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Safety and pharmacokinetics of nintedanib and pirfenidone in idiopathic pulmonary fibrosis

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ABSTRACT A randomised, double-blind, phase II, dose escalation trial was conducted to assess the safety, tolerability and pharmacokinetics of the tyrosine kinase inhibitor nintedanib, alone and when added to ongoing pirfenidone therapy, in Japanese patients with idiopathic pulmonary fibrosis.

50 Japanese patients were randomised to receive nintedanib or placebo in one of three cohorts (nintedanib 50 mg twice daily or 100 mg twice daily for 14 days, or 150 mg twice daily for 28 days). Patients receiving pirfenidone at inclusion were stratified to every nintedanib dose group and placebo.

Adverse events were reported in nine out of 17 patients receiving nintedanib alone and 10 out of 21 patients receiving nintedanib added to pirfenidone. All adverse events were mild or moderate in intensity. Gastrointestinal disorders were the most common adverse event. Maximum plasma concentration and area under the curve at steady state for nintedanib and its metabolites tended to be lower when nintedanib was added to pirfenidone. Nintedanib had no effect on the pharmacokinetics of pirfenidone.

In conclusion, further study is needed to evaluate the safety and tolerability profile of nintedanib when added to pirfenidone in patients with idiopathic pulmonary fibrosis. There was a trend toward lower exposure of nintedanib when it was added to pirfenidone.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease characterised by fibrosis of the lung alveoli and interstitium [1, 2]. Estimates of the worldwide prevalence of IPF range from two to 43 cases per 100000 people [2]. IPF has a poor prognosis [2] and there is a clinical need for novel therapies to improve outcomes in patients with IPF.

The pathogenesis of IPF is hypothesised to involve abnormal wound healing in response to epithelial injury [3]. The development of new treatments has focused on the signalling pathways involved in this response. Nintedanib (formerly known as BIBF 1120; Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany) is a potent intracellular inhibitor of tyrosine kinases that has been developed for the treatment of IPF and a number of cancer types. Nintedanib blocks the kinase activity of the platelet-derived growth factor, vascular endothelial growth factor and fibroblast growth factor receptors, all of which have been shown to be involved in the development of fibrosis [4, 5]. The results of the phase II To Improve Pulmonary Fibrosis with BIBF-1120 (TOMORROW) trial suggested that nintedanib 150 mg twice daily reduced decline in lung function in patients with IPF , with fewer acute exacerbations and preserved health-related quality of life [6]. Recently, the results of the two replicate phase III INPULSIS trials demonstrated that nintedanib reduced disease progression in patients with IPF by significantly reducing the rate of decline in forced vital capacity (FVC) [7]. In patients treated with nintedanib, the most common adverse events were gastrointestinal disorders, which accounted for the majority of discontinuations of study medication due to adverse eventss [7].

Pirfenidone (Shionogi & Co. (Osaka, Japan) and InterMune Inc. (Brisbane, CA, USA)) was approved for the treatment of IPF in Japan in 2008 (Shionogi & Co.) and for the treatment of adult patients with mild to moderate IPF in the European Union in 2011. In the phase III CAPACITY (Clinical Studies Assessing Pirfenidone in IPF: Research of Efficacy and Safety Outcomes) 2 trial, 72 weeks' treatment with pirfenidone 2403 mg·day^{-1} significantly reduced the decline in percentage predicted FVC in patients with IPF *versus* placebo, but in the concurrent CAPACITY 1 trial, a significant difference from placebo was not observed [8]. Recently, the 52-week, phase III Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis (ASCEND) trial demonstrated a benefit of pirfenidone *versus* placebo on change from baseline in percentage predicted FVC [9]. In a phase III study in Japanese patients with IPF, 52 weeks' treatment with pirfenidone 180 mg·day^{-1} significantly reduced the decline in vital capacity compared with placebo, with an adjusted mean change in vital capacity of -0.09 L with pirfenidone 180 mg·day^{-1} compared with -0.16 L with placebo [10]. Photosensitivity was the most frequent adverse event in the phase III study in Japanese patients, experienced by 51.4% of patients on pirfenidone 180 mg·day^{-1} *versus* 22.4% of patients on placebo [10]. However, in the international CAPACITY and ASCEND trials, the adverse event reported most frequently in patients treated with pirfenidone was nausea [8, 9]. A recent review of adverse events reported in patients treated with pirfenidone based on a data set with a cumulative total exposure of 2059 person-exposure years reported that nausea and vomiting were reported by 40% and 18%, respectively, of patients treated with pirfenidone [11].

There is some overlap in the adverse-event profiles of pirfenidone and nintedanib in patients with IPF in terms of gastrointestinal events and increases in liver enzymes [6–9]. However, pirfenidone and nintedanib have different metabolic profiles; pirfenidone is metabolised by various cytochrome P450 enzymes and predominantly excreted *via* the urine as the primary metabolite 5-carboxy-pirfenidone [12], whereas the metabolism of nintedanib is predominantly characterised by ester cleavage yielding BIBF 1202 ZW. BIBF 1202 ZW is subsequently glucuronidated by various uridine diphosphate glucuronosyltransferases (UGTs) in the intestine and by UGT1A1 in the liver to form BIBF 1202 glucuronide. Both nintedanib metabolites are excreted *via* the biliary system into the faeces [13].

This phase II study was conducted to determine the safety, tolerability and pharmacokinetics of nintedanib and its metabolites, alone and when added to ongoing pirfenidone therapy, in Japanese patients with IPF. The pharmacokinetics of pirfenidone (alone and when nintedanib was co-administered) were also investigated.

Materials and methods

Study subjects

Patients eligible for inclusion were aged ⩾40 years, with IPF diagnosed according to the American Thoracic Society/European Respiratory Society consensus statement [1] and the fourth version of the diagnostic guidelines for idiopathic interstitial pneumonia in Japan [14] <5 years before screening, and high-resolution computed tomography within 12 months of randomisation that was consistent with a diagnosis of IPF. Inclusion criteria included an FVC of ⩾50% of predicted value (according to the Japanese predicted normal equations) [15] and single-breath diffusing capacity for carbon monoxide

(*D*LCO) of 30–79% of predicted value. Exclusion criteria included: elevated liver enzymes (>1.5 times the upper limit of the normal range); relevant airway obstruction; requirement for ≥ 15 h·day^{-1} supplemental oxygen; treatment with oral corticosteroids at unstable doses or in excess of the equivalent of prednisone 15 mg·day^{-1}, or with ketoconazole or atazanavir; an expectation of undergoing lung transplantation or of having rapidly deteriorating disease; or a life expectancy of <3 months from screening. Patients who had been receiving a steady dose of pirfenidone for ≥ 3 months were eligible for inclusion and were enrolled according to a pre-specified stratification scheme (described in the following section).

The trial was carried out in compliance with the Declaration of Helsinki (October 1996), and in accordance with the International Conference on Harmonisation Good Clinical Practice (GCP) guidelines and Japanese GCP regulations (Ministry of Health and Welfare Ordinance Number 28; March 27, 1997). All patients provided written informed consent before entering the study. The patients' safety was monitored by an independent data monitoring committee (IDMC). The trial was registered at www.clinicaltrials.gov with identifier number NCT01136174.

Study design

This study was a randomised, double-blind (with respect to nintedanib), placebo-controlled (within dose group), multicentre, dose-escalation trial. It consisted of a screening visit occurring 5–21 days before the start of treatment, a 14-day (cohorts 1 and 2) or 28-day (cohort 3) treatment period, an end-of-treatment visit 7 days after the last dose (or on premature treatment discontinuation) and a follow-up visit 3 weeks after the end-of-treatment visit (fig. 1). The treatment period included four (cohorts 1 and 2) or six (cohort 3) visits for pharmacokinetic sampling and safety assessments after the initiation of nintedanib treatment.

Patients were randomised to three cohorts using a stepwise approach, with IDMC safety review before transition to a higher dose group. Patients in cohort 1 were randomised to receive nintedanib 50 mg twice daily or placebo for 14 days; patients in cohort 2 were randomised to receive nintedanib 100 mg twice

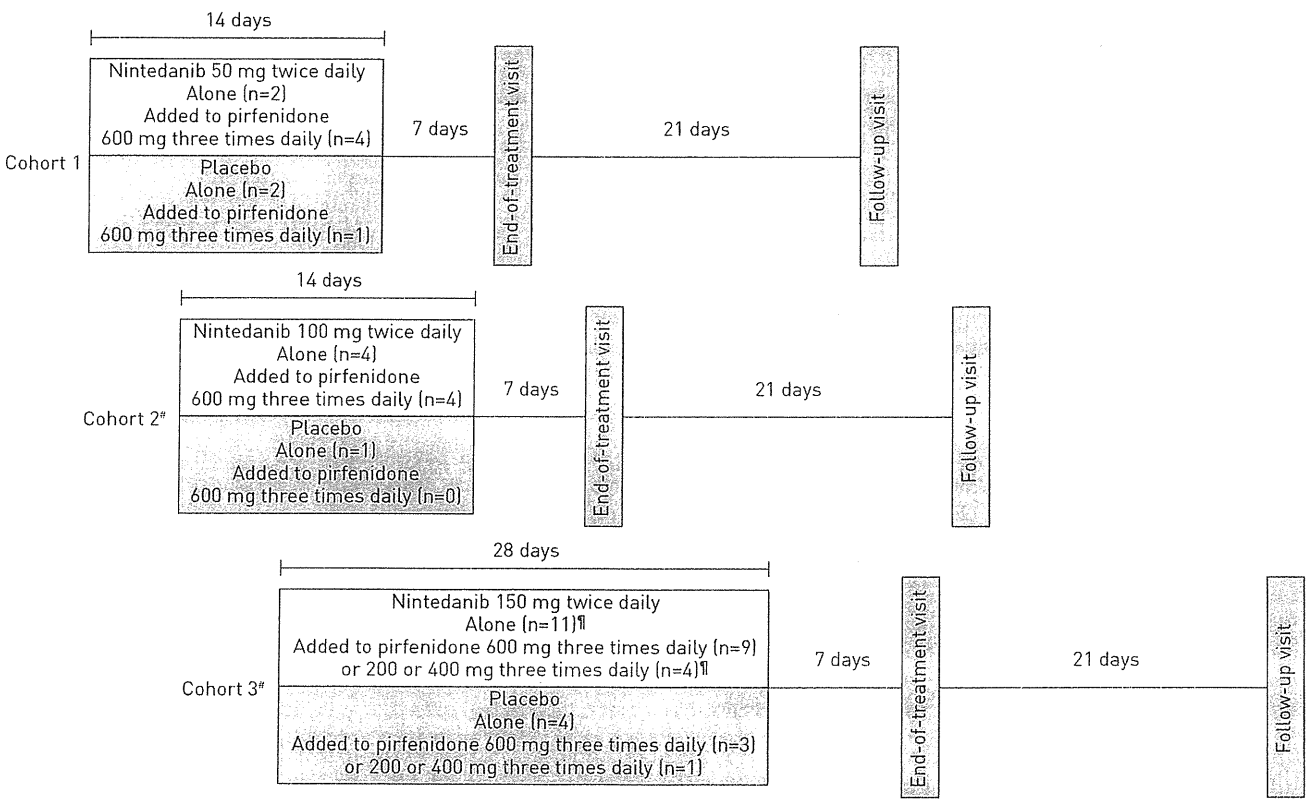

FIGURE 1 Study design and distribution of patients. #: patients' safety was reviewed by an independent data monitoring committee before patients were transitioned to these cohorts; ¶: two patients withdrew before study completion.

daily or placebo for 14 days; and patients in cohort 3 were randomised to nintedanib 150 mg twice daily or placebo for 28 days (fig. 1). Patients who had been receiving a steady dose of pirfenidone 600 mg three times daily for ≥3 months prior to inclusion were stratified to each cohort, and were included in the safety and pharmacokinetic analyses. Patients on a steady dose of pirfenidone 200 or 400 mg three times daily for ≥3 months prior to inclusion were allowed to participate in cohort 3 only and were included in safety analyses, but not in the pharmacokinetic analysis. It was planned that approximately half of every nintedanib and placebo group would be taking pirfenidone, except the placebo group in cohort 3, in which it was planned that two-thirds of the patients would be receiving pirfenidone. Pirfenidone was given as prescribed, after breakfast, lunch and dinner.

Safety analyses

All treated patients were included in the safety analyses. The safety end-points assessed were the incidence and intensity (mild, moderate or severe) of adverse events, withdrawal due to adverse events, routine laboratory tests, lung function measurements (FVC, forced expiratory volume in 1 s (FEV_1) and D_{LCO}), blood pressure and pulse rate. Analyses of adverse events focused on treatment-emergent events, defined as those occurring up to 28 days after the completion of study medication, or starting before the first drug intake and deteriorating during treatment. Laboratory tests, lung function and vital signs were measured at screening, baseline, on days 2, 7 and 14 (plus days 21 and 28 for cohort 3) of treatment, and at the end-of-treatment visit. Safety results for patients receiving placebo with or without pirfenidone were grouped across all cohorts.

Pharmacokinetic analyses

For quantification of plasma concentrations of nintedanib, its metabolites (BIBF 1202 ZW and BIBF 1202 glucuronide) and pirfenidone, ~4 mL of venous blood was collected during study visits (pre-dose and at time-points from 30 min to 72 h after drug administration at steady state). Samples for pharmacokinetic assessment of pirfenidone were taken before and after the breakfast and lunch doses (pre-dose and at time-points from 30 min to 12 h after drug administration). Plasma concentrations of nintedanib, its metabolites and pirfenidone were determined using a validated liquid chromatography–tandem mass spectrometry assay (Nuvisan Pharma Services GmbH & Co. KG, Neu-Ulm, Germany).

The pharmacokinetic parameters calculated for nintedanib and pirfenidone included: the area under the concentration–time curve of the analyte in plasma at a steady state over a uniform dosing interval τ ($AUC_{\tau,ss}$) and over the time interval from t1 to t2 ($AUC_{t1-t2,ss}$); maximum concentration of the analyte in plasma at steady state over a uniform dosing interval τ ($C_{max,ss}$); time from dosing to maximum concentration of the analyte in plasma at steady state over a uniform dosing interval τ ($t_{max,ss}$); terminal half-life of the analyte in plasma at steady state ($t_{1/2,ss}$); apparent clearance of the analyte in plasma after extravascular administration at steady state ($CL/F_{,ss}$) (nintedanib only); apparent volume of distribution during the terminal phase λz following extravascular administration at steady state ($Vz/F_{,ss}$) (nintedanib only); accumulation ratios based on $AUC_{t1-t2,ss}$ and $C_{max,ss}$ (nintedanib only); and ratios of $C_{max,ss}$ and $AUC_{t1-t2,ss}$ of the test treatment to the $C_{max,ss}$ and $AUC_{t1-t2,ss}$ of the reference treatment (pirfenidone only). Pharmacokinetics were assessed for nintedanib and its metabolites when it was given alone and when it was added to ongoing pirfenidone therapy (parallel-group comparison), and for pirfenidone with and without nintedanib co-administration (intra-individual comparison).

Results

Patients

A total of 66 patients were screened over eight sites, of whom 50 were randomised: six patients were randomised to receive nintedanib 50 mg twice daily, eight to nintedanib 100 mg twice daily, 24 to nintedanib 150 mg twice daily and 12 to placebo (fig. 1). At screening, 26 patients were being treated with pirfenidone, five of whom entered cohort 1 (four randomised to nintedanib 50 mg twice daily and one to placebo), four entered cohort 2 (all randomised to nintedanib 100 mg twice daily) and 17 entered cohort 3 (13 randomised to nintedanib 150 mg twice daily and four to placebo) (fig. 1). Of those randomised, 46 (92.0%) patients completed the study; four patients from the 150 mg twice daily group discontinued prematurely. There were no notable differences in baseline characteristics between groups (table 1). The mean age was 65.2 years and 70.0% of subjects were male. 10 patients were receiving systemic corticosteroids at baseline and four were receiving acetylcysteine.

Safety outcomes

Safety was assessed in all 50 randomised patients. A total of 23 (46.0%) patients experienced at least one adverse event: four (50.0%) patients receiving nintedanib 100 mg twice daily, 15 (62.5%) patients receiving nintedanib 150 mg twice daily and four (33.3%) patients receiving placebo (table 2). The adverse events were

TABLE 1 Baseline patient demographics and characteristics

	Placebo	Nintedanib 50 mg twice daily	Nintedanib 100 mg twice daily	Nintedanib 150 mg twice daily	Total
Subjects n	12	6	8	24	
Males	11 (91.7)	4 (66.7)	4 (50.0)	16 (66.7)	35 (70.0)
Age years	64.1±10.3	66.7±2.9	67.5±7.4	64.7±8.5	65.2±8.2
Height cm	166.2±7.0	159.3±7.2	158.3±7.5	159.5±7.8	160.9±7.9
Weight kg	69.1±12.1	58.6±7.5	63.9±9.7	62.1±13.2	63.6±12.1
Smoking status					
Ex-smokers	9 (75.0)	5 (83.3)	5 (62.5)	17 (70.8)	36 (72.0)
Never-smokers	3 (25.0)	1 (16.7)	3 (37.5)	7 (29.2)	14 (28.0)
FVC L	2.63±0.7	2.14±0.6	2.13±0.5	2.39±0.7	2.38±0.7
FVC % predicted	72.9±14.7	68.4±9.4	73.4±10.4	76.3±15.6	74.1±13.9
FEV_1 L	2.22±0.6	1.85±0.5	1.72±0.4	1.98±0.5	1.98±0.5
D_{LCO} mL·min^{-1}·mmHg^{-1}	11.37±3.7	11.10±2.7	10.08±3.3	9.31±4.0	10.14±3.7
D_{LCO} % predicted	59.2±13.6	67.8±10.5	58.5±16.9	53.0±13.8	57.2±14.4
P_{aO_2} mmHg	76.73±8.0	77.67±7.1	83.24±19.9	84.08±12.8	81.41±12.8

Data are presented as n (%) or mean±SD, unless otherwise stated. FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide; P_{aO_2}: arterial oxygen tension.

mild (87%) or moderate (13%) in intensity. The most common adverse events reported with nintedanib 150 mg twice daily were vomiting (five patients, all receiving nintedanib in addition to ongoing pirfenidone therapy) and nausea (five patients, four receiving nintedanib in addition to ongoing pirfenidone therapy). One serious adverse event (malignant hepatic neoplasm) was reported in the nintedanib 150 mg twice daily group during the follow-up period; this was not considered to be related to the study drug (previous computed tomography scans showed that the tumour was possibly present before study enrolment). Drug-related adverse events were reported by the investigator for 13 (26.0%) patients, most of which occurred in patients receiving nintedanib 150 mg twice daily (10 patients, seven receiving nintedanib in addition to ongoing pirfenidone therapy). The adverse events that led to discontinuation of study medication were increases in transaminase levels in three patients (all with nintedanib 150 mg twice daily, one with co-administration of pirfenidone 200 mg three times daily) and vomiting in one patient receiving nintedanib 150 mg twice daily and pirfenidone 200 mg three times daily. These adverse events resolved after treatment discontinuation. Photosensitivity was reported in one patient receiving pirfenidone alone and rash in one patient receiving pirfenidone with nintedanib 150 mg twice daily. FVC, FEV_1 and D_{LCO} remained stable in all groups. There were no consistent changes in blood pressure or pulse rate and observed changes were not considered related to the study medication by the investigator.

Pharmacokinetic outcomes

After multiple dosing, maximum plasma concentrations of nintedanib were reached 2–4 h after dosing and a steady state was reached by day 7. Mean plasma concentrations of nintedanib after multiple dosing (day 14 for cohorts 1 and 2, day 28 for cohort 3) are shown in figure 2. For the 150 mg twice daily dose, mean plasma concentrations of nintedanib were lower when nintedanib was added to ongoing pirfenidone therapy, but high variability was observed.

After 28 days' treatment with nintedanib 150 mg twice daily, geometric means (gMean) of $C_{max,ss}$ and $AUC_{\tau,ss}$ of nintedanib were 41% lower (23.5 *versus* 39.7 ng·mL^{-1}) and 32% lower (149 *versus* 218 h·ng·mL^{-1}), respectively, when nintedanib was added to ongoing pirfenidone therapy, but the distribution of individual values overlapped (fig. 3). Values for gMean $t_{1/2,ss}$ and median $t_{max,ss}$ were similar when nintedanib was given alone as when given in addition to ongoing pirfenidone therapy (27.5 *versus* 28.4 h and 3.9 *versus* 3.9 h, respectively) (table 3). Mean $CL/F_{,ss}$ was 11 500 mL·min^{-1} in the absence of pirfenidone and 16 800 mL·min^{-1} when nintedanib was added to pirfenidone, and mean $V_{z/F,ss}$ was 27 300 L in the absence of pirfenidone and 41 200 L when added to ongoing pirfenidone (table 3). Mean $R_{A,AUC_{0-12}}$ was 1.5 in the absence of pirfenidone and 1.7 when added to ongoing pirfenidone and mean $R_{A,C_{max}}$ was 1.1 in the absence of pirfenidone and 1.3 when added to ongoing pirfenidone (table 3). Pirfenidone therapy had no effect on nintedanib accumulation ratios ($R_{A,C_{max}}$ and $R_{A,AUC_{0-12}}$) after multiple doses of nintedanib 150 mg twice daily (table 3). The effect of adding nintedanib to ongoing pirfenidone therapy on the pharmacokinetic parameters of nintedanib was similar for the nintedanib 100 mg twice daily dose as for the 150 mg twice daily dose (table 3). Measurements of pharmacokinetic

TABLE 2 Adverse events (AEs)

	Placebo[#]		Nintedanib 50 mg twice daily[¶]		Nintedanib 100 mg twice daily[+]		Nintedanib 150 mg twice daily[§]	
	Alone	Added to ongoing pirfenidone	Alone	Added to ongoing pirfenidone	Alone	Added to ongoing pirfenidone	Alone	Added to ongoing pirfenidone
Subjects n	7	5	2	4	4	4	11	13
Any AE	2 (28.6)	2 (40.0)	0	0	3 (75.0)	1 (25.0)	6 (54.5)	9 (69.2)
Serious AEs	0	0	0	0	0	0	1 (9.1)	0
Investigator-defined drug-related AEs	1 (14.3)	1 (20.0)	0	0	1 (25.0)	0	3 (27.3)	7 (53.8)
Most common AEs[f]								
Vomiting	0	0	0	0	0	0	0	5 (38.5)
Nausea	0	0	0	0	0	0	1 (9.1)	4 (30.8)
Diarrhoea	0	0	0	0	0	0	2 (18.2)	2 (15.4)
Nasopharyngitis	0	0	0	0	1 (25.0)	0	0	2 (15.4)
Abdominal discomfort	0	1 (20.0)	0	0	0	0	1 (9.1)	0
Stomatitis	0	0	0	0	1 (25.0)	0	0	1 (7.7)
Alanine aminotransferase increased[##]	0	0	0	0	0	0	2 (18.2)	0
Aspartate aminotransferase increased[##]	0	0	0	0	0	0	2 (18.2)	0
AEs leading to discontinuation of study drug	0	0	0	0	0	0	2 (18.2)	2 (15.4)
Transaminases increased	0	0	0	0	0	0	2 (18.2)	1 (7.7)
Vomiting	0	0	0	0	0	0	0	1 (7.7)

Data are presented as n (%) unless otherwise stated. "With pirfenidone" group included all pirfenidone doses. [#]: n=12; [¶]: n=6; [+]: n=8; [§]: n=24; [f]: reported in two or more patients; [##]: increases were reported based on the judgment of the investigator.

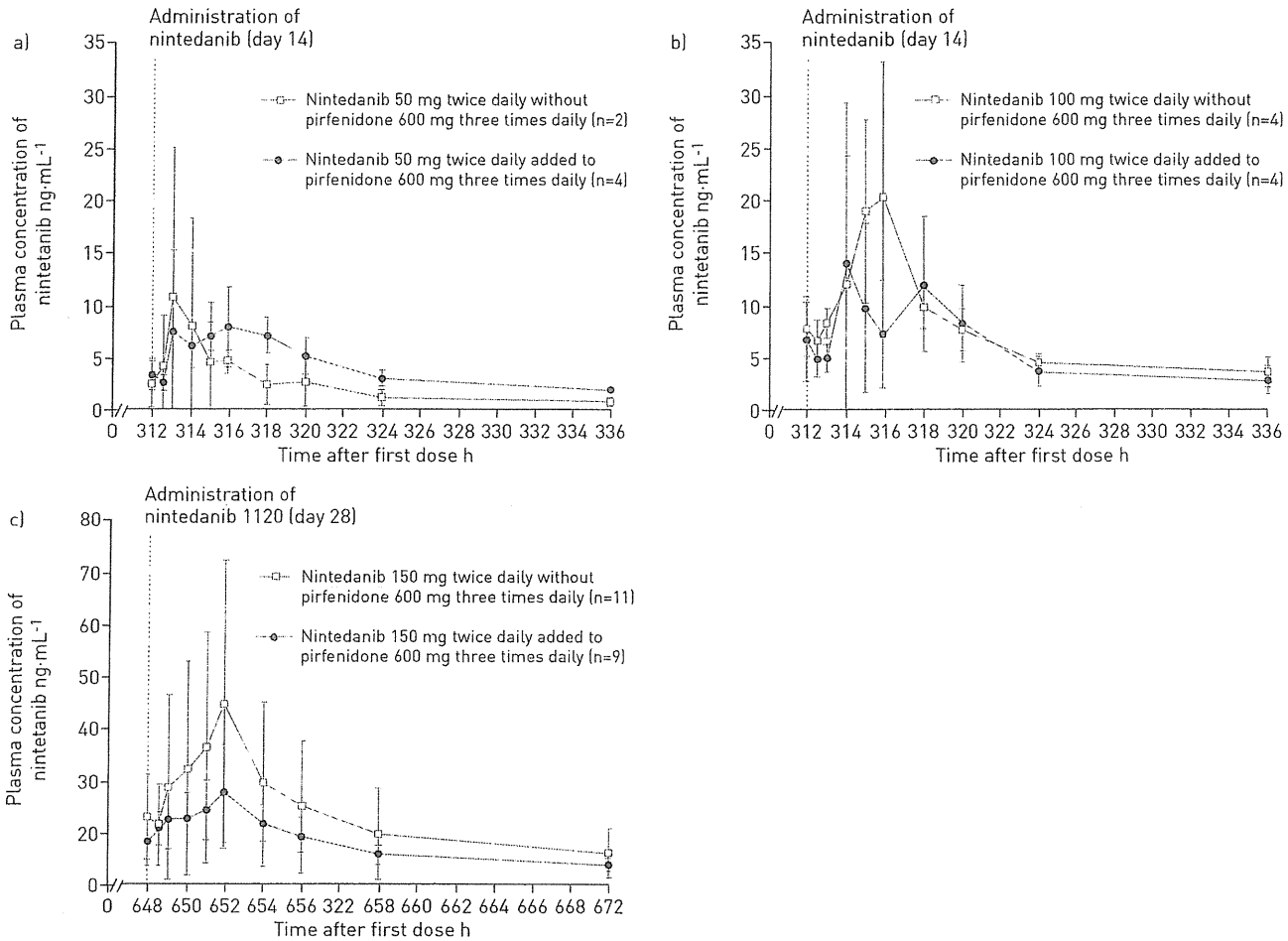

FIGURE 2 Arithmetic mean±SD plasma concentration–time profiles of nintedanib after a) multiple dosing of nintedanib 50 mg twice daily (day 14), b) 100 mg twice daily (day 14) and c) 150 mg twice daily (day 28) given alone and added to ongoing pirfenidone therapy (600 mg three times daily).

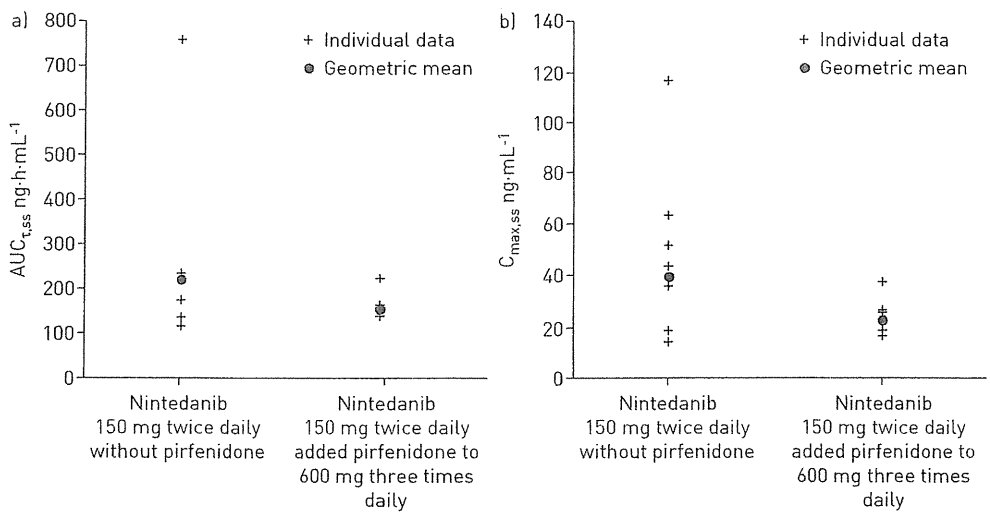

FIGURE 3 Individual and geometric mean area under the concentration–time curve of the analyte in plasma at a steady state over a uniform dosing interval τ ($AUC_{\tau,ss}$) and maximum concentration of the analyte in plasma at steady state over a uniform dosing interval τ ($C_{max,ss}$) values for nintedanib 150 mg twice daily given alone and added to ongoing pirfenidone therapy (600 mg three times daily).

TABLE 3 Pharmacokinetic parameters of nintedanib after multiple doses (steady state)

	Nintedanib 50 mg twice daily			Nintedanib 100 mg twice daily			Nintedanib 150 mg twice daily		
	Patients without/ with ongoing pirfenidone therapy	Alone	Added to ongoing pirfenidone 600 mg three times daily	Patients without/ with ongoing pirfenidone therapy	Alone	Added to ongoing pirfenidone 600 mg three times daily	Patients without/ with ongoing pirfenidone therapy	Alone	Added to ongoing pirfenidone 600 mg three times daily
$AUC_{\tau,ss}$ $h \cdot ng \cdot mL^{-1}$	2/4	33.7 (165)	67.9 (16.7)	4/3	115.0 (32.4)	86.0 (62.7)	9/7	218 (58.3)	149 (18.0)
$C_{max,ss}$ $ng \cdot mL^{-1}$	2/4	9.1 (173)	10.9 (50.3)	4/3	20.0 (64.5)	13.8 (113.0)	9/7	39.7 (68.1)	23.5 (27.2)
$t_{max,ss}$ h	2/4	2.4 (1.0–3.9)	3.9 (1.0–6.0)	4/3	3.4 (2.0–4.1)	2.0 (2.0–6.0)	9/7	3.9 (1.0–4.0)	3.9 (1.0–4.0)
$t_{1/2,ss}$ h	0/4	NA	25.4 (25.5)	4/3	23.4 (22.4)	30.5 (20.1)	9/7	27.5 (20.1)	28.4 (22.7)
$CL_{/F,ss}$ $mL \cdot min^{-1}$	2/4	24700 (165.0)	12300 (16.7)	4/3	14500 (32.4)	19400 (62.7)	9/7	11500 (58.3)	16800 (18.0)
$V_{z/F,ss}$ L	0/4	NA	27000 (39.5)	4/3	29300 (54.7)	51200 (76.7)	9/7	27300 (58.9)	41200 (33.8)
$R_{A,AUC_{0-12}}$	0/3	NA	2.2 (13.8)	4/3	2.0 (91.2)	1.5 (22.3)	9/6	1.5 (34.9)	1.7 (92.6)
$R_{A,C_{max}}$	2/4	2.3 (26.6)	1.9 (62.1)	4/3	1.5 (74.5)	1.4 (35.7)	9/6	1.1 (57.3)	1.3 (99.8)

Data are presented as n, geometric mean (geometric coefficient of variation %) or median (range). $AUC_{\tau,ss}$: area under the concentration–time curve of the analyte in plasma at a steady state over a uniform dosing interval τ; $C_{max,ss}$: maximum concentration of the analyte in plasma at steady state over a uniform dosing interval τ; $t_{max,ss}$: time from dosing to maximum concentration of the analyte in plasma at steady state over a uniform dosing interval τ; $t_{1/2,ss}$: terminal half-life of the analyte in plasma at steady state; $CL_{/F,ss}$: apparent clearance of the analyte in plasma after extravascular administration at steady state; $V_{z/F,ss}$: apparent volume of distribution during the terminal phase λz following extravascular administration at steady state; $R_{A,AUC_{0-12}}$: accumulation ratio based on $AUC_{0-12,ss}$; $R_{A,Cmax}$: accumulation ratio based on $C_{max,ss}$; NA: not applicable.

parameters were not obtained from enough patients receiving nintedanib 50 mg twice daily to adequately evaluate whether ongoing pirfenidone therapy had any effect.

After multiple doses of nintedanib alone, maximum plasma concentrations of the nintedanib metabolites BIBF 1202 ZW and BIBF 1202 glucuronide were reached 3–4 and 0.8–4.0 h, respectively, after drug administration, with gMean $t_{1/2,ss}$ values of approximately 23 and 46–56 h, respectively. When nintedanib was added to ongoing pirfenidone therapy, values for $t_{max,ss}$ were 3–5 and 0.7–8.0 h for BIBF 1202 ZW and BIBF 1202 glucuronide, respectively, while $t_{1/2,ss}$ was 27–26 h for BIBF 1202 ZW and 38–43 h for BIBF 1202 glucuronide. For the nintedanib 150 mg twice daily dose, gMean $C_{max,ss}$ was 51% lower (15.4 *versus* 33.2 ng·mL^{-1}) for BIBF 1202 ZW and 16% lower (107 *versus* 128 ng·mL^{-1}) for BIBF 1202 glucuronide when nintedanib was given in addition to ongoing pirfenidone therapy. $AUC_{\tau,ss}$ was 50% lower (118 *versus* 237 h·ng·mL^{-1}) for BIBF 1202 ZW and 20% lower (1100 *versus* 1380 h·ng·mL^{-1}) for BIBF 1202 glucuronide when nintedanib was given in addition to ongoing pirfenidone therapy. The effect of pirfenidone therapy on the pharmacokinetic parameters of BIBF 1202 ZW and BIBF 1202 glucuronide in the nintedanib 100 mg twice daily group was similar to that seen in the 150 mg twice daily group.

Maximum plasma concentrations of pirfenidone administered alone at the steady state were reached 1–1.6 h after the breakfast dose and 1–2 h after the lunch dose, with a gMean $t_{1/2,ss}$ of approximately 3–4 h (table 4). Plasma concentrations and pharmacokinetic parameters of pirfenidone were not affected by co-administration with nintedanib (table 4).

Discussion

The results of this study show that nintedanib 150 mg twice daily had an acceptable safety and tolerability profile in Japanese patients with IPF when given alone or when added to ongoing pirfenidone therapy, but with more reports of nausea and vomiting when nintedanib was added to ongoing pirfenidone than when given alone. All the adverse events reported in this trial were mild or moderate in intensity. The most common adverse events reported in patients receiving nintedanib were gastrointestinal side-effects, which were reported by approximately one-third of patients taking nintedanib alone or nintedanib in addition to already prescribed pirfenidone therapy. Nausea, vomiting and diarrhoea were reported only by patients in the nintedanib 150 mg twice daily group: five (20.8%) patients on this dose reported nausea, five (20.8%) patients reported vomiting and four (16.7%) patients reported diarrhoea. Gastrointestinal adverse events were not unexpected, as gastrointestinal side-effects have been observed in previous trials of nintedanib (at doses up to 150 mg twice daily) and pirfenidone (at doses up to 3600 mg·day^{-1}) in patients with IPF [6–9, 16], and in phase I and II studies of nintedanib at doses of 50 mg once daily to 300 mg twice daily in patients with advanced solid tumours and advanced non-small cell lung cancer [17, 18]. In this study, of the patients receiving nintedanib 150 mg twice daily in combination with pirfenidone, 69.2% reported adverse events, compared to 54.5% of patients receiving nintedanib 150 mg twice daily alone. The difference was mostly due to nausea (reported by four (30.8%) patients given nintedanib 150 mg twice daily in addition to pirfenidone and one (9.1%) patient given nintedanib 150 mg twice daily alone) and vomiting (reported by five (38.5%) of patients given nintedanib 150 mg twice daily in addition to pirfenidone and none given nintedanib alone); diarrhoea was not more frequently reported when nintedanib 150 mg twice daily was given in addition to pirfenidone than when it was given alone. Vomiting led to discontinuation of study medication in one patient (treated with nintedanib 150 mg twice daily in addition to pirfenidone 200 mg three times daily). Other adverse events associated with pirfenidone (but not nintedanib) include a dose-related increase in skin photosensitivity and rash [8, 11, 12]. The incidence of these adverse events did not increase when pirfenidone was co-administered with nintedanib in this study.

Increases in transaminase levels led to discontinuation of study medication in three patients (all treated with nintedanib 150 mg twice daily). The elevations in transaminases were reversible and resolved after treatment discontinuation. In a phase I study in Japanese patients with advanced solid tumours, liver enzyme elevations led to treatment discontinuation in three (25%) patients treated with nintedanib 200 mg twice daily [19]. In the phase II TOMORROW trial in patients with IPF, clinically significant elevations in liver enzyme levels were observed in six (7.1%) patients receiving nintedanib 150 mg twice daily [6]; these elevations were reversible. In the phase III INPULSIS trials, investigators were given recommendations for management of liver enzyme elevations through treatment interruption, dose reduction or treatment discontinuation. Across the two trials, elevations in liver transaminases (three or more times the upper limit of normal for aspartate aminotransferase or alanine aminotransferase) were observed in 5.0% of patients in the nintedanib groups and 0.7% of patients in the placebo groups. In general, elevations in liver enzymes returned to normal following treatment interruption, dose reduction or treatment discontinuation. There were no cases of Hy's law in patients treated with nintedanib [7].

TABLE 4 Pharmacokinetic parameters (steady state) of pirfenidone 600 mg three times daily

	Cohort 1			Cohort 2			Cohort 3		
	Patients without/ with ongoing pirfenidone therapy	Alone	With nintedanib 50 mg twice daily	Patients without/ with ongoing pirfenidone therapy	Alone	With nintedanib 100 mg twice daily	Patients without/ with ongoing pirfenidone therapy	Alone	With nintedanib 150 mg twice daily
After breakfast									
$AUC_{0-4,ss}$ h·ng·mL^{-1}	4/4	34400 (36.3)	34300 (39.9)	3/3	45800 (26.6)	35000 (32.2)	9/7	32500 (21.2)	35900 (21.8)
$C_{max,ss}$ ng·mL^{-1}	4/4	11900 (28.9)	12800 (44.3)	4/3	14600 (41.5)	15300 (51.1)	9/8	11200 (26.6)	12600 (27.2)
$t_{max,ss}$ h	4/4	1.6 (1.0–3.0)	0.7 (0.5–2.0)	4/3	1.5 (0.5–3.0)	2.0 (0.5–2.0)	9/8	1.1 (0.5–3.0)	0.8 (0.5–3.9)
$R_{AUC_{0-4,ss},T/R}$	0/4	1.0 (32.2)		0/2	0.7 (51.8)		0/7	1.1 (13.1)	
$Rc_{max,ss,T/R}$	0/4	1.1 (45.1)		0/3	1.0 (38.6)		0/8	1.1 (12.4)	
After lunch									
$AUC_{0-8,ss}$ h·ng·mL^{-1}	4/4	72800 (40.7)	71000 (40.8)	3/3	84100 (11.4)	71500 (19.1)	8/6	60900 (22.9)	63600 (27.7)
$C_{max,ss}$ ng·mL^{-1}	4/4	14600 (20.9)	12000 (37.3)	4/3	15100 (19.5)	12100 (10.7)	9/8	12900 (30.2)	12500 (23.0)
$t_{max,ss}$ h	4/4	1.0 (0.5–3.1)	2.5 (1.0–3.9)	4/3	2.0 (1.0–3.0)	4.0 (2.0–4.0)	9/8	1.0 (0.4–6.0)	2.0 (0.5–4.4)
$t_{1/2,ss}$ h	4/3	3.4 (50.5)	4.0 (31.7)	4/1	3.5 (49.0)	3.6 (NC)	8/5	3.1 (40.6)	3.2 (39.1)
$R_{AUC_{0-8,ss},T/R}$	0/4	1.0 (4.7)		0/2	0.9 (21.2)		0/5	1.0 (14.6)	
$Rc_{max,ss,T/R}$	0/4	0.8 (19.7)		0/3	0.8 (20.2)		0/8	0.9 (25.6)	
$AUC_{0-12,ss}$# h·ng·mL^{-1}	4/4	108000 (36.8)	105000 (40.3)	3/3	130000 (16.0)	107000 (22.4)	8/6	92000 (18.3)	102000 (22.2)
$R_{AUC_{0-12,ss},T/R}$	0/4	1.0 (9.9)		0/2	0.8 (30.8)		0/5	1.1 (12.2)	

Data are presented as n, geometric mean (geometric coefficient of variation %) or median (range). $AUC_{t1-t2,ss}$: area under the concentration–time curve of the analyte in plasma at a steady state over the time interval from t1 to t2; ; $C_{max,ss}$: maximum concentration of the analyte in plasma at steady state over a uniform dosing interval τ; $t_{max,ss}$: time from dosing to maximum concentration of the analyte in plasma at steady state over a uniform dosing interval τ; $R_{AUC_{t1-t2,SS,T/R}}$: ratio of $AUC_{t1-t2,ss}$ of the test treatment to $AUC_{t1-t2,ss}$ of the reference treatment $Rc_{max,ss,T/R}$: ratio of $C_{max,ss}$ of the test treatment to $C_{max,ss}$ of the reference treatment; $t_{1/2,ss}$: terminal half-life of the analyte in plasma at steady state. #: $AUC_{0-12,ss}=AUC_{0-4,ss}$ (post-dose after breakfast)+$AUC_{0-8,ss}$ (post-dose after lunch). NA: not applicable; NC: not calculated.

A limitation of this study in evaluating the safety and tolerability of nintedanib was its relatively short duration. An extension trial investigating the long-term safety and tolerability of nintedanib given in addition to pirfenidone is ongoing (www.clinicaltrials.gov identifier number NCT01417156).

The pharmacokinetic profile of nintedanib has previously been described in Japanese and Caucasian patients with advanced solid tumours [18, 19]. Those studies suggest there is no difference in the pharmacokinetic behaviour of nintedanib between Japanese and Caucasian patients. Pharmacokinetic analyses of nintedanib revealed moderately fast absorption with a terminal half-life suitable for once- or twice-daily dosing. Maximum plasma concentrations and exposure increased with doses from 50 mg once daily to 300 mg twice daily, both after single administration and at a steady state [17]. Previous reports revealed all pharmacokinetic variables displayed a moderate–high variability, as expected for an oral compound [17, 19]. After multiple doses of nintedanib 150 mg twice daily in patients with advanced solid tumours, values for t_{max} and half-life were similar to those observed in the 150 mg twice daily group in this study. In this study, the exposure (maximal concentration and $AUC_{\tau,ss}$) of nintedanib and its metabolites tended to be lower when nintedanib was added to ongoing pirfenidone therapy than when given alone; however, the distribution of individual values overlapped. Values for $CL/F_{,ss}$ and $Vz/F_{,ss}$ of nintedanib tended to be higher when nintedanib was added to ongoing pirfenidone therapy, indicating that the bioavailability of nintedanib may be decreased by co-administration of pirfenidone. As the pathway of metabolism of the two drugs is different, the lower bioavailability of nintedanib when pirfenidone is co-administered with it may reflect reduced absorption. Nintedanib had no effect on the pharmacokinetics of pirfenidone.

In conclusion, further study is needed to evaluate the safety and tolerability profile of nintedanib when added to pirfenidone in patients with IPF. There was a trend toward lower exposure of nintedanib and its metabolites when nintedanib was added to ongoing pirfenidone therapy. Co-administration with nintedanib had no effect on the pharmacokinetics of pirfenidone. The efficacy of a pirfenidone/nintedanib regimen may be investigated in the future.

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Pleuroparenchymal fibroelastosis from a consecutive database: a rare disease entity?

To the Editor:

Pleuroparenchymal fibroelastosis (PPFE) is a rare condition characterised by predominantly upper lobe involvement with pleural fibrosis and subjacent parenchymal fibroelastosis [1, 2]. Idiopathic PPFE (IPPFE), which was included in the rare idiopathic interstitial pneumonias (IIPs) in the update of the international multidisciplinary classification of IIPs published in 2013 [3], was first described in the Japanese literature by AMITANI *et al.* in 1992 [4]. PPFE has been reported to be associated with drugs, chronic hypersensitivity pneumonia, collagen vascular diseases, infections, and bone marrow transplantations [5–8]. However, the frequency of PPFE occurrence has been uncertain. We hypothesised that PPFE was not a rare disease entity and conducted this study. Informed consent was obtained from all patients, and the Institutional Review Board of the National Hospital Organization Kinki-Chuo Chest Medical Center (KCCMC) (Sakai City, Japan) approved this study.

To prove the hypothesis, we retrospectively reviewed our database of diagnostic pathology archives from 205 consecutive patients who had undergone a surgical lung biopsy (SLB) to diagnose diffuse lung diseases at the KCCMC from 2004 to 2012, and selected 14 cases in which the key words "atelectatic fibrosis", "pleuroparenchymal fibroelastosis" or "parenchymal fibroelastosis" were identified. The 14 cases were re-evaluated in multidisciplinary discussions using histopathological and radiological criteria for the diagnosis of PPFE [1, 2, 5]. Two cases were excluded from a diagnosis of PPFE; one did not fulfil the radiological criteria and the other showed a pathological pattern of usual interstitial pneumonia (UIP), with only focal elastosis.

We evaluated the pathology according to the report by REDDY *et al.* [5]. Patients with upper zone subpleural elastosis, intra-alveolar collagen deposition and pleural thickening with fibrosis were categorised as definite PPFE. Patients without pleural thickening were categorised as consistent with PPFE. For the radiological findings from high-resolution computed tomography (HRCT) pleural thickening associated with subpleural fibrosis was observed mainly in the upper lobes, with less marked or no involvement of the lower lobes. Features suggesting comorbid disease were allowed to be present elsewhere in the lung. Pathological and radiological patterns of interstitial lung diseases (ILDs) were determined by the criteria previously reported [3, 9, 10]. A radiological pattern of nonspecific interstitial pneumonia (NSIP) was defined according to a previous report [11].

Of the 205 consecutive patients who had undergone a SLB for ILDs, 12 (5.9%) cases were identified as PPFE after multidisciplinary discussion (definite PPFE: eight cases; consistent with PPFE: four cases). In the same period, the number of patients presenting ILDs on HRCT and receiving bronchoalveolar lavage was 1622, including the 205 (12.6%) cases with SLB. Of the 205 cases, 77 cases were diagnosed as IIPs. Clinical characteristics of the PPFE cases are summarised in table 1. Seven (58%) were male and the median age was 62 years old. Seven (58%) had never-smoked. Eight (67%) developed spontaneous pneumothoraces during the course of their disease and six (50%) experienced pneumothoraces repeatedly. Eight (3.9%) patients undergoing SLB were categorised as IPPFE, while four (2.0%) were categorised as secondary PPFE (SPPFE). Thus, the frequency of IPPFE was not rare among IIPs (10.4%).

The HRCT findings of patients with PPFE are summarised in table 1. All 12 patients revealed bilateral irregular pleuroparenchymal thickening in the upper zone. 10 demonstrated elevated hilar shadows suggesting volume reduction in the upper lobes. Notably, 11 (92%) demonstrated coexistent ILD in the lower lobes (UIP pattern: five cases; possible UIP pattern: four cases; NSIP pattern: one case; and an undefined pattern: one case).

Follow-up HRCT images were available for 10 patients (follow-up period: 13–69 months, median 22.5 months). Of these patients, seven (70%) demonstrated progression of pleuroparenchymal thickening, and four (40%) had increased or newly apparent honeycombing at their last HRCT. In seven (70%) out of the 10 discrete cysts increased or enlarged. In one of these cases, a ball of fungus appeared in the upper lobe cyst.

TABLE 1 Summary of the 12 cases of pleuroparenchymal fibroelastosis (PPFE)

Subjects n	12
Idiopathic/secondary PPFE n/n[#]	8/4
Age years[¶]	62 (27–70)
Sex	
Males	7 (58)
Females	5 (42)
BMI kg·m^{-2}[¶]	20.0 (13.5–24.2)
Smoking habits[¶]	
Never-smoker	7 (58)
Current or ex-smoker	5 (42)
Clinical symptoms[¶]	
Asymptomatic	3 (25)
Symptomatic	9 (75)
Dyspnoea on exertion	7 (58)
Dry cough	5 (42)
Chest pain	1 (8)
Pneumothorax	8 (67)
HRCT findings[+]	
Pleuroparenchymal thickening	12 (100)
Elevated hilar shadows	10 (83)
Coexistent ILD in lower lobes	11 (92)
UIP pattern	5 (42)
Possible UIP pattern	4 (33)
NSIP pattern	1 (8)
Others	1 (8)
Pathological findings	
Subpleural elastosis	12 (100)
Intra-alveolar collagen deposition	12 (100)
Pleural thickening with fibrosis	8 (67)
Preserved alveolar structure	12 (100)
Coexistent ILD in lower lobes	9 (75)
UIP pattern	8 (67)
Non-classifiable interstitial pneumonia pattern	1 (8)
Pulmonary function test (n=8)	
FVC % predicted[¶]	70.6 (53.8–108.6)
FVC decline mL·year^{-1}	−187 (−878–4)
TLC % predicted[¶]	71.7 (50.3–133.9)
TLC decline mL·year^{-1}	−310 (−1335–−54)
Medication	
Steroid	6 (50)
Immunosuppressant	7 (58)
Pirfenidone	4 (33)
Median survival time days	
From the first visit	2459 (55–2996)
From SLB	838 (29–2014)

Data are presented as median (range) or n (%) unless otherwise stated. BMI: body mass index; HRCT: high-resolution computed tomography; ILD: interstitial lung disease; UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; FVC: forced vital capacity; TLC: total lung capacity; SLB: surgical lung biopsy. [#]: Of the four secondary PPFE cases one was a cyclophosphamide-induced case and the remaining three cases coexisted with chronic hypersensitivity pneumonia, rheumatoid arthritis or Sjögren's syndrome; [¶]: the data were obtained at the first visit; [+]: the data were obtained before the SLB.

For pathological findings, 10 patients underwent SLBs in the upper lobes, with the remaining two undergoing biopsies in the middle lobes. All patients exhibited subpleural elastosis and intra-alveolar collagen deposition; however, four (33%) did not have pleural thickening with fibrosis. Notably, nine (75%) showed coexistent ILDs (eight with UIP pattern and one with non-classifiable interstitial pneumonia pattern) (table 1).

Pulmonary function test data were available for eight patients without the complication of pneumothoraces. The baseline levels of median forced vital capacity (FVC) and total lung capacity (TLC) were 70.6 and 71.7 % predicted, respectively. There was a marked decline in FVC and TLC.

Eight patients received medication. Six were treated with low-dose corticosteroids. Four out of these six patients received additional immunosuppressant therapy (cyclosporine (n=2) and azathioprine (n=2)). The other two of these six patients received both immunosuppressant therapy (azathioprine) and pirfenidone. Of the remaining two patients, one received both immunosuppressant therapy (azathioprine) and pirfenidone, while the other was treated only with pirfenidone (table 1). However, we did not find any improvement in pulmonary function tests, HRCT or symptoms.

The median survival time for PPFE patients from the first hospital visit and from the SLB were 2459 days and 838 days, respectively. The survival from SLB seemed to be poor. The number of patients was too small to tell the difference between the survival time for IPPFE and SPPFE patients, and of those with definite PPFE and consistent with PPFE. Seven patients were alive at the last follow-up (four of whom required home oxygen therapy), while the remaining five died from respiratory failure due to disease progression.

Although fibrotic thickening of the pleura is one of the features of PPFE patients [1], four patients (three IPPFE and one cyclophosphamide-induced case) did not have pleural thickening in the present study. These four cases were diagnosed as consistent with PPFE. The three IPPFE cases among these four cases did not have radiotherapy, chemotherapy or inhalational injuries, which are known aetiologies of intra-alveolar fibrosis with septal elastosis. Some reports have included PPFE cases without pleural thickening [4, 5, 8, 12, 13]. Further studies are required to clarify the significance of pleural thickening in the diagnosis of PPFE.

Patients with a coexistent ILD other than fibroelastosis were observed in the present study as previously reported [5, 12–14]. The frequency of such cases was 75% in our report and might be higher than the report by REDDY *et al.* [5] (43%); however, the patients in the other reports did not always accept SLB of the lower lobe. WATANABE *et al.* [13] mentioned eight out of nine cases of idiopathic upper lobe fibrosis, which is similar to PPFE, showed lower lobe lesions on HRCT although they were not pathologically evaluated. Thus, coexistent ILD is supposedly more frequently observed when histologically examined.

In pulmonary function tests FVC declined rapidly in most patients. In the report by WATANABE *et al.* [13] respiratory function also declined remarkably in PPFE patients. These findings suggest that PPFE is a progressive disease. However, in the current study drug therapies including pirfenidone were not effective. Given this, at present, lung transplantation would be the only effective treatment for PPFE.

From these findings, IPPFE is an acceptable disease entity among IIPs, and is not as rare as previously reported. PPFE is a progressive disease with the frequent complication of pneumothorax and there is no effective therapy. Development of effective anti-fibrotic and/or anti-elastotic treatment is required.

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Idiopathic pleuroparenchymal fibroelastosis is an acceptable entity among IIPs and not as rare as previously reported http://ow.ly/I5NEz

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Original article

Tracheobronchial lesions in eosinophilic pneumonia

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Bronchoscopy

ABSTRACT

Background: Eosinophilic pneumonia (EP) is characterized by eosinophil infiltration in the lung parenchyma. However, tracheobronchial lesions associated with the disease have been poorly described. To clarify the frequency and characteristics of cases with tracheobronchial lesions in EP, we performed a retrospective review of EP patients.

Methods: We included 36 EP cases seen from January 2004 to December 2007 at the Kinki-Chuo Chest Medical Center. The incidence of tracheobronchial nodules and associated clinical features were analyzed.

Results: Of these 36 patients, 29 had chronic eosinophilic pneumonia (CEP); 1, acute EP; 3, drug-induced EP; 2, allergic bronchopulmonary aspergillosis; and 1, parasite-related EP. Only 2 of the 29 CEP cases had tracheobronchial lesions. For both of these cases, bronchoscopy revealed multiple whitish nodules on the tracheobronchial mucosa. The associated histopathological findings revealed squamous metaplasia and eosinophil infiltration in the subepithelial region. In both cases, the nodules disappeared after steroid therapy. The prevalence of tracheobronchial lesions was 6.9% in CEP patients and 5.6% in EP patients overall. EP patients were divided into 3 groups: CEP with nodules ($n=2$), CEP without nodules ($n=27$), and other EP ($n=7$). We found that the CEP with nodules group showed a relatively higher incidence of respiratory symptoms, higher white blood cell (WBC) count, and higher levels of peripheral and bronchoalveolar eosinophilia than the other groups.

Conclusions: Tracheobronchial nodules represent rare observations within the EP population, which are likely to reflect a severe disease condition.

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1. Introduction

Eosinophilic pneumonia (EP) is characterized by the infiltration of eosinophils in the lung parenchyma with or without circulating eosinophilia [1–4]. The condition can be caused by a variety of stimuli, including fungi, parasitic infections, and drugs [2,5,6]. EP can be further divided into various subtypes: chronic eosinophilic pneumonia (CEP), acute eosinophilic pneumonia (AEP), drug-induced EP, allergic bronchopulmonary aspergillosis (ABPA), Churg-Strauss syndrome (CSS), and others [7,8]. CEP was originally reported to be characterized by severe dyspnea, weight loss, and fever lasting months or years, with a typical chest radiograph showing peripheral pulmonary infiltrates [4]. Non-segmental air space consolidations that are detectable using chest-computed tomography (CT) have also been reported [9,10]. Compared to pulmonary parenchymal lesions, which are well described in the context of CEP, tracheobronchial mucosal lesions have not been studied extensively. Only 2 reported cases of CEP have involved multiple small nodules with eosinophilic infiltration that localized to large airways [11,12]. Few reports have examined the prevalence and features of such mucosal lesions in patients with EP. The purpose of this study was to clarify the frequency and characteristics of cases of EP involving tracheobronchial lesions. Some of our data were previously reported in the form of an abstract [13].

2. Materials and methods

We retrospectively reviewed our clinical charts and found 36 cases of EP seen from January 2004 to December 2007 at the Kinki-Chuo Chest Medical Center (Osaka, Japan). The present study included patients diagnosed with EP after pathological examination revealed the infiltration of eosinophils admixed with histiocytes and other inflammatory cells into the airspaces and alveolar interstitium with preservation of the background structure of the lung [7,8].

We modified the criteria established by Mochizuki et al. [14] for the diagnosis of CEP. Inclusion in this study require fulfillment of both of the criteria outlined below

(A) CEP was suspected because of clinical symptoms and abnormal chest shadows that had existed for more than 1 month, with the exclusion of other diseases (e.g., infection) and eosinophilic pneumonias of determined origin.
(B) At least one of the following conditions was satisfied:
  (1) Histopathological diagnosis of CEP as determined by a surgical lung biopsy.
  (2) The presence of numerous eosinophils in transbronchial lung biopsy (TBLB) specimen.

The diagnoses of AEP, ABPA, and drug-induced EP were based on the criteria proposed by Allen et al. [2], Tillie-Leblond et al. [15], and Allen et al. [16], respectively. In brief, BAL was performed by instilling a total of 150 mL of normal saline from three 50-mL aliquots and retrieved using a handheld syringe. The procedure has previously been described in detail [17].

Table 1 – Laboratory data on admission.

	Case 1	Case 2
Blood examinations		
WBC (/μL)	24,900	20,300
Neutrophils (%)	33.4	21.0
Lymphocytes (%)	9.2	8.9
Monocytes (%)	1.9	3.2
Eosinophils (%)	55.4	66.8
Basophils (%)	0.1	0.1
Hb (g/dL)	10.5	11.9
Ht (%)	33.9	36.5
PLT ($\times 10^4$/μL)	41.9	42.3
AST (IU/L)	21	129
ALT (IU/L)	20	279
LDH (IU/L)	257	379
CRP (mg/dL)	4.26	3.74
ANA	$< \times 40$	$< \times 40$
PR3-ANCA (EU)	<10	<10
MPO-ANCA (EU)	<10	66
IgE RIST (IU/mL)	1316	172
Site	Right $B^3{}_b$	Right B^4
BALF analysis		
Total cell count ($\times 10^5$/mL)	11.25	7.07
Macrophages (%)	4.1	15.6
Lymphocytes (%)	3.8	2.8
Neutrophils (%)	2.2	0
Eosinophils (%)	87.7	81.2
Basophils/mast cells (%)	2.2	0.4
CD4/CD8	1.22	0.73

WBC, white blood cells; Ht, hematocrit; PLT, platelets; T-Bil, total-bilirubin; ALP, alkaline phosphatase; AST, aspartate amino transferase; ALT, alanine amino transferase; CPK, creatine phosphokinase; CRP, C-reactive protein; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic autoantibody and RIST, radio immunosorbent test.

To analyze the characteristics of EP patients with tracheobronchial nodules with respect to the overall population of EP patients, we investigated the following variables: age, sex, smoking status, respiratory symptoms, percutaneous oxygen saturation, pulmonary function, and laboratory data. This retrospective study was approved by the Ethics Committee of the National Hospital Organization, Kinki-Chuo Chest Medical Center (Approved date: September 8, 2010; Approved #: 287). All data in Table 2 are expressed as the median (range).

3. Results

3.1. *Frequency*

A total of 36 patients with EP were included in this study: 29 patients with CEP, 1 patient with AEP, 3 patients with drug-induced EP, 2 patients with ABPA, and 1 patient with parasite-related EP. All 36 patients underwent bronchoscopic examination at the time of diagnosis. Two CEP patients had nodules in the tracheobronchial mucosa. The prevalence of tracheobronchial nodules was 6.9% (2/29) in CEP patients and 5.6% (2/36) in EP patients overall. These 2 cases are described below.

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Table 2 – Clinicopathological features of EP with tracheo-bronchial nodules.

	CEP Nodules (+), $n=2$	CEP Nodules (–), $n=27$	Other EP Nodules (–), $n=7$
Age[a]	43 (36–50)	63 (22–79)	60 (37–69)
Female no. (%)	1 (50)	14 (52)	3 (43)
No history of smoking (%)	2 (100)	14 (52)	4 (57)
Fever no.[b] (%)	2 (100)	8 (30)	2 (29)
Cough no. (%)	2 (100)	19 (70)	4 (57)
Sputum no. (%)	2 (100)	5 (19)	1 (14.3)
SpO_2 room air[a] (%)	96.5 (94–99)	95 (91–98)	96 (95–98)
Peripheral WBC[a] (/μL)	21400 (20300–22500)	8900 (2800–38000)	12500 (5600–16000)
Peripheral eosinophils[a] (%)	61.9 (57–66.8)	19.3 (0.5–82.2)	16.7 (9.4–26.2)
Peripheral eosinophils[a] (/μL)	13192.7 (12825–13560.4)	1690.6 (63.5–31236)	1708.2 (854.4–4427.8)
IgE[a] (IU/mL)	744 (172–1316)	533 (42–4329)	150 (22–21030)
BALF TCC[a] ($\times 10^5$/mL)	9.2 (7.1–11.3)	1.8 (0.2–27.0)	1.9 (1.4–4.1)
BALF eosinophils[a] (%)	89.5 (81.2–97.7)	22.3 (0–93.8)	13.2 (0.6–55.6)
CD4/CD8[a]	0.98 (0.73–1.22)	0.97 (0.26–5.38)	0.96 (0.6–2.0)

CEP, chronic eosinophilic pneumonia; EP, eosinophilic pneumonia; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; BALF, bronchoalveolar lavage fluid and TCC, total cell count.

[a] Data were presented as median (range).

[b] Body temperature is 37.0 °C and over.

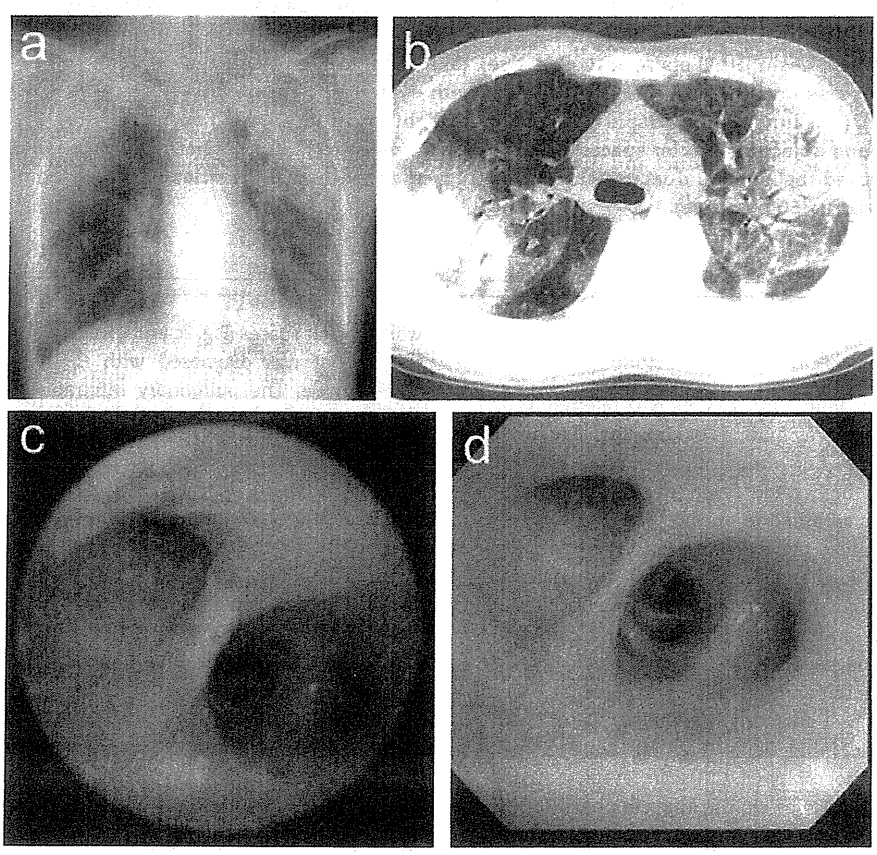

Fig. 1 – Radiological and bronchoscopic findings in Case 1. (a) Chest radiograph at admission showing bilateral consolidations in the upper and middle lung fields. (b) Computed tomography of the chest at admission showing bilateral consolidations in the relative periphery of the lungs. (c) Multiple whitish nodules on the right middle and inferior bronchial mucosa, as revealed by fiberoptic bronchoscopy 4 days after admission. (d) Disappearance of the tracheobronchial nodules 40 days after steroid therapy began.

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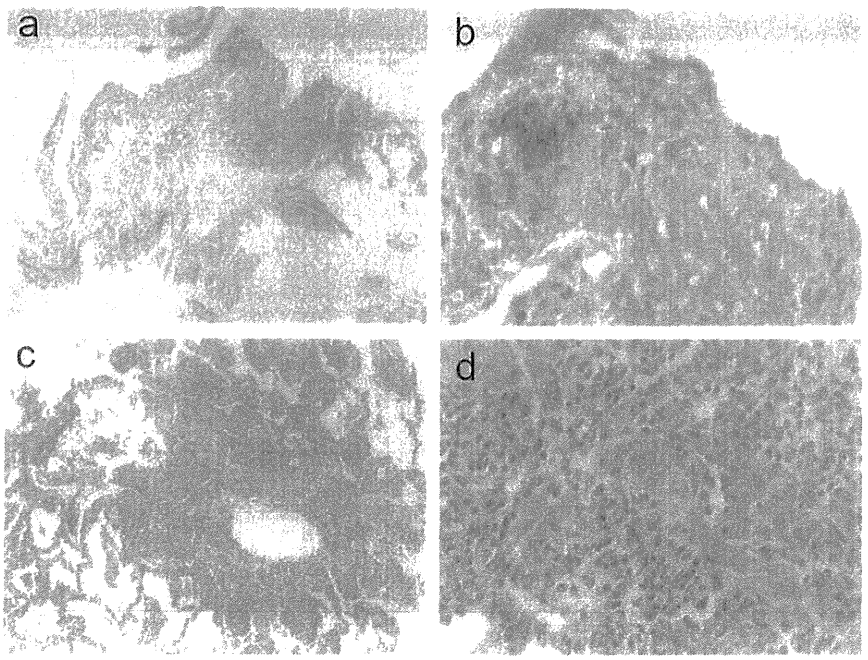

Fig. 2 – Histopathological findings in Case 1. Bronchoscopic biopsy samples taken at the time point depicted in Fig. 1(c). (a) The biopsy sample at the right main bronchus reveals squamous metaplasia of the epithelial layer, subepithelial hyalinous exudates measuring 40 μm in width, and infiltration of eosinophils and lymphoid cells in the epithelial and subepithelial layers. (Hematoxylin and eosin [H&E] stain, ×10 objective). (b) A higher magnification of (a). A cluster of eosinophils measuring 25 × 30 μm was noted in the subepithelial layer with evidence of eosinophilic granulocytes degranulation (H&E stain, ×60 objective). (c) A lung tissue sample taken from the right upper lobe (rt S^2_b) shows marked eosinophil infiltration in the alveolar duct and adjacent alveolar spaces (H&E stain, ×10 objective). (d) A higher magnification of (c). Numerous eosinophils have packed the alveolar duct and the adjacent alveolar space, with associated infiltration of lymphocytes and plasma cells (H&E stain, ×60 objective).

3.2. *Cases*

Case 1. A 36-year-old woman with rhinitis was referred to our hospital because of chest X-ray findings of abnormal shadows in the left upper lung field during a medical check-up. One month later, she developed a high-grade fever, cough, and dyspnea upon exertion, and was admitted to our hospital. No rales were heard on chest auscultation, nor were skin lesions or neurological findings present. A blood examination revealed an increased white blood cell (WBC) count with eosinophilia and a high IgE titer. Myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) testing was negative. BAL fluid analysis revealed that both the total cell count and the eosinophil percentage were elevated (Table 1). A chest radiograph revealed bilateral consolidations in the upper lung fields (Fig. 1a), while a high-resolution computed tomography (HRCT) scan revealed consolidations and ground glass opacities in the lung periphery (Fig. 1b). Bronchoscopy revealed macroscopic findings of multiple whitish nodules on the tracheobronchial mucosa (Fig. 1c). Histopathological analysis of the nodules revealed squamous metaplasia of the epithelial cells, fibrination, and eosinophil infiltration in the subepithelial region (Fig. 2a and b). In the TBLB specimens, numerous eosinophil infiltrates were observed in the alveolar walls and air spaces (Fig. 2c and d). On the basis of these findings, the patient was diagnosed with CEP and was treated with prednisolone. The pulmonary infiltrates and tracheobronchial nodules resolved 40 days after steroid therapy was initiated (Fig. 1d). Repeated biopsy specimens of the bronchial mucosa confirmed the absence of eosinophil infiltration.

Case 2. A 50-year-old man presented complaining of a cough with sputum, fever, and dyspnea. His chest radiograph revealed abnormal shadows, and his blood tests revealed peripheral eosinophilia. Treatment with antibiotics proved ineffective, and 1 month later, he was referred to our hospital. His history included allergic rhinitis and bronchial asthma. He had no symptoms indicating mono- or polyneuropathy. A blood examination showed an increased WBC count with eosinophilia. His elevated serum transaminase level was considered an adverse effect of the antibiotics (Table 1). BAL fluid analysis showed that the total cell count and eosinophil percentage were elevated. The MPO-ANCA test was positive (Table 1). A chest radiograph revealed bilateral consolidations in the upper lung fields (Fig. 3a), while an HRCT scan revealed consolidations in the relative periphery of the lungs (Fig. 3b). Bronchoscopy revealed multiple whitish nodules on the tracheobronchial mucosa (Fig. 3c). Histopathological examination of the nodule in the first

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