Suboptimal Dosing And Discontinuation Of Antifibrotic Agents In Patients With Idiopathic Pulmonary Fibrosis (IPF)

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Introduction

- Idiopathic pulmonary fibrosis (IPF) is a life-threatening rare disease characterized by decline in lung function due to progression of fibrosis in the interstitium of the lung.[1]
- Two US Food and Drug Administration (FDA) approved antifibrotic medications, nintedanib and pirfenidone, have been found to reduce the rate of IPF progression if taken according to the recommended dosing, in both clinical trials and real-world evidence.[2-6]
- Previous real-world studies have compared adherence/discontinuation patterns for nintedanib and pirfenidone and found similar adherence patterns for both drugs.[7,8] However, these studies did not consider the differential dosing regimens between these two drugs and corresponding incidence of suboptimal dosing. Nintedanib is given twice daily for a full dose of 300 mg, whereas pirfenidone is given three times daily for a full dose of 2403 mg.[9,10]

Objective

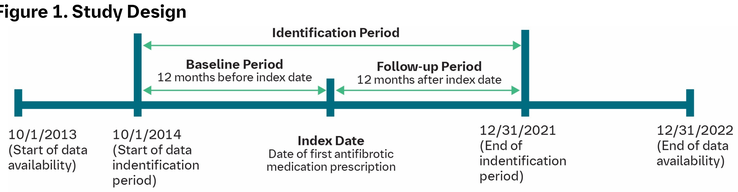
- Evaluate suboptimal dosing and discontinuation of antifibrotic agents, nintedanib and pirfenidone, among patients with IPF.

Methods

Study Design

- The study utilized a retrospective cohort design. The study used data from the Optum Research Database (ORD), a claims database containing approximately 14 million commercial enrollees and 4 million Medicare Advantage enrollees.
- Patients with IPF who initiated either nintedanib or pirfenidone were identified between October 1, 2014 and December 31, 2021. The date of the first prescription of either nintedanib or pirfenidone was assigned as index date (Figure 1). Two separate cohorts were created based on initiation of nintedanib or pirfenidone.
- All outcomes were assessed in the 12 months post-index period. A 12-month time-period prior to the index date was used as the baseline period for determining baseline characteristics.

Figure 1. Study Design



Inclusion Criteria:

- At least one nintedanib or pirfenidone prescription during the identification period (10/1/2014 to 12/31/2021), and
- At least one inpatient or two outpatient claims (≥14 days apart) with a diagnosis code for IPF (ICD-9-CM 516.31 or ICD-10-CM J84.112) during the study period (10/1/2013 to 12/31/2022), and
- At least 18 years old at the index date, and
- At least 12 months of continuous enrollment in the health plan during pre-index period and at least 12 months of continuous enrollment in post-index period

Exclusion Criteria:

- Any history of lung transplant during the 12-month baseline period
- Any claims for a skilled nursing facility, a long-term care facility or hospice care during the 12-month baseline period
- Evidence (≥2 ICD-9-CM or ICD-10-CM diagnostic codes on different dates) of non-IPF chronic fibrosis ILD or connective tissue diseases during the 12-month baseline period
- Missing demographic information (i.e., age or sex)

Outcomes

Suboptimal dosing definition

- The main outcome of our study was incidence of suboptimal dosing, calculated separately for nintedanib and pirfenidone. For each patient, average daily dose was calculated separately in each month in the post-index period. Suboptimal dosing was defined as a dose not following the prescribing information (PI), for 90 days continuously, which corresponds to a daily dose of less than 200 mg[10] (66.67% of full dose) for nintedanib or a daily dose of less than 1607 mg[9] (66.67% of full dose) for pirfenidone.

Medication discontinuation definition

- Discontinuation of nintedanib and pirfenidone in the follow-up period was defined as a gap of at least 90 days in filling of prescription (a gap of 90 days after the prescription date + days of supply for the current prescription).

Data Analysis:

- Nintedanib initiators were matched to pirfenidone initiators using nearest neighbor match on the demographic and baseline clinical characteristics reported in Table 1.
- Doubly-robust matching was performed, with adjustments of baseline variables with standardized differences >10% in the final multivariable models.
- Semiparametric Cox proportional hazards model was used to assess time to suboptimal dosing and discontinuation.
- Multinomial logistics regression was used for assessing association between cumulative dose categories and antifibrotic agents.

Results

- Among patients with IPF, a total of 1,389 new users of nintedanib were matched to equal number of new pirfenidone users.
- After propensity score matching, all variables except index year had a standardized difference below 10% (Table 1). Mean age was 73.4 years in the nintedanib group with 61.5% male while mean age was 73.9 years and 60.5% male in the pirfenidone group. About 87% of patients in both groups were Medicare. The mean Charlson Comorbidity Index score was 2.1.

Table 1. Baseline characteristics post-matching by antifibrotic agent type

Characteristics	Nintedanib n=1389		Pirfenidone n=1389		Standardized difference (%)
Demographic characteristics					
Age as of index (in years), mean (SD)	73.4	(7.6)	73.9	(7.6)	6%
Male, n (%)	855	(61.5%)	840	(60.5%)	2%
Geographic region, n (%)					9%
East	133	(9.6%)	163	(11.7%)	
Midwest	301	(21.7%)	295	(21.2%)	
South	582	(41.9%)	539	(38.8%)	
West	373	(26.9%)	392	(28.2%)	
Plan type, n (%)					
Commercial	183	(13.2%)	177	(12.7%)	1%
Medicare	1206	(86.8%)	1212	(87.3%)	
Index year, n (%)					**28%**
2014	5	(0.4%)	5	(0.4%)	
2015	130	(9.4%)	245	(17.6%)	
2016	156	(11.2%)	165	(11.8%)	
2017	181	(13.0%)	210	(15.1%)	
2018	196	(14.1%)	217	(15.6%)	
2019	251	(18.1%)	224	(16.1%)	
2020	244	(17.6%)	164	(11.8%)	
2021	226	(16.2%)	159	(11.5%)	
Clinical characteristics					
Charlson Comorbidity Index, mean (SD)	2.1	(1.8)	2.1	(1.8)	2%
Select comorbidities, n (%)					
Pulmonary hypertension	189	(13.6%)	181	(13.0%)	2%
COPD	679	(48.9%)	695	(50.0%)	2%
Asthma	234	(16.9%)	234	(16.9%)	0%
Lung cancer	19	(1.4%)	21	(1.5%)	1%
Type 2 diabetes	483	(34.8%)	508	(36.6%)	4%
Hypertension	1036	(74.6%)	1046	(75.3%)	2%
Heart failure	249	(17.9%)	282	(20.3%)	6%

- Patients who initiated pirfenidone had 34% higher risk of suboptimal dosing (below 66.67%) vs. nintedanib [Hazard ratio (HR) – 1.34 (95% CI - 1.15 to 1.56), *P*<0.001] (Table 2).
- Patients who initiated pirfenidone had 16% higher risk of discontinuing vs. nintedanib [HR – 1.16 (95% CI – 1.04 to 1.28), *P* = 0.007] (Table 2).

Table 2. Rates of suboptimal dosing and discontinuation among pirfenidone versus nintedanib cohorts

Outcome	Ratio of association (95% CI)	P value
Suboptimal dosing		
Hazard ratio (95% CI)	**1.34 (1.15 to 1.56)**	**<.00001**
Drug discontinuation		
Hazard ratio (95% CI)	**1.16 (1.04 to 1.28)**	**0.007**
Suboptimal dosing categories (in patients who don't discontinue)		
Above 90% vs. between 90% to 67%	**2.20 (1.73 to 2.78)**	**<.00001**
Above 90% vs. between 66% to 51%	**1.81 (1.21 to 2.71)**	**0.003**
Above 90% vs. below 50%	**2.39 (1.04 to 5.50)**	**0.04**

- Patients who initiated pirfenidone and did not discontinue had 120% higher odds of having drug dose below 90% vs. nintedanib (Odds ratio - 2.20 (1.73 to 2.78), *P*<.00001).

Figure 2. Time to suboptimal dosing for patients with IPF treated with nintedanib or pirfenidone

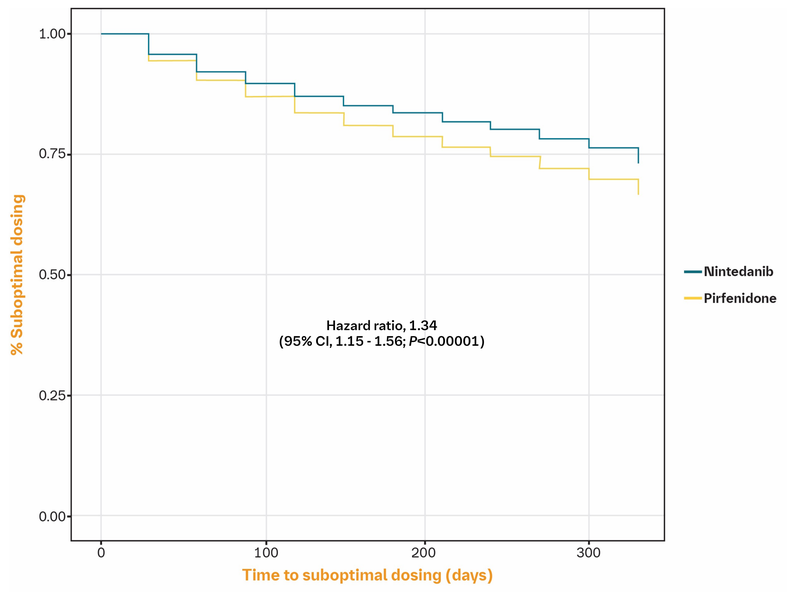
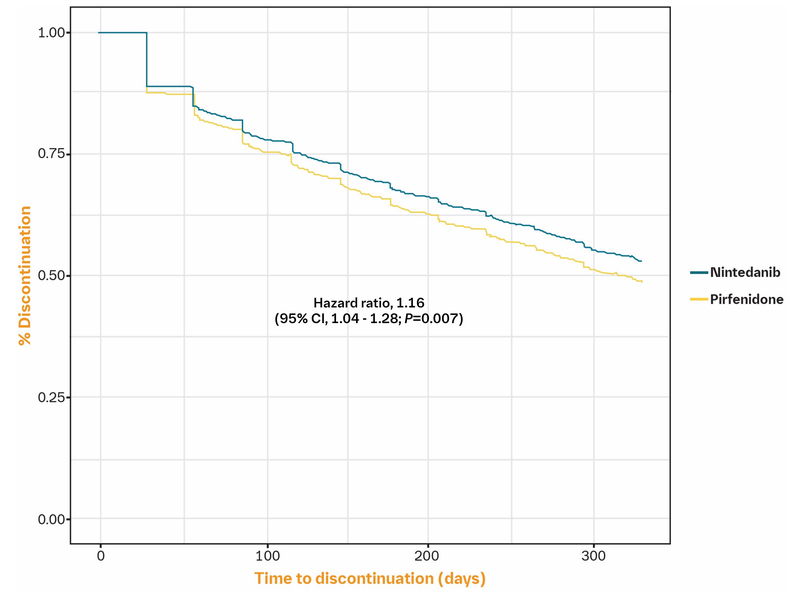


Figure 3. Time to drug discontinuation for patients with IPF treated with nintedanib or pirfenidone



Limitations

- Administrative claims data lack information on symptoms and clinical information, and could not be studied. Dose reduction and or discontinuation may have been influenced by severity of IPF. However, severity information was unavailable and could not be studied.
- This study could not ascertain reasons for discontinuations and/or dose reductions as this information is not captured in the administrative claims database.

Conclusions

- Patients on pirfenidone had a significantly higher risk of suboptimal dosing and discontinuation compared to patients on nintedanib.
- This study helps decision makers understand the impact of differential complexities in dosing regimen. Patients with IPF and treated with pirfenidone may not fully benefit from the therapy due to possible suboptimal dosing and early discontinuation, as compared to patients treated with nintedanib.

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