could not be classified according to standard definitions,

Table 4 Annualized Healthcare Utilization and Adjusted Costs[a]

Parameter	COPD-related utilization/costs			All-cause utilization/costs		
	Early roflumilast treatment (N = 280)	Delayed roflumilast treatment (N = 715)	*P* value[b]	Early roflumilast treatment (N = 280)	Delayed roflumilast treatment (N = 715)	*P* value[b]
Utilization						
Hospitalizations, N (%)	50 (17.9)	181 (25.3)	.012	73 (26.1)	248 (34.7)	.009
Hospitalizations per patient, mean, N (SD)	2.7 (1.6)	3.0 (1.9)	.317	2.9 (1.8)	3.1 (2.1)	.430
Inpatient length of stay, mean, days (SD)	16.9 (18.7)	16.8 (16.1)	.967	16.2 (17.1)	17.4 (18.9)	.622
Outpatient visits, N (%)	262 (93.6)	679 (95.0)	.383	277 (98.9)	713 (99.7)	.112
Outpatient visits per patient, mean, N (SD)	19.1 (14.8)	26.1 (23.1)	<.001	41.1 (25.8)	50.6 (31.5)	<.001
Emergency department visits, N (%)	41 (14.6)	129 (18.0)	.200	76 (34.9)	261 (36.5)	.005
Emergency department visits per patient, mean, N (SD)	2.4 (1.1)	2.9 (1.6)	.035	3.5 (2.4)	3.6 (2.7)	.740
Procedures/therapies, N (%)	129 (46.1)	390 (54.5)	.016	154 (55.0)	457 (63.9)	.009
Procedures and therapies per patient, mean, N (SD)	19.4 (12.0)	21.0 (6.9)	.324	20.5 (12.2)	21.5 (16.8)	.513
Costs, mean						
Total, $ (SD)	20,503 (36,186)	27,776 (44,063)	.014	41,973 (57,961)	56,084 (68,312)	.002
Hospital services, $ (SD)	52,902 (63,015)	55,369 (60,209)	.780	57,561 (72,878)	60,746 (66,775)	.726
Outpatient services, $ (SD)	5458 (9532)	7214 (12,452)	.040	15,802 (19,750)	21,936 (33,419)	.004
Emergency department services, $ (SD)	1830 (2301)	1948 (2716)	.803	2436 (3674)	2386 (3278)	.909
Procedures/therapies, $ (SD)	2164 (2710)	3035 (8564)	.257	2291 (2541)	2969 (7971)	.300
Medications, $ (SD)	4464 (3290)	4909 (3216)	.326	9412 (8051)	10,385 (8691)	.105
Medications, N (%)	280 (100.0)	714 (99.9)	—	280 (100.0)	714 (99.9)	—

[a]Costs (in US dollars) were adjusted to 2013 by 5% Consumer Price Index.
[b]Multivariate analysis conducted using a generalized linear model with a log-link function and gamma distribution, adjusted for baseline age, sex, COPD complexity, nutritional abnormalities, insurance plan type, and preindex comorbidities and costs, to compare the between-group healthcare costs.
COPD indicates chronic obstructive pulmonary disease; SD, standard deviation.

because of inadequate documentation that is inherent in any retrospective analysis, and the predicted risk for exacerbation was adjusted only by the observed variables and the available data.

Spirometric measurements, such as forced expiratory volume in 1 second, and other outcomes are not available to confirm a diagnosis of COPD or disease severity or to assess the number of exacerbations or other outcomes during follow-up.

In addition, because asthma and COPD can be difficult to differentiate, miscoding errors can occur. Thus, a diagnosis of asthma was not an exclusionary criterion, nor was it assessed as a comorbidity, because excluding all patients with asthma would have greatly reduced our sample size.

Furthermore, not all COPD exacerbations can be detected in claims data, because medical care is not always sought, and it is possible that the patients with severe asthma were misdiagnosed as having COPD.

The imbalance in the number of patients within the

Table 5 Adjusted Total COPD-Related and All-Cause Per-Patient Annual Costs of Healthcare Services[a]

Variable	PPPY COPD-related costs			PPPY all-cause costs		
	Estimate (SE)[b]	95% confidence interval	*P* value	Estimate (SE)[b]	95% confidence interval	*P* value
Treatment initiation						
Early vs delayed roflumilast treatment	–0.3839 (0.0777)	–0.5363 to –0.2316	<.0001	–0.3058 (0.0641)	–0.4315 to –0.1802	<.001
Age	–0.0060 (0.0034)	–0.0127 to 0.0007	.082	–0.0064 (0.0028)	–0.0120 to –0.009	.023
Male vs female	–0.0143 (0.0716)	–0.1547 to 0.1260	.841	–0.0206 (0.0579)	–0.1340 to 0.0928	.721
Preindex diagnosis, yes/no						
Asphyxia and respiratory arrest	0.0873 (0.0761)	–0.0620 to 0.2365	.252	–0.0772 (0.0632)	–0.2012 to 0.0467	.222
Respiratory infection	–0.1682 (0.0891)	–0.3428 to 0.0063	.060	–0.1283 (0.0740)	–0.2732 to 0.0167	.083
Nutritional abnormalities	0.2177 (0.1386)	–0.0539 to 0.4893	.116	0.0709 (0.1144)	–0.1533 to 0.2952	.536
Pneumonia	0.3501 (0.0917)	0.1704 to 0.5297	.0001	0.2018 (0.0754)	0.0540 to 0.3497	.007
Osteoporosis	–0.1167 (0.1230)	–0.3576 to 0.1243	.343	–0.1037 (0.1015)	–0.3026 to 0.0952	.307
COPD disease complexity						
Lesser vs unclassified	0.1143 (0.2046)	–0.2868 to 0.5154	.577	0.3382 (0.1653)	0.0142 to 0.6622	.041
Greater vs unclassified	0.1380 (0.0761)	–0.0111 to 0.2872	.070	0.0365 (0.0630)	–0.0869 to 0.1599	.562
Insurance plan type						
Indemnity vs PPO	–0.1314 (0.0816)	–0.2914 to 0.0285	.107	–0.1286 (0.0685)	–0.2629 to 0.0057	.061
HMO vs PPO	0.2456 (0.1210)	0.0084 to 0.4828	.043	0.0795 (0.1000)	–0.1165 to 0.2754	.427
POS vs PPO	–0.2169 (0.1304)	–0.4726 to 0.0387	.096	–0.2333 (0.1072)	–0.4434 to –0.0233	.029
Unknown vs PPO	0.1144 (0.4064)	–0.6820 to 0.9109	.778	0.6390 (0.3395)	–0.0264 to 1.3044	.060
Log of annualized preindex COPD-related cost	0.5118 (0.0580)	0.3981 to 0.6255	<.0001	0.8218 (0.0683)	0.6880 to 0.9556	<.001
Intercept	8.4563 (0.3457)	7.7787 to 9.1339	<.0001	7.8153 (0.3578)	7.1141 to 8.5165	<.001

[a]Multivariate analysis conducted using a generalized linear model with a log-link function and gamma distribution, which was adjusted for baseline age, sex, COPD complexity, nutritional abnormalities, insurance plan type, and preindex comorbidities and costs, to compare the between-group healthcare costs.

[b]Estimate statement of linear function based on a generalized linear model.

COPD indicates chronic obstructive pulmonary disease; HMO, health maintenance organization; PPO, preferred provider organization; POS, point of service; PPPY, per-patient per-year; SE, standard error.

early roflumilast treatment group (N = 280) versus the delayed roflumilast treatment group (N = 715) may reflect prescribing practices (eg, patients receiving earlier treatment with roflumilast might have had greater disease complexity, as is shown in Table 1 [70.4% of the early roflumilast treatment group had greater disease complexity compared with 60.6% in the delayed roflumilast treatment group; *P* = .004]). Because our information comes from insurance claims data, the distribution of patients into each treatment group could not be predicted nor can the reasons for the disparity be confirmed; however, a multivariate analysis was used to control for disease complexity.

Roflumilast was approved by the US Food and Drug Administration in 2011, placing our study period within the first 2 years that roflumilast was available on the market. Thus, patients receiving treatment with roflumilast within the time frame of the study might have had different results from patients who are currently receiving the drug, because of changes in prescribing patterns as roflumilast becomes established in the COPD pharmacopoeia.

As previously mentioned, the adoption of the ACA during the data collection time frame of this study might also have affected our results.

In addition, because roflumilast is the only approved oral PDE-4 inhibitor for COPD, the effects of the timing

of roflumilast could not be compared with that of other PDE-4–inhibiting drugs, and thus, it is unknown if early treatment with other PDE-4 inhibitors could confer the same benefit.

Early treatment of COPD-related exacerbations with oral corticosteroids and/or antibiotics also has been shown to improve health outcomes.[18] However, because patients in the present study would also have received treatment with oral corticosteroids and/or antibiotics for COPD exacerbations, it is not possible to compare the effects of early versus late roflumilast treatment with that of oral corticosteroids and antibiotics.

Conclusion

Previous evidence has shown that early treatment of COPD exacerbations with corticosteroids or antibiotics improves patient outcomes.[18] This current analysis of patient claims data suggests that the early initiation of roflumilast treatment after a hospitalization or an emergency department visit for a COPD exacerbation is beneficial in lowering the risk for subsequent exacerbations, as well as reducing COPD-related and all-cause healthcare utilization and costs. In addition to reducing disease-related costs, minimizing the impact of an active exacerbation and decreasing the risk for future exacerbations may lead to improvements in patient outcomes. The timely use of roflumilast could represent a valuable treatment in a select group of patients with severe COPD that is associated with chronic bronchitis and a history of exacerbations. ■

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Author Disclosure Statement

Dr Lee is a consultant to Forest Laboratories. Dr Sun and Ms Mocarski were employees of Allergan (Legacy Forest Laboratories) at the time this study was conducted.

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STAKEHOLDER PERSPECTIVE

Continuing Challenges in COPD Management, Despite Its Prevalence and High Economic Burden

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PAYERS: Chronic obstructive pulmonary disease (COPD) is a high priority for the majority of US payers. Despite improvements in smoking rates, the prevalence of COPD continues to rise.[1] The medical costs associated with COPD are also increasing; it is estimated that by 2020, the annual cost of COPD in the United States will reach $49.9 billion, of which $29.5 billion will be attributed to direct healthcare expenditures.[1] Medical costs outweigh pharmacy costs in COPD, especially as a patient's condition progresses to more advanced stages of the disease. Spending associated with hospitalizations accounts for approximately 85% of direct medical costs associated with COPD, and the majority of that cost can be attributed to disease exacerbations.[1]

Reducing acute exacerbations of COPD is therefore a priority for payers, because these often lead to costly hospitalizations. Therefore, many payers offer relatively open access to pharmaceutical therapies for COPD. Add-on therapy increases overall pharmacy spending, which could result in members paying higher copayments or coinsurance for nonpreferred medications. Preferred status for a medication is typically determined in negotiations between the health plan or the pharmacy benefit management and the drug manufacturer.[1]

PROVIDERS: The current clinical guidelines for the treatment of patients with COPD may not provide sufficient guidance for the management of this condition, particularly for primary care physicians. A lack of objective disease markers in COPD complicates the process of patient assessment. Furthermore, limited confidence in the use of spirometry to assess patients' airflow limitations, and the perception that current therapeutic options have limited efficacy, also limit providers' ability to effectively treat this disease.[1] Although pulmonologists acknowledge the central role of primary care physicians in treating patients with stable COPD, they maintain that specialists possess the training and resources to accurately diagnose COPD and appropriately manage patients' care.[1]

Alternative payment programs, including accountable care organizations, bundled-payment initiatives, and the Centers for Medicare & Medicaid Services (CMS)'s Independence at Home demonstration, include incentives for providers to lower hospital admission and readmission rates. CMS has also begun allowing physicians to bill Medicare for "transitional care management" after a Medicare beneficiary has been discharged from the hospital.[2] All these programs have the potential to lead to an uptake of roflumilast in the management of patients with COPD, which has been demonstrated in the current retrospective analysis by Lee and colleagues to have the ability to reduce costs associated with COPD exacerbations.[3]

PATIENTS: Several barriers to access may prevent patients with COPD from adhering to their roflumilast treatment regimen. Many patients with this disease represent underserved populations that may be difficult to reach. These patients may have financial, transportation, or cultural barriers that cause difficulties in continuing smoking-cessation efforts, attending regular office visits, and remaining adherent to their medication.[1] ■

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