Uptake of Antifibrotics for Patients with Idiopathic Pulmonary Fibrosis: 2016–2022

To the Editor:

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrosing interstitial lung disease (ILD) with a poor prognosis (1). In 2014, two antifibrotic agents, nintedanib and pirfenidone, were approved by the U.S. Food and Drug Administration to slow the progression of the disease (2–4). Subsequently, studies among patients enrolled in IPF registries reported antifibrotic agent uptake rates among eligible patients with IPF as high as 70% (5, 6), whereas adoption among insured patients in the general population and veterans was lower (approximately 17–25%) (7, 8). The uptake of and factors associated with antifibrotic agent use in socioeconomically diverse populations is unclear. We evaluated the adoption of antifibrotic medications for patients with IPF in a large, multicenter, all-payer database.
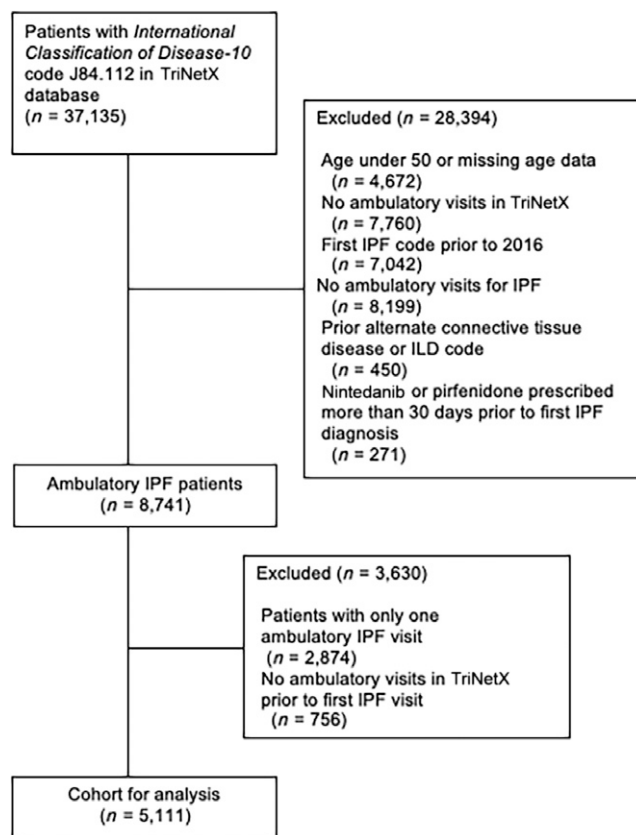
Methods

We used the TriNetX Analytics Platform Research Network (https://trinetx.com/), an electronic health record and claims database with inpatient and outpatient data on all patients treated at more than 76 healthcare organizations across the United States (regardless of insurance/payer), including academic and community facilities. We defined incident cases of IPF from January 1, 2016, to December 22, 2022, as patients ≥50 years of age (1) with at least one ambulatory visit without an IPF diagnosis (*International Classification of Diseases, Tenth Revision* code J84.112 [9]) followed by at least two subsequent ambulatory visits with an IPF diagnosis. Patients with another ILD or connective tissue disease before the first IPF code or medication initiation more than 30 days before the first IPF visit were excluded; our cohort definition is intentionally more specific than previously published cohort definitions (7, 8).

We calculated the annual incidence rate of antifibrotic agents by assessing the number of antifibrotic prescriptions prescribed divided by the total person-time accumulated within each calendar year. Patients contributed person-time to only the year in which they were first diagnosed with IPF. Person-time was censored at death, new connective tissue disease or interstitial lung disease diagnosis code, or

Figure 1. Flow diagram of cohort selection. IPF = idiopathic pulmonary fibrosis; ILD = interstitial lung disease.

the last encounter in the database before the end of the calendar year of the diagnosis.

We used multivariable regression analysis to assess factors associated with the receipt of antifibrotic agents within 1 year of diagnosis. The included factors were demographic characteristics (age, sex, race [White/non-Hispanic versus non-White/Hispanic/unknown]), adverse social determinants of health, comorbidities (modified individual components of the combined comorbidity score [10, 11]), prior testing (pulmonary function testing, echocardiography, oximetry), and prior healthcare encounters (emergency visit, inpatient admission). The presence of prior testing and prior healthcare encounters were assessed in the year before the first IPF code. Codes used to define the variables can be found at https://osf.io/x6dw7/?view_only=08c77e52720c46729b007ccef57fb6b2. Statistical testing was two-tailed, with an α of 0.05, and was conducted using R (version 4.0.2; R Foundation for Statistical Computing). This study was deemed exempt by the Boston University Institutional Review Board (H-43331).

Results

We identified 5,111 patients with IPF who met the inclusion criteria (Figure 1) (mean age, 71.0 yr; 61.8% male; 62.0% White/non-Hispanic); 839 patients (16.4%) received an antifibrotic agent after an initial IPF diagnosis. Among patients who received an antifibrotic agent, the median time to initiation was 43 days (interquartile range, 0–224.5 d). Patient characteristics stratified by antifibrotic treatment are depicted in Table 1.

Table 1. Baseline characteristics and factors associated with receipt of antifibrotic agents within 1 year of IPF diagnosis

Patient Characteristic	No Antifibrotic (n = 4,272)	Antifibrotic (n = 839)	aOR (95% CI)
Mean age ± SD, yr	71.1 ± 8.35	70.9 ± SD 8.04	0.94 (0.86–1.03)
Sex			
Male (reference)	2,581 (60.4%)	579 (69.0%)	–
Female	1,518 (35.5%)	249 (29.7%)	0.71 (0.59–0.85)*
Unknown	173 (4.0%)	11 (1.3%)	0.12 (0.04–0.28)*
Race and ethnicity			
White/non-Hispanic (reference)	2,549 (59.7%)	619 (73.8%)	–
Non-white, Hispanic, and/or unknown race/ethnicity	1,723 (40.3%)	220 (26.2%)	0.65 (0.54–0.79)*
Adverse social determinants of health[†]	142 (3.3%)	13 (1.5%)	0.60 (0.28–1.14)
Geographic region			
Northeast (reference)	580 (13.6%)	209 (24.9%)	–
Midwest	247 (5.8%)	57 (6.8%)	0.47 (0.31–0.68)*
South	2,152 (50.4%)	301 (35.9%)	0.33 (0.26–0.43)*
West	1,144 (26.8%)	270 (32.2%)	0.68 (0.53–0.87)*
Unknown	149 (3.5%)	2 (0.2%)	0.03 (0.00–0.13)*
Ischemic heart disease[‡]	1,226 (28.7%)	211 (25.1%)	0.85 (0.68–1.06)
Congestive heart failure[‡]	550 (12.9%)	88 (10.5%)	0.74 (0.54–1.00)
Liver disease[‡]	384 (9.0%)	55 (6.6%)	0.78 (0.55–1.08)
Gastrointestinal composite[§]	1,715 (40.1%)	343 (40.9%)	0.98 (0.81–1.18)
Renal failure	500 (11.7%)	79 (9.4%)	0.99 (0.73–1.35)
Alcohol abuse	121 (2.8%)	23 (2.7%)	0.96 (0.55–1.61)
Any tumor	384 (9.0%)	67 (8.0%)	0.82 (0.59–1.12)
Cardiac arrythmias	1,002 (23.5%)	179 (21.3%)	0.85 (0.67–1.07)
Chronic pulmonary disease	1,765 (41.3%)	282 (33.6%)	0.68 (0.56–0.82)*
Coagulopathy	275 (6.4%)	49 (5.8%)	0.76 (0.51–1.11)
Complicated diabetes	505 (11.8%)	89 (10.6%)	0.91 (0.67–1.22)
Anemia	237 (5.5%)	36 (4.3%)	0.86 (0.56–1.29)
Fluid and electrolyte disorder	586 (13.7%)	120 (14.3%)	1.10 (0.83–1.45)
HIV/AIDS	27 (0.6%)	3 (0.4%)	1.13 (0.26–3.49)
Hypertension	2,012 (47.1%)	401 (47.8%)	0.98 (0.81–1.20)
Metastatic cancer	190 (4.4%)	19 (2.3%)	0.58 (0.32–0.99)*
Peripheral vascular disease	664 (15.5%)	106 (12.6%)	0.89 (0.68–1.16)
Psychosis	24 (0.6%)	5 (0.6%)	1.08 (0.24–3.35)
Pulmonary circulation disorder	696 (16.3%)	117 (13.9%)	0.93 (0.72–1.20)
Weight loss	336 (7.9%)	44 (5.2%)	0.81 (0.54–1.19)
Dementia	60 (1.4%)	6 (0.7%)	0.83 (0.31–1.90)
Hemiplegia	58 (1.4%)	6 (0.7%)	0.79 (0.26–1.94)
Pulmonary function tests[‖]	1,907 (44.6%)	462 (55.1%)	1.42 (1.18–1.70)*
Echocardiogram[‖]	765 (17.9%)	195 (23.2%)	1.21 (0.96–1.53)
Oximetry[‖]	400 (9.4%)	131 (15.6%)	1.48 (1.15–1.90)*
Emergency department visit[‖]	466 (10.9%)	145 (17.3%)	1.89 (1.47–2.41)*
Inpatient visit[‖]	725 (17.0%)	196 (23.4%)	1.68 (1.34–2.10)*

Definition of abbreviations: AIDS = acquired immunodeficiency syndrome; aOR = adjusted odds ratio; HIV = human immunodeficiency virus; SD = standard deviation.
*The value signifies that the adjusted odds ratio does not cross 1.
[†]Social determinants of health identified by *International Classification of Diseases, 10th Revision* coding.
[‡]Modified from combined comorbidity score as defined by Quan et al. and Sun et al. (10, 11)
[§]Gastrointestinal composite comprising *International Classification of Diseases* codes for gastrointestinal reflux disease, irritable bowel syndrome, aphagia, and nausea.
[‖]Prior testing and visits occurring as long as 1 year before the presence of the first idiopathic pulmonary fibrosis code.

Annual rates of antifibrotic agent uptake remained stable to slightly increasing until 2021, after which nintedanib use increased and pirfenidone use remained stable (Figure 2). The factors associated with the receipt of antifibrotic agents after full model adjustment are shown in Table 1. The odds of receiving antifibrotic agents within 1 year of a IPF diagnosis was lower in patients who were female (odds ratio [OR], 0.71; 95% confidence interval [CI], 0.59–0.85; reference category, male), were of non-White/Hispanic/unknown race or ethnicity (OR, 0.65; 95% CI, 0.54–0.79; reference category, White/non-Hispanic), had chronic pulmonary disease (OR, 0.68; 95% CI, 0.56–0.82), or had metastatic cancer (OR, 0.58; 95% CI, 0.32–0.99). Pulmonary testing and healthcare encounters in the 1 year before the

IPF diagnosis were associated with increased odds of receiving an antifibrotic agent within 1 year of diagnosis.

Discussion

Using a large, multicenter, all-payer claims-based database, from 2016 to 2022, we found that the uptake of antifibrotic medications was lower than prior registry-based estimates but has increased over time. We observed disparities in prescription rates along gender and racial lines.

Society guidelines recommend the use of antifibrotic therapy in patients with mild to moderate IPF (12). The adoption of antifibrotic agents in our study (16%) is lower than previously observed in

Antifibrotic Prescriptions per Annual Person Years Among Incident Cases of IPF
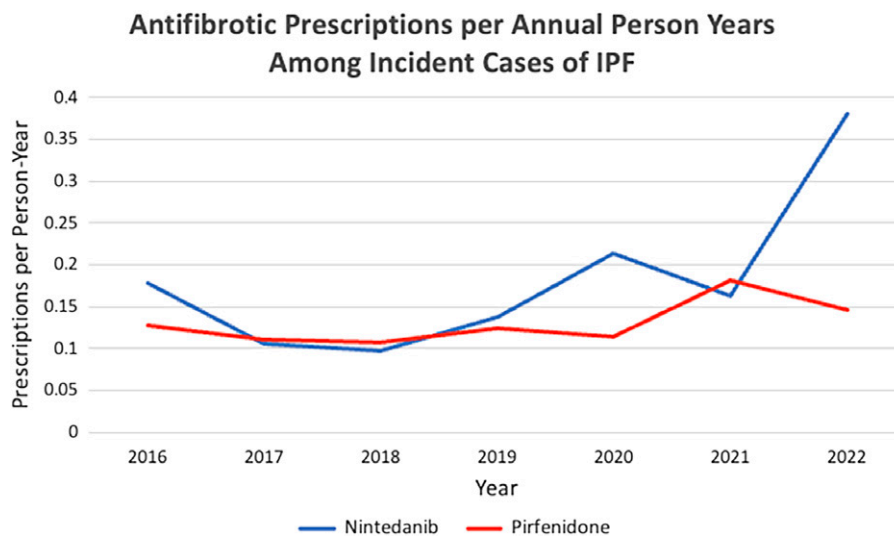
Figure 2. Antifibrotic prescriptions per annual person-year among incident cases of IPF. IPF = idiopathic pulmonary fibrosis.

registry-based studies (58–70%), a study using private insurance/Medicare Advantage administrative data (25%), and a study in the U.S. Veterans Affairs Health Care System (17%) (5–8). Registry-based studies are susceptible to selection bias because participants are often carefully selected patients at ILD centers, and adoption of new practices at ILD centers may differ widely from those at nonspecialty centers. Our slightly lower adoption rate compared with insured patients or veterans (7, 8) may be due to our inclusion of uninsured/underinsured patients without universal medication coverage, suggesting that costs may be a barrier to the receipt of antifibrotic agents. For example, out-of-pocket costs for a 30-day supply of an antifibrotic agent are $5–$11 for veterans but may be as high as $400 for the general population (2, 7). Despite generally low prescribing rates for antifibrotic agents, rates of nintedanib use increased after approval expanded to the treatment of progressive pulmonary fibrosis in 2019 (13); the expanded indication may have increased provider familiarity with nintedanib. Nintedanib is also dosed twice daily, compared with pirfenidone's thrice-daily dosing, possibly leading some providers and patients to favor nintedanib (14).

Our cohort was more diverse than prior registry-based or population-specific administrative studies (i.e., 62% male and 62% White/non-Hispanic vs. 75–95% male and 90–95% White [5, 6, 8]). Additionally, we intentionally used narrow, highly specific inclusion criteria to best isolate a population of patients with true and incident IPF who were receiving ambulatory care (and therefore eligible for antifibrotic agent initiation) within the healthcare systems captured in TriNetX; even though our resulting cohort is smaller, there is a decreased risk for misclassification than in previously published work using the same dataset (15). Similar to prior studies, we found that women and participants of minority race had lower odds of receiving antifibrotic therapy even after adjusting for social determinants of health, a pattern that has also been noted in the initiation of immunomodulatory and antifibrotic treatments in a larger cohort of patients with ILD (16). Further studies are needed to identify the reasons for the large disparities in antifibrotic agent prescribing.

Our study has limitations. First, there is the possibility of misclassification bias in the identification of our cohort within administrative data, and there is a possibility that patients with non-IPF fibrotic ILDs were misclassified as patients with IPF. However, we chose to use a validated definition of IPF to increase the probability of identifying true cases of IPF (17). Second, we were unable to completely adjust for the severity of IPF. We were also unable to assess for practice pattern clusters because healthcare organizations were deidentified. Finally, even though TriNetX represents a highly socioeconomically diverse cohort, the majority of included health organizations are academic centers, and antifibrotic agent uptake may be even lower in other settings.

Conclusions. Antifibrotic agent uptake in an incident IPF population is low but increasing in recent years. Future work should focus on addressing potential gender bias, structural racism, and cost barriers to improve the equitable uptake of antifibrotic agents in eligible populations. ∎

Divya A. Shankar, M.D.*
Finn Hawkins, M.B. B.Ch.
Konstantinos-Dionysios Alysandratos, M.D., Ph.D.
Kevin C. Wilson, M.D.
Allan J. Walkey, M.D., M.Sc.
Nicholas A. Bosch, M.D., M.Sc.
Anica C. Law, M.D., M.S.
Boston University School of Medicine
Boston, Massachusetts

ORCID IDs: 0000-0002-2433-4895 (D.A.S.); 0000-0002-2246-6448 (F.H.); 0000-0002-5611-0343 (K.-D.A.); 0000-0003-4429-2263 (K.C.W.); 0000-0003-4685-6894 (A.J.W.); 0000-0001-7161-5254 (N.A.B.); 0000-0003-3616-0316 (A.C.L.).

*Corresponding author (e-mail: divyas@bu.edu).

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Disease Manifestations in Siblings with Primary Ciliary Dyskinesia

To the Editor:

Primary ciliary dyskinesia (PCD) is a multiorgan disease with symptoms related to ineffective or absent beating of motile cilia in different body systems (1, 2). Although siblings share the same disease-causing pathogenic variant and are exposed to similar environmental and social factors, disease heterogeneity has been described for other monogenetic diseases (3–5). To date, no study has evaluated disease manifestations in siblings with PCD.

Methods

We compared presenting symptoms and clinical outcomes in a retrospective cohort study of pediatric sibling pairs with a confirmed diagnosis of PCD according to the American Thoracic Society Clinical Practice Guidelines (6) who were seen at the Hospital for Sick Children in Toronto, Ontario, Canada, between 2000 and 2022. The study was approved by the hospital's research ethics board (no. 1000080423). For the longitudinal analysis of clinical parameters, siblings had to have a minimum of 3 years of follow-up data with assessments performed at a similar age (within 1 yr) for each sibling pair. Sibling pairs were divided into two groups, younger sibling (YS) and older sibling (OS), with siblings born after the older sibling with PCD categorized as YSs.

The primary outcome measure for the longitudinal analysis was forced expiratory volume in 1 second (FEV_1) percent predicted at the last clinic visit (at similar age). Secondary outcomes included body mass index (BMI), the presence of bronchiectasis, and the presence of persistent airway infection, as well as the cumulative prevalence of typical PCD pathogens.

Descriptive analysis was performed for baseline demographic, clinical, and diagnostic characteristics of the sibling cohort. For the comparison of the two groups (YS vs. OS), continuous variables that did not meet parametric criteria were compared by Wilcoxon matched pairs signed rank test. Statistical analysis was performed using GraphPad Prism (version 9.5.0; GraphPad Software).