Real-world safety profiles of pirfenidone and nintedanib in idiopathic pulmonary fibrosis patients

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Abstract (247/300)

Introduction. While pirfenidone and nintedanib have greatly influenced the treatment of idiopathic pulmonary fibrosis (IPF), both drugs have significant early adverse drug reactions (ADRs) and almost nothing is known of their rare and delayed ADRs. We collected and analyzed pirfenidone- or nintedanib- related ADRs identified in a French rare lung disease center, recorded their profiles and identified potential safety signals.

Methods. We analyzed the medical records of IPF patients treated with pirfenidone or nintedanib between January, 2011 and January, 2020 at the Rennes University Hospital to estimate the incidence of serious and non-serious ADRs cases due to each drug and the incidence of ADRs involving the cardiovascular, hepatobiliary, gastro-intestinal, dermatological, and metabolic/nutritional systems.

Results. The 176 patients included 115 (65%) initially treated with pirfenidone and 61 (35%) given nintedanib. ADRs occurred in 78.3% of those given pirfenidone and in 70.5% of those given nintedanib. The incidence of first serious ADRs cases was about 33 per 100 person-years (100 PY) for both drugs; first non-serious pirfenidone ADRs cases were 102 per 100 PY and 130 per 100 PY for nintedanib. The incidence involving each organ system were quite similar, except for the gastro-intestinal and skin disorders. Cardiovascular disorders occurred in about 10 cases per 100 PY in both pirfenidone and nintedanib patients.

Discussion. Most ADRs were consistent with the expected antifibrotic drug safety profiles. As arterial and venous thromboembolic events are rare, it is important to assess the risk associated with using antifibrotics by a dedicated pharmacoepidemiological study.

Highlights

- The study included a representative population of IPF patients, compared with trials and registries
- Most ADRs were consistent with the expected antifibrotic safety profiles
- Serious ADRs occurred with both drugs (about 33 per 100 patient-years)
- Incidence of cardiovascular ADRs was about 10 per 100 patient-years with both drugs
- Thromboembolic risk should be assessed pharmacoepidemiologically

1. Introduction

While idiopathic pulmonary fibrosis (IPF) is a rare disease (incidence < 10 per 100 000 person-years[1]), it is the most common type of idiopathic interstitial pneumonia [2]. It occurs mostly in men over 65 years old and the median survival time from diagnosis is 2 to 5 years.

Two recently introduced antifibrotic drugs, pirfenidone (Esbriet®, Roche Registration GmbH), a TGF-ß inhibitor, and nintedanib (Ofev®, Boehringer Ingelheim International GmbH), a multikinase inhibitor, have profoundly changed IPF care [1]. As the course of IPF varies and the efficacy of antifibrotics varies between patients, it is important to understand the safety profiles of these drugs in order to evaluate their risk/benefit ratio for each individual [3–5].

Phase III clinical trials and real-world studies (some with few patients) indicate that adverse drug reactions (ADRs) to both drugs most frequently involve gastrointestinal (nausea, diarrhea, abdominal discomfort, etc.), metabolic (anorexia / weight loss), hepatic, or skin-related disorders [6–10] that can result in drug discontinuation or dose reduction. Pirfenidone is not expected to affect the cardiovascular safety profile [11]. However, nintedanib can produce ADRs leading to myocardial infarction and bleeding, and thromboembolic events (venous and arterial) and heart failure are mentioned as important potential risks in the risk management plan [12].

Post-marketing drug safety surveillance is an essential component of overall drug safety profiling as it can signal safety problems (especially serious events), provide information on rare and/or delayed ADRs, and data for patients not included in clinical trials due to comorbidities. The results in pharmacovigilance databases cannot readily be extrapolated to the real world because of reporting bias. As previously shown in other health areas[13,14], hospital clinical records can identify ADRs in IPF patients who are hospitalized or have been followed up in hospital.

We carried out the "SAPIN" (SAfety of PIrfenidone and Nintedanib) pharmacovigilance study on a cohort of IPF patients who were new users pirfenidone and nintedanib at the Rennes University Hospital, France in order to collect and describe individual cases of ADRs, with a special focus on cardiovascular events, and to identify safety signals. We estimated the incidence of the initial serious and non-serious ADRs occurring after antifibrotic initiation and the incidences of ADRs in selected organ systems.

2. Methods

IPF patients are followed in 23 expert centers in France, one of which is the Rennes University Hospital [15]. This retrospective pharmacovigilance study was carried out on a cohort of patients followed at the Rennes University Hospital between January, 2011 and May, 2020.

2.1 Data source

We used the electronic clinical data records in the Rennes University Hospital "eHop" warehouse [16,17], which includes all types of documents related to care (including hospitalization and consultation) and drug prescriptions, both structured and unstructured data, produced by the hospital information system. It also contains information on follow-up visits and phone calls with patients. Keyword-based queries can be used to retrieve documents for a specific time period.

2.2 Study population and exposure

We used the keywords "idiopathic pulmonary fibrosis", "IPF", "pirfenidone", "esbriet", "nintedanib" and "ofev", to identify all deidentified electronic medical records of patients who had been hospitalized or followed-up for IPF between January 1, 2011 and January 28, 2020. As a reminder, pirfenidone and nintedanib were launched in France in 2012 and 2016, respectively.

Patients were selected who satisfied the following criteria: started on pirfenidone or nintedanib between January 1, 2011 and January 28, 2020, treated for IPF, and followed-up at the Rennes University Hospital throughout. Exclusion criteria were: IPF patients included in pirfenidone or nintedanib clinical trials, pirfenidone / nintedanib not used, follow-up at another health care facility. End of the study was 30 May, 2020.

Patients were assigned to one of two groups according to the first antifibrotic given. The date of pirfenidone / nintedanib initiation was the start of follow-up.

2.3 Outcomes

All records were reviewed to identify individual cases of ADRs suspected by clinicians to be linked to pirfenidone or nintedanib. A case of ADRs was defined as a set of ADRs occurring in a patient at a given time; a patient could suffer from multiple ADRs *i.e.,* several occurrences of ADRs, during follow-up.

The primary outcome was dual including both first serious and non-serious cases of ADRs. ADRs were also classified using the Medical Dictionary for Regulatory Activities (MedDRA) according to their system organ class, simply named 'organ system' in the article [18]. Drug imputability was assessed according to the chronological, semiological and bibliographic criteria outlined in the French Pharmacovigilance method [19]. Serious ADRs were defined as disorders that were incapacitating or life-threatening, prevented work or normal activity, resulted in hospitalization, persistent or clinically significant problems, or a congenital anomaly or birth defect, or deemed serious for any other reason.

Secondary outcomes included unexpected ADRs among the first serious ADR cases, defined as disorders not mentioned in the product characteristics. Finally, taking into account the first and subsequent ADR cases, we focused on ADRs affecting specific organ systems: gastro-intestinal, cardiovascular, hepatobiliary, skin-related, and metabolic/ nutritional.

2.4 Covariates

Baseline patient characteristics, medical co-morbidities, IPF characteristics (diffusing capacity of the lung for carbon monoxide [DLCO], forced vital capacity [FVC], age at IPF diagnosis, and time between diagnosis and antifibrotic initiation), and antifibrotic therapy prescribing information (drug, dose) were collected.

2.5 Data analysis

We described the baseline characteristics of the pirfenidone and nintedanib patient groups. Comparisons between groups were performed using the $\chi 2$ test for discrete variables, and Student test for continuous variables.

Each ADR was assigned a seriousness ranking, an organ system and its unexpected nature (serious cases). Cases simultaneous serious and non-serious ADRs were classified as serious. A patient with several ADRs affecting more than one organ system was assigned to the organ system most seriously impaired or which led to treatment discontinuation. This provided a principal organ system (with a main clinical entity) while allowing each ADR to involve another organ system. The IPF therapy following an ADR was also described, as was any other ADR case.

We estimated the crude incidence of first serious and non-serious ADRs cases related to pirfenidone or nintedanib separately, by dividing the number of each type of ADR case by the cumulative drug exposure time of all exposed patients (from drug initiation to the date of the first appropriate ADRs case, the date the drug was stopped or switched, or the last follow-up for patients who had no outcome of interest), expressed in person-years plus 95% confidence interval (95% CI). While patients could experience multiple ADRs occurences, only the first one was used to estimate the incidence, since the second ADR occurence may be influenced by the first.

For the secondary outcome, regardless the seriousness, we estimated the crude incidence of ADRs cases of cardiovascular, hepatobiliary, gastrointestinal, skin and subcutaneous tissue, and metabolic and nutrition disorders organ systems, counting each ADR case in the organ system. Thus, an ADR was counted each time it involved an organ system, but the organ system was counted only once regardless of the number of its ADRs. The ADR case incidence for each organ system was estimated independently by dividing the number of ADR case involved by the cumulative drug exposure of all patients. All ADRs occurrences related to the first antifibrotic exposure were considered for this outcome, not only the first ADR case, unlike the main outcome. ADRs occurring after a drug switch were not considered.

Our description of serious cardiovascular ADRs provides details of the event, the drugs involved, the time to onset, and the cardiovascular risk (CV risk). We considered patients to be at “high CV risk” if they had a history of atherosclerotic cardiovascular disease (including acute coronary syndrome, unstable angina, stroke or transient ischemic attack) and/or one or more CV risk factors (age over 50 (men) or 60 (women), hypertension, diabetes, dyslipidemia, tobacco use and obesity) at baseline, and at “low CV risk” if they had no history of atherosclerotic cardiovascular disease and no CV risk factors at baseline.

2.6 Quality assessment

All the de-identified medical records were reviewed independently by two pharmacovigilance specialists (*DF and MNO or LMS*). Each new ADR was reviewed by two pharmacovigilance experts and a pulmonologist before it was recorded in the French Pharmacovigilance database as an individual case safety report. Disagreement between experts were resolved by arbitration.

Patient records that included ADRs were reidentified to verify that all spontaneously reported ADRs recorded in the French Pharmacovigilance database were identified in the hospital clinical data records, so ensuring completeness. The electronic medical record of an ADR was reidentified to check for duplicates recorded in the Pharmacovigilance center. New ADRs were registered in the French Pharmacovigilance Database using the MedDRA classification.

2.7 Ethics

This research was authorized by the CNIL *'Commission Nationale Informatique et Liberté'* (Authorization 2020-028, February 27, 2020). All patients were informed via a welcome booklet upon their arrival at the hospital and could oppose the use of their data for research. The use of patients' personal and clinical data is authorized by a European Directive that states that pharmacovigilance systems should use all appropriate measures to obtain accurate, verifiable information for the scientific evaluation of suspected adverse reaction reports, including re-identification of records identifying ADRs [20].

3. Results

3.1 Population

A search of the clinical data warehouse identified 386 IPF patients followed-up between January 1, 2011 and January 28, 2020 and 176 of them met the inclusion criteria; 115 (65%) were initially treated with pirfenidone and 61 (35%) were initially given nintedanib (Figure 1). The median age at IPF diagnosis was 73 years and the median follow-up was 15.3 months (Q1, Q3: 6.8, 25.6) (Table 1). The diagnosis of IPF was made in all cases after multidisciplinary discussion.

Table 1. Baseline characteristics of the population.

	Overall population	Pirfenidone	Nintedanib	P value
Number of patients	176	115	61	
Men, % (n)	79.5 (140)	81.7 (94)	75.4 (46)	0.322
Length of follow-up in months Mean ± SD Median (Q1, Q3)	 20.0 ± 16.8 15.3 (6.8, 25.6)	 22.3 ± 18.2 17.4 (7.8, 30.0)	 15.5 ± 12.7 14.5 (6.3, 20.1)	0.005
Mean age at the IPF diagnosis ± SD in years	71.8 ± 8.4	72.4 ± 7.9	70.6 ± 9.2	0.198
IPF diagnosis Lung biopsy / cryobiopsy, % (n) Clinical-radiographic criteria, % (n)	 26.1 (46) 73.4 (130)	 22.6 (26) 77.4 (89)	 32.8 (20) 67.2 (41)	0.144
Mean FVC* ± SD, %	82.6 ± 18.3	82.1 ± 18.9[$]	83.5 ± 17.3[£]	0.621
Mean DLCO* ± SD, %	46.7 ± 12.4	46.7 ± 12.0[€]	46.7 ± 13.2[€]	0.991
Time between IPF diagnosis and antifibrotic initiation in days Mean ± SD Median (Q1, Q3)	 139.9 ± 459.2 25.5 (5.0, 75.5)	 127.7 ± 431.9 30.0 (4.5, 76.0)	 162.8 ± 509.7 24.0 (5.0, 69.0)	0.648
Mean BMI ± SD	27.1 ± 3.8	26.9 ± 4.0	27.3 ± 3.4	0.478
History of smoking, % (n)	64.2 (113)	62.6 (72)	67.2 (41)	0.593
Mean number of cigarette pack-years ± SD	27.4 ± 21.7	25.1 ± 19.9[£]	31.3 ± 24.1	
History of obstructive sleep apnea syndrome, % (n)	11.9 (21)	13.0 (15)	9.8 (6)	0.532
High risk of CV disorders, % (n)	60.2 (106)	61.7 (71)	57.4 (35)	0.573
Low risk of CV disorders, % (n)	39.8 (70)	38.2 (44)	42.6 (26)	

BMI, body mass index; CV, cardiovascular; DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; Q1, Q3: first and third quartile; SD: standard deviation.

* at the time of IPF diagnosis.

[$] data was missing for 1 patient.

[£] data was missing for 2 patients.

[€] data was missing for 3 patients.

3.2 Patients experiencing ADRs

Most pirfenidone (78.3%; n = 90) and nintedanib (70.5%; n = 43) patients had one or more ADR cases (figure 2). Serious reactions to either drug resulted in the antifibrotic being switched or discontinued (Appendix eFigure 1). Non-serious ADRs did not lead to the IPF management being modified in most patients (antifibrotic was continued in 45% - 62%). Some patients who continued their antifibrotic treatment had new ADRs (different from their first ADR); one pirfenidone patient experienced atrial fibrillation and another developed ischemic heart disease with stent implantation, while a nintedanib patient suffered a myocardial infarction.

3.3 ADRs and incidences

Most of the 90 pirfenidone-related ADRs cases were not serious (n = 68, 75.6 %); they were mainly gastrointestinal, skin, or metabolism and nutrition disorders. The 22 serious ADRs cases included a fatal pulmonary embolism in a patient on pirfenidone. Unexpected serious ADRs were tooth loss, a burning sensation, tachycardia and palpitation, hypertension, erectile dysfunction, depression, loss of drug efficacy and IPF worsening.

Most of the 43 nintedanib-related ADRs cases were not serious (n = 34, 79%). They were largely gastrointestinal disorders (n = 27, 79%) and none was fatal. The 9 serious unexpected ADRs included loss of consciousness, retinal artery occlusion and loss of drug efficacy.

While the crude incidence of serious ADRs cases was about 33 per 100 person-years with both drugs, it could be as high as 130 non-serious ADRs cases per 100 person-years with nintedanib (Table 2).

Table 2. Crude incidence of serious and non-serious ADRs cases to antifibrotic drugs

	Number of ADRs*	Person-years	Crude incidence per 100 person-years	95 % CI	P value
Serious					
Pirfenidone	22	66.4	33.1	19.3 – 46.9	0.922
Nintedanib	9	26.2	34.4	11.9 – 56.9	
Non-serious					
Pirfenidone	68	66.4	102.3	78.0-126.7	0.254
Nintedanib	34	26.2	130.0	86.3 – 173.7	

ADRs: adverse drug reactions; CI: confidence interval.

* Only the first ADR of a given patient was considered, regardless of seriousness.

3.4 ADRs of specific organ systems

The crude incidences are shown in Table 3. Gastrointestinal ADRs to both drugs included nausea/vomiting, diarrhea, and abdominal pain, but no colitis or gastrointestinal perforation. Most ADRs involving metabolism/nutrition were loss of appetite and weight loss. ADRs leading to hepatobiliary disorders were mainly due to increased transaminase activity. Pirfenidone produced most skin ADRs, resulting in photosensitivity and isolated rashes with or without pruritus. Most cardiovascular ADRs to both drugs were serious (Table 4). Serious ADRs cases involving other organ systems are shown in Appendix eTable 1.

Table 3. Crude incidence of ADRs cases: organ systems and antifibrotic drugs.

	Gastrointestinal		Cardiovascular		Hepatic		Skin		Metabolism and nutrition	
	Pirfenidone	Nintedanib	Pirfenidone	Nintedanib	Pirfenidone	Nintedanib	Pirfenidone	Nintedanib	Pirfenidone	Nintedanib
Number of ADR case*	37	34	9	3	4	4	26	1	40	20
% Serious (n)	18.9 (7)	11.7 (4)	66.7 (6)	100.0 (3)	25.0 (1)	0.0 (0)	23.1 (6)	0.0 (0)	17.5 (7)	4.0 (5)
Person-years	75.9	27.2	78.1	30.2	75.8	31.3	77.2	31.3	76.9	29.9
Crude incidence per 100 person-years	48.8	124.8	11.5	9.9	5.3	12.8	33.7	3.2	52.0	66.8
95 % CI	33.1 - 64.5	82.9 - 166.8	4.0 - 19.1	0 - 21.2	0.1 - 10.5	0.3 - 25.3	20.7 - 46.7	0 - 9.5	35.9 - 68.1	37.5 - 96.1

CI: confidence interval

* All ADRs cases per patient are included, not just the first.

ADR time-to-onset for each organ system are shown in appendix (eFigure 2, eFigure 3).

Table 4. Serious cardiovascular ADRs cases*.

Antifibrotic drug	Nintedanib cases			Pirfenidone cases					
CV disorder	ACS with stent implantation	ACS, no stent implantation, general condition change, weight loss, anorexia	Myocardial infarction	Pulmonary embolism, deep and superficial vein thromboses	Ischemic heart disease with stent implantation	Pulmonary embolism and hemoptysis	Palpitation, tachycardia	Ischemic stroke	Atrial fibrillation
Age	58	86	65	59	65	85	76	66	66
Gender	Male	Male	Male	Male	Male	Male	Female	Male	Male
Duration of follow-up (months)	20	9	20	17	31	8	7	16	52
CV risk	High	High	Low	High	Low	High	Low	Low	Low
Onset time from antifibrotic initiation (months)	7	6	20	3	17	8	7 days	16	45
Seriousness	Hospitalization	Hospitalization	Life-threatening	Hospitalization	Serious for any other reason	Death	Serious for any other reason	Hospitalization	Hospitalization
Subsequent IPF management	Nintedanib continued	Switch to pirfenidone	Antifibrotic stop	Pirfenidone continued	Pirfenidone continued	/	Antifibrotic stop	Pirfenidone continued	No information

ADR: adverse drug reaction; ACS: acute coronary syndrome; CV: cardiovascular; IPF: idiopathic pulmonary fibrosis.

* All ADRs for a single patient are included, not just the first.

4. Discussion

This independent pharmacovigilance "SAPIN" study was carried out to improve our knowledge of antifibrotics safety because the study population was more representative of the target population. Our inclusion criteria were less selective than those of trials and open-label studies, including patients very severe and also with normal or supranormal lung function [21,22]; we included patients with a history of cardiovascular disease and users of antithrombotics. Unlike clinical trials or registries, the hospital clinical data warehouse allowed an analysis of previously collected data, so limiting recall bias or refusal to participate. Under-reporting bias in pharmacovigilance databases and classifications bias in other studies could explain differences in the published rates of ADR [6,23].

4.1 Serious and non-serious ADRs

About three-quarters of new pirfenidone and nintedanib users experienced ADRs. Non-serious ADRs cases to both drugs were initially frequent (crude incidence in pirfenidone new users: 102 per 100 person-years, and for nintedanib: 130 per 100 person-years; serious ADRs: 33 per 100 person-years for pirfenidone and 34 per 100 person-years for nintedanib). Most ADRs were consistent with the expected antifibrotic safety profiles, including data from international registries [7,8,10,21,23–26], which can be reassuring.

Patient management for ADR depends on the severity of the ADR and contains an inherent degree of subjectivity[27–30]. An update of the French IPF guidelines provide information on the prevention and management related to some expected ADRs of pirfenidone and nintedanib (for gastrointestinal and metabolic/nutritional disorders, hepatic disorders and skin disorders) [31]. Overall, the decision to keep a patient on antifibrotic therapy should be specific to each patient.

4.2 ADRs for specific organ systems

Gastrointestinal and metabolic/nutritional disorders, hepatic disorders and skin disorders were also consistent with the respective safety profiles of the antifibrotics.

Diarrhea is a common early ADR related to tyrosine kinase inhibitors (including nintedanib, a multikinase inhibitor) that can result in intestinal damage and reduced healing of the intestinal epithelium [32]. Gastrointestinal perforation and ischemic colitis may also occur [33,34].

Hepatic disorders are frequent, mostly non-serious, responses to both drugs. The French Health Authority Agency 'ANSM' published safety information about the potentially serious (including fatal) pirfenidone-induced liver injury in October 2020, and the need for monitoring before and during treatment [35].

Almost all skin ADRs were related to pirfenidone (34 cases per 100 person-years), and mostly were, as expected, photosensitivity / phototoxic reactions [8,24,36,37].

4.3 Cardiovascular

Cardiovascular ADRs to nintedanib included myocardial infarctions, in agreement with others [6,12,23,34]. Through post-marketing experiences, the incidence of myocardial infarction and, more broadly, of major cardiovascular events can be from 0.4 to 29 events per 100 patient-years [6,23]. Venous and arterial thromboembolisms (excluding myocardial infarction) have also been identified as important potential risks of nintedanib [12], which makes our case of retinal artery occlusion all the more interesting. It echoes a meta-analysis suggestion that the cardiovascular risk of tyrosine kinase inhibitors is due to their anti-VEGF (vascular endothelial growth factor) activity [38]. The authors also suggest that nintedanib is involved in atheromatous processes (including plaque instability) by inhibiting PDGF (platelet-derived growth factor), FGF (fibroblast growth factor), and VEGF, and could also exacerbate myocardial infarction in acute coronary syndrome [39].

The summary of product characteristics of nintedanib does not contraindicate its use in patient with high risk of cardiovascular disorders but advises "caution"[34], which, from a pragmatic clinical point of view does not help the physician in charge of the patient... The French recommendations for managing IPF indicate also that nintedanib should be used with caution in IPF patients on anticoagulants, or high-dose antiplatelet therapy, or who are at risk of ischemic heart disease [31,40]. It is recommended in such patients to avoid nintedanib as first line treatment in IPF patients[31]. As a reminder, over half our patients were at high risk of cardiovascular disorders, about 57% of those on nintedanib and 62% of those on

pirfenidone. In practice, clinicians from French expert centers seem prefer pirfenidone initiation in those patients, since the latter is not expected to provoke cardiovascular disorders [11,41]. However, we identified serious cases of arterial or venous thromboembolism with pirfenidone. The cardiovascular safety of nintedanib is probably why clinicians are reporting twice as many cases with pirfenidone in our study. Overall, given these data and that some events of interest are rare, perform a pharmacoepidemiological study is relevant to assess the safety signal of a potential risk of arterial and venous thromboembolism with nintedanib, taking into account the cardiovascular risk of each patient in IPF patients. It should be noted that a French population-based study recently suggested that nintedanib might be linked to greater all-cause mortality and a lower risk of discontinuation at 12 months than pirfenidone [42]. The authors provided no information on the cardiovascular history of their patients, neither did they discuss channeling bias.

Also commonly expected with nintedanib and more widely with tyrosine kinase inhibitors[43], no bleeding case was reported with nintedanib in our study, even in patients concomitantly exposed to antiplatelets. Considering the bleeding risk of nintedanib, authors recommended that pirfenidone may be preferred to treat patients at increased risk of bleeding, especially patients on a high dose of anticoagulant [44].

4.4 Strengths

We believe that our cohort of patients is representative of the IPF population in France, despite the few patients followed elsewhere. Regarding ADRs, using the clinical data warehouse, we believe we have identified almost all ADRs in our catchment area as our hospital is an expert center for IPF patient follow-up. But it is possible that patients forgot to mention some ADRs or that the ADRs were managed at another facility and not recorded.

A clinician checked all ADRs to ensure that the drug etiology (antifibrotic) could be a cause.

4.4 Weaknesses

The seriousness of the ADRs could reflect the perception of the patient and/or clinician, especially for the criterion “serious for any other reason” (French pharmacovigilance

criterion). For instance, diarrhea with several stools per day may be acceptable for a retired patient but troublesome for a working person.

As they looked for safety signals, the reporting by pulmonologists of events that are potentially not related to antifibrotics may have overestimated the incidence of ADRs.

Allocating the most severe ADR of a patients suffering from multiple disorders or the ADR leading to treatment discontinuation to a specific organ system potentially masked some (non-serious) events in the primary outcome analysis.

5. Conclusion

Conducting this study in a French expert center for rare lung diseases allowed us to evaluate the real-life safety profiles of pirfenidone and nintedanib in newly treated IPF patients. The selection criteria were less restrictive than those of trials and registries and the patient cohort was more representative of the target population. Nevertheless, our results are consistent with published findings for the most frequent ADRs. The safety signal of arterial and venous thromboembolic events with nintedanib should be evaluated in a dedicated pharmacoepidemiological study, because they are so rare.

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Author contributions

Drs Fournier, Scailteux, Osmont, and Bouzillé had full access to all the data used to generate the study population. They are responsible for the integrity of the data and the accuracy of the data analysis.

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Manuscript drafting: Osmont, Scailteux.

Critique of completed data analysis and interpretation in the manuscript: Jouneau.

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Statistical analysis: Fournier, Scailteux.

Administrative, technical, or material support: Osmont, Scailteux.

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Figure 1. Flowchart

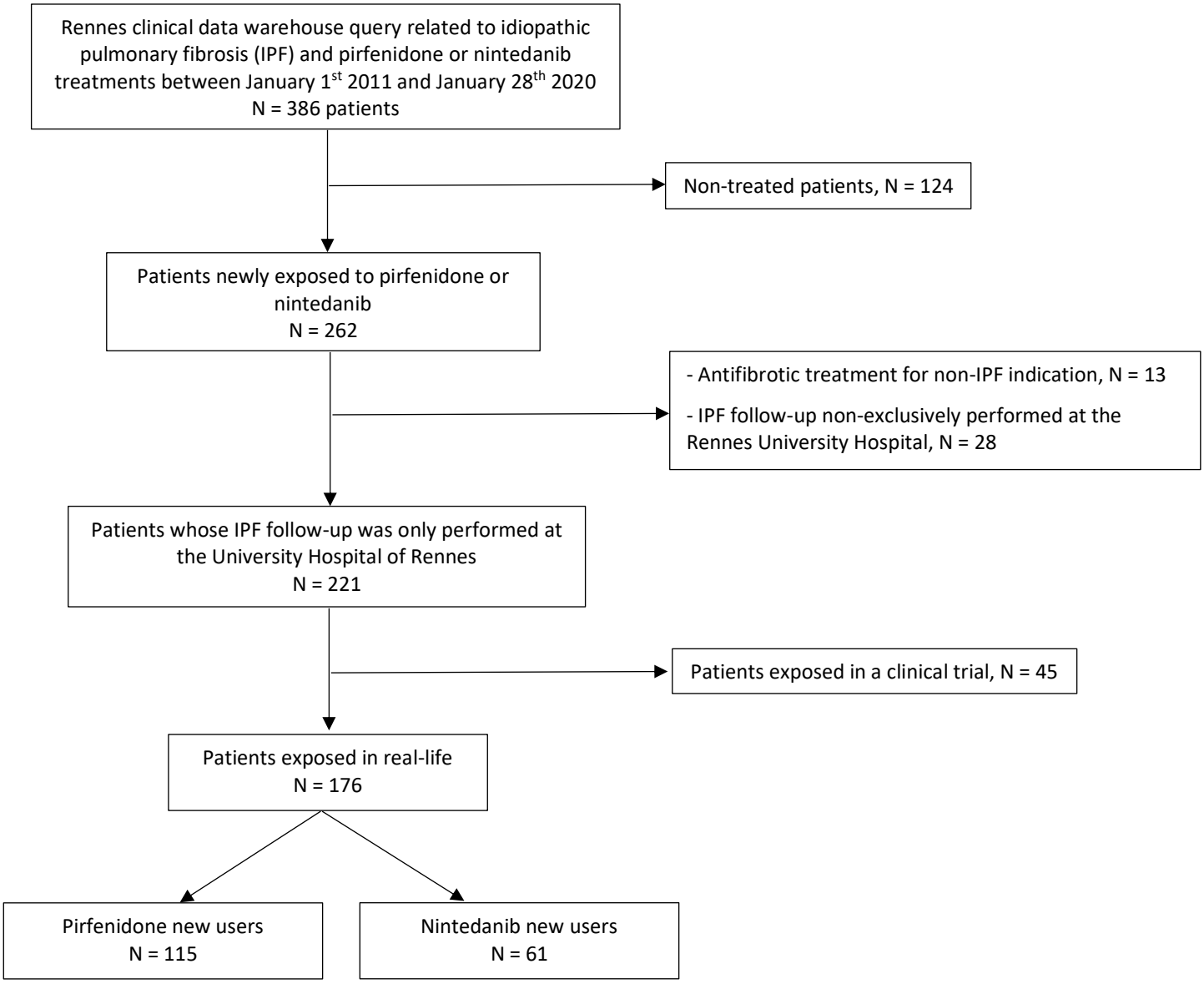

Figure 2. Number of patients with adverse drug reactions under pirfenidone or nintedanib and subsequent idiopathic pulmonary fibrosis care.