Real-world study of antifibrotic drugs-related adverse events based on the United States Food and Drug Administration Adverse Event Reporting System and VigiAccess databases

Mneglin He[1], Jian Zhou[2], Taoran Yang[2], Xuehan Li[2], and Rurong Wang[2]

[1]Affiliation not available
[2]West China Hospital of Sichuan University

June 14, 2023

Abstract

Aims: To analyze and compare the adverse events (AEs) and adverse drug reaction (ADRs) associated with pirfenidone and nintedanib, two antifibrotic drugs commonly used in the treatment of idiopathic pulmonary fibrosis (IPF), based on real-world data. Methods: We collected reports from the FD Adverse Event Reporting System (FAERS) and VigiAccess databases. Two main disproportional analysis, including reporting odds ratio (ROR) and proportional reporting ratio (PRR), were conducted to determine the association of these drugs with signals at both the preferred term (PT) and system organ class (SOC) levels. Results: A total of 55,949 reports for pirfenidone and 35,884 reports for nintedanib were obtained from the FAERS database. Correspondingly, the VigiAccess database provided 37,187 reports for pirfenidone and 23,134 reports for nintedanib. Male patients and individuals over the age of 65 were more likely to report AEs for both drugs. Gastrointestinal disorders emerged as the most significant signal at SOC level for both pirfenidone and nintedanib. Additionally, signals such as nausea, diarrhoea and decreased appetite were notable at PT level. Furthermore, we also identified signals, including hemiplegic migraine for pirfenidone and asthenia, constipation, as well as flatulence for nintedanib, which were previously unknown or underestimated risks. Conclusion: This study identified AEs and ADRs of pirfenidone and nintedanib in the treatment of IPF, confirming the most of the corresponding label information is relatively safe. However, some unexpected risk signals should be taken seriously, and further research is needed to manage the safety profiles of these drugs in IPF patients.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive interstitial lung disease (ILD) characterized by the development of excessive fibrotic tissue in the lungs, leading to impaired respiratory function, and an increased risk of respiratory failure or complications causing mortality.[1] Despite extensive research efforts, the exact etiology of IPF remains elusive, and its prognosis remains poor, with a median survival time of only 2-3 years after diagnosis, not to mention the elderly over the age of 65 years.[2] Nonpharmacologic interventions play a crucial role in enhancing the overall well-being and quality of life for IPF patients, enabling them to lead healthier lives.[3] Moreover, among the limited treatment options currently, two antifibrotic drugs, nintedanib and pirfenidone, are recommended as first-line treatment for IPF, which have shown promise in slowing progression, preserving lung function, and improving patient outcomes.[4]

Pirfenidone exerts regulatory effects on fibrogenic growth factors, especially transforming growth factor (TGF)-β1, thereby mitigating the proliferation of fibroblasts, differentiation into myofibroblasts, as well as the synthesis and deposition of collagen, fibronectin, and other extracellular matrix (ECM) components.[5] It has been shown to reduce the decline in forced vital capacity (FVC) and improve progression-free survival in patients with IPF.[6] Pirfenidone was firstly approved for treatment of IPF in Japan, and has subsequently gained clinical recognition in America and Europe. Nintedanib, a triple angiokinase inhibitor, stands as

another disease-modifying therapy approved and indicated for the treatment of IPF. It targets key pathways involved in fibrogenesis, including platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) signaling.[7] Clinical trials such as INPULSIS trials have demonstrated that nintedanib reduces the annual decline in FVC and slows disease progression in IPF patients, leading to its first approval as a treatment option for IPF in the United States in 2014.[8]

Despite demonstrating favorable therapeutic effects, drugs can similarly bring the inevitable risk of causing unforeseen harm known as adverse events (AEs), affecting effects of drug, prognosis and outcome of patients.[9] In addition, adverse drug reactions (ADRs), defined as the unexpected and harmful response that occurs during drug administration, should also be taken seriously.[10] The administration of pirfenidone in clinic has been associated with gastrointestinal symptoms, skin rashes and the occurrence of significant liver function abnormalities, necessitating regular monitoring as recommended.[11] Moreover, ADRs related to pirfenidone demonstrate a dose-dependent relationship and can be ameliorated through adjustments in mode and dose of administration.[12] The reported common ADRs associated with nintedanib were diarrhea, bronchitis, nasopharyngitis and cough.[13] And the occurrence of these in hospitalized patients not only imposes financial burden on patients, but also prolongs their hospital stay, and in severe cases, poses a threat to their life. Therefore, it is crucial for clinicians to have a thorough understanding of these potential ADRs, as close monitoring and prompt management can help mitigate the impact of these ADRs.

While clinical trials play a crucial role in establishing the efficacy of novel medications and identifying common ADRs, they may not capture all real-world scenarios due to the potential for rare and severe events that may only emerge after widespread administration of the drug in clinical settings. Fortunately, the emergence of pharmacovigilance (PV) analysis compensates for this deficiency. PV analysis plays a crucial role in monitoring and evaluating the safety profile of pharmaceutical products. Data sources such as the FDA Adverse Event Reporting System (FAERS) and the World Health Organization's VigiAccess database enable the collection, analysis, and assessment of ADRs and other medication-related safety issues on a population level.[14]

In the present study, we conducted a statistical analysis of the data gathered from the FAERS and VigiAccess databases to identify the AEs and ADRs signals associated with pirfenidone and nintedanib. In addition, we visually depicted the categories of AEs for both drugs and compared the the risk of ADRs between them, so as to provide valuable insights into the safety of clinical medication and support evidence-based decision-making in drug selection.

2. Methods

2.1 Data source

OpenVigil 2.1 (https://openvigil.sourceforge.net/) is an online tool used for data mining and pharmacovigilance data analysis, which has been widely utilized in pharmacovigilance research.[15] In this study, we employed this online tool to retrieve data from the FAERS database. The search period was set from January 1, 2013, to January 1, 2023 for pirfenidone and January 1, 2014, to January 1, 2023 for nintedanib according to their respective launch dates. Various pharmaproduct names of pirfenidone (such as 'esbriet', 'pirfenidone aet', 'pirfenidone axunio', 'pirfenidone viatris', 'truemed group llc') and 'ofev' or 'vargatef' for nintedanib were used as search terms. Only primary suspect roles were considered for the analysis.

2.2 Data standardization

AEs doucumented in the FAERS database were systematically categorized and encoded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Each individual record is assigned a preferred term (PT), which can be further classified into various systems according to System Organ Class (SOC).

2.3 Statistical analysis

Disproportionality analysis is a data mining algorithm extensively employed in the global monitoring of ADRs. This algorithm demonstrates a notable level of sensitivity and is capable of reducing numerous biases.

Each identified signal derived from this approach represents a statistical association between a specific drug and an AE. In this study, a combination of proportional reporting ration (PRR)[16] and reporting odds ratio (ROR)[17], both recognized for their heightened sensitivity, were utilized for signal mining. The screening criterias for PRR are: N[?]3; χ2[?]4; PRR[?]2, and for ROR are: N[?]3; lower limit of 95% CI>1. The signal value obtained from these two algorithms directly represents the strength of statistical correlation between an AE and the drug. AEs satisfied with both PRR and ROR criteria were subjected to further analysis.

3. Results

3.1Characteristic analysis of AE reports

The FAERS databse contained a total of 55,949 AE reports associated with pirfenidone and 35,884 reports associated with nintedanib (Figure 1). These numbers exceeded the corresponding figures reported in the VigiAccess database (37,187 and 23,134). Furthermore, the occurrence of cases was more frequent in males than in females for both drugs in both databases (Pirfenidone: 60.09% vs. 36.73% in the FAERS database; 63.36% vs. 33.45% in the VigiAccess database, Nintedanib: 55.98% vs. 38.66% in the FAERS database; 59.17% vs. 34.94% in the VigiAccess database). In terms of age distribution in the FAERS database, patients over the age of 65 were more likely to report AE, accounting for 16,716 (29.88%) in pirfenidone and 20,330 (56.65%) in nintedanib. Similar results were shown in the VigiAccess database (14,409, 38.75%; 13,245, 57.25%). However, more than half of cases (20,047, 53.91%) lacked age information for pirfenidone. The main reporting continent was Americas for both drugs in both databases. Among the all cases, the most severe outcome was hospitalization (10,869, 19.43% for pirfenidone; 17,433, 48.58% for nintedanib). In addition, AE reports for these drugs showed an increasing trend over the years.

3.2 Signal detection at PT level

A combination of PRR and ROR algorithms was utilized to analyze AEs and assess their adherence to various screening criteria. In the FAERS database, a total of 150 PTs related to pirfenidone was screened, and the top 20 PTs, presented in Figure 2, are ranked by their lower 95% CI values. The top five robust PTs were idiopathic pulmonary fibrosis (lower 95% CI: 52.21), lung diffusion test decreased (lower 95% CI: 48.29), forced vital capacity decreased (lower 95% CI: 36.64), forced vital capacity abnormal (lower 95% CI: 35.99), and sunburn (lower 95% CI: 30.91). And 422 PTs related to nintedanib were identified, and the top five strongest PTs were idiopathic pulmonary fibrosis (lower 95% CI: 978.10), oxygen saturation increased (lower 95% CI: 88.89), cough decreased (lower 95% CI: 86.22), oxygen consumption (lower 95% CI: 49.93), and lung transplant (lower 95% CI: 48.95) (Figure 3). In the VigiAccess database, the top 20 PTs were ranked by case numbers. The top five PTs for pirfenidone were death (case number: 6240), nausea (case numbers: 5013), fatigue (case number: 3760), decreased appetite (case number: 3733), diarrhoea (case number: 2895) (Table 1). And the top five PTs for nintedanib were diarrhoea (case numbers: 9676), nausea (case number: 3770), weight decreased (case number: 2888), decreased appetite (case number: 2671), vomiting (case number: 2302).

3.3 Signal detection at SOC level

In the FAERS database, gastrointestinal disorders ranked first among 19 SOCs for pirfenidone (case number: 9,927; 30.63%), and also ranked first among 23 SOCs for nintedanib (case number: 8,988; 35.88%) (Table 2,3). Additionally, in the VigiAccess database, gastrointestinal disorders ranked second among 27 SOCs for pirfenidone (case number: 11,442, 15.75%), following general disorders and administration site conditions (case number: 15,378, 21.17%) (Table 4). For nintedanib, gastrointestinal disorders remained the top SOC (case number: 13,433, 22.77%), followed by general disorders and administration site conditions (case number: 7,425, 12.59%) (Table 5).

4. Discussion

Pirfenidone and nintedanib have undergone rigorous clinical trials to establish their efficacy and safety, emerging as major therapeutic agents for IPF patients.[18] However, the related post-marketing surveillance studies and pharmacovigilance analysis, which can provide valuable insights into the long-term safety profiles

of drugs, are limited. In this study, we analyzed and compared the AEs and ADRs induced by these drugs based on the FAERS and VigiAccess databases in the real-world practice, thereby guiding clinicians in their use for the management of IPF patients.

In our analysis, we found that male patients or patients over the age of 65 accounts for a large part of AE reports in the two databases, which is consistent with previous study indicating that older age and male sex are risk factors associated with IPF.[19] This epidemic character might be explained by that male individuals tend to be smoker and its occupational exposures. Hence, it is worth noting that the need for heightened vigilance when administering pirfenidone or nintedanib, especially in elderly and male individuals who may be more susceptible to AEs.

ADRs manifest during routine clinical practice, contributing to approximately 5% of hospitalization, affecting 10-20% of hospitalized individuals.[20] It has been reported that pirfenidone and nintedanib are both associated with several ADRs, with pirfenidone primarily linked to gastrointestinal disorders, skin rashes or photosensitivity, and nintedanib primarily linked to gastrointestinal disorders, bleeding, cardiovascular events or myocardial infarction[21, 22]. In this study, we aimed to find new and unexcepted ADRs, so as to remind clinicians to beforehand detect potential ADRs and timely make correct choice in decision-making process. For pirfenidone in the FAERS database, the top five signals at PT level are idiopathic pulmonary fibrosis, lung diffusion test decreased, forced vital capacity decreased, forced vital capacity abnormal, and sunburn. These signals notice us that although pirfenidone can delay the decline in lung function in patients with IPF, it is still unable to completely halt the progression of the disease, highlighting the importance of regularly monitor various relevant indicators. And if the respiratory symptoms are time-dependently worse with the use of pirfenidone, temporary dosage reductions or discontinuations may be required.[23] Moreover, wearing sunscreen and protective clothing daily to avoid exposure to sunlight and sunlamps should be recommended. For nintedanib, the top five are idiopathic pulmonary fibrosis, oxygen saturation increased, cough decreased, oxygen consumption, lung transplant, which also indicates that professional caregivers should prevent and control the advent of these ARDs. In the VigiAccess database, gastrointestinal disorders, including nausea, vomiting and diarrhoea, accounts for majority ADRs of reports. It is imperative to provide supportive care including antiemetic or antidiarrheal therapy at first signs. Additionally, attention should be paid to signals that were not mentioned in these drugs labels. Hemiplegic migraine occurred in the use of pirfenidone, and asthenia, constipation, as well as flatulence occurred in the use of nintedanib. This may indicate the need for greater consideration to potential risks related to these ADRs during the administration of pirfenidone and nintedanib.

5. Limitations

It is important to acknowledge the limitations of this study. First, the major is the underreporting of AEs by healthcare professionals, leading to incomplete data and an inaccurate representation of the true safety profile of drug. Second, the quality of data in pharmacovigilance databases can vary and hinder the analysis and interpretation of safety signals. Third, pharmacovigilance data often lacks comprehensive information about confounding factors that could contribute to AEs. Therefore, it is important to consider these limitations when interpreting pharmacovigilance data, as well as making decisions regarding drug and risk management. However, this study identified signals, such as hemiplegic migraine, asthenia, constipation, and flatulence, that are previously unknown or underestimated risk associated with pirfenidone or nintedanib, and provides an opportunity to assess ADRs that may not be detected during pre-approval clinical trials, which typically involve a limited number of patients.

6. Conclusion

Our analysis provides valuable insights into the safety profiles of pirfenidone and nintedanib in real-world practice. The findings emphasize the importance of monitoring and managing specific ADRs and highlight the need for continued pharmacovigilance efforts to ensure patient safety in the long-term use of these drugs for IPF treatment.

Acknowledgements

This work was funded by the National Natural Science Foundation of China (No. 82170079) and Natural Science Foundation of Sichuan province (No. 2023NSFSC1457).

Competing interests

The authors report no conflicts of interest in this work.

Contributors

Rurong Wang and Xuehan Li: designed the study; Menglin He and Jian Zhou: performed data collection and statistical analysis; Taoran Yang: wrote the first draft of manuscript. All members participated in discussion and approved the final manuscript.

Data availability statement

The data included in this study are available on the request from the corresponding author or the first author.

Table

Table 1 The signals of AEs of pirfenidone and nintedanib at the PT level in the VigiAccess database

PT Name	Case Numbers	PT Name	Case Numbers
Death	6240	Diarrhoea	9676
Nausea	5013	Nausea	3770
Fatigue	3760	Weight decreased	2888
Decreased appetite	3733	Decreased appetite	2671
Diarrhoea	2895	Vomiting	2302
Dyspnoea	2527	Dyspnoea	2243
Weight decreased	2455	Fatigue	2078
Rash	2345	Cough	1536
Dizziness	2004	Abdominal pain upper	1426
Cough	1751	Death	1424
Abdominal discomfort	1602	ldopathic pulmonary fbrosis	1326
Pneumonia	1586	Asthenia	1162
Vomiting	1566	Constipation	1139
Pruritus	1398	Headache	1075
Asthenia	1376	Abdominal discomfort	1056
Abdominal pain upper	1329	Abdominal pain	1035
Malaise	1321	Pneumonia	971
Dyspepsia	1271	Dizziness	813
Headache	1246	Productive cough	728
Photosensitivity reaction	1194	Flatulence	708

Abbreviations: AEs, adverse events; PT, preferred term.

Table 2 The signals of AEs of pirfenidone at the SOC level in the FEARS database

SOC Name	Case Number	PT	Percentage
Gastrointestinal disorders	9927	21	30.63%
General disorders and administration site conditions	8009	8	24.71%
Respiratory, thoracic and mediastinal disorders	4694	44	14.48%

SOC Name	Case Number	PT	Percentage
Metabolism and nutrition disorders	2168	7	6.69%
Skin and subcutaneous tissue disorders	1969	9	6.08%
Investigations	1925	21	5.94%
Cardiac disorders	1343	6	4.14%
Psychiatric disorders	759	5	2.34%
Injury, poisoning and procedural complications	748	6	2.31%
Nervous system disorders	406	4	1.25%
Immune system disorders	228	2	0.70%
Renal and urinary disorders	69	1	0.21%
Vascular disorders	66	5	0.20%
Surgical and medical procedures	66	5	0.20%
Social circumstances	14	1	0.04%
Musculoskeletal and connective tissue disorders	8	1	0.02%
Reproductive system and breast disorders	6	2	0.02%
Infections and infestations	3	1	0.01%
Ear and labyrinth disorders	3	1	0.01%

Abbreviations: AEs, adverse events; SOC, system organ class; FAERS, Food and Drug Administration Adverse Event Reporting System; PT, preferred term.

Table 3 The signals of AEs of nintedanib at the SOC level in the FEARS database

SOC Name	Case Number	PT	Percentage
Gastrointestinal disorders	85	8988	35.88%
Respiratory, thoracic and mediastinal disorders	65	4384	17.50%
General disorders and administration site conditions	18	2712	10.83%
Investigations	49	1987	7.93%
Metabolism and nutrition disorders	14	1467	5.86%
Immune system disorders	4	950	3.79%
Vascular disorders	28	891	3.56%
Cardiac disorders	22	759	3.03%
Nervous system disorders	16	548	2.19%
Hepatobiliary disorders	19	465	1.86%
Injury, poisoning and procedural complications	14	455	1.82%
Surgical and medical procedures	24	322	1.29%
Renal and urinary disorders	13	243	0.97%

SOC Name	Case Number	PT	Percentage
Infections and infestations	14	224	0.89%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8	200	0.80%
Musculoskeletal and connective tissue disorders	6	201	0.80%
Psychiatric disorders	5	100	0.40%
Blood and lymphatic system disorders	6	66	0.26%
Skin and subcutaneous tissue disorders	4	38	0.15%
Eye disorders	2	26	0.10%
Reproductive system and breast disorders	3	12	0.05%
Social circumstances	2	9	0.04%
Ear and labyrinth disorders	1	6	0.02%

Abbreviations: AEs, adverse events; SOC, system organ class; FAERS, Food and Drug Administration Adverse Event Reporting System; PT, preferred term.

Table 4 The signals of AEs of pirfenidone at the SOC level in the VigiAccess database

SOC Name	Case Number	PT	Percentage
General disorders and administration site conditions	15378	146	21.17%
Gastrointestinal disorders	11442	246	15.75%
Respiratory, thoracic and mediastinal disorders	6260	196	8.62%
Skin and subcutaneous tissue disorders	5773	158	7.95%
Nervous system disorders	5511	161	7.59%
Investigations	5012	304	6.90%
Metabolism and nutrition disorders	4362	63	6.01%
Infections and infestations	4177	222	5.75%
Injury, poisoning and procedural complications	3513	190	4.84%
Psychiatric disorders	2366	107	3.26%

SOC Name	Case Number	PT	Percentage
Musculoskeletal and connective tissue disorders	1769	112	2.44%
Cardiac disorders	1427	103	1.96%
Vascular disorders	1048	75	1.44%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	796	198	1.10%
Surgical and medical procedures	671	99	0.92%
Renal and urinary disorders	660	67	0.91%
Eye disorders	591	75	0.81%
Hepatobiliary disorders	447	51	0.62%
Ear and labyrinth disorders	346	26	0.48%
Blood and lymphatic system disorders	331	49	0.46%
Immune system disorders	328	23	0.45%
Social circumstances	158	27	0.22%
Reproductive system and breast disorders	109	49	0.15%
Product issues	79	30	0.11%
Endocrine disorders	51	19	0.07%
Congenital, familial and genetic disorders	18	11	0.02%
Pregnancy, puerperium and perinatal conditions	3	2	0.00%

Abbreviations: AEs, adverse events; SOC, system organ class; PT, preferred term.

Table 5 The signals of AEs of nintedanib at the SOC level in the VigiAccess database

SOC Name	Case Number	PT	Percentage
Gastrointestinal disorders	13433	303	22.77%
General disorders and administration site conditions	7425	172	12.59%
Respiratory, thoracic and mediastinal disorders	6388	178	10.83%
Investigations	6084	361	10.31%
Nervous system disorders	3670	198	6.22%

SOC Name	Case Number	PT	Percentage
Metabolism and nutrition disorders	3577	84	6.06%
Infections and infestations	3474	275	5.89%
Musculoskeletal and connective tissue disorders	1908	125	3.23%
Injury, poisoning and procedural complications	1886	217	3.20%
Skin and subcutaneous tissue disorders	1501	136	2.54%
Psychiatric disorders	1375	114	2.33%
Cardiac disorders	1363	101	2.31%
Vascular disorders	1360	94	2.31%
Hepatobiliary disorders	1002	58	1.70%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	995	170	1.69%
Renal and urinary disorders	824	82	1.40%
Surgical and medical procedures	734	174	1.24%
Blood and lymphatic system disorders	694	65	1.18%
Eye disorders	445	76	0.75%
Immune system disorders	230	25	0.39%
Ear and labyrinth disorders	220	26	0.37%
Reproductive system and breast disorders	134	49	0.23%
Social circumstances	130	32	0.22%
Product issues	58	26	0.10%
Endocrine disorders	48	11	0.08%
Congenital, familial and genetic disorders	22	18	0.04%
Pregnancy, puerperium and perinatal conditions	3	3	0.01%

Abbreviations: AEs, adverse events; SOC, system organ class; PT, preferred term.

Figure legends

Figure 1. Characteristic analysis of AE reports in the FAERS and VigiAccess databases.

Figure 2. The ROR(A) and PRR(B) disproportionality analysis of signals at PTs level associated with pirfenidone in the FAERS database. ROR, reporting odds ratio; PRR, proportional reporting ratio; PTs,

preferred terms; FAERS, Food and Drug Administration Adverse Event Reporting System; 95% CI, 95% credibility interval.

Figure 3. The ROR(A) and PRR(B) disproportionality analysis of signals at PTs level associated with nintedanib in the FAERS database. ROR, reporting odds ratio; PRR, proportional reporting ratio; PTs, preferred terms; FAERS, Food and Drug Administration Adverse Event Reporting System; 95% CI, 95% credibility interval.

References:

1. Lederer DJ, Martinez FJ: **Idiopathic Pulmonary Fibrosis.***N Engl J Med* 2018, **378:** 1811-1823.

2. Podolanczuk AJ, Thomson CC, Remy-Jardin M, Richeldi L, Martinez FJ, Kolb M, Raghu G: **Idiopathic pulmonary fibrosis: state of the art for 2023.** *Eur Respir J* 2023, **61** .

3. Liu GY, Budinger GRS, Dematte JE: **Advances in the management of idiopathic pulmonary fibrosis and progressive pulmonary fibrosis.***BMJ* 2022, **377:** e066354.

4. Richeldi L, Fletcher S, Adamali H, Chaudhuri N, Wiebe S, Wind S, Hohl K, Baker A, Schlenker-Herceg R, Stowasser S, Maher TM: **No relevant pharmacokinetic drug-drug interaction between nintedanib and pirfenidone.** *Eur Respir J* 2019, **53** .

5. Ruwanpura SM, Thomas BJ, Bardin PG: **Pirfenidone: Molecular Mechanisms and Potential Clinical Applications in Lung Disease.***Am J Respir Cell Mol Biol* 2020, **62:** 413-422.

6. Takehara K, Koga YA-O, Hachisu YA-O, Utsugi M, Sawada Y, Saito Y, Yoshimi S, Yatomi M, Shin Y, Wakamatsu I, et al: **Differential Discontinuation Profiles between Pirfenidone and Nintedanib in Patients with Idiopathic Pulmonary Fibrosis. LID - 10.3390/cells11010143 [doi] LID - 143.**

7. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, Richeldi L, Kolb M, Tetzlaff K, Stowasser S, et al: **Nintedanib in Progressive Fibrosing Interstitial Lung Diseases.** *N Engl J Med* 2019, **381:** 1718-1727.

8. Crestani B, Huggins JT, Kaye M, Costabel U, Glaspole I, Ogura T, Song JW, Stansen W, Quaresma M, Stowasser S, Kreuter M: **Long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: results from the open-label extension study, INPULSIS-ON.** *Lancet Respir Med* 2019, **7:** 60-68.

9. Feagins LA, Abdelsayed GG, Schairer J: **Reporting Adverse Drug Events.**

10. Basile AO, Yahi A, Tatonetti NP: **Artificial Intelligence for Drug Toxicity and Safety.**

11. Lancaster LH, de Andrade JA, Zibrak JD, Padilla ML, Albera C, Nathan SD, Wijsenbeek MS, Stauffer JL, Kirchgaessler KU, Costabel U:

Pirfenidone safety and adverse event management in idiopathic pulmonary fibrosis. LID - 10.1183/16000617.0057-2017 [doi] LID - 170057.

12. Kang J, Chung MP, Park MS, Oh IJ, Lee HB, Kim YW, Park JS, Uh ST, Kim YS, Jegal Y, Song JW: **Clinical outcomes of dose modification during pirfenidone treatment for IPF: A nationwide post-marketing surveillance study.**

13. Li R, Jia Y, Kong X, Nie Y, Deng Y, Liu Y: **Novel drug delivery systems and disease models for pulmonary fibrosis.**

14. Rong L, Xie M, Jiang M, Qiu H, Kong LA-O: **A post-marketing pharmacovigilance study of avapritinib: Adverse event data mining and analysis based on the United States Food and Drug Administration Adverse Event Reporting System database. LID - 10.1111/bcp.15673 [doi].**

15. Böhm R, von Hehn L, Herdegen T, Klein HJ, Bruhn O, Petri H, Höcker J: **OpenVigil FDA - Inspection of U.S. American Adverse Drug Events Pharmacovigilance Data and Novel Clinical Applications.**

16. Evans SJ, Waller Pc Fau - Davis S, Davis S: **Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports.**

17. Rothman KJ, Lanes S Fau - Sacks ST, Sacks ST: **The reporting odds ratio and its advantages over the proportional reporting ratio.**

18. Justet A, Klay D, Porcher RA-O, Cottin VA-O, Ahmad K, Molina Molina M, Nunes H, Reynaud-Gaubert M, Naccache JM, Manali E, et al:

Safety and efficacy of pirfenidone and nintedanib in patients with idiopathic pulmonary fibrosis and carrying a telomere-related gene mutation. LID - 2003198 [pii] LID - 10.1183/13993003.03198-2020 [doi] FAU - Justet, Aurélien.

19. Zhao M, Wang L, Wang M, Zhou S, Lu Y, Cui H, Racanelli AC, Zhang L, Ye TA-O, Ding BA-O, et al: **Targeting fibrosis, mechanisms and cilinical trials.**

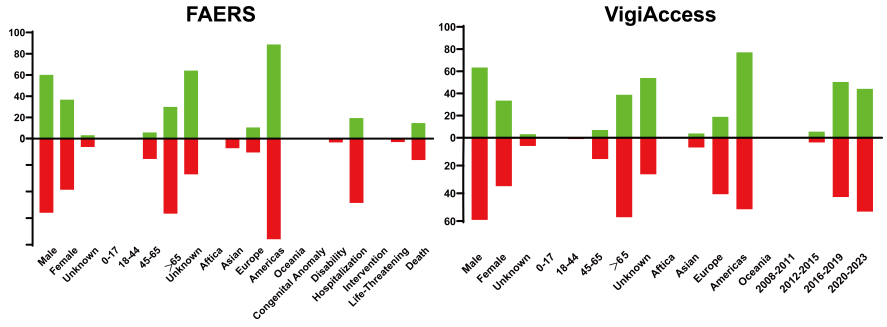
20. Staniszewka S: **A patient-researcher partnership for rare cancer research.** *Nat Med* 2020, **26:** 164-165.

21. Petnak T, Lertjitbanjong P, Thongprayoon C, Moua T: **Impact of Antifibrotic Therapy on Mortality and Acute Exacerbation in Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis.**

22. Rogliani P, Calzetta L, Cavalli F, Matera MG, Cazzola M:

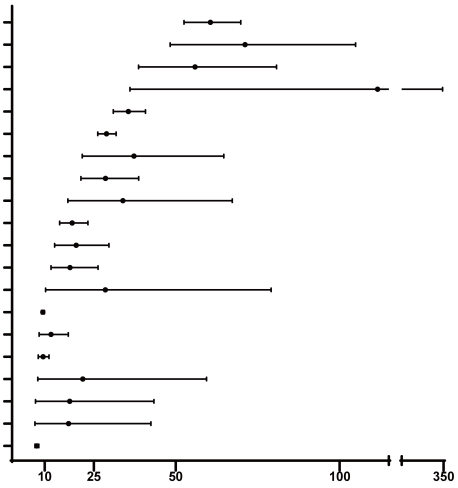
Pirfenidone, nintedanib and N-acetylcysteine for the treatment of idiopathic pulmonary fibrosis: A systematic review and meta-analysis.

23. Meyer KC, Decker CA: **Role of pirfenidone in the management of pulmonary fibrosis.**



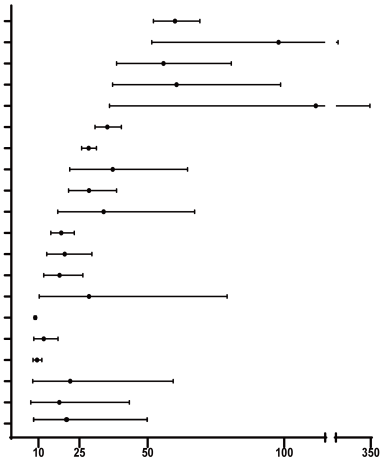
A

P T	Case Number	CI(95 %CI)
Idiopathic pulmonary fibrosis	225	60.55(52.21-69.82)
Lung diffusion test decreased	31	71.16(48.29-104.87)
Forced vital capacity decreased	33	55.86(36.64-80.77)
Forced vital capacity abnormal	4	111.60(35.99-346.05)
Sunburn	224	35.50(30.91-40.76)
Photosensitivity reaction	447	28.85(26.18-31.81)
Dependence on oxygen therapy	14	37.21(21.42-64.65)
Pulmonary function test abnormal	45	28.52(21.03-38.68)
Solar dermatitis	9	33.86(17.06-67.22)
Pulmonary function test decreased	75	18.36(14.55-23.18)
Total lung capacity decreased	24	19.61(12.99-29.61)
Sputum increased	26	17.71(11.93-26.27)
FEV1/FVC ratio decreased	4	28.49(10.26-79.09)
Decreased appetite	1838	9.43(8.98-9.89)
Fibrosis	30	11.93(8.28-17.17)
Pulmonary fibrosis	135	9.50(8.00-11.28)
Heavy exposure to ultraviolet light	4	21.60(7.86-59.37)
Hemiplegic migraine	5	17.62(7.17-43.32)
Pulmonary artery dilatation	5	17.26(7.02-42.40)
Dyspepsia	657	7.56(6.99-8.17)



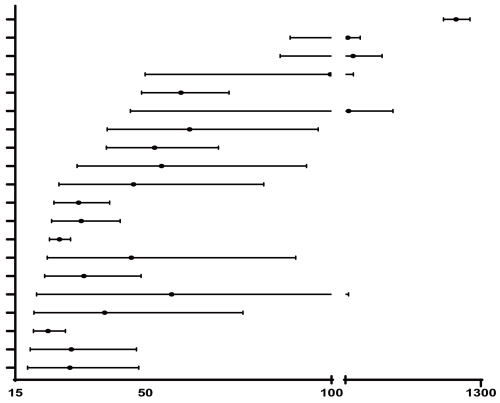
B

P T	Case Number	CI(95 %CI)
Idiopathic pulmonary fibrosis	225	60.01(52.10-69.13)
Lung diffusion test decreased	31	97.97(51.50-186.40)
Forced vital capacity decreased	33	55.79(38.60-80.63)
Forced vital capacity abnormal	4	60.57(37.16-98.72)
Sunburn	224	111.58(35.99-345.95)
Photosensitivity reaction	447	35.19(30.68-40.36)
Dependence on oxygen therapy	14	28.36(25.77-31.20)
Pulmonary function testa bnormal	45	37.19(21.42-64.60)
Solar dermatitis	9	28.48(21.01-38.60)
Pulmonary function test decreased	75	33.85(17.06-67.18)
Total lung capacity decreased	24	18.31(14.52-23.10)
Sputum increased	26	19.59(12.99-29.57)
FEV1/FVC ratio decreased	4	17.69(11.93-26.24)
Decreased appetite	1838	28.49(10.26-79.07)
Fibrosis	30	8.80(8.28-9.21)
Pulmonary fibrosis	135	11.91(8.28-17.14)
Heavy exposure to ultraviolet light	4	9.46(7.97-11.21)
Hemiplegic migraine	5	21.60(7.86-59.36)
Pulmonary artery dilatation	5	17.62(7.17-43.30)
Dyspepsia	657	17.25(7.02-42.39)



A

P T	Case Number	CI(95 %CI)
Idiopathic pulmonary fibrosis	788	1086.75(978.10-1207.46)
Oxygen saturation increased	16	151.42(88.89-257.92)
Cough decreased	7	196.34(86.22-447.12)
Oxygen consumption	9	99.67(49.93-198.96)
Lung transplant	108	59.56(48.95-72.47)
Paroxysmal arrhythmia	3	157.70(45.95-541.35)
Chronic respiratory failure	21	61.88(39.71-96.42)
Oxygen consumption increased	51	52.46(39.50-69.64)
Forced vital capacity decreased	14	54.33(31.63-93.30)
Systemic scleroderma	13	46.78(26.75-93.30)
Faeces soft	75	32.03(25.41-40.37)
Pulmonary function test decreased	52	32.73(24.79-43.21)
Productive cough	374	26.89(24.21-29.87)
Lung diffusion test decreased	9	46.19(23.60-90.38)
Oxygen saturation abnormal	28	33.44(22.91-48.82)
Lung diffusion disorder	4	57.03(20.71-157.03)
Orthopaedic procedure	9	39.04(20.01-76.20)
Pneumothorax	125	23.82(19.91-28.48)
Pneumomediastinum	19	30.09(19.03-47.57)
Sputum increased	17	29.71(18.31-48.21)



B

P T	Case Number	CI(95 %CI)
Idiopathicpulmonaryfibrosis	788	996.38(900.46-1102.52)
Oxygensaturationincreased	16	151.16(88.81-257.29)
Coughdecreased	7	196.19(86.19-446.57)
Oxygenconsumption	9	99.57(49.91-198.65)
Lungtransplant	108	58.89(48.50-71.50)
Paroxysmalarrhythmia	3	157.66(45.95-541.00)
Chronicrespiratoryfailure	21	61.74(39.66-96.12)
Oxygenconsumptionincreased	51	52.17(39.35-69.17)
Forcedvitalcapacitydecreased	14	54.25(31.61-69.17)
Systemicscleroderma	13	46.71(26.73-93.10)
Faecessoft	75	31.79(25.26-39.99)
Pulmonaryfunctiontestdecreased	52	32.56(24.70-42.92)
Productivecough	374	25.87(23.39-28.61)
Lungdiffusiontestdecreased	9	54.84(17.06-176.29)
Oxygensaturationabnormal	28	33.35(22.87-48.63)
Lungdiffusiondisorder	4	57.01(20.71-156.91)
Orthopaedicprocedure	9	39.01(20.00-76.08)
Pneumothorax	125	23.51(19.70-28.06)
Pneumomediastinum	19	30.03(19.01-47.44)
Sputumincreased	17	29.66(18.29-48.08)