Impact of Roflumilast on COPD Exacerbations, Healthcare Utilization and Costs in a Medicare Advantage Population

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BACKGROUND

- Chronic obstructive pulmonary disease (COPD)-related exacerbations have serious health consequences and are associated with declines in lung function, reductions in health related quality of life, and increases in hospitalizations and mortality[1]
- The economic impact of exacerbations is evidenced by the cost of COPD exacerbation-related hospitalizations accounting for the largest share of COPD direct medical costs[2]
- Roflumilast is indicated as a treatment option to reduce the risk of exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations[3]
- An assessment of real-world utilization of roflumilast is essential to better understand the characteristics of COPD patients to whom it is prescribed, the appropriateness of its use, and associated outcomes

OBJECTIVE

- To examine exacerbations, COPD-related healthcare utilization (HCU) and costs associated with roflumilast compared with the standard of care (SOC) in a predominantly elderly, Medicare Advantage Prescription Drug (MAPD) plan COPD population

METHODS

Study Design

- Retrospective cohort study using administrative claims data from a large, national MAPD health plan

Subject Selection

- Medical and pharmacy claims data from May 1, 2010 to December 31, 2012 were used to identify potential subjects, to measure baseline characteristics, and to examine the outcomes of interest

Inclusion Criteria

Roflumilast Cohort

- MAPD members between 40 and 89 years of age with ≥1 COPD diagnosis (ICD-9-CM diagnosis codes of 491.x, 492.x, or 496.x)
- At least one pharmacy claim for roflumilast (first date of the roflumilast claim as index date)
- 12 months of continuous pre-index enrollment, 12 months of continuous post-index enrollment
- At least one pre-index COPD exacerbation of any severity (Table 1)

SOC Cohort

- Same criteria as roflumilast cohort, except without a pharmacy claim for roflumilast at any time during the study period
  - Proxy index dates were randomly assigned to this cohort and based on the distribution of the difference between pre-index exacerbation date and index date of the roflumilast group so that the distribution of time-at-risk was similar between cohorts[4]

Outcomes and Statistical Analyses

- Type and number of exacerbations were assessed (Table 1)
- The quantity and costs of COPD-related and total inpatient and outpatient services received (including inpatient hospitalizations, emergency room visits, outpatient office visits, and pharmacy claims) were assessed for both the pre-index and post-index periods
- Chi-square or Fisher's exact tests and Wilcoxon rank sum tests were used to evaluate the statistical significance of differences in categorical and continuous variables, respectively
- A univariate difference-in-difference (DID) analytic approach was utilized to contrast changes in healthcare utilization, costs, and exacerbations of the roflumilast cohort compared with SOC cohort

Table 1. Exacerbation Type Definitions and Identification Algorithm[5,6]

Exacerbation Type (ranked by decreasing severity)	Identification Method
Inpatient hospitalized exacerbation	Presence of an inpatient hospital stay with a principal diagnosis of COPD with acute exacerbation (ICD-9-CM codes 491.21, 491.22, 493.22), emphysema (ICD-9-CM, 492.8), or a principal diagnosis of respiratory failure (ICD-9-CM codes 518.81, 518.82, 518.84) combined with a secondary diagnosis of COPD with acute exacerbation or emphysema
Emergency room visit exacerbation	Presence of an emergency room visit with a primary diagnosis of COPD (ICD-9 code 491.x, 492.x, or 496.x)
Ambulatory exacerbation identified by qualifying diagnosis	Presence of an office or outpatient non-emergency room visit with any of the following diagnosis codes in the first position: 136.3, 466.0-466.19, 480-486, 487.0, 490, 491.21, 491.22, 493.02, 493.12, 493.22, 493.92, 494.1, 506.0-506.3, 507-507.8, 511.0-511.1, 512-512.8, 517.1, 518.0, 518.81, 518.82, 518.84, 770.84
Ambulatory exacerbation identified by qualifying antibiotic	Presence of a pharmacy claim for the following oral antibiotics commonly used for respiratory infections: amoxicillin, beta-lactamase inhibitors, second or third-generation cephalosporins, macrolides, or doxycycline
Ambulatory exacerbation identified by qualifying systemic steroid	Presence of a pharmacy claim for systemic steroids (oral, intramuscular, or intravenous)

COPD=chronic obstructive pulmonary disease

RESULTS

- Baseline demographics were similar across cohorts except for age, low income subsidy (Table 2), certain comorbid conditions (Table 3), and medications of interest (Table 4)

Table 2. Baseline Demographics

Trait	Roflumilast Cohort n=500	SOC Cohort n=60,145	*P*-value*
Age, years, mean (SD)	69.7 (8.3)	72.3 (9.1)	<0.0001
Age group, n (%)			
40-49	7 (1.40)	1064 (1.77)	<0.0001
50-59	50 (10.00)	4711 (7.83)	
60-69	181 (36.20)	14,540 (24.17)	
70-79	204 (40.80)	26,165 (43.50)	
80-89	58 (11.60)	13,665 (22.72)	
Sex (female), n (%)	271 (54.20)	33,758 (56.10)	0.3870
Race/ethnicity, n (%)			
White	451 (90.20)	52,948 (88.03)	0.1471
Black	39 (7.80)	5265 (8.75)	
Hispanic	2 (0.40)	974 (1.62)	
Other	8 (1.60)	958 (1.59)	
Geographic region, n (%)			
Northeast	11 (2.20)	954 (1.59)	0.0825
Midwest	111 (22.20)	13,674 (22.74)	
South	354 (70.80)	40,985 (68.14)	
West	24 (4.80)	4532 (7.54)	
Low income subsidy, n (%)	243 (48.60)	15,052 (25.03)	<0.0001

*Continuous variables compared via Wilcoxon rank sum test, categorical variables compared via Chi-square or Fisher's exact test, as appropriate.
SD=standard deviation; SOC=standard of care

Table 3. Baseline Comorbid Conditions

Trait	Roflumilast Cohort n=500	SOC Cohort n=60,145	*P*-value*
Deyo-Charlson Comorbidity Index score, mean (SD)	2.63 (1.84)	2.61 (2.31)	0.8569
Comorbidity, n (%)			
Myocardial infarction	60 (12.00)	5956 (9.90)	0.1182
Congestive heart failure	120 (24.00)	10,553 (17.55)	0.0002
Peripheral vascular disease	70 (14.00)	8,000 (13.3)	0.6468
Cerebrovascular disease	53 (10.60)	8112 (13.49)	0.0596
Dementia	8 (1.60)	740 (1.23)	0.4123
Chronic pulmonary disease	485 (97.00)	39,431 (65.56)	<0.0001
Connective tissue disease	23 (4.60)	3,193 (5.31)	0.4812
Peptic ulcer disease	11 (2.20)	1089 (1.81)	0.5159
Mild liver disease	7 (1.40)	606 (1.01)	0.3623
Diabetes without complications	160 (32.00)	20,217 (33.61)	0.4468
Diabetes with complications	27 (5.40)	7039 (11.70)	<0.0001
Paraplegia and hemiplegia	3 (0.60)	521 (0.87)	0.8055
Renal disease	64 (12.80)	11,739 (19.52)	0.0002
Cancer (including leukemia and lymphoma)	52 (10.40)	7146 (11.98)	0.3078
Moderate or severe liver disease	2 (0.40)	249 (0.41)	1.0000
Metastatic carcinoma	1 (0.20)	820 (1.36)	0.0175
AIDS	2 (0.40)	98 (0.16)	0.1997
Respiratory tract cancer	16 (3.20)	1490 (2.48)	0.3011
Cystic fibrosis	0 (0.00)	24 (0.04)	1.0000
Fibrosis from tuberculosis	0 (0.00)	4 (0.01)	1.0000
Bronchiectasis	31 (6.20)	1128 (1.88)	<0.0001
Pneumoconiosis	16 (3.20)	1076 (1.79)	0.0181
Pulmonary fibrosis	50 (10.00)	2693 (4.48)	<0.0001
Pulmonary tuberculosis	1 (0.20)	86 (0.14)	0.5136
Pulmonary sarcoidosis	2 (0.40)	49 (0.08)	0.0664

*Continuous variables compared via Wilcoxon rank sum test, categorical variables compared via Chi-square or Fisher's exact test, as appropriate.
AIDS=acquired immunodeficiency syndrome; SD=standard deviation; SOC=standard of care

Table 4. Baseline COPD Treatment Medications

Treatment	Roflumilast Cohort n=500	SOC Cohort n=60,145	*P*-value*
COPD medication class of interest (not mutually exclusive), n (%)			
SABA	449 (89.80)	25,608 (42.58)	<0.0001
LABA	55 (11.00)	658 (1.09)	<0.0001
ICS + LABA combination product	345 (69.00)	12,629 (21.00)	<0.0001
Anticholinergics (short-acting)	259 (51.80)	9424 (15.67)	<0.0001
LAMA	308 (61.60)	7216 (12.00)	<0.0001
Methylxanthines	90 (18.00)	1404 (2.33)	<0.0001
Oral/IV corticosteroids	446 (89.20)	34,643 (57.60)	<0.0001
ICS	99 (19.80)	3389 (5.63)	<0.0001
Antibiotics	477 (95.40)	53,503 (88.96)	<0.0001
Long-term oxygen use	330 (66.00)	10,607 (17.64)	<0.0001
Combination regimen of interest, n (%)			
ICS + LABA + LAMA combination**	253 (50.60)	4057 (6.75)	<0.0001

*Categorical variables compared via Chi-square or Fisher's exact test, as appropriate.
** "ICS + LABA + LAMA combination" use indicates that a member utilized each of these drug classes at least once during the pre-index period. Concomitant use was not required. Use of individual drug classes (ICS, LABA, and/or LAMA) is reflected under "COPD Medication Class of Interest."
COPD=chronic obstructive pulmonary disease; ICS=inhaled corticosteroids; IV=intravenous; LABA=long-acting β_2-agonists; LAMA=long-acting muscarinic antagonists; SABA=short-acting β_2-agonists; SOC=standard of care

Summary of Results

- DID assessments favored the roflumilast cohort for all exacerbation types (Table 5; negative values favor roflumilast)
- While both the roflumilast cohort and SOC cohort displayed reductions across the majority of COPD-related utilization and cost outcomes during the post-index period, the roflumilast cohort exhibited significantly greater reductions in:
  - Mean COPD-related hospitalizations (annualized at -0.22 vs -0.02; p=0.009)
  - Mean COPD-related outpatient visits (annualized at -3.04 vs -0.74; p<0.0001)
  - Mean COPD-related outpatient costs (annualized at -$376 vs -$55; p<0.0001)
  - Mean COPD-related inpatient costs (annualized at -$1717 vs -$135; p=0.0346)

Table 5. Difference-in-Difference Analyses

Measure	Roflumilast Cohort			SOC Cohort			Roflumilast Change Minus SOC Change	
	Pre-index Period	Post-index Period	Change	Pre-index Period	Post-index Period	Change	DID*	*P*-value**
COPD-related utilization per 30 days, mean (SD)								
Hospitalizations	0.0740 (0.1503)	0.0557 (0.1093)	-0.0182 (0.1444)	0.0092 (0.0426)	0.0079 (0.0391)	-0.0013 (0.0441)	-0.0169	0.009
ER visits	0.0335 (0.1159)	0.0254 (0.0904)	-0.0081 (0.1153)	0.0040 (0.0277)	0.0035 (0.0244)	-0.0005 (0.0318)	-0.0076	0.1434
Outpatient visits	0.7575 (0.7032)	0.5075 (0.4967)	-0.2500 (0.6264)	0.2129 (0.3073)	0.1523 (0.2519)	-0.0606 (0.2945)	-0.1894	<0.0001
COPD-related costs per 30 days, mean (SD)								
Total costs	$843 ($802)	$780 ($797)	-$62 ($850)	$130 ($333)	$110 ($280)	-$19 ($314)	-$43	0.2580
Outpatient-related costs	$43 ($52)	-$30 ($119)	$43 ($52)	$14 ($38)	$9 ($25)	-$4 ($40)	-$26	<0.0001
Inpatient-related costs	$588 ($1,304)	$447 ($1,015)	-$141 ($1,371)	$78 ($492)	$67 ($462)	-$11 ($593)	-$130	0.0346
ER-related costs	$18 ($63)	$14 ($53)	-$4 ($63)	$2 ($17)	$2 ($15)	$0 ($20)	-$4	0.1529
Pharmacy costs	$328 ($259)	$330 ($250)	$2 ($203)	$58 ($123)	$51 ($105)	-$7 ($70)	$9	0.2840
Exacerbations per 30 days, mean (SD)								
Number of exacerbations	0.6584 (0.4366)	0.4589 (0.3210)	-0.1995 (0.3161)	0.3471 (0.2752)	0.2309 (0.2248)	-0.1162 (0.2193)	-0.0833	<0.0001
Number of severe exacerbations	0.0593 (0.1121)	0.0451 (0.0866)	-0.0143 (0.1064)	0.0068 (0.0313)	0.0056 (0.0261)	-0.0011 (0.0327)	-0.0131	0.0060
Number of moderate exacerbations, ER	0.0237 (0.0790)	0.0145 (0.0447)	-0.0091 (0.0693)	0.0029 (0.0185)	0.0024 (0.0155)	-0.0005 (0.0208)	-0.0087	0.0055
Number of moderate exacerbations, OP	0.1373 (0.1847)	0.0829 (0.1167)	-0.0544 (0.1517)	0.0487 (0.0878)	0.0318 (0.0646)	-0.0169 (0.0888)	-0.0375	<.0001
Number of moderate exacerbations, steroid	0.2752 (0.3217)	0.1957 (0.2360)	-0.0794 (0.2611)	0.1169 (0.2053)	0.0816 (0.1556)	-0.0353 (0.1562)	-0.0442	0.0002
Number of moderate exacerbations, antibiotics	0.1629 (0.1732)	0.1207 (0.1520)	-0.0422 (0.1801)	0.1718 (0.1804)	0.1094 (0.1364)	-0.0624 (0.1584)	0.0202	0.0129

*Roflumilast cohort mean difference minus SOC cohort mean difference; positive values favor SOC cohort.
**t-test, unequal variances assumed.
COPD=chronic obstructive pulmonary disease; DID=difference-in-difference; ER=emergency room; OP=outpatient; SD=standard deviation; SOC=standard of care

DISCUSSION AND LIMITATIONS

- Clinical measures, such as forced expiratory volume in 1 second (FEV_1), and symptom frequency and severity were not available to adjust for true COPD severity
- As with all claims-based studies, the validity of subject identification and diagnostic classification, as well as the identification of disease-related utilization and costs, may be impacted by provider, region, or site-specific coding practices
- While the administrative claims data utilized for this study are from a large national health plan with members residing in a broad array of geographic regions, the results may not be generalizable to the entire COPD population

CONCLUSION

- One-year post-initiation of roflumilast revealed directionally desirable outcomes for exacerbations and some markers of HCU, notably severe exacerbations requiring hospitalization
- The directional decrease in the majority of exacerbation types for the roflumilast cohort was observed and in accordance with previous findings in severe to very severe COPD patients initiated on roflumilast[7-9]
- To better control for differences in disease severity, future research should identify methods to combine the robust patient populations found via administrative claims-based research and the validated COPD severity assessments found in patient-reported outcomes methodologies

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