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Baseline history of patients using selexipag for pulmonary arterial hypertension

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Abstract

Introduction: Since its introduction to the market in 2016, selexipag has been an alternative oral therapy among both treatment-naïve patients and those with mono or dual therapy failure; however, limited information is available regarding the presentation and management of patients with pulmonary arterial hypertension (PAH) prior to selexipag initiation. This study examined treatment patterns, healthcare utilization, and costs in the 12 months prior to and the 6 months following selexipag initiation.

Methods: This was a retrospective study of adult commercial and Medicare Advantage with Part D (MAPD) health plan members with a medical or pharmacy claim for selexipag from 1 January 2016 through 31 May 2017, a diagnosis of pulmonary hypertension, and continuous health plan enrollment for 12 months prior to selexipag initiation (baseline period). Treatment patterns, healthcare utilization, and costs were measured over the baseline period and the 6 months following selexipag initiation (among patients with ⩾6 months of follow up).

Results: After inclusion and exclusion criteria were applied, 95 patients were included in the analysis. At study start, 57.9% of patients were prescribed combination therapy, increasing to 69.5% immediately prior to selexipag initiation. Approximately 60% of patients had one baseline regimen. Emergency visits and inpatient admissions during the baseline period occurred in 63.2% and 48.4% of patients, respectively. Baseline medical costs rose steadily, increasing 266.8% in commercial and 26.7% in MAPD enrollees from the beginning to the end of the 12-month baseline period. PAH-related healthcare costs accounted for more than 80% of total costs. Mean medical costs in the 6 months following selexipag initiation were US$17,215 in commercial and US$23,976 in MAPD enrollees.

Conclusions: The majority of patients with PAH remained on the same therapy in the 12 months prior to selexipag initiation despite high rates of healthcare utilization and increasing costs. Mean medical costs appeared to decrease after adding or switching to selexipag.

Keywords: costs, pulmonary arterial hypertension, treatment patterns, utilization

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Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by increased pulmonary vascular resistance caused by pulmonary arteriopathy. If left untreated, PAH may result in right heart failure and death. Data from the United States (US) and European registries estimate a prevalence of 10–26 cases per million population and an incidence of approximately 2–8 cases per million annually.[1–4] Patients with PAH typically present with multiple comorbidities that may contribute to worse clinical outcomes and poor response to therapy.[5–9] In the REVEAL registry, hypertension, obesity, diabetes, and chronic obstructive pulmonary disease (COPD) were associated with significantly worse 6-minute walk test distances; obesity and COPD were associated with worse World Health Organization functional

class; and diabetes and COPD were associated with increased mortality among patients with PAH.[9]

Patients with PAH should be treated with an appropriate initial medication regimen upon diagnosis with close monitoring and treatment escalation as required. Current European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines recommend treatment decisions be guided by a multi-parameter risk assessment to determine a patient's risk for deterioration or mortality.[10] In patients with an inadequate clinical response to mono or dual therapy with endothelin receptor antagonists (ERAs), soluble guanylate cyclase stimulators (sGCSs), or phosphodiesterase type 5 inhibitors (PDE-5is), an additional agent targeting the prostacyclin (PGI_2) pathway should be considered.[10] Previously, medications targeting the PGI_2 pathway were generally only used for patients with severe disease given the complex routes of administration and the potential for administration side effects; however, the advent of oral PGI_2-targeted therapies has opened up the option for earlier use of PGI_2 therapy. Due to the progressive nature of PAH, some argue that triple combination therapy that targets all three pathogenic pathways should be started immediately upon diagnosis to delay pulmonary vascular remodeling.[11]

Selexipag, an oral highly selective IP PGI_2-receptor agonist, entered the market in 2016 and appears to offer improved tolerability compared with other medications in the PGI_2 class with more convenient dosing for patients.[12] In the GRIPHON study, selexipag provided a 40% risk reduction in the first event of death or PAH-related complication compared with placebo.[13,14] Additionally, selexipag increased cardiac index and reduced pulmonary vascular resistance among patients who received previous treatment for PAH.[15]

There is currently limited information about the presentation and management of patients with PAH prior to initiation with selexipag. The purpose of this study was to examine medication treatment patterns, healthcare utilization, and costs for patients with PAH in the 12 months prior to initiation with selexipag. As a secondary objective, healthcare costs and utilization in the 6 months immediately following selexipag initiation was also examined among a subset of patients with adequate follow-up time.

Methods

Data sources

This was a retrospective database study that used medical and pharmacy claims and enrollment information from 01 January 2015 to 31 May 2017 (study period) from commercial and Medicare Advantage with Part D (MAPD) health plan members in the Optum Research database (ORD). Commercial coverage encompasses health insurance not provided by a government agency and MAPD is a health insurance and prescription drug plan offered by private companies approved by Medicare for patients ⩾65 years of age or for younger patients with qualifying disabilities. The ORD is geographically diverse and nationally representative of the US population, containing data on approximately 13.5 million lives annually. Claims for inpatient and outpatient services are presented as International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis and procedure codes, Current Procedural Terminology version 4 (CPT-4) procedure codes, Healthcare Common Procedure Coding System codes and place of service codes. Outpatient pharmacy claims included national drug codes for dispensed medications, quantity dispensed, and dose and days' supply. No identifiable protected health information was extracted or accessed during the study, thus Institutional Review Board approval or waiver of authorization was not required.

Study sample selection

To be eligible for study inclusion, patients must have had ⩾1 medical or pharmacy claim for selexipag from 1 January 2016 through 31 May 2017. The date of the first selexipag claim was considered the index date. Patients were also required to have ⩾1 medical claim with a diagnosis for pulmonary hypertension (PH) (ICD-9-CM codes 416.0, 416.8, or 416.9; ICD-10-CM codes I27.0, I27.2, I27.81, I27.89, I27.9) in any position between the 12-month period prior to (baseline period) and including the index date, continuous enrollment in the health plan with medical and pharmacy benefits for ⩾12 months during the baseline period, and be ⩾18 years of age as of the index year. Patients with an unlisted sex, geographic region, or insurance plan type were excluded from study analyses.

Measures

Baseline demographic and clinical characteristics. Baseline characteristics were measured over the 12-month baseline period and included age, sex, insurance type, pharmacy coverage, geographic region, and comorbidity based on the Charlson comorbidity index (a measure of 1-year mortality risk based on weighted comorbid conditions with higher scores indicating more risk)[16,17] and Clinical Classifications software managed by the Agency for Healthcare Research (AHRQ).[18]

Outcomes. Treatment patterns were recorded during the baseline period. The first and last PAH treatment regimens filled in the baseline period were recorded and included the following drug classes: ERAs (ambrisentan, bosentan, macitentan), PDE-5is (sildenafil, tadalafil), PGI_2s (treprostinil, epoprostenol, iloprost), and sGCS (riociguat). Medication adherence was calculated using proportion of days covered (PDC), defined as the number of days medication was available divided by the number of days between the first prescription claim and the end of the study period. A threshold of 80% was used to categorize patients as highly adherent.[19] Persistence was calculated as the number of months from the start of the first fill until therapy discontinuation. Whether a patient switched, discontinued, or augmented their baseline treatment regimen was also identified. Discontinuation was defined as a gap in therapy of ⩾90 days after the run-out of days' supply of the last prescription filled prior to the gap in therapy. Patients with an addition or fill for a new PAH-related medication prior to the discontinuation of the ongoing regimen were considered to have augmented therapy and patients with evidence of discontinuation of a PAH-related medication and a fill for a new PAH-related medication were considered to have switched. The PAH regimen at selexipag initiation was also recorded.

Baseline all-cause and PAH-related healthcare utilization was calculated as the number and percentage of patients with ambulatory visits (office and outpatient), emergency visits, and inpatients stays. Utilization was considered PAH-related if the medical claim had a diagnosis code for PH in the first or second position. All-cause healthcare utilization was also calculated for the 6 months following selexipag initiation among patients who had ⩾6 months of continuous health plan enrollment.

Mean baseline all-cause and PAH-related healthcare costs were calculated over the 12-month baseline period and quarterly. Costs included the combined health plan and patient-paid amounts adjusted for inflation from 2015 to 2016 using the annual medical care component of the Consumer Price Index. Costs were presented in subcategories or pharmacy, ambulatory, emergency services, inpatient, and other medical costs. Other medical costs included costs related to the site of service, including independent clinics that are not part of a hospital, urgent care facilities, home health care, group homes, assisted living facilities, and laboratories independent of an institution. Costs were considered PAH-related if the claim had a diagnosis code for pulmonary hypertension in the primary or secondary position or if there was an outpatient pharmacy claim for a PAH-related medication. Mean follow-up all-cause medical costs were also calculated as above for patients with ⩾6 months of continuous follow-up health plan enrollment. A paired analysis was conducted among the subset of patients with ⩾6 months of follow-up duration to determine the mean difference in all-cause and PAH-related medical costs from baseline to follow up.

Statistical analysis

A Kaplan–Meier analysis was performed to show the time to discontinuation, augmentation, and switch for the first PAH regimen during the baseline period. Mean healthcare utilization and costs over the 12-month base period and the 6-month follow-up period were calculated and presented separately for commercial and MAPD health plan members due to the differences in demographics and cost structures between these two health plans.

Results

Baseline measures

Study sample and baseline characteristics. In the claims data, 176 patients with ⩾1 medical or pharmacy claim for selexipag from 1 January 2016 to 31 May 2017 were identified. Of these patients, 95 met the study inclusion and exclusion criteria. The mean age was 61.8 ± 13.8 years and the majority of patients (70.5%) were female (Table 1). The mean Charlson comorbidity score was 3.6 ± 2.3, with 46.3% of patients

Table 1. Baseline demographic and clinical characteristics.

Patient characteristics	Overall sample ($N = 95$)
Age (years), mean (SD)	61.8 (13.8)
Female sex, *n* (%)	67 (70.5)
Insurance plan type, *n* (%)	
Commercial	31 (32.6)
MAPD	64 (67.4)
Charlson comorbidity score, mean (SD)	3.6 (2.3)
Charlson comorbidity score, *n* (%)	
0–1	22 (23.2)
2–3	29 (30.5)
4+	44 (46.3)
Common comorbidities, *n* (%)	
Other lower respiratory disease	85 (89.5)
Hypertension	77 (81.1)
Heart failure	61 (64.2)
Other connective tissue disease	51 (53.7)
Respiratory failure, insufficiency, arrest	50 (52.6)
Diseases of the urinary system	49 (51.6)
Disorders of lipid metabolism	48 (50.5)
Respiratory infections	48 (50.5)
Chronic obstructive pulmonary disorder	47 (49.5)
Sleep apnea	39 (41.1)
Obesity	29 (30.5)
Thyroid disease	27 (28.4)
Type 2 diabetes	25 (26.3)

MAPD, Medicare Advantage with Part D; SD, standard deviation.

having a score ⩾4. Notable comorbidities in this population included chronic respiratory diseases [COPD and bronchiectasis (52.6%) and sleep apnea (41.4%)], circulatory diseases [hypertension (81.1%) and heart failure (64.2%)], and endocrine and metabolic diseases [obesity (30.5%), thyroid disease (28.4%), and type 2 diabetes (26.3%)].

Baseline treatment patterns. Prior to initiating selexipag, only 5.3% of patients had no evidence of a prior PAH medication (Figure 1). Most patients were treated with combination therapy as the first baseline regimen (57.9%), usually an ERA + PDE-5i (35.8%) or an ERA + PDE-5i + PGI_2 (11.6%). The remaining patients were treated with monotherapy (36.9%), most often an

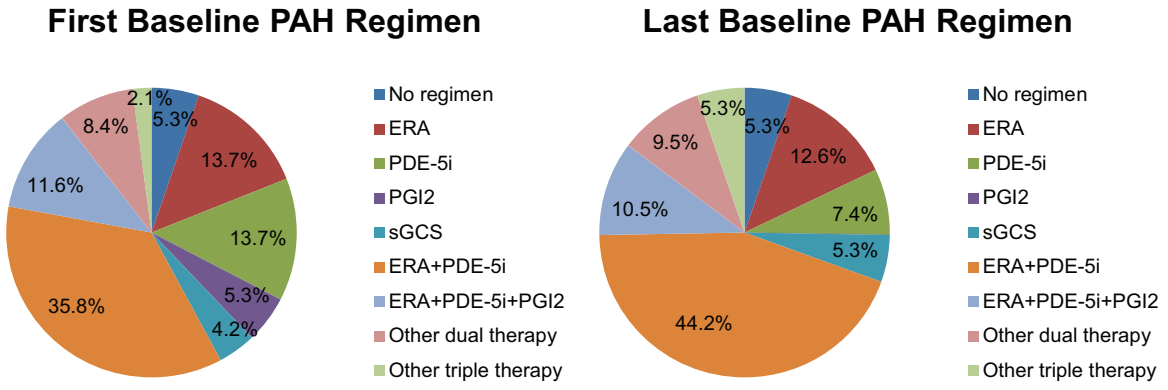

Figure 1. Baseline PAH medication regimens.
ERA, endothelin receptor antagonist; PDE-5i, phosphodiesterase type 5 inhibitor; PGI_2, prostacyclin; sGCS, soluble guanylate cyclase stimulator.

Table 2. PAH medication adherence, persistence, discontinuation and switching during the baseline period.

Measure	Patients with PAH Regimen (n = 90)
Persistence with PAH therapy (days) during baseline, mean (SD)	289.8 (108.4)
Discontinuation of any PAH therapy during baseline, *n* (%)	3 (3.3)
PDC with PAH therapy, mean (SD)	0.9 (0.1)
PDC ⩾0.8, *n* (%)	80 (89.9)
Freedom from discontinuation of first baseline PAH regimen at 12 months	97.2%
Freedom from augmentation of first baseline PAH regimen at 12 months	78.6%
Freedom from switching first PAH regimen at 12 months	76.9%

PAH, pulmonary arterial hypertension; PDC, proportion of days covered; SD, standard deviation.

ERA (13.7%) or PDE-5i (13.7%). Patients remained on their first baseline regimen for a mean duration of 223.6 ± 139.7 days. In the last regimen prior to selexipag initiation, the percentage of patients on combination therapy increased to 69.5%, most commonly an ERA + PDE-5i (44.2%) or an ERA + PDE-5i + PGI_2 (10.5%). The majority of patients had only one PAH regimen (60.0%) and 34.7% had 2–4 regimens during the 12-month baseline period (Table 2). The mean time to discontinuation with any baseline PAH medication therapy was 289.8 ± 108.4 days and the mean adherence, measured by PDC, was 94%. Over the 12-month baseline period, the Kaplan–Meier probabilities of discontinuation, augmentation, and switch of PAH therapy were 2.8%, 21.4% and 23.1%, respectively.

Baseline healthcare utilization and costs. Baseline healthcare resource utilization is shown in Table 3. Over the 12-month baseline period, all patients had an all-cause ambulatory visit and averaged approximately 39.1 and 37.8 visits among commercial and MAPD enrollees, respectively. At least one all-cause emergency room visit occurred in 63.2% of patients and at least one all-cause inpatient admission occurred in 48.4%. PAH-related inpatient admissions occurred in 38.7% and 42.2% of commercial and MAPD enrollees, respectively. Among patients with a PAH-related inpatient admission (n = 39), 43.6% were readmitted during the baseline period, with 94% of readmissions being PAH-related (data not shown).

Table 3. Baseline healthcare resource utilization.

Measure	Total (n = 95)	Commercial (n = 31)	MAPD (n = 64)
All-cause utilization			
Ambulatory visits, *n* (%)	95 (100.0)	31 (100.0)	64 (100.0)
Count, mean (SD)	38.2 (24.8)	39.1 (34.2)	37.8 (19.0)
Emergency visit, *n* (%)	60 (63.2)	20 (64.5)	40 (62.5)
Count, mean (SD)	1.8 (2.2)	1.7 (1.9)	1.8 (2.3)
Inpatient visit, *n* (%)	46 (48.4)	13 (41.9)	33 (51.6)
Count, mean (SD)	0.9 (1.2)	0.6 (0.8)	1.0 (1.4)
PAH-related utilization			
Ambulatory visit, *n* (%)	95 (100.0)	31 (100.0)	64 (100.0)
Count, mean (SD)	10.9 (7.1)	9.3 (4.9)	11.7 (7.8)
Emergency visit, *n* (%)	11 (11.6)	4 (12.9)	7 (10.9)
Count, mean (SD)	0.2 (0.7)	0.2 (0.6)	0.2 (0.7)
Inpatient visit, *n* (%)	39 (41.1.)	12 (38.7)	27 (42.2)
Count, mean (SD)	0.7 (1.1)	0.5 (0.7)	0.8 (1.2)

MAPD, Medicare Advantage with Part D; PAH, pulmonary arterial hypertension; SD, standard deviation.

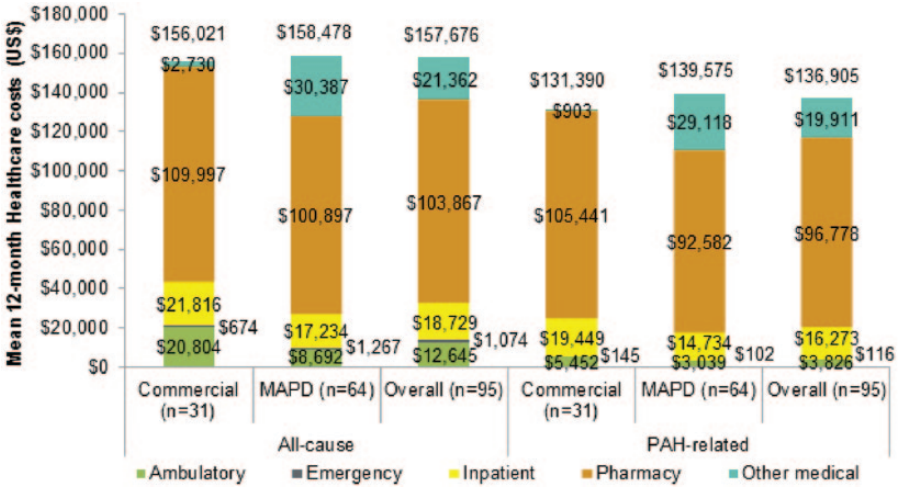

Figure 2. Baseline healthcare costs.
MAPD, Medicare Advantage with Part D; PAH, pulmonary arterial hypertension.

Baseline mean all-cause healthcare costs were similar among commercial and MAPD enrollees (US$156,021 ± US$114,989 *versus* US$158,478 ± US$101,125; Figure 2). Pharmacy costs accounted for 65.9% of total all-cause costs. All-cause mean medical costs were slightly higher among MAPD enrollees compared with commercial enrollees (US$57,581 ± US$74,074

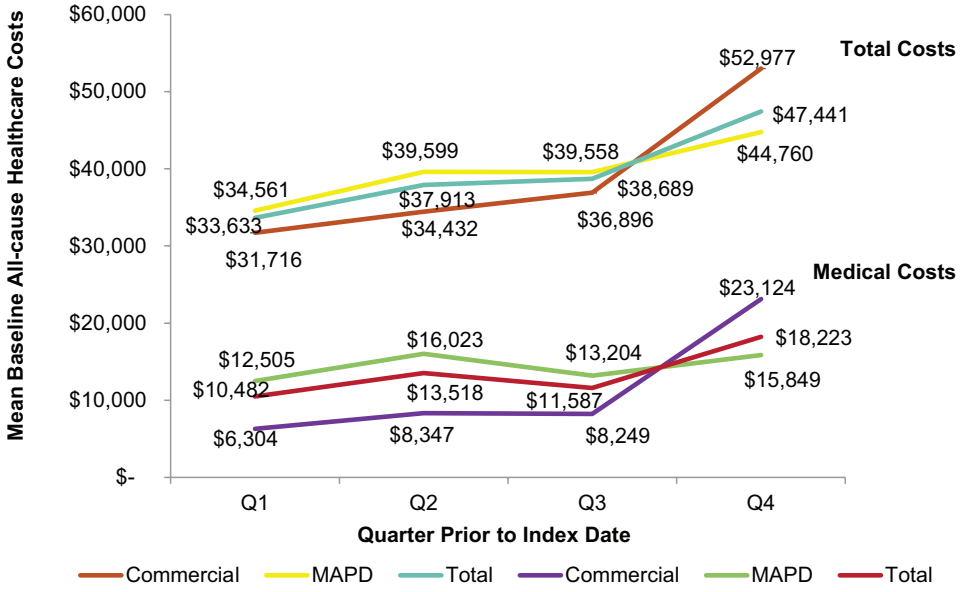

Figure 3. Baseline healthcare costs by quarter.
MAPD, Medicare Advantage with Part D.

versus US$46,024 ± US$76,392). This was primarily due to higher other medical costs, mainly home healthcare expenses, in a small subset of patients (n = 13, 20.3%) who incurred 94.2% of the total baseline other medical costs among MAPD enrollees.

Total baseline healthcare costs rose steadily each quarter for both commercial and MAPD enrollees during the 12-month baseline period (Figure 3). Mean all-cause baseline medical costs increased 266.8% and 26.7% among commercial and MAPD enrollees, respectively, from the first to the last quarter prior to selexipag initiation. This increase was driven primarily by increased inpatient costs. A small subset (n = 7, 22.6%) of the commercial patient sample accounted for 76.5% of the total baseline costs due to particularly high costs in the last quarter prior to selexipag initiation. Pharmacy costs increased moderately each quarter, increasing 17.5% and 31.1% among commercial and MAPD enrollees, respectively from quarter 1 to quarter 4.

Mean healthcare costs related to PAH were US$131,390 ± US$106,877 among commercial enrollees and US$139,575 ± US$96,630 among MAPD enrollees (Figure 2), and consisted of approximately 84% and 88% of all-cause costs, respectively. PAH-related costs were driven by pharmacy costs, which represented 66% of all-cause costs and 71% of PAH-related costs.

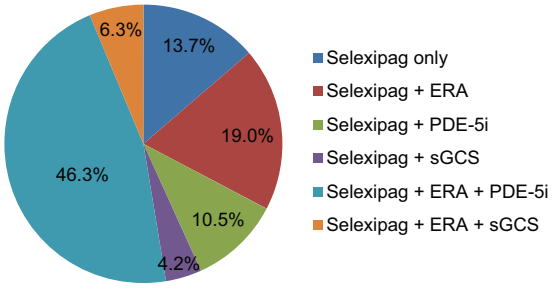

Figure 4. Index PAH medication regimens.
ERA, endothelin receptor antagonist; PAH, pulmonary arterial hypertension; PDE-5i, phosphodiesterase type 5 inhibitor; PGI2, prostacyclin; sGCS, soluble guanylate cyclase stimulator.

Follow-up measures

Selexipag was initiated as monotherapy for 13.7% of patients and as combination therapy with an ERA + PDE-5i in 46.3% (Figure 4). In the 6 months following selexipag initiation, among patients that had ⩾6 months of follow up (total = 42; 29 = MAPD, 13 = commercial), healthcare utilization remained high. All patients had an ambulatory visit, with an average of 15.8 and 21.2 visits for commercial and MAPD enrollees, respectively; and 15.4% and 41.4% of commercial and MAPD enrollees, respectively had an inpatient admission. Total all-cause mean healthcare costs during the 6-month follow-up period were US$157,904 ± US$70,367 in commercial

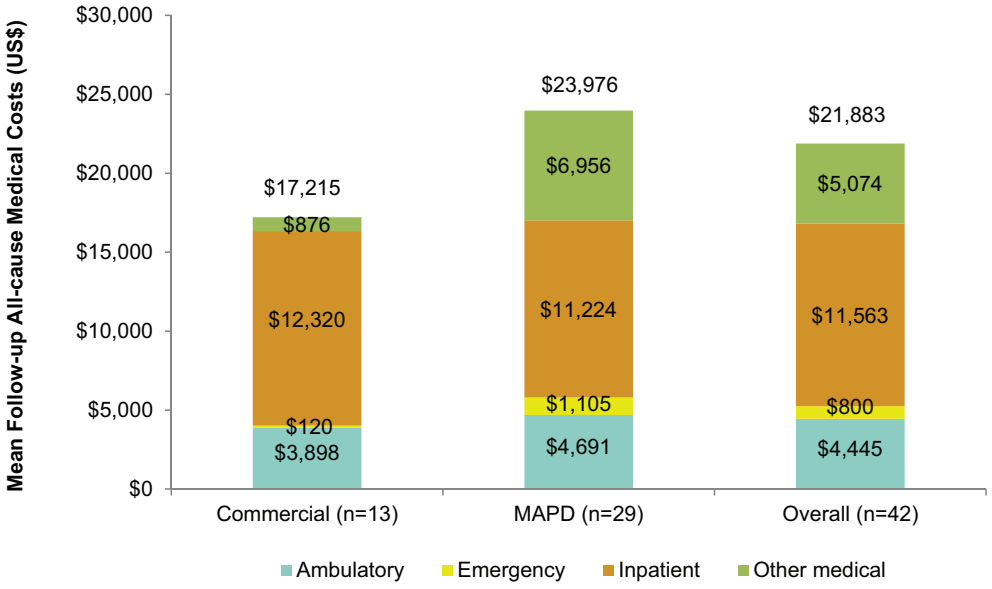

Figure 5. Six-month mean follow-up all-cause medical costs.
MAPD, Medicare Advantage with Part D.

enrollees and US$182,238 ± US$85,293 in MAPD enrollees, driven heavily by pharmacy costs. Follow-up mean all-cause medical costs appeared lower in commercial versus MAPD enrollees (US$17,215 ± US$40,306 versus US$23,976 ± US$36,130; Figure 5). The higher medical costs in MAPD enrollees were mostly a result of higher other medical costs (US$6,956 *versus* $876). Inpatient costs accounted for 71.6% of total medical costs in commercial enrollees and 46.8% in MAPD enrollees. In a paired analysis among patients with ⩾6 months of follow-up duration (n = 42), all-cause medical costs decreased 18% and PAH-related medical costs decreased 29% from baseline to follow up.

Discussion

In the year prior to selexipag initiation, approximately 58% of patients received combination therapy as their first baseline PAH medication regimen, increasing to almost 70% immediately prior to starting selexipag. This is slightly higher than the 45% of patients on combination therapy in the REVEAL registry[20] and much higher than the proportion receiving combination therapy reported in previous claims studies, ranging from 5% to 20%.[5,21–23] The high rates of combination therapy use among patients in our study population likely reflect the fact that patients had prevalent disease and were not newly diagnosed or treatment-naïve like those in many previous studies. As PAH is a progressive disease, these were likely changes in prescribing patterns based on recent research supporting the use of upfront combination therapy as well as recommendations to treat to a 'low-risk' status.

As in previous studies,[5–8,20] comorbidities were prevalent in this population. The average Charlson comorbidity index score was 3.6 and almost half of the patient population had a score of 4 or greater. Comorbidities associated with worse outcomes and greater mortality among patients with PAH, such as hypertension, COPD, obesity, and diabetes were notably present in a majority of patients. The REVEAL registry noted many of the same comorbidities including systemic hypertension (40%), obesity (33%), clinical depression (25%), obstructive airway disease not considered the cause of PAH (22%), sleep apnea (21%), and diabetes mellitus (12%).[24]

Ambulatory visits during the 12 months prior to selexipag initiation averaged more than three visits per month and approximately 42% (commercial) and 52% (MAPD) of patients were hospitalized. Among those that were hospitalized, 85% had a PAH-related hospitalization. The high rate of inpatient utilization observed in this study is consistent with that found in previous studies.[5,25,26] Burger and colleagues showed that 57%

of patients newly diagnosed with PAH had ⩾1 hospitalization post-enrollment and 52.4% of hospitalizations were PAH-related.[26] Several clinical trials have provided evidence that treatment with appropriate PAH therapy can reduce the risk and frequency of hospitalization.[14,27,28]

Consistent with the high rate of healthcare utilization, healthcare costs were also high in this population, as well as in previous studies of patients with PAH.[5,6,22,29] Pharmacy costs were the major cost driver; however, costs for inpatient care accounted for approximately one-third of total medical costs. Pharmacy costs doubled from quarter 1 to quarter 4 of the baseline period, which is likely due to the progressive nature of PAH and patient deterioration. Similar to previous estimates,[6,22] PAH-related costs represented a significant portion of total all-cause healthcare costs, accounting for 81% (commercial) and 88% (MAPD) of total healthcare costs in this study population. Driven primarily by increased inpatient costs, mean total healthcare costs rose steadily each quarter for both commercial and MAPD enrollees, increasing approximately 267% and 27%, respectively in the last quarter prior to selexipag initiation. Among patients who had ⩾6 months of follow up after selexipag initiation, mean medical costs appeared to decrease over the follow-up period, particularly among commercial enrollees.

Despite the high healthcare utilization and rising costs observed in this population that should have triggered therapy escalation, 60% remained on the same therapy for the entire 12-month period prior to selexipag initiation. This highlights the need for more frequent PAH risk assessments to determine treatment adequacy to allow patients to escalate to a more effective treatment strategy prior to experiencing clinical deterioration leading to higher healthcare utilization and costs. The trend of increasing costs we observed, particularly in the last quarter of selexipag initiation, warrants additional research to determine whether initiation with a PGI_2 earlier in the course of disease may decrease the burden to the patient and healthcare system.

Limitations

Results of this study were limited to patients in a large US managed care population with PAH who initiated selexipag, thus results may not be representative of all patients with a PAH diagnosis. Additionally, the ICD-10-CM codes used to identify patients were for pulmonary hypertension, not PAH specifically, and therefore patients may have been misidentified; however, both National Drug Code pharmacy codes and ICD-10-CM diagnosis codes were used to decrease the likelihood of misidentification. It is possible that some patients with group 2 or 3 PH were inaccurately treated with selexipag, which is indicated only for PAH. Medications prescribed for PAH prior to the 12-month baseline period were not captured in this study, and medications provided as part of a clinical trial may not have been accounted for in the claims data. Dispensed medication can be identified from pharmacy claims; however, it does not indicate that the medication was consumed or taken as prescribed by the patient. Lastly, in the analysis of healthcare costs, monetary amounts estimated to be paid by other payers for a total paid amount were not incorporated resulting in more conservative cost estimates.

Conclusion

The majority of patients with PAH remained on the same therapy in the 12 months prior to selexipag initiation despite high rates of healthcare utilization and rising healthcare costs. Adherence to PAH medications was high and therapy adjustments were less common before augmenting with or switching to selexipag. Mean all-cause baseline healthcare costs, driven to a large degree by pharmacy costs, increased substantially over time, but mean medical costs appeared to decrease after treatment augmentation or a switch to selexipag. Patients should receive regular PAH risk assessments to verify treatment adequacy and to allow for potential therapeutic escalation prior to clinical deterioration.

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Conflict of interest statement

KH is on the Speaker's Bureau and has received grants/contracts from Actelion Pharmaceuticals.

MH and CE are employees of Optum, which was funded by Actelion Pharmaceuticals to conduct this study. JP, YT, and WD are employees of Actelion Pharmaceuticals.

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