Safety and Tolerability of Nintedanib in Patients with Systemic Sclerosis-associated Interstitial Lung Disease in Clinical Practice

Interim Analysis of Post-marketing Surveillance in Japan

Aiko Saito[1),*] Akira Takahashi[2)]

ABSTRACT

Background: Nintedanib, an oral anti-fibrotic agent, was approved for treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD) in Japan in December 2019.

Objective: To evaluate the safety and tolerability of nintedanib in routine clinical practice in Japan.

Methods: This prospective, non-interventional, post-marketing surveillance of nintedanib began on 15 April 2020 (ClinicalTrials.gov: NCT04325217). The primary endpoint is the incidence of adverse drug reactions (ADRs) (i.e., adverse events [AEs] to which nintedanib has a possible causal relationship). Other outcomes include the incidence of serious AEs. We analyzed safety data for patients who received ≧1 dose of nintedanib and had ≧1 post-baseline visit (safety analysis set) with 12-week case reports by 15 October 2022.

Results: The safety analysis set comprised 181 patients, 137 (75.69%) female. Mean baseline age, body mass index, SSc-ILD duration, and forced vital capacity were 64.0 years, 21.78 kg/m^2, 5.03 years, and 2045.8 mL, respectively. Most patients began treatment with the approved dosages of 150 mg (41.99%) or 100 mg twice daily (33.70%), mean/median treatment duration was 225/148 days. ADRs occurred in 96 patients (53.04%), mostly commonly diarrhoea (n=56, 30.94%), abnormal hepatic function (n=21, 11.60%), and nausea (n=18, 9.94%). Serious AEs were reported in 21 patients (11.60%), including serious ADRs of abnormal hepatic function (n=2), nephrotic syndrome, decreased appetite, drug-induced liver injury, and hepatic enzyme increased (n=1 each). All serious ADRs resolved.

Conclusion: In this interim analysis, the safety profile of nintedanib in SSc-ILD

Key words: Adverse drug reactions, Nintedanib, Post-marketing surveillance, Systemic sclerosis-associated interstitial lung disease (SSc-ILD), Safety

[1)]Therapeutic Area Pulmonary Fibrosis/Specialty Care Medicine, Nippon Boehringer Ingelheim Co., Ltd., Tokyo, Japan [2)]PMS Center, EPS Corporation, Tokyo, Japan *Corresponding author

patients in routine clinical practice in Japan was consistent with previous studies, with no new concerns.

INTRODUCTION

Systemic sclerosis (SSc) is a rare chronic autoimmune rheumatic disease characterized by diffuse fibrosis of connective tissue in the skin, joints, and internal organs. People with SSc frequently develop interstitial lung disease (ILD), usually within a few years of SSc onset[1,2]. SSc-associated ILD (SSc-ILD) has a heterogenous clinical course but is overall a leading cause of premature mortality in these individuals[3,4].

There are limited options for SSc-ILD patients requiring treatment. Haematopoietic stem cell transplantation is generally only considered for highly selected SSc-ILD patients at risk of rapid disease progression, due to the risk of treatment-related mortality, while lung transplant is reserved for advanced refractory cases[5,6]. Thus, pharmacotherapy is the mainstay of treatment for SSc-ILD, but few agents have been specifically approved for this condition. Non-specific immunosuppression with off-label cyclophosphamide or mycophenolate mofetil has historically been the most common treatment strategy[5,6].

More recently, the anti-fibrotic agent nintedanib (Ofev®) became the first pharmacotherapy to be specifically approved for SSc-ILD[7]. Nintedanib is an orally administered small-molecule inhibitor of multiple receptor tyrosine kinases, including platelet-derived growth factor receptors α and β, fibroblast growth factor receptors 1, 2 and 3, and vascular endothelial growth factor receptors 1, 2 and 3[8] ——all of which appear to be involved in pro-fibrotic signalling pathways[9]. Nintedanib has demonstrated anti-fibrotic and therapeutic effects in animal models of SSc-ILD[7]. In a pivotal phase Ⅲ, randomized, multinational clinical trial in patients with SSc-ILD (SENSCIS), nintedanib reduced the annual rate of decline in forced vital capacity (FVC) by 44% compared with placebo, with a safety profile characterized mainly by gastrointestinal adverse events[10]. The effects of nintedanib in the Japanese subgroup of the SENSCIS trial were consistent with the overall findings[11]. Consequently, nintedanib was approved to slow the rate of decline in pulmonary function in people with SSc-ILD in the United States (in 2019) and the European Union (2020), and approved for treatment of SSc-ILD in Japan (2019).

Post-marketing surveillance of nintedanib in SSc-ILD patients in Japan began in April 2020 to evaluate its long-term safety and effectiveness in routine clinical practice. We describe here the first interim results of this post-marketing surveillance.

PATIENTS AND METHODS

1 Study design and patient cohort

This non-interventional, prospective post-marketing surveillance involves patients at approximately 200 clinical sites in Japan. It began on 15 April 2020 and has a planned observation period of two years (104 weeks) per patient (ClinicalTrials.gov: NCT04325217; European Union electronic Register of Post-Authorisation Studies: EUPAS32905). The surveillance includes SSc-ILD patients prescribed nintedanib for the first time. There are no formal exclusion criteria or constraints on factors such as concomitant medications, as this is an observational study of clinical practice.

Patients beginning treatment with ninte-

danib are registered by their attending physician in a centralized electronic database using case report forms, with additional case report forms collected at 12 weeks, 52 weeks, and 104 weeks after starting treatment. This interim analysis evaluated data for patients whose 12-week case report forms had been cleaned by 15 October 2022.

This post-marketing surveillance of nintedanib is being conducted in accordance with the Good Post-Marketing Study Practice (GPSP) and Good Vigilance Practice ordinances from the Ministry of Health, Labour and Welfare, which regulates medicines in Japan together with the Pharmaceuticals and Medical Devices Agency (PMDA). GPSP does not require either informed consent from patients or ethical approval by an institutional review board or ethics committee for non-interventional observational studies. Patient confidentiality in this post-marketing surveillance is ensured by de-identifying their data prior to collection in case report forms.

2 Outcomes

The primary outcome is the incidence of adverse drug reactions (ADRs), defined as adverse events for which either the physician reporting the event or a sponsor-employed physician cannot exclude a causal relationship with nintedanib. Other outcomes include the incidences of serious adverse events, adverse events leading to treatment discontinuation, adverse events leading to dose reduction, adverse events leading to death, and gastrointestinal symptoms including diarrhoea and nausea. Serious adverse events are defined as those that result in death, are life-threatening, require or prolong hospitalization, result in persistent or significant disability or incapacity, or are congenital anomalies/birth defects. Gastrointestinal symptoms are an important identified risk in the Japanese risk management plan for nintedanib (i.e., an already confirmed ADR). ADRs are classified using the Medical Dictionary for Regulatory Activities (MedDRA), which was at version 25.0 for this interim analysis.

The effectiveness outcomes are the annual rate of decline in FVC over 52 and 104 weeks, annual rate of decline in FVC in percent predicted over 52 and 104 weeks, and change from baseline in FVC at 52 and 104 weeks.

3 Statistical analysis

The planned sample size is approximately 500 patients, based on investigator-defined serious gastrointestinal disorders (MedDRA system organ class) occurring in 1.0% and 0% of patients receiving nintedanib and placebo, respectively, in the SENSCIS trial. If the true incidence of investigator-defined serious gastrointestinal disorders with nintedanib is actually 3.0%, including 428 patients would provide 90% power to reject the null hypothesis (incidence of 1.0%) with a two-sided significance level of 0.05, while including 500 patients allows for anticipated discontinuations. Safety data are analyzed descriptively for all patients who received at least one dose of nintedanib and visited the clinic at least once after their initial visit (the safety analysis set). Effectiveness outcomes will be reported in a later publication when sufficient FVC data at weeks 52 and 104 have been analyzed.

RESULTS

1 Patient disposition

A total of 338 patients had been enrolled by the cut-off date for this interim analysis (15 October 2022). Case report forms at 12 weeks after beginning nintedanib treatment have been collected to date from 211 patients and cleaned for 183 so far. Of the latter, 181 patients were included in the safety analysis set for this interim analysis, after excluding 2 who have not yet returned after their first visit (**Fig. 1**).

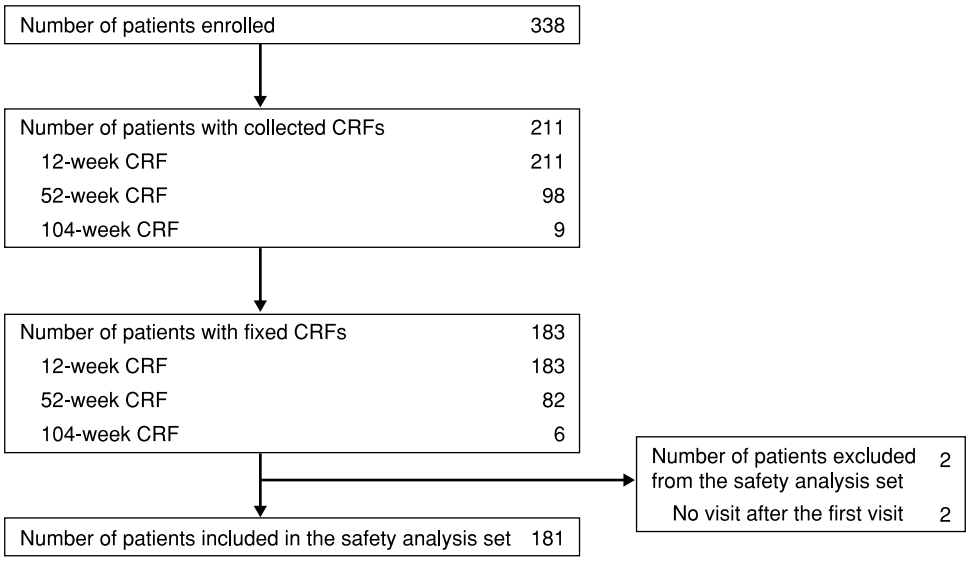

Fig. 1 Patient disposition
CRF: case report form

2 Patient demographics and clinical characteristics at baseline

The baseline demographic and clinical characteristics of the 181 patients in the safety analysis set are shown in **Table 1**. A total of 137 patients (75.69%) are female. Overall, mean age of the 181 patients was 64.0 years, while mean body weight, body mass index and body surface area were 54.57 kg, 21.78 kg/m^2, and 1.540 m^2, respectively. The mean duration of SSc was 6.25 years, and 116 patients (64.09%) had diffuse cutaneous disease while 60 (33.15%) had limited cutaneous disease. Mean duration of SSc-ILD was 5.03 years, mean extent of ILD lesions was 29.1%, and most patients had mild (31.49%) or moderate SSc-ILD (36.46%). Mean FVC was 2045.8 mL and mean % FVC was 72.103%. A total of 130 patients (71.82%) were taking concomitant medications for SSc-ILD/SSc, most commonly steroids (45.30%) and mycophenolate mofetil (23.76%).

3 Exposure to nintedanib

In the 181 patients in the safety analysis set, most were initially prescribed the licensed dosages of nintedanib: 150 mg twice daily (300 mg/day) in 76 patients (41.99%) and 100 mg twice daily (200 mg/day) in 61 (33.70%) (**Table 2**). Among the other 44 patients (24.31%), the initial dose was 100 mg once daily in 29 individuals, 150 mg once daily in 13 individuals, 50 mg once daily in 1 individual, and unknown in 1 individual. Thirty patients (16.57%) discontinued treatment, due to adverse events (n=27, 14.92%), patient's request (n=5, 2.76%), and other personal reasons (n=2, 1.10%). The mean/median duration of treatment to date is 225 days/148 days.

4 Safety and tolerability

1) ADRs

ADRs were reported in 96 (53.04%) of the 181 patients in the safety analysis set, but serious ADRs were reported in only 6 patients (3.31%). **Table 3** shows ADRs occurring in at least 1% of patients. **Table 4** shows ADRs occurring in at least 1% of patients by baseline demographic and clinical characteristics.

Gastrointestinal disorder ADRs were re-

Table 1　Demographic and clinical characteristics of patients at baseline (1)

Characteristic	Safety analysis set (n=181*)
Sex, n (%)	
Male	44 (24.31)
Female	137 (75.69)
Age, years, mean±SD	64.0±12.2
Body weight, kg, mean±SD (n=166)	54.57±11.83
Body mass index, kg/m^2, mean±SD (n=165)	21.78±3.90
Body surface area, m^2, mean±SD (n=165)	1.540±0.186
FVC, mL, mean±SD (n=165)	2045.8±694.2
%FVC (%), mean±SD (n=165)	72.103±17.029
Smoking history, n (%)	
Never smoker	113 (62.43)
Former smoker	51 (28.18)
Current smoker	4 (2.21)
Unknown	13 (7.18)
Hepatic dysfunction†, n (%)	10 (5.52)
Child-Pugh classification of hepatic impairment	
A (mild impairment)	2 (1.10)
B (moderate impairment)	0
C (severe impairment)	0
Unknown	3 (1.66)
SSc duration, years (n=170)	
Mean±SD	6.25±7.37
Median (Q1, Q3)	3.28 (1.22, 8.40)
SSc subtypes, n (%)	
Diffuse cutaneous sclerosis	116 (64.09)
Limited cutaneous sclerosis	60 (33.15)
Unknown	5 (2.76)
Duration of SSc-ILD, years (n=164)	
Mean±SD	5.03±5.44
Median (Q1, Q3)	2.88 (1.00, 6.96)
Extent of ILD lesions, %, mean±SD (n=148)	29.1±17.3

*n=181 unless otherwise indicated, †Based on the following 4 MedDRA SMQs: Drug related hepatic disorders-comprehensive search (narrow); Liver-related investigations, signs and symptoms (broad); Cholestasis and jaundice of hepatic origin (narrow); Hepatitis, non-infectious (broad)

FVC: forced vital capacity, ILD: interstitial lung disease, MedDRA: Medical Dictionary for Regulatory Activities, version 25.0, Q: quartile, SD: standard deviation, SMQ: Standardized MedDRA Query, SSc: systemic sclerosis, SSc-ILD: systemic sclerosis-associated interstitial lung disease

ported in 73 (40.33%) patients, including diarrhoea in 56 (30.94%), nausea in 18 (9.94%), vomiting in 6 (3.31%), abdominal pain in 5 (2.76%), and haematochezia in 1 (0.55%) (**Table 5**). None of these ADRs were serious. Hepatic function disorder ADRs were reported in 28 patients (15.47%), including hepatic function abnormal in 21 patients (11.60%) and gamma-glutamyltransferase increased in 3 patients (1.66%) (**Table 5**). Of these, serious

Table 1　Demographic and clinical characteristics of patients at baseline(2)

Characteristic	Safety analysis set（n=181*）
Severity of SSc-ILD‡	
0（normal）	1（0.55）
1（mild）	57（31.49）
2（moderate）	66（36.46）
3（severe）	35（19.34）
4（very severe）	10（5.52）
Unknown	12（6.63）
Concomitant medications for SSc-ILD/SSc, n（%）	130（71.82）
Steroids	82（45.30）
Mycophenolate mofetil	43（23.76）
Azathioprine	16（8.84）
Tacrolimus	13（7.18）
Cyclophosphamide	5（2.76）
Other immunosuppressants	3（1.66）
Tocilizumab	3（1.66）
Rituximab	1（0.55）
Unknown	1（0.55）

*n=181 unless otherwise indicated
‡Based on SSc-ILD severity scale：0（no lesions on HRCT）；1（<20% spread of lesions）；2（>20% spread of lesions with %FVC>70%）；3（<70%%FVC without the need for oxygen therapy）；4（requiring oxygen therapy）
HRCT：high-resolution computed tomography, SSc-ILD：systemic sclerosis-associated interstitial lung disease

Table 2　Patient exposure to nintedanib

	Safety analysis set（n=181）
Duration of treatment, days	
Mean±SD	225.3±173.7
Median（Q1, Q3）	148.0（85.0, 371.0）
Initial dose, n（%）	
150 mg b.i.d.	76（41.99）
Dose reduction from initial 150 mg b.i.d. to 100 mg b.i.d.	26（34.21）
100 mg b.i.d.	61（33.70）
Dose increase from initial 100 mg b.i.d. to 150 mg b.i.d.	12（19.67）
Other*	44（24.31）
Patients who discontinued nintedanib, n（%）†	30（16.57）
Adverse event	27（14.92）
Patient's request	5（2.76）
Other personal reasons	2（1.10）

*100 mg once daily in 29 patients, 150 mg once daily in 13 patients, 50 mg once daily in 1 patient, unknown in 1 patient, †≧1 reason in some patients
b.i.d.：twice daily, Q：quartile

Table 3　ADRs occurring in ≧1% of patients

ADRs	Safety analysis set（*n*＝181）
Any ADR	96（53.04）
ADR reported in ≧1% of patients*	
Diarrhoea	56（30.94）
Hepatic function abnormal	21（11.60）
Nausea	18（9.94）
Decreased appetite	7（3.87）
Vomiting	6（3.31）
Abdominal pain	5（2.76）
Abdominal discomfort	3（1.66）
Gamma-glutamyltransferase increased	3（1.66）
Constipation	2（1.10）
Faeces soft	2（1.10）
Rash	2（1.10）

*Preferred terms from MedDRA version 25.0

ADR：adverse drug reaction, MedDRA：Medical Dictionary for Regulatory Activities

Table 4　ADRs occurring in ≧1% of patients by demographic and clinical characteristics at baseline

ADRs	Age		Hepatic dysfunction*		Renal dysfunction†	
	＜65 years（*n*＝83）	≧65 years（*n*＝98）	No（*n*＝171）	Yes（*n*＝10）	No（*n*＝171）	Yes（*n*＝10）
Any ADR	44（53.01）	52（53.06）	89（52.05）	7（70.00）	91（53.22）	5（50.00）
ADR reported in ≧1% of patients‡						
Diarrhoea	29（34.94）	27（27.55）	52（30.41）	4（40.00）	52（30.41）	4（40.00）
Hepatic function abnormal	10（12.05）	11（11.22）	19（11.11）	2（20.00）	20（11.70）	1（10.00）
Nausea	9（10.84）	9（9.18）	16（9.36）	2（20.00）	17（9.94）	1（10.00）
Decreased appetite	2（2.41）	5（5.10）	7（4.09）	0	6（3.51）	1（10.00）
Vomiting	2（2.41）	4（4.08）	5（2.92）	1（10.00）	6（3.51）	0
Abdominal pain	4（4.82）	1（1.02）	5（2.92）	0	5（2.92）	0
Abdominal discomfort	2（2.41）	1（1.02）	3（1.75）	0	3（1.75）	0
Gamma-glutamyltransferase increased	0	3（3.06）	3（1.75）	0	3（1.75）	0
Constipation	1（1.20）	1（1.02）	2（1.17）	0	2（1.17）	0
Faeces soft	1（1.20）	1（1.02）	1（0.58）	1（10.00）	2（1.17）	0
Rash	1（1.20）	1（1.02）	2（1.17）	0	2（1.17）	0

*Based on the following 4 MedDRA SMQs：Drug related hepatic disorders-comprehensive search（narrow）；Liver-related investigations, signs and symptoms（broad）；Cholestasis and jaundice of hepatic origin（narrow）；Hepatitis, non-infectious（broad）

†Based on MedDRA SOC（Renal and urinary disorders）or HLT（Renal function analyses）

‡Preferred terms from MedDRA version 25.0

ADR：adverse drug reaction, HLT：high level term, MedDRA：Medical Dictionary for Regulatory Activities, SMQ：Standardized MedDRA Query, SOC：system organ class

ADRs occurred in 4 patients（hepatic function abnormal：*n*＝2［1.10%］；hepatic enzyme increased：*n*＝1［0.55%］；drug-induced liver injury：*n*＝1［0.55%］）——all of these resolved. A serious ADR of nephrotic syndrome was reported in 1 patient（0.55%），which resolved.

Table 5　ADRs for important identified risks*

ADRs	Safety analysis set（n＝181）
Gastrointestinal disorders†	73（40.33）
Diarrhoea	56（30.94）
Nausea	18（9.94）
Vomiting	6（3.31）
Abdominal pain	5（2.76）
Abdominal discomfort	3（1.66）
Constipation	2（1.10）
Faeces soft	2（1.10）
Gastrointestinal disorder	1（0.55）
Haematochezia	1（0.55）
Hepatic function disorder†	28（15.47）
Hepatic function abnormal	21（11.60）
Gamma-glutamyltransferase increased	3（1.66）
Liver disorder	1（0.55）
Hepatic enzyme increased	1（0.55）
Drug-induced liver injury	1（0.55）
Liver function test increased	1（0.55）
Nephrotic syndrome†	1（0.55）
Nephrotic syndrome	1（0.55）

*ADRs occurring in this PMS for important identified risks in the Japanese risk management plan for nintedanib

†Main categories（gastrointestinal disorders, hepatic function disorder, nephrotic syndrome） are important identified risks; subcategories are preferred terms from MedDRA version 25.0

ADR: adverse drug reaction, MedDRA: Medical Dictionary for Regulatory Activities, PMS: post-marketing surveillance

The only other serious ADR was decreased appetite in 1 patient（0.55%）, which also resolved.

2）Adverse events

Of the 181 patients in the safety analysis set, adverse events leading to dose reduction were reported in 41 patients（22.65%）, most commonly diarrhoea in 26（14.36%）, nausea in 6（3.31%）, and hepatic function abnormal in 4（2.21%）（**Table 6**）.

Adverse events leading to discontinuation were reported in 27（14.92%）patients: diarrhoea in 9（4.97%）; nausea in 6（3.31%）; hepatic function abnormal in 6（3.31%）; abdominal pain in 2（1.10%）; and gastrointestinal disorder, vomiting, faeces soft, nephrotic syndrome, C-reactive protein increased, hepatic enzyme increased, bronchopulmonary aspergillosis, pulmonary hypertension, and pyrexia in 1 patient each（0.55%）.

Serious adverse events were reported in 21 patients（11.60%）: hepatic function abnormal, nephrotic syndrome, ILD, pulmonary hypertension, and pulmonary arterial hypertension in 2 patients each（1.10%）; and decreased appetite, drug-induced liver injury, hepatic enzyme increased, bronchopulmonary aspergillosis, osteomyelitis, subarachnoid haemorrhage, cardiac failure, left ventricular failure, respiratory disorder, large intestine polyp, cholangitis, renal failure, pyrexia, fall, femoral neck fracture, and

Table 6 Adverse events leading to dose reduction

AEs	Safety analysis set (n=181)
Gastrointestinal disorders*	41 (22.65)
Diarrhoea	26 (14.36)
Nausea	6 (3.31)
Abdominal discomfort	2 (1.10)
Abdominal pain	2 (1.10)
Vomiting	2 (1.10)
Constipation	1 (0.55)
Hepatobiliary disorders*	
Hepatic function abnormal	4 (2.21)
Metabolism and nutrition disorders*	
Decreased appetite	3 (1.66)
Skin and subcutaneous tissue disorders*	
Skin ulcer	1 (0.55)
Investigations*	
Liver function test increased	1 (0.55)

*Main categories (gastrointestinal disorders, hepatobiliary disorders, metabolism and nutrition disorders, skin and subcutaneous tissue disorders, and investigations) are system organ classes from MedDRA; subcategories are preferred terms from MedDRA

AE: adverse event, MedDRA: Medical Dictionary for Regulatory Activities, version 25.0

contusion in 1 patient each (0.55%).

Adverse events leading to death were reported in 3 patients (1.66%), consisting of 1 event each of bronchopulmonary aspergillosis, pyrexia, cardiac failure and renal failure——the latter 2 of which occurred in the same patient. All adverse events leading to death were considered unrelated to nintedanib.

DISCUSSION

Nintedanib was approved for treatment of SSc-ILD in Japan on 20 December 2019, based on clinical trial data. In 2020, the Japan Respiratory Society and Japan College of Rheumatology jointly proposed a treatment algorithm for SSc-ILD that recommends nintedanib in addition to immunomodulators[12]. Therefore, as an increasing number of Japanese SSc-ILD patients may be prescribed this medication in coming years, it is important to evaluate its safety and effectiveness in routine clinical practice.

This interim analysis of post-marketing surveillance in Japan found that after a mean of 225 days of treatment to date, 53.04% of the 181 patients had reported ADRs, most commonly diarrhoea in 30.94%, abnormal hepatic function in 11.60%, and nausea in 9.94%. However, these ADRs were serious in only 3.31% of patients, all of whom recovered. There were no notable differences in the occurrence of ADRs by baseline age, liver dysfunction and renal dysfunction.

The Japanese risk management plan for nintedanib (a standard document required by the PMDA for pharmacovigilance of any licensed medication) includes gastrointestinal disorders, hepatic function disorder, and nephrotic syndrome as "important identified risks" (i.e., known ADRs) and haematochezia as an "important

potential risk" (i.e., a suspected but not confirmed ADR), based on clinical trials. In this interim analysis, gastrointestinal ADRs occurred in 40.33% of patients but none were serious. Hepatic function disorder ADRs occurred in 15.47% of patients and were serious in 2.21%, but all patients recovered. There was only 1 haematochezia ADR (0.55% of patients), which was not serious.

In the overall cohort of the multinational SENSCIS trial in SSc-ILD patients, diarrhoea was the most common adverse event, reported by 75.7% and 31.6% of the nintedanib and placebo groups, respectively, followed by nausea (31.6% and 13.5%, respectively)[10]. Diarrhoea was also the most common adverse event in the Japanese subgroup of the SENSCIS trial, occurring in 82.4% and 32.6% of nintedanib and placebo patients, respectively, while nausea occurred in 20.6% and 8.3%, respectively, and liver disorder occurred in 17.6% and 0%, respectively; these gastrointestinal and liver disorder events were mostly of mild-to-moderate severity[11].

Nintedanib is also approved for treatment of other fibrotic lung diseases in Japan; specifically, progressive fibrosing ILD and idiopathic pulmonary fibrosis (IPF). Interim post-marketing surveillance of 5578 patients with IPF receiving nintedanib found that 3767 (67.5%) reported ADRs[13]. Hepatic function abnormal and diarrhoea were the most common ADRs causing discontinuation (in 18.8% and 13.2% of patients, respectively)[13].

In the current interim analysis of SSc-ILD patients, only 42% of patients were initially prescribed 150 mg twice daily, the usual recommended dosage based mainly on a phase Ⅱ dose evaluation trial in IPF[14], while the other patients received lower starting doses. Although the nintedanib prescribing information in the United States[15] and Europe[16] recommends a lower dose (100 mg twice daily) for patients with mild hepatic impairment (Child-Pugh class A), the Japanese prescribing information does not make this recommendation[17] and only 2 patients in the current interim analysis had mild hepatic impairment. Thus, the lower-than-recommended dose in over half the patients may represent caution by the prescribing physicians, possibly because of the generally low body weight (mean of 54.57 kg) and body surface area (mean 1.540 m^2) of the patients, given that previous studies have suggested that low body weight and low body surface area may predict nintedanib-associated adverse events in Japanese patients with IPF[18,19]. Furthermore, a population pharmacokinetic analysis in IPF patients found that Asian race and low body weight were associated with a small-to-moderate increase in nintedanib plasma exposure[20], while exposure-safety analysis of nintedanib in patients with fibrotic lung diseases (including SSc-ILD) revealed weak-to-moderate correlation between plasma drug levels and elevations in hepatic enzymes[21]. However, *a priori* dose reduction must be balanced with the need to optimize treatment effectiveness, given the high morbidity and mortality associated with SSc-ILD. Furthermore, the rate of treatment discontinuation in this interim analysis (16.57% of patients), which was mostly due to adverse events (14.92%), was similar to that in Japanese patients in the SENSCIS trial (17.6%) where all patients began treatment with 150 mg twice daily[11]. The discontinuation rate was, however, much lower than in Japanese patients with IPF in clinical practice (approximately 50%)[13,19,22].

Overall, therefore, the safety and tolerability profile of nintedanib in SSc-ILD patients in routine clinical practice in Japan in this interim analysis of post-marketing surveillance is consistent with other data from routine clinical practice in

Japan as well as clinical trials.

This study has some noteworthy strengths and limitations. To the best of our knowledge, it is the first robust investigation of the safety and tolerability of nintedanib in SSc-ILD patients in routine clinical practice in Japan. The sample size in this interim analysis ($n=181$) should be considered in the context of the rarity of SSc-ILD, which was recently estimated to have a prevalence of only 13.9 per 100,000 people in Japan[23]. However, the usual limitations of post-marketing surveillance also apply here, including the lack of a control group, which complicates the interpretation of causality between nintedanib treatment and the observed adverse events (despite the expert judgement of the physicians who attributed them to be either possible ADRs or unrelated to nintedanib).

CONCLUSION

In Japanese patients with SSc-ILD, the safety and tolerability profile of nintedanib in routine clinical practice in this interim analysis of post-marketing surveillance was consistent with previous studies, and no new safety signals were observed. The final safety and effectiveness results will be published when the planned two years of surveillance per patient has been completed.

CONFLICTS OF INTEREST

AS is an employee of Nippon Boehringer Ingelheim Co. Ltd. AT is an employee of EPS Corporation, which was contracted by Nippon Boehringer Ingelheim for this study.

FUNDING

This study is sponsored by Nippon Boehringer Ingelheim Co. Ltd.

DATA AVAILABILITY

To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the International Committee of Medical Journal Editors criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data after publication of the primary manuscript and secondary analyses in peer-reviewed journals and regulatory and reimbursement activities are completed, normally within 1 year after the marketing application has been granted by major regulatory authorities. Researchers should use the https://vivli.org/ link to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

ACKNOWLEDGMENTS

We thank the investigators involved in this study. We also thank Katsumi Tanaka (formerly of Nippon Boehringer Ingelheim Co. Ltd) for his contribution to the study. Medical writing assistance was provided by Giles Brooke, PhD, of Envision Pharma Group, which was contracted and compensated by Nippon Boehringer Ingelheim Co. Ltd.

REFERENCES

1) Jaeger VK, Wirz EG, Allanore Y, Rossbach P, Riemekasten G, Hachulla E, et al. Incidences and risk factors of organ manifestations in the early course of systemic sclerosis: a longitudinal EUSTAR study. PLoS One 2016;11:e0163894.
2) Bergamasco A, Hartmann N, Wallace L, Verpillat P. Epidemiology of systemic sclerosis and systemic sclerosis-associated interstitial lung disease. Clin Epidemiol 2019;11:257-73.
3) Elhai M, Meune C, Boubaya M, Avouac J, Hachulla E, Balbir-Gurman A, et al. Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis 2017;76:1897-905.
4) Nikpour M, Baron M. Mortality in systemic sclerosis: lessons learned from population-based and observational cohort studies. Curr Opin Rheumatol 2014;26:131-7.
5) Fischer A, Patel NM, Volkmann ER. Interstitial lung disease in systemic sclerosis: focus on early detection and intervention. Open Access Rheumatol 2019;11:283-307.
6) Cottin V, Brown KK. Interstitial lung disease associated with systemic sclerosis (SSc-ILD). Respir Res 2019;20:13.

7) Kuwana M, Azuma A. Nintedanib: new indication for systemic sclerosis-associated interstitial lung disease. Mod Rheumatol 2020;30:225-31.
8) Hilberg F, Roth GJ, Krssak M, Kautschitsch S, Sommergruber W, Tontsch-Grunt U, et al. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res 2008;68:4774-82.
9) Chaudhary NI, Roth GJ, Hilberg F, Muller-Quernheim J, Prasse A, Zissel G, et al. Inhibition of PDGF, VEGF and FGF signalling attenuates fibrosis. Eur Respir J 2007;29:976-85.
10) Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med 2019;380:2518-28.
11) Kuwana M, Ogura T, Makino S, Homma S, Kondoh Y, Saito A, et al. Nintedanib in patients with systemic sclerosis-associated interstitial lung disease: A Japanese population analysis of the SENSCIS trial. Mod Rheumatol 2021;31:141-50.
12) Kondoh Y, Makino S, Ogura T, Suda T, Tomioka H, Amano H, et al. 2020 guide for the diagnosis and treatment of interstitial lung disease associated with connective tissue disease. Respir Investig 2021;59:709-40.
13) Ogura T, Inoue Y, Azuma A, Homma S, Kondoh Y, Tanaka K, et al. Real-world safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: interim report of a post-marketing surveillance in Japan. Adv Ther 2023;40:1474-93.
14) Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med 2011;365:1079-87.
15) Boehringer Ingelheim Pharmaceuticals, Inc.. OFEV (nintedanib) Prescribing Information: 10/2022. Available at: https://content.boehringer-ingelheim.com/DAM/b5d67da8-329b-4fa4-a732-af1e011fc0a5/ofev-us-pi.pdf
16) Boehringer Ingelheim International GmbH. Ofev (nintedanib) Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/ofev-epar-product-information_en.pdf (Accessed 8 November, 2023)
17) Nippon Boehringer Ingelheim. Ofev (nintedanib) Japanese package insert. https://www.pmda.go.jp/ (Accessed 8 November, 2023)
18) Ikeda S, Sekine A, Baba T, Yamanaka Y, Sadoyama S, Yamakawa H, et al. Low body surface area predicts hepatotoxicity of nintedanib in patients with idiopathic pulmonary fibrosis. Sci Rep 2017;7:10811.
19) Dobashi M, Tanaka H, Taima K, Itoga M, Ishioka Y, Shiratori T, et al. The efficacy of nintedanib in 158 patients with idiopathic pulmonary fibrosis in real-world settings: A multicenter retrospective study. SAGE Open Med 2021;9:20503121211023357.
20) Schmid U, Doege C, Dallinger C, Freiwald M. Population pharmacokinetics of nintedanib in patients with idiopathic pulmonary fibrosis. Pulm Pharmacol Ther 2018;48:136-43.
21) Schmid U, Weber B, Sarr C, Freiwald M. Exposure-safety analyses of nintedanib in patients with chronic fibrosing interstitial lung disease. BMC Pulm Med 2021;21:244.
22) Kato M, Sasaki S, Tateyama M, Arai Y, Motomura H, Sumiyoshi I, et al. Clinical significance of continuable treatment with nintedanib over 12 months for idiopathic pulmonary fibrosis in a real-world setting. Drug Des Devel Ther 2021;15:223-30.
23) Kuwana M, Saito A, Sakamoto W, Raabe C, Saito K. Incidence rate and prevalence of systemic sclerosis and systemic sclerosis-associated interstitial lung disease in Japan: analysis using Japanese claims databases. Adv Ther 2022;39:2222-35.

＜Received on November 8, 2023＞