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RESEARCH ARTICLE

Evaluation of the potential complication of interstitial lung disease associated with antifibrotic drugs using data from databases reporting spontaneous adverse effects

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Abstract

Interstitial lung disease (ILD), as an adverse effect of certain drugs, leads to inflammation and damage in the walls of the alveoli, making it difficult for the alveoli to take up oxygen. Interstitial pneumonia with no identifiable cause is called idiopathic interstitial pneumonia (IIP), and, among the major IIPs, idiopathic pulmonary fibrosis (IPF) is diagnosed in about half of patients. Current treatment options are limited, among which the antifibrotic drugs nintedanib (Ofev) and pirfenidone (Pirespa) are the first-line drugs. In this study, we investigated the incidence of ILD possibly caused by antifibrotic agents using data from the Japanese Adverse Drug Event Report (JADER) database, a database of spontaneous adverse event reports published by the Pharmaceuticals and Medical Devices Agency (PMDA), and the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), published by the FDA. We used the FAERS and JADER to detect the signals of adverse events on the basis of reporting odds ratios. The relationship between indications and adverse events was clarified by separating indications and adverse events using the spontaneous adverse event reporting database with novel drug involvement. Regarding the involvement of nintedanib and pirfenidone in the development of ILD, JADER and FAERS showed signals for both nintedanib and pirfenidone as suspect drugs, and no signals for nintedanib or pirfenidone as concomitant drug interactions were detected. We highlight this because there are only a few effective drugs for IPF, and effective and safe drug therapies should be implemented by taking into consideration drug-induced ILD.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

In this study, we aimed to analyze the association of the onset of interstitial lung disease (ILD) as an adverse event with the use of the drugs nintedanib and pirfenidone. These antifibrotic agents are widely used as the first-line treatment for idiopathic pulmonary fibrosis (IPF).

WHAT QUESTION DID THIS STUDY ADDRESS?

We analyzed data from two widely used postmarket adverse reporting databases, the Japanese Adverse Drug Event Report (JADER) database and the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS). We calculated reporting odds ratios and confidence intervals to determine signals for the adverse event of ILD associated with nintedanib and pirfenidone.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The results of the database analysis suggest that nintedanib and pirfenidone are not only used for the treatment of ILD but are also suspected of causing ILD. As only a limited number of effective drugs for IPF are available, effective and safe drug therapy should be implemented by taking into consideration drug-induced ILD.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Through clinical pharmacology and translational science, this study may lead to the creation of safer and more effective therapies for the treatment of sudden pulmonary fibrosis, which currently has only limited treatment options, namely antifibrotic agents.

INTRODUCTION

Interstitial pneumonia with no identifiable cause is known as idiopathic interstitial pneumonia (IIP). Nine types, six major IIPs, two rare IIPs, and one unclassifiable IIP, are known. Approximately half of the patients with major IIPs are diagnosed with idiopathic pulmonary fibrosis (IPF). The average survival time of patients after a confirmed diagnosis of IPF is 3–5 years.[1] The prevalence of IPF is estimated to be 14–43 cases per 100,000 IIP cases worldwide.[2,3] IPF is characterized by progressive scarring, thickening, and stiffening of the lung tissue and a decline in respiratory function over time.[4] As the tissue thickens and stiffens, the lungs lose their ability, leading to insufficient oxygen consumption into the bloodstream and delivery to major organs.[5] IPF is a pulmonary fibrosis disease that eventually leads to death, with only limited treatment options.[6] Among them, the antifibrotic drugs nintedanib (Ofev) and pirfenidone (Pirespa) are administered as first-line treatment.[6]

Pirfenidone was launched in 2008.[7] The two effects of pirfenidone, the suppression of mRNA expression of transforming growth factor (TGF)-β and production of TNF-α, are anticipated to play an important role in the antifibrotic mechanism of the drug.[8,9] Nintedanib is a molecularly targeted drug that targets growth factor receptors, especially platelet-derived growth factor (PDGF) receptors, fibroblast growth factor (FGF) receptors, and vascular endothelial growth factor (VEGF) receptors, which have been implicated in the pathogenesis of pulmonary fibrosis.[4,10–12]

Pirfenidone has been reported to cause interstitial lung disease (ILD) as an adverse event in clinical trials.[13] Nintedanib has also been shown to cause ILD in clinical trials in patients with non-small cell lung cancer. Other tyrosine kinase inhibitors are known to be high-risk factors of ILD.[14–16] More than 100 causes of ILD are known, including the influence of drugs, such as anticancer drugs, Chinese herbal medicine, and anti-inflammatory analgesics.[17] The package insert for nintedanib, but not for pirfenidone, lists ILD as an adverse effect,[11,18] although there have been confirmed cases of ILD in patients whose underlying disease is not IPF. Furthermore, information on the occurrence of ILD as a serious adverse effect of antifibrotic agents is limited.[13,15] Such information is essential in Japan as well as other countries due to the lack of detailed reports on the differences between the two drugs, which exhibit equivalent antifibrotic activity, in terms of the description of ILD in the package insert distributed. Each database can assign a "drug role," including suspect drugs, concomitant drugs, and interactions, for individual drugs when multiple drugs are prescribed to a patient with an adverse event, such as ILD, and can appropriately reflect the data registrant's assumptions for the drugs being prescribed.

However, in each database, both the primary disease and the adverse event are entered as disease names based on MedDRA, and the primary disease IPF is broadly classified into one of the ILDs, which are adverse events with multiple disease names; hence, in some cases, the primary disease and the adverse event are both IPFs. For instance, database analysis could not distinguish between new and exacerbated pulmonary fibrosis. This suggests that

although antifibrotic agents can be used to treat pulmonary fibrosis, they may also induce interstitial pneumonia. Further research is needed to investigate this thoroughly.

In the present study, to investigate the possible development of ILD attributed to antifibrotic agents in clinical practice, we used the Japanese Adverse Drug Event Report (JADER) database, which records spontaneous adverse event reports published by the Pharmaceuticals and Medical Devices Agency (PMDA). This database is a useful tool for analyzing postmarketing adverse event reports. We used the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) published by the FDA and the reporting odds ratio (ROR) to analyze the signals corresponding to adverse events. To determine the association between antifibrotic drugs and ILDs, we attempted to distinguish the adverse events induced by drugs that are predisposing factors in patients, based on the information on the involvement of drugs available in the databases. We also aimed to analyze drug-induced ILD after distinguishing primary diseases from adverse events.

METHODS

Data

This study was exempted from the requirements of ethical approval and informed consent by the ethics committee of Shujitsu University as the study involved the use of anonymized data in an open-access database. Data from JADER were downloaded from the PMDA website (https://www.pmda.go.jp/, accessed on October 16, 2020). JADER consists of four files: DEMO, DRUG, REAC, and HIST. DEMO contains basic patient information, such as sex, age, and weight, and DRUG contains the generic name of drugs, involvement of the drugs, route of drug administration, and start and end dates of administration. REAC contains the name of the adverse events, outcomes, and date of onset of the adverse event. HIST contains information on the patients' primary diseases. FAERS data were downloaded from the FDA website (http://www.fda.gov/, accessed on March 4, 2021). FAERS consists of seven files: DEMO, DRUG, REAC, OUTC, RPSR, INDI, and THER. DEMO contains basic patient information such as sex, age, date of onset of the adverse event, and the reporting country of the adverse event. DRUG contains information, such as the drug name, drug involvement, route of administration, and dose. REAC contains the name of the adverse event. OUTC contains the outcome of the case. RPSR contains the source of adverse event information. INDI contains the indication, and THER contains the start and end dates of adverse events and the treatment date. The analysis period of this study was from April 2004 to June 2020 for JADER and from January 2004 to December 2020 for FAERS.

Analysis target

The International Conference on Harmonization (ICH) Medical Dictionary for Regulatory Activities (MedDRA) basic preferred terms (PTs) are classified as either narrow (for highly relevant cases) or broad (for all possible cases). The term classification was assigned to the included PTs. The name of the adverse event used in the analysis was the basic PT with a narrow scope for ILD as described in MedDRA version 23.1J standardized MedDRA queries (Table S1). The only two antifibrotic agents currently indicated for IPF, nintedanib and pirfenidone, were included in the analysis (Figure S1).

Using the drug involvement information in the database, we separated the primary disease from adverse events. The drugs have an entry for "drug involvement," which is divided into "suspect drug" (S), "concomitant drug" (C), and "interaction" (I). FAERS also specifies "role codes" that indicate the role of the drug in the event, and they are divided into "primary suspect drug" (PS), "secondary suspect drug" (SS), "concomitant" (C), and "interacting" (I). In the present analysis, "S," "PS," and "SS" were considered as suspected ILD adverse events, and "C" and "I" were not considered as suspected ILD events.

Analysis method

Access 2016 (Microsoft) was used to create a database for the JADER data. NaviCat for SQLite (Premium Soft, Grand Century Place) was used to create a database for FAERS. ROR, a signal detection method, was used to evaluate the safety of each antifibrotic drug (Figure S1). Using the following formula, RORs were calculated using a 2×2 contingency table divided by the presence of drug use and the onset of specific adverse events, where "*a*" represents cases that belong to the group and were identified as ILD; "*b*" represents cases that did not belong to the group but were identified as ILD; "*c*" represents cases that belong to the group and were not identified as ILD; and "*d*" represents cases that did not belong to the group and were not identified as ILD.[19] A signal was considered to be present when the lower limit of the 95% confidence interval (CI) of the calculated ROR exceeded 1. "P" and ["PS" + "SS"] were analyzed as cases suspected to have ILDs, and ["C" + "I"] were analyzed as cases not suspected to have ILDs.

$$\mathrm{ROR} = \frac{\frac{a}{c}}{\frac{b}{d}}, 95\%\,\mathrm{CI} = \exp\left\{\log(\mathrm{ROR}) \pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}\right\}$$

RESULTS

The total number of JADER reports was 646,779 and that of ILD reports was 35,396 (5.57%). The lower limit of the 95% CI of the ROR was higher than one for nintedanib and pirfenidone analyzed, and a signal was detected (Table 1). The number of reports in FAERS was 12,920,505 and that in ILD was 76,277 (0.60%). The lower limit of the 95% CI of the RORs for nintedanib and pirfenidone analyzed was greater than one, and a signal was detected (Table 2).

In JADER, 124 cases of "S" and 13 cases of "C" were reported for nintedanib, but no cases of "I" were reported. Pirfenidone was reported as "S" in 45 cases and "C" in 23 cases, but no cases of "I" were reported for this drug (Table 3). Regarding the involvement of each medication in the onset of ILD reported in FAERS, nintedanib was reported as "PS" in 1152 cases, "SS" in 114 cases, "C" in 40 cases, and "I" in two cases. Pirfenidone was reported as "PS" in 361 cases, "SS" in 89 cases, "C" in 94 cases, and "I" in one case (Table 4).

The lower limit of the 95% CI of "S" for ROR was greater than one for both drugs. For both drugs, the lower limit of the 95% CI of the ROR for "S" was greater than one and a signal was detected, but the lower limit of the 95% CI of the ROR for "C" and "I" combined was less than one and no signal was detected (Table 5). The lower limit of the 95% CI of the ROR for ["PS" + "SS"] was greater than one for both drugs. For both drugs, the lower limit of the 95% CI of the ROR for ["PS" + "SS"] was greater than one, and a signal was detected. However, the lower limit of the 95% CI of the ROR for "C" and "I" combined was less than one, and no signal was detected (Table 6). It is important to analyze the possibility of ILD, which is different from IPF, in patients with IPF treated with antifibrotic agents based on radiological and pathological characteristics. However, factors unrelated to drug-induced ILD, such as radiation-induced ILD, have not been reported in either the FAERS or JADER database; hence, it was not possible to completely investigate the progression of the primary disease. Depending on the use of suspicious drugs, concomitant medications, and interactions detailed in the FAERS and the JADER databases, we could differentiate the occurrences of primary disease from adverse events. However, it was difficult to differentiate between these cases and those in which underlying pulmonary fibrosis was exacerbated (Tables S2 and S3).

TABLE 1 Number of reports and the reporting odds ratio for each antifibrotic agent in JADER

Drug	Total number of adverse events	Number of ILD cases	ROR (95% CI)
Nintedanib	705	137	4.2 (3.5–5.0)
Pirfenidone	379	68	3.8 (2.9–4.9)

Abbreviations: CI, confidence interval; ILD, interstitial lung disease; JADER, Japanese Adverse Drug Event Report; ROR, reporting odds ratio.

TABLE 2 Number of reports and the reporting odds ratio for each antifibrotic agent in FAERS

Drug	Total number of adverse events	Number of ILD cases	ROR (95% CI)
Nintedanib	12,154	1308	20.6 (19.5–21.9)
Pirfenidone	23,460	545	4.0 (3.7–4.4)

Abbreviations: CI, confidence interval; FAERS, US Food and Drug Administration Adverse Event Reporting System; ILD, interstitial lung disease; ROR, reporting odds ratio.

DISCUSSION

In this study, we reviewed the information on the occurrence of ILD as an adverse effect of pirfenidone and nintedanib in patients whose underlying disease is not IPF, which implies that the development of ILD is due to exacerbation of underlying IPF, even though ILD has been indicated in the package insert. Both nintedanib and pirfenidone are used to treat IPF.[11,18] In this study, the analyses of data obtained from both JADER and FAERS demonstrated an inverse signal (odds ratio < 1) for nintedanib and pirfenidone limited to ["C" + "I"]. The results of the ["C" + "I"] analysis of data regarding nintedanib and pirfenidone are RORs (95% CI) of 0.3 (0.2–0.6) and 1.1 (0.7–1.7), respectively, according to JADER and 0.6 (0.4–0.8) and 0.7 (0.6–0.8), respectively, according to FAERS (Tables 5 and 6). These results suggest that both nintedanib and pirfenidone have therapeutic effects. When the analysis of these drugs was limited to "S" or ["PS" + "SS"], the signal indicating the therapeutic effect of ILD disappeared and that indicating potential complications of ILD (odds ratio > 1) was detected. The "S" analysis of data in JADER indicated that the RORs (95% CI) of nintedanib and pirfenidone were 3.7 (3.0–4.5) and 2.3 (1.7–3.2), respectively, whereas ["PS" + "SS"] analysis of FAERS indicated that the RORs (95% CI) were 19.9 (18.8–21.1) and 3.3 (3.0–3.6), respectively (Tables 5 and 6). In the package insert of nintedanib, ILD is listed as an adverse effect, whereas it is not listed in the package insert of pirfenidone.[11,18] In this study, we successfully verified

TABLE 3 Number of reports and odds ratios based on the role of antifibrotic agents reported for the concerned events in JADER

Drug	Total	*a*/*c*	*b*/*d*
Nintedanib			
Suspect drug	705	124/581	35,272/610,802
Concomitant	705	13/692	35,383/610,691
Interacting	0	0/0	0/0
Pirfenidone			
Suspect drug	379	45/334	35,351/611,049
Concomitant	379	23/356	35,373/611,027
Interacting	0	0/0	0/0

Note: "*a*" represents cases that belong to the group identified as ILD. "*b*" represents cases that did not belong to the group but were identified as ILD. "*c*" represents cases that belong to the group and were not identified as ILD. "*d*" represents cases that did not belong to the group and were not identified as ILD.

Abbreviations: ILD, interstitial lung disease; JADER, Japanese Adverse Drug Event Report.

TABLE 4 Number of reports and odds ratios by ratios based on the role of antifibrotic agents reported for the concerned events in FAERS

Drug	Total	*a*/*c*	*b*/*d*
Nintedanib			
Primary suspect drug	12,154	1152/11,002	75,125/12,833,226
Secondary suspect drug	12,154	114/12,040	76,163/12,832,188
Concomitant	12,154	40/12,114	76,237/12,832,114
Interacting	12,154	2/12,152	76,275/12,832,076
Pirfenidone			
Primary suspect drug	23,460	361/23,099	75,916/12,821,129
Secondary suspect drug	23,460	89/23,371	76,188/12,820,857
Concomitant	23,460	94/23,366	76,183/12,820,862
Interacting	23,460	1/23,459	76,276/12,820,769

Note: "*a*" represents cases that belong to the group identified as ILD. "*b*" represents cases that did not belong to the group but were identified as ILD. "*c*" represents cases that belong to the group and were not identified as ILD. "*d*" represents cases that did not belong to the group and were not identified as ILD.

Abbreviations: FAERS, US Food and Drug Administration Adverse Event Reporting System; ILD, interstitial lung disease.

through the data from two databases that both drugs, which have common underlying antifibrotic effects, require attention regarding potential complications of ILD. A major limitation of adverse event databases involves the reporting of patient bias. A signal is detected owing to a bias in drug use or the onset of adverse events attributed to the patient's predisposing factors, such as diseases.[20] Although nintedanib and pirfenidone are effective as therapeutic agents for IPF, they also cause ILDs as adverse drug reactions. However, it is difficult to properly analyze ILD signals because the effects of antifibrotic agents on IPF may be related to the underlying disease being treated or may be caused by other drugs taken simultaneously. In the present study, by separating the data into the categories of suspected and concomitant medications and interactions, we were able to separate the analysis between the underlying disease and adverse events.

Nintedanib is a molecularly targeted antifibrotic agent that inhibits tyrosine kinases of three growth factor receptors (PDGF, FGF, and VEGF). In contrast, pirfenidone inhibits the production of inflammatory cytokines, such as TNF-α, IL-1, and IL-6; enhances the production of anti-inflammatory cytokines, such as IL-10; suppresses the reduction in the expression of IFN-γ; and inhibits the production of growth factors involved in fibrosis, namely, TGF-β1, b-FGF, and PDGF. Nintedanib is an antifibrotic agent that modulates the production of various cytokines and growth factors and exhibits different mechanisms of action. Similar to other tyrosine kinase inhibitors, it acts on macrophages, which are responsible for immune responses, and the onset of ILD may be influenced by the secretion of two inflammatory substances, IL-1β and HMGB1.[21] However, the mechanism underlying the onset of ILD due to pirfenidone, as with other adverse effects, remains unclear. The drug is involved in light-induced genetic damage, which may affect ILD onset.[13,22]

Nintedanib inhibits the production of interleukins and fibrotic mediators, such as TGF, by blocking the action of Src kinase and Lck during the process of inflammation and immune abnormalities. Gefitinib, a tyrosine kinase inhibitor similar to nintedanib, has been found to promote the secretion of two inflammatory substances, IL-1β and HMGB1, by acting on macrophages responsible for the immune response. This suggests that these mechanisms are involved in the development of ILD.[21] Pirfenidone exerts its antifibrotic effects on TGF-β, which is continuously produced by alveolar macrophages and epithelial cells in the lungs, and is a representative fibrogenic growth factor along with PDGF.[9] In addition, TGF-β acts on pulmonary fibroblasts to promote their proliferation and migration, and is also gaining attention as a factor that induces the differentiation of pulmonary fibroblasts into myofibroblasts.[23] TGF-β is a growth factor that has been implicated in lung remodeling after acute inflammation. During the inflammatory phase, macrophages are the main producers of TGF-β; however, as fibrosis progresses, the bronchial epithelium

TABLE 5 Involvement and odds ratio of the suspect drug in antifibrotic events in JADER

Drug	Total number of adverse events	Number of ILD cases	ROR (95% CI)
S			
Nintedanib	705	124	3.7 (3.0–4.5)
Pirfenidone	379	45	2.3 (1.7–3.2)
C + I			
Nintedanib	705	13	0.3 (0.2–0.6)
Pirfenidone	379	23	1.1 (0.7–1.7)

Note: C, Concomitant; I, Interacting; S, Suspect drug.

TABLE 6 Number of reports and the reporting odds ratio for each antifibrotic agent in FAERS

Drug	Total number of adverse events	Number of ILD cases	ROR (95% CI)
PS + SS			
Nintedanib	12,154	1266	19.9 (18.8–21.1)
Pirfenidone	23,460	450	3.3 (3.0–3.6)
C + I			
Nintedanib	12,154	42	0.6 (0.4–0.8)
Pirfenidone	23,460	95	0.7 (0.6–0.8)

Note: C, Concomitant; I, Interacting; S, Primary suspect drug; SS, Secondary suspect drug.

Abbreviations: CI, confidence interval; ILD, interstitial lung disease; JADER, Japanese Adverse Drug Event Report; ROR, reporting odds ratio.

produces TGF-β.[6] In the present study, an association, not a causal relationship, between the two drugs and the occurrence of adverse effects was found. Analyses using databases such as FAERS and JADER cannot analyze the "risk" of adverse effects, but can only indicate the "potential complications of adverse events" using ROR.

The data from JADER and FAERS could not be analyzed based on the severity of the disease owing to the lack of detailed information on the patient background, such as symptoms and medication status. Hence, the signals detected in this study suggest a statistical association between drugs and adverse events but do not indicate a causal relationship. Another limitation of this study involves the presence of bias attributed to the generation of the dataset from reported cases. Therefore, it should be noted that not all factors affecting the results, such as concomitant medications, were reported. As JADER and FAERS comprise data from reports, the population of patients using these drugs is unknown. Accordingly, as a surrogate, patients with reports other than the adverse events of interest were treated as the population.[19] As the adverse event databases accumulate cases that are suspected to be caused by drugs according to medical personnel; the data in these databases depends on the diagnoses of these adverse events. As the diagnostic criteria are not constant, it is challenging to analyze the pathological aspects of ILD development without considering the effects of radiation and other factors.

The relationship between indications and adverse events was elucidated by separating indications and adverse events using a database of spontaneous adverse drug reaction reports with drug involvement. The results of the database analysis suggest that nintedanib is not only used for the treatment of ILD but also a suspected drug for ILD. As only a limited number of effective drugs for IPF are available, efficacious and safe drug therapy should be implemented by taking into consideration drug-induced ILD. This study underscores the need to improve the efficacy and safety of antifibrotic agents used in IPF treatment.

AUTHOR CONTRIBUTIONS

H.N. wrote the manuscript. H.N., H.H., M.G., Y.Z., and K.I. designed the research. H.N. and Y.Z. performed the research. H.N., H.H., T.N., K.M., and K.Y. analyzed the data. H.H., T.N., M.G., Y.Z., and K.I. contributed new reagents/analytical tools.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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