Research Article

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Healthcare use and costs among Medicare enrollees on pirfenidone versus nintedanib for idiopathic pulmonary fibrosis

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Aim: Compare healthcare utilization and costs between Medicare beneficiaries with idiopathic pulmonary fibrosis (IPF) receiving pirfenidone or nintedanib. **Methods:** Retrospective cohort study of Medicare beneficiaries (100% Research Identifiable Files) with IPF who initiated pirfenidone or nintedanib between 15 October 2014 and 31 December 2015. Inverse probability of treatment weighting using propensity scores adjusted for baseline covariates. Outcomes: hospitalization and monthly costs. **Results:** Hazard and incidence rate ratios (95% CI) for all-cause (0.79 [0.68–0.91]; 0.69 [0.59–0.82]) and respiratory-related (0.80 [0.65–0.97]; 0.71 [0.57–0.90]) hospitalizations favored pirfenidone versus nintedanib. Monthly inpatient costs were lower for pirfenidone versus nintedanib patients; outpatient and pharmacy costs were similar. **Conclusion:** In patients with IPF, pirfenidone compared with nintedanib has a moderate but significant protective effect on hospitalization, corresponding to lower inpatient costs.

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Keywords: healthcare costs • hospitalization • idiopathic pulmonary fibrosis • lung diseases • treatment outcome

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrotic interstitial lung disease (ILD) of unknown cause that is characterized by a specific radiologic or pathologic pattern of usual interstitial pneumonia (UIP) [1]. A 2011 estimate of US IPF prevalence among those aged 65 and older was 495 per 100,000 [2]. Prognosis is poor and associated with a high risk of comorbidities [3].

Effective treatments for IPF were not available prior to 2014. In 2014, two novel antifibrotic drugs, pirfenidone and nintedanib, were demonstrated to slow disease progression in randomized clinical trials (RCT) and became the first US FDA approved treatments for IPF. Past treatment modalities failed to improve quality of life [4,5], and other treatment recommendations were mainly supportive [6]. Moreover, disease management often required hospitalization to manage complications and comorbidities [3,7,8].

Despite the acceptance of antifibrotic drug therapy into IPF treatment guidelines and routine clinical practice, real-world evidence comparing the effectiveness of pirfenidone and nintedanib on healthcare utilization is limited [9]. A recent US claims study found an overall decreased risk of all-cause acute hospitalizations in antifibrotic-treated versus untreated IPF patients, although it did not compare hospitalizations between the drugs [10]. Other evidence is confined to clinical trial data comparing individual antifibrotic agents to placebo treatment. Pooled RCT data have demonstrated a lower risk of respiratory-related hospitalizations in IPF patients treated with pirfenidone as compared with placebo [11]. Similarly, two replicate Phase III trials of nintedanib versus placebo showed a slowing of disease progression, but did not examine any measures of healthcare resource utilization or cost [12].

This study aimed to address the dearth of evidence on the comparative effectiveness of two antifibrotic treatments. Using real-world data from Medicare beneficiaries, we compared both healthcare resource utilization and costs between beneficiaries with IPF receiving pirfenidone and those receiving nintedanib.

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Materials & methods

Study design & data source

This comparative effectiveness and cost study used a retrospective cohort design for a head-to-head comparison of utilization and costs among IPF beneficiaries initiating pirfenidone and nintedanib. We used Medicare beneficiary- and fee-for-service claim-level administrative data from a 100% sample of Medicare beneficiaries (Research Identifiable Files). This study was exempt from review by an institutional review board.

Patient population & timeframe

We identified all beneficiaries diagnosed with IPF who initiated antifibrotic therapy (pirfenidone or nintedanib) in the identification (ID) period between 15 October 2014 (the US FDA approval date for both agents) and 31 December 2015. Beneficiaries were included if they had at least one claim for a prescription fill of pirfenidone or nintedanib during the ID period (with the date of the first claim for either agent serving as the index date); had at least one inpatient or one outpatient claim with IPF as a listed diagnosis (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] codes: 516.3, 516.30 and 516.31; 10th Revision [ICD-10-CM] codes: J84.111, J84.112), occurring on or before the index date; and were at least 67 years old on the index date, allowing for 2 years of observation prior to index (baseline period) and the identification of newly diagnosed beneficiaries (i.e., those whose first observed IPF diagnosis date was within 1 year prior to index). We excluded beneficiaries who received a lung transplant prior to index, were not continuously enrolled in fee-for-service Medicare (Parts A and B) or Medicare Part D, or who were enrolled in Medicare Advantage (Part C) in the baseline period.

Beneficiaries were followed until receiving a lung transplant, index medication switching or discontinuation, death, end of enrollment in fee-for-service Medicare (Parts A and B), in Medicare Part D or study end (31 December 2015), whichever came first; thus, no minimum follow-up time was required. Beneficiaries who discontinued index treatment were identified by a gap in treatment of more than 60 days, with the discontinuation date on day 60.

Stabilized inverse probability of treatment weighting & measures

Stabilized inverse probability of treatment weighting (IPTW) using the propensity score [13,14] was implemented to approximate covariate balance between the treatment groups that is normally achieved by randomization. The following baseline characteristics were derived from Medicare data and used to estimate the propensity score, or probability of receiving the index treatment: age, gender, region, Charlson comorbidity index [15,16] (CCI, modified by excluding chronic pulmonary disease), chronic obstructive pulmonary disease (COPD), newly diagnosed IPF, pneumonia in 3 months prior to index, quartile of median income of beneficiary residential area [17], and distance from residential area (based on ZIP code) to interstitial lung disease (ILD) specialty center [18]. The variables were chosen based on observed differences between the study groups or clinical relevance determined by a specialist in IPF. The inverse probability of receiving the index treatment weight was then calculated. To control for unstable IPTW arising from very small or large propensity scores, stabilized IPTW was computed by multiplying the IPTW by the marginal probability of a given treatment received [14].

The primary outcomes were the risk and rate of inpatient hospitalization (both all cause and respiratory-related) in the post-index period. Other utilization outcomes (both all cause and respiratory related) in the post-index period were the number of monthly inpatient hospitalizations, emergency department (ED) visits, and physician office visits. Monthly costs (all cause, respiratory-related and IPF specific), which correlate with utilization, were also measured for inpatient, outpatient and pharmacy services. Respiratory-related care was defined by an inpatient claim with a principal discharge diagnosis of respiratory disease (ICD-9-CM: 460.xx-519.xx; ICD-10-CM: J00.xx-J99.xx) or an outpatient claim with any diagnosis of respiratory disease or a pharmacy claim for an antifibrotic medication, inhaled corticosteroids, azathioprine, n-acetylcysteine, mycophenolate mofetil or an antibiotic filled within 15 days of a medical claim with a pneumonia diagnosis that can be treated with antibiotics. IPF-specific care was defined as a claim for an antifibrotic medication.

In addition to the baseline characteristics used in the weighting procedure, we reported race and the number of Healthcare Cost and Utilization Project (HCUP) chronic conditions [19]. Additionally, we measured the following comorbidities: obstructive sleep apnea, lung cancer, pneumothorax, gastroesophageal reflux, obesity and cardiovascular conditions (pulmonary hypertension, ischemic heart disease, congestive heart failure, venous thromboembolism, atrial fibrillation and cor pulmonale). We also reported several proxy measures of disease severity in the baseline period: recent respiratory-related hospitalizations (in the 3 months prior to index), oxygen use in

the 1 year prior to index, pulmonary rehabilitation in the 1 year prior to index, and computerized tomography (CT) scan in the 1 year prior to index. Other measures reported descriptively were adherence to index treatment (measured as proportion of days covered [PDC] ≥80%), and follow-up time after index. PDC was determined by dividing the number of available days of index therapy by days of follow-up [20]. Treatment discontinuation was defined as a gap in use of at least 60 days.

Statistical analysis

Descriptive statistics were generated for all measures among the treatment groups. To compare monthly cost measures and number of office visits, t-test weighted by stabilized IPTW was used. For number of ED visits and hospitalizations, Wald Chi-square test based on weighted negative binomial model was used. We compared the weighted risk of all-cause and respiratory-related hospitalization between pirfenidone and nintedanib using cumulative probability curves and Cox proportional hazards regression. The proportional hazard assumption was checked for all covariates. Additionally, we compared the incidence rate of all-cause and respiratory-related hospitalizations using negative binomial regression. The final Cox model and negative binomial model included all variables used in stabilized IPTW, irrespective of statistical significance, to adjust for potential residual confounding.

Results

Baseline characteristics

We identified 7237 Medicare beneficiaries who received antifibrotic therapy in the ID period (15 October 2014 to 31 December 2015). Of these, 3546 beneficiaries were at least 67 years old upon initiation of antifibrotic therapy, were continuously enrolled in Medicare Part A, B, and D, were not recipients of a lung transplant, and had ≥1 medical claim with a diagnosis of IPF on or before their index date. The final treatment groups comprised 2082 beneficiaries initiating pirfenidone and 1464 initiating nintedanib (Table 1).

At baseline, mean (standard deviation, SD) age was 75.6 (5.5) years for initiators of pirfenidone and 76.3 (5.9) years for nintedanib initiators. A smaller percentage of pirfenidone initiators compared with nintedanib initiators were female (33.3 vs 40.5%). Beneficiaries in both groups were mostly white (both 95%) and represented all US geographic regions, while predominantly from the South (both >38%). Pirfenidone initiators more often resided in areas representing the highest quartile of median household income than nintedanib initiators (37.2 vs 27.2%). Distances between beneficiary residential area and the nearest ILD specialty center were similar between both groups (Table 1, unweighted).

For other baseline characteristics, about half of pirfenidone initiators and a higher percentage of beneficiaries starting nintedanib were newly diagnosed with IPF within 1 year prior to index (50.9 vs 57.5%). Pirfenidone initiators had a lower overall comorbidity burden versus nintedanib initiators (mean modified CCI 3.2 [2.9] vs 3.4 [2.9]). In addition, pirfenidone compared with nintedanib initiators had lower proportions of several individual comorbidities: COPD (57.0 vs 61.1%), stroke (7.1 vs 8.9%), and pneumonia within the 3 months prior to index (9.7 vs 12.0%). Rates of other selected comorbidities were similar at baseline between the study groups. The proxy measures of disease severity were mostly similar between treatment groups, with the exception of pirfenidone initiators having fewer CT scans in 1 year prior to index (73.8 vs 77.4%) (Table 1, unweighted).

After implementation of the IPTW procedure, the baseline characteristics included in weighting were nearly identical (Table 1).

Medication adherence & follow-up length

Following index, pirfenidone initiators had longer mean follow-up time compared with those on nintedanib (184.4 [97.7] days vs 161.2 [103.9] days). In that period, the percentage of beneficiaries who were adherent to index medication was greater among pirfenidone versus nintedanib initiators (65.4 vs 60.5%) (results not displayed).

Healthcare resource utilization

Monthly weighted respiratory-related utilization following initiation of antifibrotic therapy was lower for pirfenidone beneficiaries compared with nintedanib beneficiaries. The mean (SD) number of respiratory-related inpatient hospitalizations per month (0.041 [0.20] vs 0.052 [0.25]) and number respiratory-related ED visits per month (0.028 [0.11] vs 0.038 [0.19]) were significantly lower among pirfenidone versus nintedanib initiators. However, there was no significant difference in respiratory-related office visits. Similar results were observed for

Table 1. Baseline demographics and clinical characteristics among Medicare beneficiaries with IPF who initiated antifibrotic therapy.

Variables	Unweighted cohorts		Weighted cohorts	
	Pirfenidone	Nintedanib	Pirfenidone	Nintedanib
Number of subjects	2082	1464	2082	1464
Age, year, mean (SD)	75.6 (5.5)	76.3 (5.9)	75.8 (5.7)	75.9 (5.7)
Age category, n (%)				
– 67–74	971 (46.6)	618 (42.2)	933 (44.8)	652 (44.6)
– 75–84	961 (46.2)	687 (46.9)	968 (46.5)	683 (46.7)
– 85+	150 (7.2)	159 (10.9)	180 (8.7)	128 (8.7)
Female, n (%)	694 (33.3)	593 (40.5)	756 (36.3)	532 (36.4)
White, n (%)	1985 (95.3)	1397 (95.4)	–	–
Region, n (%)				
– Midwest	507 (24.4)	389 (26.6)	523 (25.1)	367 (25.1)
– Northeast	384 (18.4)	207 (14.1)	348 (16.7)	245 (16.8)
– South	798 (38.3)	670 (45.8)	863 (41.5)	607 (41.5)
– West	393 (18.9)	198 (13.5)	347 (16.7)	244 (16.6)
Quartile of median income of residential area[†], n (%)				
– Quartile 1	344 (16.5)	331 (22.6)	399 (19.1)	281 (19.2)
– Quartile 2	391 (18.8)	351 (24.0)	434 (20.8)	305 (20.8)
– Quartile 3	531 (25.5)	362 (24.7)	523 (25.1)	367 (25.1)
– Quartile 4	775 (37.2)	398 (27.2)	689 (33.1)	484 (33.1)
– Unknown	41 (2.0)	22 (1.5)	37 (1.8)	26 (1.8)
Distance from residential area to an ILD specialty center (miles), mean (SD)	100 (175.7)	98 (138.3)	100.4 (160.2)	100.2 (163.2)
Newly diagnosed with IPF, n (%)	1,059 (50.9)	842 (57.5)	1,114 (53.5)	784 (53.6)
Modified Charlson comorbidity index[‡], mean (SD)	3.2 (2.9)	3.4 (2.9)	3.2 (2.9)	3.3 (2.9)
Number of chronic conditions, mean (SD)	7.7 (2.0)	7.8 (2.0)	7.7 (2.0)	7.8 (2.0)
Stroke, n (%)	147 (7.1)	130 (8.9)	163 (7.8)	114 (7.8)
COPD, n (%)	1187 (57.0)	895 (61.1)	1224 (58.8)	862 (58.9)
Pneumonia in 3 months prior to index, n (%)	201 (9.7)	176 (12.0)	219 (10.5)	154 (10.5)
Obstructive sleep apnea, n (%)	627 (30.1)	431 (29.4)	–	–
Lung cancer, n (%)	56 (2.7)	50 (3.4)	–	–
Pneumothorax, n (%)	163 (7.8)	91 (6.2)	–	–
Gastroesophageal reflux, n (%)	1,230 (59.1)	863 (58.9)	–	–
Obesity, n (%)	501 (24.1)	348 (23.8)	–	–
Cardiovascular conditions, n (%)	1508 (72.4)	1066 (72.8)	–	–
– Pulmonary hypertension	254 (12.2)	178 (12.2)	–	–
– Ischemic heart disease	1180 (56.7)	839 (57.3)	–	–
– Congestive heart failure	608 (29.2)	448 (30.6)	–	–
– Venous thromboembolism	203 (9.8)	143 (9.8)	–	–
– Atrial fibrillation	500 (24.0)	319 (21.8)	–	–
– Cor pulmonale	106 (5.1)	83 (5.7)	–	–
Smoking cessation therapy, n (%)	73 (3.5)	54 (3.7)	–	–
Respiratory hospitalization in 3 months prior to index	200 (9.6)	164 (11.2)	–	–
Oxygen use in 1 year prior to index[§]	1743 (83.7)	1215 (83.0)	–	–
Pulmonary rehabilitation in 1 year prior to index	1985 (95.3)	1388 (94.8)	–	–
Computerized tomography scan in 1 year prior to index	1536 (73.8)	1133 (77.4)	–	–

[†]Income quartiles based on an external population derived from Healthcare Cost and Utilization Project Nationwide Inpatient Sample.
[‡]Excludes chronic pulmonary disease.
[§]Numbers of patients with evidence of an oxygen flow rate of ≥4 liters/min were 5 and 4 for pirfenidone and nintedanib users, respectively.
COPD: Chronic obstructive pulmonary disease; ILD: Interstitial lung disease; IPF: Idiopathic pulmonary fibrosis; SD: Standard deviation.

Table 2. Healthcare utilization and costs† after initiation of antifibrotic therapy among Medicare beneficiaries with IPF, weighted‡.

Variables	Beneficiaries who initiated antifibrotic therapy	
	Pirfenidone	Nintedanib
Number of subjects	2082	1464
Utilization per patient month, mean (SD)		
All-cause		
– Office visits	1.7 (1.5)	1.7 (1.4)
– ED visits	0.055 (0.33)§	0.060 (0.22)
– Hospitalizations	0.080 (0.28)§	0.106 (0.38)
Respiratory-related		
– Office visits	0.73 (1.03)	0.72 (0.77)
– ED visits	0.028 (0.11)§	0.038 (0.19)
– Hospitalizations	0.041 (0.20)§	0.052 (0.25)
Costs per patient month, mean (SD)		
All-cause		
Total	$10,993 (13,161.8)§	$12,006 (14,953.3)
– Outpatient service	$1042 (1453.6)	$1072 (1462.8)
– Inpatient service	$1129 (3992.6)§	$1494 (5317.7)
– Pharmacy	$8822 (12,018.9)	$9441 (13,565.7)
Respiratory-related		
Total	$9521 (12,458.1)	$10,383 (14,217.9)
– Outpatient service	$541 (933.6)	$550 (804.8)
– Inpatient service	$581 (2559.1)§	$833 (4180.1)
– Pharmacy	$8399 (11,967.8)	$9001 (13,413.5)
IPF-specific		
Total	$8784 (12,179.1)	$9440 (13,787.0)
– Antifibrotic medication	$8394 (11,967.9)	$8994 (13,413.8)

†Adjusted to 2015 USD.
‡Weighted by stabilized inverse probability of treatment weight.
§Represents statistical significance at $p < 0.05$, compared with nintedanib cohort.
ED: Emergency department; IPF: Idiopathic pulmonary fibrosis; SD: Standard deviation.

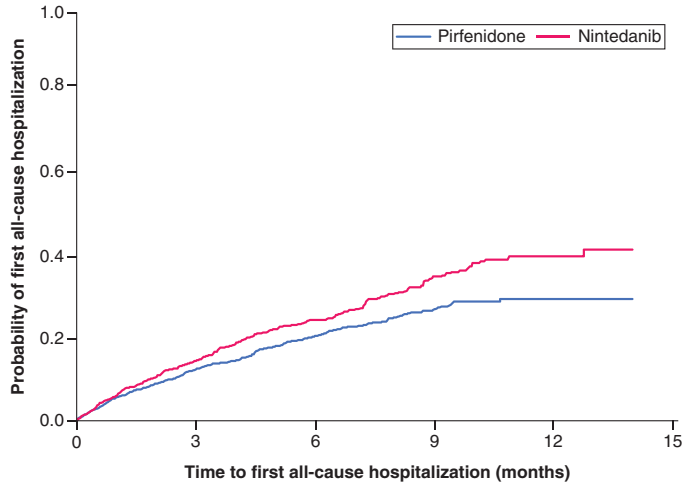
monthly weighted all-cause hospitalizations (0.080 [0.28] vs 0.106 [0.38]), ED visits (0.055 [0.33] vs 0.060 [0.22]), and office visits (1.7 [1.5] vs 1.7 [1.4]) (Table 2).

Healthcare costs

Mean (SD) weighted total costs per month in the post-index period (both all-cause and respiratory-related) were lower among pirfenidone compared with nintedanib beneficiaries. Group differences in all-cause total costs were driven by costs for inpatient services, but for other service categories (outpatient and pharmacy), cost differences were nominal (<7%) and were not statistically significant. Mean (SD) all-cause inpatient costs per beneficiary per month were $1129 (3992.6) in pirfenidone initiators versus $1494 (5317.7) in nintedanib initiators (Table 2). Mean (SD) respiratory-related inpatient costs per beneficiary per month were similarly lower in pirfenidone initiators ($581 [2559.1] vs $833 [4180.1]). For both treatment groups, pharmacy services (treatment costs) accounted for the largest share of total costs per month, followed by costs for inpatient services, and then outpatient services; this pattern was similar for respiratory-related and IPF-specific costs (Table 2).

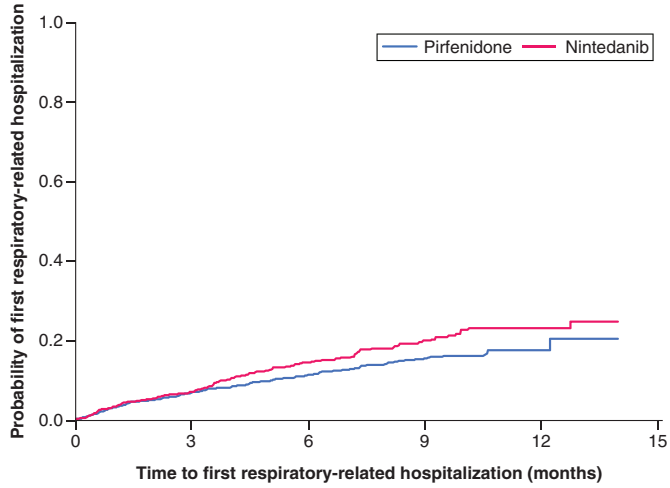
Risk & rate of hospitalization

Following index, the weighted 1-year probability of hospitalization-free survival for initiators of pirfenidone versus nintedanib was 0.294 (95% CI: 0.265–0.343) compared with 0.359 (0.320–0.401), respectively (Figure 1). The difference in cumulative probability of all-cause hospitalization between study groups was statistically significant. Similarly, 1-year probability of respiratory-related hospitalization-free survival for initiators of pirfenidone versus nintedanib was 0.173 (95% CI: 0.147–0.203) compared with 0.244 (0.196–0.301) (Figure 2). The difference in



	At 90 day		At 180 day		At 270 day		At 365 day		At 428 day	
	Survival probability (95% CI)	At risk	Survival probability (95% CI)	At risk	Survival probability (95% CI)	At risk	Survival probability (95% CI)	At risk	Survival probability (95% CI)	At risk
Pirfenidone	0.123 (0.109–0.138)	1411	0.201 (0.182–0.221)	916	0.266 (0.242–0.291)	444	0.294 (0.265–0.343)	22	0.294 (0.265–0.343)	0
Nintedanib	0.142 (0.124–0.163)	858	0.241 (0.215–0.270)	448	0.344 (0.307–0.384)	209	0.359 (0.320–0.401)	46	0.359 (0.320–0.401)	0

Figure 1. Cumulative risk of first all-cause hospitalization after initiation of antifibrotic therapy among Medicare beneficiaries, weighted†.
†Weighted by stabilized inverse probability of treatment weight.
95% CI.
CI: Confidence interval.



	At 90 day		At 180 day		At 270 day		At 365 day		At 428 day	
	Survival probability (95% CI)	At risk	Survival probability (95% CI)	At risk	Survival probability (95% CI)	At risk	Survival probability (95% CI)	At risk	Survival probability (95% CI)	At risk
Pirfenidone	0.067 (0.056–0.079)	1482	0.109 (0.094–0.125)	1003	0.150 (0.131–0.170)	499	0.173 (0.147–0.203)	26	0.201 (0.141–0.281)	0
Nintedanib	0.069 (0.056–0.084)	920	0.143 (0.122–0.168)	483	0.192 (0.163–0.226)	230	0.244 (0.196–0.301)	54	0.244 (0.196–0.301)	0

Figure 2. Cumulative risk of first respiratory-related hospitalization after initiation of antifibrotic therapy among Medicare beneficiaries, weighted†.
†Weighted by stabilized inverse probability of treatment weight.
95% CI.
CI: Confidence interval.

Table 3. Comparative risk and rate of hospitalization after initiation of antifibrotic therapy among Medicare beneficiaries with IPF, weighted[†].

Variables	Risk of hospitalization		Rate of hospitalization per month	
	All-cause hospitalization	Respiratory-related hospitalization	All-cause hospitalization	Respiratory-related hospitalization
	HR (95% CI)	HR (95% CI)	IRR (95% CI)	IRR (95% CI)
Age				
– 67–74 vs 85+	0.65 (0.51–0.84)	0.98 (0.68–1.41)	0.65 (0.48–0.88)	0.94 (0.60–1.45)
– 75–84 vs 85+	0.72 (0.56–0.91)	0.94 (0.65–1.36)	0.71 (0.52–0.95)	0.93 (0.60–1.44)
Female vs male	0.92 (0.79–1.08)	0.99 (0.81–1.21)	0.90 (0.75–1.07)	0.90 (0.71–1.15)
Region				
– Midwest vs Northeast	0.92 (0.73–1.15)	1.02 (0.75–1.39)	1.03 (0.78–1.35)	1.06 (0.74–1.52)
– South vs Northeast	0.97 (0.78–1.20)	1.07 (0.79–1.43)	1.06 (0.82–1.38)	1.06 (0.75–1.50)
– West vs Northeast	0.73 (0.55–0.96)	0.69 (0.47–1.01)	0.82 (0.59–1.12)	0.74 (0.48–1.14)
Quartile of median income of residential area[‡]				
– Quartile 2 vs Quartile 1	0.99 (0.79–1.24)	0.94 (0.68–1.29)	1.14 (0.87–1.49)	1.12 (0.77–1.64)
– Quartile 3 vs Quartile 1	0.99 (0.80–1.24)	1.26 (0.93–1.69)	1.12 (0.86–1.46)	1.44 (1.00–2.05)
– Quartile 4 vs Quartile 1	0.88 (0.70–1.10)	1.09 (0.80–1.48)	1.03 (0.80–1.34)	1.37 (0.96–1.95)
– Unknown vs Quartile 1	1.42 (0.86–2.33)	1.63 (0.85–3.12)	1.41 (0.74–2.67)	2.49 (1.16–5.38)
Distance from residential area to an ILD specialty center (miles)[§]	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Newly diagnosed IPF beneficiaries (y/n)	0.91 (0.78–1.05)	0.79 (0.65–0.96)	0.85 (0.72–1.01)	0.78 (0.62–0.98)
Modified Charlson comorbidity index[¶]	1.06 (1.04–1.09)	1.04 (1.01–1.08)	1.08 (1.05–1.11)	1.04 (0.99–1.08)
Stroke (y/n)	1.17 (0.92–1.50)	1.07 (0.76–1.52)	1.05 (0.77–1.43)	1.04 (0.69–1.58)
COPD (y/n)	1.47 (1.26–1.72)	1.54 (1.24–1.91)	1.51 (1.26–1.81)	1.61 (1.27–2.06)
Pneumonia (3 months before index) (y/n)	1.74 (1.43–2.12)	2.15 (1.68–2.75)	1.97 (1.53–2.53)	2.48 (1.81–3.40)
Pirfenidone (n = 2082) **vs Nintedanib** (n = 1464)	0.79 (0.68–0.91)[#]	0.80 (0.65–0.97)[#]	0.69 (0.59–0.82)[#]	0.71 (0.57–0.90)[#]

[†]Weighted by stabilized inverse probability of treatment weight.
[‡]Income quartiles based on an external population derived from Healthcare Cost and Utilization Project Nationwide Inpatient Sample.
[§]Missing values for <11 pirfenidone beneficiaries replaced with 100 miles (the average distance for pirfenidone patients).
[¶]Excludes chronic pulmonary disease.
[#]Represents statistical significance at $p < 0.05$, compared with nintedanib cohort (shown for treatment variable only).
COPD: Chronic obstructive pulmonary disease; HR: Hazard ratio; ILD: Interstitial lung disease; IPF: Idiopathic pulmonary fibrosis; IRR: Incidence rate ratio.

cumulative probability of respiratory-related hospitalization between study groups was also statistically significant.

The Cox proportional hazards regression showed the weighted risk of both all-cause (hazard ratio [HR] = 0.79; 95% CI = 0.68–0.91) and respiratory-related (HR = 0.80; 95% CI = 0.65–0.97) hospitalization to be lower among pirfenidone initiators versus nintedanib initiators. In the weighted negative binomial regression, the rates of all-cause (incidence rate ratio [IRR] = 0.69; 95% CI = 0.59–0.82) and respiratory-related hospitalizations (IRR = 0.71; 95% CI = 0.57–0.90) per month were also lower among pirfenidone initiators versus nintedanib initiators (Table 3).

Discussion

This real-world study, which directly compares the impact of two antifibrotic treatments on healthcare utilization and costs among Medicare beneficiaries who are diagnosed with IPF, may be the first of its kind. Our analysis showed that Medicare beneficiaries with IPF who initiated pirfenidone had a significantly lower risk of all-cause and respiratory-related hospitalizations compared with those treated with nintedanib after adjusting for baseline differences. Beneficiaries treated with pirfenidone had a 21% lower risk of being admitted to the hospital for any reason compared with those taking nintedanib; pirfenidone beneficiaries had a 20% lower risk of respiratory-related hospitalizations versus nintedanib beneficiaries.

We also observed that beneficiaries treated with pirfenidone had a significantly lower incidence of hospitalization – both all-cause and respiratory-related – compared with initiators of nintedanib after adjusting for confounders. Beneficiaries treated with pirfenidone had 31 and 29% fewer all-cause and respiratory-related hospitalizations per month, respectively, compared with patients on nintedanib. In other words, if 100 patients are treated with nintedanib versus an equal number of patients treated with pirfenidone, we would expect to see in 1 year about

127 versus 87 all-cause and 62 versus 44 respiratory-related hospital admissions (based on applying the adjusted model results in Table 3 to the observed hospitalizations per month for nintedanib in Table 2).

We believe these findings are important for several reasons. Our study suggests that pirfenidone may have a protective effect against hospitalization for IPF patients, in terms of both risk of being admitted and the overall number of hospital admissions. This finding is especially salient as prior work has shown a correlation between respiratory hospitalization and death [7,11]. In addition, this analysis generated real-world evidence on the effectiveness of antifibrotic therapy among elderly patients with advanced age, a population with a higher prevalence of IPF and who are underrepresented in real-world claims studies [2,21].

Studies on resource utilization and costs associated with pirfenidone and nintedanib use are limited. The most recent analysis of utilization in claims found a lower risk of all-cause acute hospitalizations in antifibrotic-treated versus untreated IPF patients, but did not compare hospitalizations between the drugs [10]. Pooled RCT data showing lower risk of respiratory-related hospitalization in pirfenidone versus placebo may be consistent with our results; however, we found no RCT evidence on impact of nintedanib on hospitalization for making an indirect comparison. We also found no prior IPF studies that examined costs after antifibrotic initiation. Only one head-to-head real-world study was identified, although it focused on end points such as lung function, not utilization or costs [22].

In addition, total monthly costs, our secondary outcome, were lower among pirfenidone compared with nintedanib patients, which was driven by differences in inpatient costs. For both pirfenidone and nintedanib initiators, antifibrotic treatment costs accounted for about three-quarters of total costs per month. Notably, pharmacy costs, of which antifibrotic treatment costs comprise a large share, were not different between the study groups; this differs from comparisons in commercially-insured populations where pharmacy cost differences exist, likely due to variation in negotiated reimbursement rates [23]. Of the remaining services, monthly inpatient costs made up a much smaller share of total costs (10–12%), with very small differences between the two groups.

Our study had several limitations. First, our short time frame for measuring outcomes contributed to a high rate of administrative censoring. Second, despite use of robust weighting procedures to balance observed characteristics between the treatment groups, unobserved and certain observed characteristics, such as disease severity, could not be fully controlled. In addition, we did not adjust for medication adherence which could contribute to differences between the study groups. Third, claims data are designed for billing, not for research; coding errors, misclassification, diagnostic uncertainty, and/or omissions could affect the reliability of the results. Fourth, our data were limited to fee-for-service Medicare beneficiaries and results may not be generalizable to other populations with different demographic and other characteristics, such as those who are commercially insured or uninsured. Lastly, the data analyzed in this study reflect practice from 2014 to 2015 and newer data on IPF treatment, and healthcare utilization and costs have since become available. However, we believe this research is still valid and relevant as current recommendations for management of IPF remain supportive care, use of nintedanib and pirenidone, participation in clinical trial, referral for lung transplant when appropriate, and treatment of comorbidities [9,24,25]. No new curative therapy options for IPF have emerged since the approval of nintedanib and pirenidone. Moreover, the findings in this study may continue to be relevant for comparison in future analyses and to examine trends over time, as the number of older adults and patients with IPF increases in the USA, so will related healthcare utilization and costs.

Conclusion

This initial look at resource utilization and costs among IPF patients treated with antifibrotic therapy, using only 14 months of data, showed pirfenidone to have a moderate but significant protective effect on hospitalization compared with nintedanib. Correspondingly, pirfenidone patients had lower inpatient costs. Future studies should examine outcomes over a longer time period to further understand and to inform clinical practice of the extended, relative impacts of two antifibrotic agents on hospitalization and costs.

Author contributions

M Corral: Conception of the work and interpretation of data; revising the work for important intellectual content; final approval. E Chang; Design of the work, acquisition and analysis of data; drafting the work for important intellectual content; final approval. MS Broder: Interpretation of data; revising the work for important intellectual content; final approval. S Gokhale: Acquisition of data; drafting the work for important intellectual content; final approval. SR Reddy: Design of the work, acquisition and interpretation of data; drafting and revising the work for important intellectual content; final approval.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

This study was exempt from review by an institutional review board.

Summary points

- A 2011 estimate of US idiopathic pulmonary fibrosis (IPF) prevalence among those aged 65 and older was 495 per 100,000.
- In 2014, two novel antifibrotic drugs, pirfenidone and nintedanib, were demonstrated to slow disease progression in randomized clinical trials and became the first US FDA approved treatments for IPF. Past treatment modalities failed to improve quality of life, and other treatment recommendations were mainly supportive.
- Real-world evidence comparing the effectiveness of pirfenidone and nintedanib on healthcare utilization is limited.
- Using real-world data from Medicare beneficiaries, we compared both healthcare resource utilization and costs between beneficiaries with IPF receiving pirfenidone and those receiving nintedanib.

Materials & methods

- We used 2012–2015 Medicare beneficiary- and fee-for-service claim-level administrative data from a 100% sample of Medicare beneficiaries.
- The study population comprised of beneficiaries who: initiated pirfenidone or nintedanib between 15 October 2014 and 31 December 2015; were ≥67 years; and had a diagnosis of IPF on or before initiation of antifibrotic therapy (index date). Patients were categorized by index antifibrotic therapy: pirfenidone or nintedanib.
- Baseline confounding factors were adjusted by stabilized inverse probability of treatment weighting using the propensity score, estimated using baseline covariates of age, gender, region, Charlson comorbidity index (modified to exclude chronic pulmonary disease), chronic obstructive pulmonary disease, stroke, newly diagnosed IPF, pneumonia ≤3 months prior to initiation, quartile of median income of patient residential area and distance from patient residential area to interstitial lung disease specialty center.
- The primary outcomes were the risk and rate of all-cause and respiratory-related inpatient hospitalization in the post-index period. Secondary outcomes included monthly costs.

Results

- After inverse probability of treatment weighting adjustment, baseline characteristics were balanced between treatment cohorts. Hazard and incidence rate ratios (95% CI) for all-cause (0.79 [0.68–0.91]; 0.69 [0.59–0.82]) and respiratory-related (0.80 [0.65–0.97]; 0.71 [0.57–0.90]) hospitalizations favored pirfenidone versus nintedanib. Accordingly, monthly inpatient costs were lower for pirfenidone versus nintedanib patients, while outpatient and pharmacy costs were similar between cohorts.

Conclusion

- This study of resource utilization and cost in patients with IPF treated with antifibrotics indicated a moderate but significant protective effect on hospitalization, and correspondingly lower inpatient costs, for pirfenidone compared with nintedanib.

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