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 $V_{z/F,ss}$ 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.

@ERSpublications
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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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.

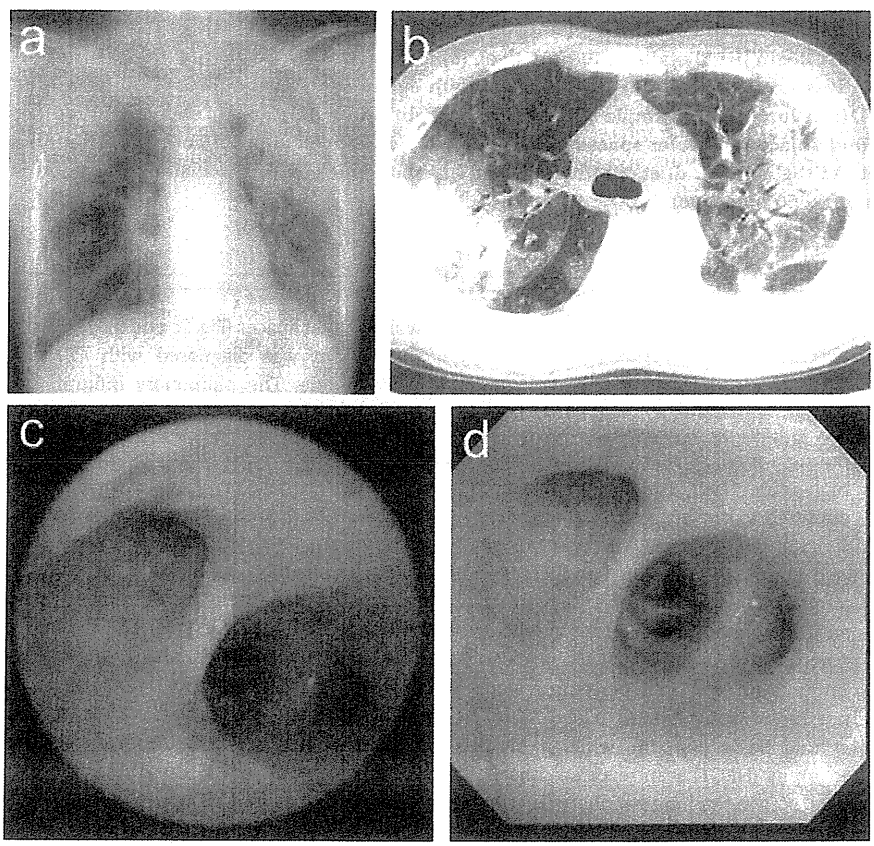

Fig. 1 – Radiological and bronchoscopic findings in Case 1. (a) Chest radiograph at admission showing bilateral consolidations in the upper and middle lung fields. (b) Computed tomography of the chest at admission showing bilateral consolidations in the relative periphery of the lungs. (c) Multiple whitish 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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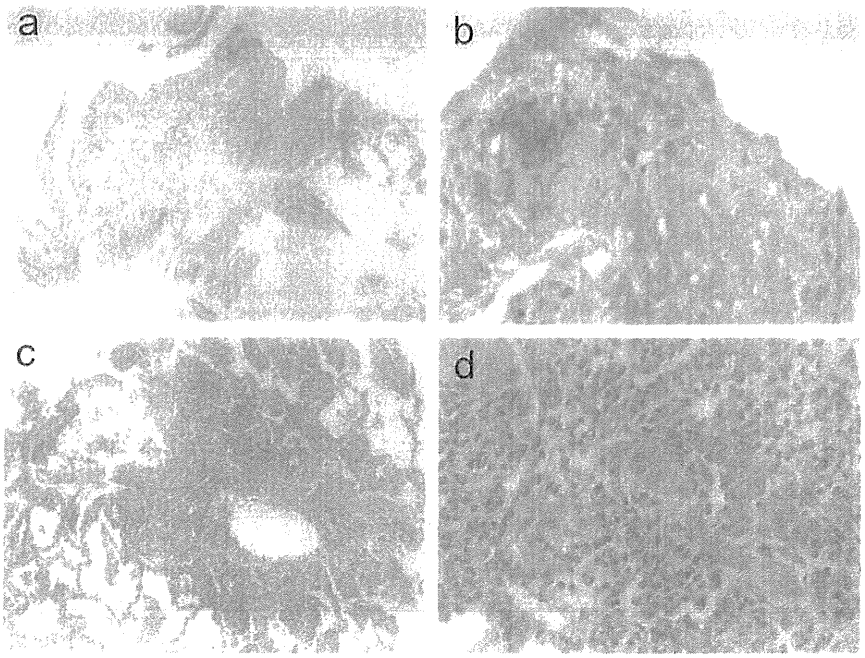

Fig. 2 – Histopathological findings in Case 1. Bronchoscopic biopsy samples taken at the time point depicted in Fig. 1(c). (a) The biopsy sample at the right main bronchus reveals squamous metaplasia of the epithelial layer, subepithelial hyalinous exudates measuring 40 μm in width, and infiltration 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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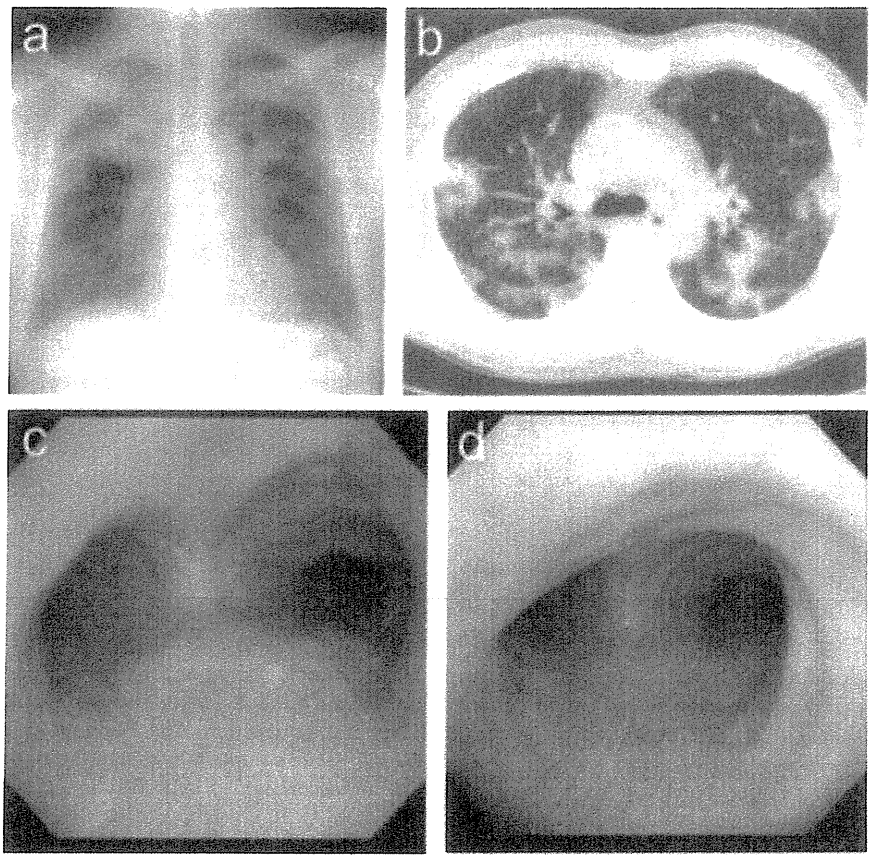

Fig. 3 – Radiological and bronchoscopic findings in Case 2. (a) Chest radiograph at admission showing bilateral consolidations in the upper lung fields. (b) Computed tomography of the chest at admission showing bilateral consolidations in the middle lung fields and periphery. (c) Multiple whitish nodules on the tracheobronchial mucosa, as revealed by fiberoptic bronchoscopy five days after admission. (d) Disappearance of the tracheobronchial nodules 21 days after steroid therapy began.

carina revealed infiltration and degranulation of eosinophils in the subepithelial layer with thickening of the associated basement membranes and squamous metaplasia (Fig. 4a and b). Histopathologic findings of TBLB tissue revealed eosinophil infiltration in the alveolar walls, which were thickened by fibrotic lesions (Fig. 4c and d). Hence, the patient was diagnosed with CEP and started on a steroid treatment regimen. The pulmonary infiltrates and bronchial nodules disappeared 21 days after the initiation of therapy (Fig. 3d).

3.3. *Characteristics*

In order to identify the clinicopathological features of EP patients with multiple nodules in the bronchial mucosa, we classified the patients into 3 groups for analysis: CEP with nodules, CEP without nodules, and Other EP. Although we could not compare the data statistically because of the small number of patients, both patients afflicted by CEP with nodules had never smoked and exhibited coughs, sputum, fevers, high peripheral WBC and eosinophil counts, high bronchoalveolar total cell counts, and eosinophilia (Table 2).

4. Discussion

Although the number of patients was small, to the best of our knowledge, this is the first study describing the frequency of tracheobronchial nodular lesions in EP, and their associated clinical features. Tracheobronchial nodules were seen in 6.9% of CEP patients and in 5.6% of EP patients as a whole. The CEP patients with tracheobronchial nodules both had severe respiratory symptoms and elevated inflammatory markers. Another strength of the present study was that the data were based on an investigation of 36 EP patients who underwent bronchoscopy.

Fox et al. described a CEP patient as having small, pale nodules in the bronchi [11], while Toyoshima et al. reported on a CEP patient with multiple nodular lesions in the trachea and bronchi. In the latter case, peripheral blood eosinophil levels were highly elevated, and a biopsy specimen of the nodule revealed necrotizing bronchial inflammation with pervasive eosinophils. These tracheobronchial lesions resolved after corticosteroid treatment [12]. Similarly, patients with CSS, which is part of the EP spectrum, have been reported to exhibit multiple tracheobronchial lesions [18,19]. Alvarez et al. described such

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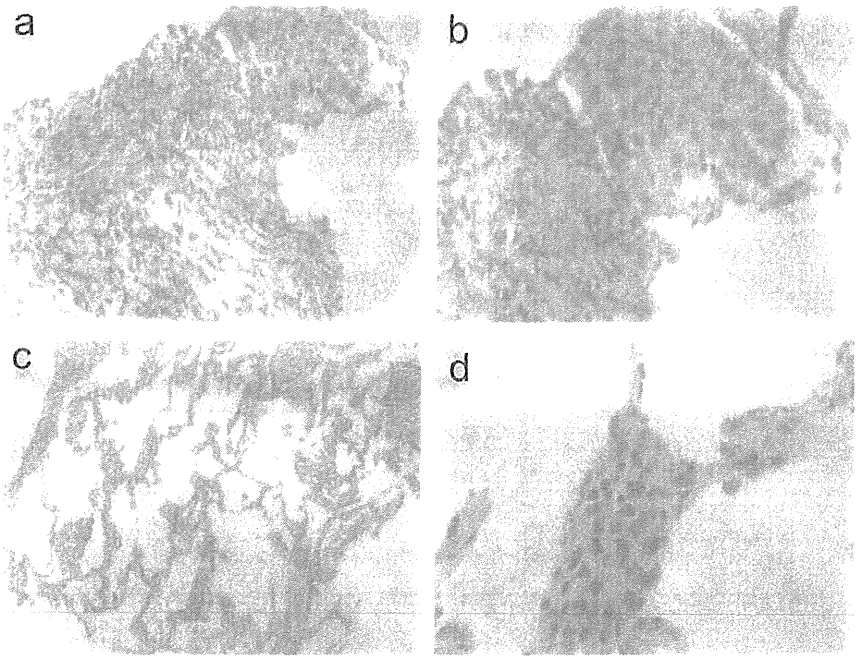

Fig. 4 – Histopathological findings in Case 2. (a–d) Bronchoscopic biopsy samples taken at the time of Fig. 3(c). (a) The biopsy sample taken at the tracheal bifurcation shows squamous metaplasia of the epithelial layer and eosinophil infiltration in the epithelial and subepithelial layers (H&E stain, ×40 objective). (b) A higher magnification of (a). Eosinophils have infiltrated the epithelial and subepithelial layers (H&E stain, ×60 objective). (c) A lung tissue sample taken from the right upper lobe (rt S^3) showing fibrotic thickening of the alveolar walls measuring upto 25 μm, accompanied by infiltration of eosinophils and lymphoid cells. Alveolar structures were kept essentially intact (H&E stain, ×10 objective). (d) A higher magnification of (c). Several eosinophils have infiltrated the alveolar wall, and 2 eosinophils are present in the adjacent alveolar space (H&E stain, ×60 objective).

a CSS patient with tracheobronchial nodules in whom histological observations of eosinophil infiltration and an elevated eosinophil count in BAL fluid were noted [18]. Matsushima et al. likewise reported 2 CSS cases with marked peripheral eosinophilia. Histopathology of the tracheobronchial mucosal lesions revealed necrotizing bronchial inflammation with numerous eosinophils. As with our CEP patients, the bronchial nodules disappeared after steroid treatment [19]. In both of our cases, histopathologic examination of the nodules on bronchial mucosa revealed eosinophil infiltration in the subepithelial regions: after steroid therapy, the nodules and infiltration disappeared (as confirmed by rebiopsy specimens), as did the consolidations observed by chest radiograph and HRCT. Furthermore, in dogs, infiltrations of the airways and/or pulmonary parenchyma by eosinophils have been described as eosinophilic bronchopneumopathy [20]. It should be noted that canine bronchial lesions are closely similar to the human equivalents in the literature and to the present cases, in terms of macroscopic bronchoscopic features, histological findings, and the response to steroids. Taken together, these findings suggest that the observed tracheobronchial nodules are one feature of EP, which disappear in association with decreased allergic inflammation after steroid treatment.

Both of the CEP patients with nodules in this study had high peripheral WBC and eosinophil counts and elevated BAL fluid total and eosinophil cell counts. Both suffered from coughing, sputum, and fever. These cases resembled the CEP patient with tracheobronchial nodules described by Fox et al. That patient also had an elevated WBC count with 30% eosinophils, a cough, and a high-grade fever [11]. Likewise, the patient reported by Toyoshima et al. had an elevated WBC count with 43.7% eosinophils [12]. These findings suggest that tracheobronchial nodules could reflect severe EP. In bronchial asthma, the extent of eosinophilic inflammation of the airways is correlated with disease severity [21]. Therefore, we conclude that the tracheobronchial inflammatory nodules observed in these cases of CEP with nodules were probably associated with a severe manifestation of EP.

Our study had some limitations. First, it was a retrospective study. Second, the positive MPO-ANCA levels observed for Case 2 indicate that the patient may have had CSS. However, his symptoms and laboratory data did not match the diagnostic criteria for CSS. Third, because of the small number of patients with CEP with nodules, we could not compare this group with the other two—CEP without nodules and Other EP—by way of statistical analysis.

5. Conclusions

The presence of tracheobronchial nodules as observed via bronchoscopy should be considered as indicative of severe

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EP. An additional, larger-scale study is necessary to elucidate the precise prevalence of this condition and to confirm the characteristics of such tracheobronchial lesions in the EP patient population.

Conflict of interest

The authors have no conflicts of interest.

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Original article

Predictors of the clinical effects of pirfenidone on idiopathic pulmonary fibrosis

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ABSTRACT

Background: Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease with a poor prognosis. Recently, pirfenidone was reported to slow the rate of decline in vital capacity and improve progression-free survival in IPF. The purpose of this study was to clarify the factors that predicted a good response to pirfenidone, as well as its adverse effects.
Methods: Forty-one IPF cases, treated with pirfenidone from January 2009 to January 2011, were enrolled in this investigation. Disease severity was classified into grades I–IV, as defined by the Japanese Respiratory Society (JRS). Short-term responsiveness to pirfenidone was evaluated by the modified criteria of the JRS. Predictors of nausea, anorexia, or both that represented important adverse effects were examined by multivariate Cox proportional

Abbreviations: IPF, Idiopathic pulmonary fibrosis; JRS, Japanese Respiratory Society; SLB, surgical lung biopsy; VC, vital capacity; NHO-KCCMC, National Hospital Organization Kinki-Chuo Chest Medical Center; UIP, usual interstitial pneumonia; HRCT, high-resolution computed tomography; ATS, American Thoracic Society; ERS, European Respiratory Society; TLC, total lung capacity; DLco, diffusing capacity of carbon monoxide; KL-6, Krebs von den Lungen-6; (SP)-D, surfactant protein-D; MRC, Medical Research Council; PaO_2, arterial oxygen tension; PPIs, proton pump inhibitors; H2RAs, histamine H2-receptor antagonists

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Anorexia
Acid-secretion inhibitors

hazard analyses. Predictors of short-time responsiveness were examined by multivariate logistic regression analyses.

Results: Diagnosed by a surgical lung biopsy (SLB), the mild cases of grade I/II were predictors of good, short-term responsiveness. Patients taking acid-secretion inhibitors, including proton pump inhibitors and histamine H2-receptor antagonists, showed less anorexia, nausea, or both. Only 1 case was administered drugs to activate gastrointestinal motility.

Conclusions: We concluded that IPF patients with a mild disease, diagnosis by SLB, or both showed indications of a good response to pirfenidone. In addition, acid-secretion inhibitors may reduce the frequency of anorexia, nausea, or both from pirfenidone.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a lung disease with a poor prognosis that includes the progressive deterioration of pulmonary function. Its etiology is unknown, and there is no proven effective therapy [1,2]. The pathophysiology of IPF is not fully understood; however, treatments targeting the fibrotic pathway and epithelial injury are supposed to attenuate IPF progression [3].

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) elicits both antifibrotic and anti-inflammatory effects in experimental pulmonary fibrosis models [4]. Open-label studies have revealed that pirfenidone stabilizes IPF disease progression [5,6]. A phase III clinical trial conducted in Japan showed that vital capacity (VC) declined to a lesser degree in pirfenidone-treated IPF patients than that of placebo-treated patients [7]. A significant difference in the progression-free survival was also observed between the 2 groups. On the basis of these findings, in 2008, pirfenidone was approved for IPF treatment in Japan. However, Noble et al. reported controversial results from 2 concurrent phase III trials in the United States [8].

The adverse effects of pirfenidone have been frequently observed. A phase II trial showed that 98.5% of pirfenidone-treated IPF patients had complications including various adverse effects as compared to that of 88.9% of the placebo group [9]. Photosensitivity, nausea, anorexia, and fatigue were observed in 43.8%, 21.9%, 31.5%, and 21.9%, respectively, of the patients; moreover, a significant increase in the frequency of these side effects was observed in the pirfenidone group than that of the placebo group. Photosensitivity can be controlled by prophylactic sunscreen use, which is recommended in the guideline of Shionogi & Co., Ltd. Gastrointestinal adverse effects are the most important dose-limiting and withdrawal-determining factors of pirfenidone.

Thus, if we can predict the responsiveness and adverse effects of pirfenidone treatment in IPF patients, treatment regimens could be better managed. In this study, we examined the predictors of responsiveness and adverse effects of pirfenidone in IPF patients treated in our institute.

2. Materials and methods

2.1. Subjects

From January 1, 2009 to January 1, 2011, 41 patients with IPF were prospectively enrolled and treated with pirfenidone (Shionogi & Co., Ltd., Osaka, Japan) in National Hospital Organization Kinki-Chuo Chest Medical Center (NHO-KCCMC). Informed consent was obtained from all subjects. The institutional review board at NHO-KCCMC approved this study (approval number: Jutaku-20-22; approval date: January 16, 2009). Twenty-three patients were clinically diagnosed with IPF with an usual interstitial pneumonia (UIP) pattern using high-resolution computed tomography (HRCT), while 18 patients were histologically diagnosed as IPF/UIP by surgical lung biopsy (SLB) specimens under the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Society guidelines for IPF [10]. HRCT patterns (*e.g.*, UIP pattern or possible UIP pattern) upon pirfenidone initiation were also evaluated in IPF/UIP cases. The patients' demographics are summarized in Table 1.

Table 1 – Patient demographics at the commencement of pirfenidone.

Parameters	Frequency or median (IQR)
Total (*n*)	41 cases
Gender, male (*n*)/female (*n*)	34/7
Age, (years)	70 (65.5–75.5)
Smoking status (*n*), CS/ES/NS	6/24/11
Diagnosis (*n*), Clinical/SLB	23/18
Modified MRC scale (*n*), grade 0/1/2/3/4	2/6/18/12/3
VC, %predicted (%)	66.7 (54.8–77.8)
Severity grade of IPF (*n*), I/II/III/IV	9/5/9/18
Serum KL-6 (U/mL)	858 (1600 – 687)
Serum SP-D (ng/mL)	187 (138–299)
Serum cholinesterase (U/L)	270 (216–327)
Long term oxygen therapy (*n*), Yes/No	22/19
Treatment before pirfenidone	
Corticosteroid alone (*n*)	3
Corticosteroid and azathioprine (*n*)	4
Corticosteroid and cyclosporine (*n*)	1
Inhalation of N-acetyl-cysteine (*n*)	1

Abbreviations: IQR, interquartile range; CS, current smokers; ES, ex-smokers; NS, non-smokers; SLB, surgical lung biopsy; MRC scale, Medical Research Council score for shortness of breath upon exertion; VC, vital capacity; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein-D.

2.2. Clinical parameter measurement

Pulmonary function tests, including VC, total lung capacity (TLC), and diffusing capacity of carbon monoxide (DLco), were performed using CHESTAC-8800 (Chest M.I., Inc., Tokyo, Japan). A 6-min walk test was performed in accordance with ATS guidelines [11]. Serum Krebs von den Lungen-6 (KL-6) and surfactant protein-D (SP)-D were measured by the enzyme-linked immunosorbent assay using commercially available kits [12]. Dyspnea was assessed by the modified Medical Research Council (MRC) scale from the ATS/ERS [13].

2.3. IPF severity grade

The IPF severity grade was classified per the JRS criteria [7] using the arterial oxygen tension (PaO_2) at rest and minimum SpO_2 during a 6-min walk test performed before pirfenidone initiation. Patients with a $PaO_2 \geq 80$ Torr were classified as grade I; ≥ 70 Torr and <80 Torr as grade II; ≥ 60 Torr and <70 Torr as grade III; and <60 Torr as grade IV. For patients with $\geq$ grade II, if the SpO_2 during a 6-min walk test was $<90\%$, then the severity grade was increased by one grade.

2.4. Pirfenidone administration

Pirfenidone daily dosing was increased in a stepwise manner from 600 to 1800 mg every 2 weeks [7]. The median maximum dose was 1800 mg (range, 600–1800 mg), and the median final dose in the treatment period was 1200 mg (range, 600–1800 mg). The dose was decreased in accordance with the occurrence of adverse events. The median observation period for each IPF patient administered pirfenidone was 400 days (range, 12–885 days).

2.5. Pirfenidone response

A comprehensive evaluation of the patients was performed regarding short-term responsiveness at 3–6 months after pirfenidone initiation to classify the patients as experiencing either an improvement (good response) or a deterioration of at least 2 of the 3 parameters (clinical symptoms, radiological findings, and physiological findings) according to modified criteria [14] of JRS, as well as King et al. [15] on the basis of a prior ATS/ERS consensus statement on IPF that was published in 2000 [16]. Stable state was defined as neither improvement nor deterioration. Evaluation of each parameter is defined in the online supplement (Table S1 in the online supplementary data).

The effects of pirfenidone in 10 IPF cases could not be evaluated because of death ($n=1$; pirfenidone treatment, 12 days), transfer to other hospitals ($n=1$; pirfenidone treatment, 88 days), or pirfenidone withdrawal because of adverse effects ($n=8$; pirfenidone treatment range, 10–65 days) within 3 months of initiation. Thus, short-term responsiveness was evaluated in 31 cases. One patient who died within 3–6 months of pirfenidone initiation was evaluated as *deteriorated*.

2.6. Evaluation and treatment of adverse effects, including anorexia, nausea, or both

Adverse effects in all cases were evaluated using the Common Terminology Criteria for Adverse Events (v. 4). Acute exacerbation of IPF was defined according to the criteria in Japan [7,14]. Of all adverse effects, we evaluated nausea or anorexia that would be classified as $\geq$ grade 2. In grade 2, oral ingestion decreased without significant weight loss; in grade 3, hospitalization was necessary because of significant weight loss secondary to inadequate oral ingestion. Drugs to protect the gastric mucosa and activate gastric motility, including proton pump inhibitors (PPIs) and histamine H2-receptor antagonists (H2RAs), were administered before IPF treatment because of comorbidities that included chronic gastritis, gastric/duodenal ulcers, and gastroesophageal reflux disease. The PPIs, including omeprazole, lansoprazole, and rabeprazole, were administered to 2, 5, and 9 cases, respectively. Cimetidine (H2RA) was administered to 3 cases. Each patient was additionally prescribed several types of drugs for gastrointestinal symptoms if nausea, anorexia, or both occurred.

2.7. Statistical analyses

Patient demographics data are presented as frequency (%) or median with a range. Correlation between pirfenidone response and IPF severity grade was examined by Fisher's exact test and Spearman rank correlation. Univariate and multivariate logistic regression analyses were performed to clarify the predictors of pirfenidone responsiveness. Each numerical parameter was divided into 2 groups by the median. For grades ≥ 2, the Kaplan–Meier method was used to assess the occurrence of nausea, anorexia, or both as adverse effects according to *time without nausea/anorexia* for IPF patients taking pirfenidone. Clinical parameters determining the occurrence of anorexia, nausea, or both were examined by univariate and multivariate Cox proportional hazard regression analyses. A P-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (v.19) (Chicago, IL, USA).

3. Results

3.1. Short-term pirfenidone response and IPF severity stage

Physiological and radiological improvements were observed in 4 cases and 2 cases, respectively. Symptoms improved in 11 cases (cough, 8 cases; shortness of breath, 6 cases). A comprehensive assessment revealed that 6 cases improved 3–6 months after pirfenidone initiation. The patients' pirfenidone response was found to be significantly associated with the IPF severity grade using the Fisher's exact test ($P=0.025$) and Spearman rank correlation ($\rho=0.5039$; $P=0.0039$) (Table 2).

3.2. Predictors of short-term pirfenidone response

Using the 2 significant parameters as determined by the univariate analysis (Table S2 in the online supplementary data), the multivariate analyses (Table 3) showed that diagnosis with

Table 2 – Short-term response to pirfenidone.

	Severity grade of IPF			
	I	II	III	IV
n	8	3	8	12
VC, %predicted (IQR) (%)	76.6 (69.7–83.2)	87.6 (86.0–88.9)	64.8 (57.7–71.7)	58.9 (47.7–64.5)
Response to pirfenidone				
Improvement (*n*)	3	2	1	0
Stable (*n*)	5	1	3	7
Deterioration (*n*)	0	0	4	5

Abbreviations: IPF, idiopathic pulmonary fibrosis; VC, vital capacity; IQR, interquartile range. Significant correlation between response to pirfenidone and severity grade of IPF was observed by Fisher's exact test ($p=0.025$). Definition of severity grade and response of pirfenidone was described in Section 2 and Table S1 in the online supplementary data.

Table 3 – Predictors of short-term good response to pirfenidone[a]

Factors	Odds ratio	95% CI	*p*-value
Severity grade (I/II)	32.988	1.813–600.319	0.018
Diagnosis (SLB)	23.651	1.265–442.125	0.034

Abbreviations: CI, confidence interval; SLB, surgical lung biopsy; IPF, idiopathic pulmonary fibrosis.

[a] Univariate logistic regression analysis was performed using age (≤70 years), smoking status (non-smoker), diagnosis by SLB, severity grade (I/II), Modified Medical Research Council scale for shortness of breath upon exertion (0–1), cholinesterase (>270 U/L), Krebs von den Lungen-6 (>858 U/mL), surfactant protein-D (>187 ng/mL) and usage of proton pump inhibitor (Table S2 in the online supplementary data). Multivariate logistic regression analysis was performed using significant parameters by univariate analysis (*e.g.* diagnosis with SLB and severity grade of IPF) (Table S2).

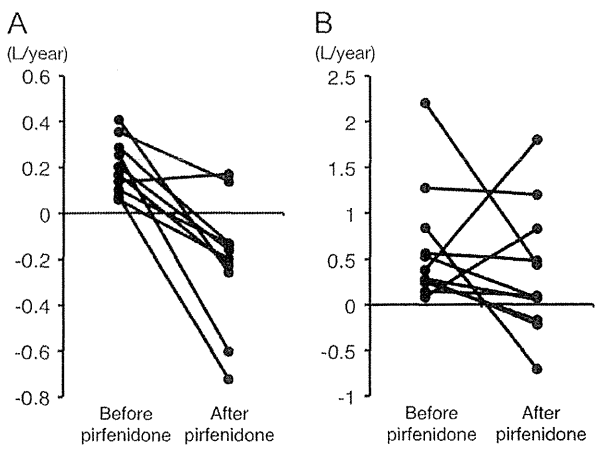

Fig. 1 – A change in vital capacity (VC; L/year) was compared with the Wilcoxon signed-rank test between 3 and 12 months before and 3 and 6 months after pirfenidone initiation with (A) severity grade I/II ($n=10$) and (B) severity grade III/IV ($n=11$). In severity grade I/II patients, the change in VC significantly decreased after pirfenidone initiation ($p=0.0039$) (A). However, the change in VC did not significantly decline in severity grade III/IV patients ($p=0.1748$) (B). The change in VC before pirfenidone administration in severity grade I/II patients was significantly smaller than that of severity grade III/IV patients with Wilcoxon rank-sum test ($p=0.0290$).

SLB specimens was a significant predictor, in addition to an IPF severity grade of I/II. Similar results were found in the evaluable short-term response cases after the addition of 1 deceased case that had died 12 days after pirfenidone initiation. No difference was observed between clinical IPF and IPF/UIP at pirfenidone initiation, except for age, gender, and HRCT patterns (Table S3 in the online supplementary data).

3.3. *VC change before and after pirfenidone initiation*

A change (L/year) in VC could be compared between 3 and 12 months before and 3 and 6 months after pirfenidone initiation by the Wilcoxon signed-rank test in 21 cases. In patients with severity grade I/II, the change in VC significantly decreased after pirfenidone initiation ($n=10$; $P=0.0039$) (Fig. 1A). However, the VC change did not significantly decline in IPF patients with severity grade III/IV ($n=11$; $P=0.1748$) (Fig. 1B). Patients with severity grade I/II experienced a VC change before pirfenidone administration that was significantly smaller than that of patients with severity grade III/IV using the Wilcoxon rank-sum test ($P=0.0290$).

3.4. *Pirfenidone adverse effects*

Adverse effects were observed in 31 of the 41 IPF patients (75.6%) following pirfenidone initiation. Anorexia, nausea, or both were observed in 24 of the 41 (58.5%) IPF patients. Other adverse effects were photosensitivity (5 cases, 12.2%), allergic skin reaction (2 cases, 4.9%), sleepiness (2 cases, 4.9%), photophobia (1 case, 2.4%), vertigo (1 case, 2.4%), diarrhea (1 case, 2.4%), and acute exacerbation (4 cases, 9.8%). Pirfenidone was ceased in 15 cases (34.1%) because of anorexia, nausea, or both (6 cases, 14.6%); disease progression including acute exacerbation (7 cases, 17.1%); and transfer to other hospitals (2 cases, 4.9%). Six cases (14.6%) died from disease progression.

3.5. *Pirfenidone induced anorexia, nausea, or both*

Nineteen IPF cases (acid-secretion inhibitor group) were taking PPIs or H2RAs before pirfenidone initiation as treatment for

Table 4 – Prophylactic effects of acid-secretion inhibitors on anorexia and/or nausea due to pirfenidone.

Drugs at the introduction of pirfenidone	No. of cases	Anorexia and/or nausea	Dose reduction of pirfenidone		
			None	Reduction	Withdrawal
Acid-secretion inhibitors[a] (*n*)	19	8	3	4	1
No acid-secretion inhibitors[b] (*n*)	22	16	7[c]	4	5

Frequency of anorexia and/or nausea was significantly less in the acid-secretion inhibitors group than that in the no acid-secretion inhibitors group as determined by the chi-square test ($p<0.05$).

[a] Proton pump inhibitors (PPIs) or histamine H2-receptor antagonists (H2RA) were administered. The PPIs, omeprazole, lansoprazole, and rabeprazole, were administered to two, five, and nine cases, respectively. The H2RA, cimetidine, was administered in three cases.

[b] Acid-secretion inhibitors were not administered, but drugs for gastritis, drugs to protect gastric mucosa or to activate motility of the gastrointestinal tract were administered. Gastrointestinal drugs in detail were shown in Table S4 in the online supplementary data.

[c] Anorexia and/or nausea improved after the additional use of PPIs after the onset of the adverse effects.

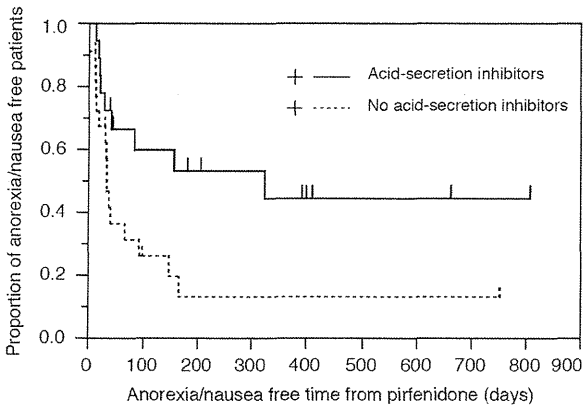

Fig. 2 – Kaplan–Meier plots of anorexia/nausea-free time in IPF patients administered pirfenidone and acid-secretion inhibitors (solid line) or pirfenidone alone (dotted line). The median anorexia/nausea-free time from pirfenidone initiation to the onset of anorexia/nausea in patients with ≥ grade 2 was significantly shorter in cases with no acid-secretion inhibitors (34 days) than in cases with acid-secretion inhibitors (324 days), as determined by log-rank test ($p=0.0211$). Cases that continued pirfenidone treatment and then stopped because of other adverse events, other than anorexia, nausea, or both, were treated as censored cases.

other comorbidities (Table 4). The other 22 cases (no acid-secretion inhibitor group) were not administered acid-secretion inhibitors but administered drugs to protect the gastric mucosa. No significant difference in frequency of coadministered gastrointestinal drugs was observed between the 2 groups (Table S4 in the online supplementary data). One case was administered drugs to activate gastrointestinal motility. There was no difference in pirfenidone dose between the 2 groups.

In the no acid-secretion inhibitor group, 16 cases (72.7%) complained of anorexia, nausea, or both, and 5 cases (22.7%) ceased taking pirfenidone; however, 7 cases continued to take pirfenidone because of additional PPI usage. In the acid-secretion inhibitor group, anorexia, nausea, or both occurred in only 8 cases (42.1%), and almost all cases remained on pirfenidone but with a dose reduction (Table 4). The χ^2 tests revealed that anorexia, nausea, or both occurred at a significantly lower frequency in the acid-secretion inhibitor group ($P<0.05$). The anorexia-free time (median, days) in the IPF patients administered pirfenidone in the acid-secretion inhibitor group was 324 days (Kaplan–Meier method), and this was significantly longer than that of the no acid-secretion inhibitor group (34 days) (Fig. 2).

Table 5 – Predictors of nausea and/or anorexia caused by pirfenidone[#]

Factors	Risk ratio	95% CI	*p*-value
Acid-secretion inhibitors (No[a])	2.346	1.053–5.591	0.037
Age (>70 years)	1.910	0.868–4.410	0.1083

Abbreviations: PPI, proton pump inhibitor; CI, confidence interval.

[#] Multivariate Cox proportional Hazard analysis was performed using two parameters with *p*-value less than 0.10 by univariate Cox proportional Hazard analysis using age (>70 years), smoking status (non-smoker), diagnosis (clinical), severity grade (IV), Modified Medical Research Council scale for shortness of breath upon exertion (0–2), serum cholinesterase (>270 U/L), no administration of acid-secretion inhibitors and administration of prednisolone described in Table S5 in the online supplementary data.

[a] PPIs and histamine H2-receptor antagonists was not administered at the commencement of pirfenidone.

3.6. *Predictors of anorexia, nausea, or both with pirfenidone administration*

A univariate analysis (Table S5 in the online supplementary data) using the Cox proportional hazard regression analyses revealed that the lack of acid-secretion inhibitors was the only significant factor. Prednisolone administration did not affect the onset of nausea, anorexia, or both. The multivariate analyses using factors with a *P*-value of <0.10 (Table 5) showed that the lack of acid-secretion inhibitors was a significant predictor of anorexia, nausea, or both.

4. Discussion

Our investigation demonstrated that the IPF severity grade (I/II) was a significant predictor of a short-term, good response to pirfenidone. Azuma et al. [17] performed an exploratory analysis in a phase III pirfenidone trial and reported that pirfenidone was effective in IPF patients with a %VC ≥ 70% or PaO_2 ≥ 70 Torr and

a SpO_2 <90% during a 6-min walk test at baseline, as compared to that of the placebo group. Their criteria for good responders corresponded to IPF cases with mild-to-moderate lung function impairment, although it was not necessarily similar to stage I/II per the JRS criteria. IPF cases with severity grade I/II also had a significant decrease in VC change after pirfenidone initiation. Thus, pirfenidone might have some effects in the unimproved grade I/II cases.

Another important predictor of a good response to pirfenidone was diagnosis by SLB specimens. Five of the 6 IPF cases with a good, short-term response to pirfenidone were diagnosed by an SLB. Similar results were reported in a bosentan clinical trial for IPF [18]. These results might be explained by the hypothesis that the beneficial effect was greater in IPF cases with a possible UIP pattern on HRCT. It is true that all the IPF/UIP cases in our study demonstrated a possible UIP pattern at diagnosis; however, the HRCT pattern in 8 of the 13 IPF/UIP cases was a definite UIP pattern upon pirfenidone initiation, and 3 of the 5 IPF/UIP cases that had a good response to pirfenidone exhibited a definite UIP pattern. Thus, other factors supposedly have an effect on a good response, although the HRCT pattern might be partially associated with a good response. A detailed reevaluation of the pathological and radiological findings may be warranted to determine the features associated with a good response to pirfenidone.

We performed a multidisciplinary evaluation of a pirfenidone response using radiological and symptomatic parameters, in addition to physiological parameters. Iwashita et al. reported that the radiological findings have improved in only 3 of the 38 cases 1 year after pirfenidone initiation [19], which is consistent to our result. However, our investigation showed that radiologic improvement could be observed in shorter treatment periods, 3–6 months after pirfenidone initiation. The degree of cough had not been evaluated in previous reports. We observed a cough improvement in some cases, although it remains unclear if this was because of a direct effect of pirfenidone. Acute exacerbation of IPF was not inhibited by pirfenidone in the phase III trials [7]. However, the incidence of acute exacerbation in our population (9.8%) was high, as compared with that of the previous clinical trials [7,9]. This may have occurred because severe cases were included in this study.

Taniguchi et al. reported that the short-term effects could predict the long-term effects of pirfenidone, using data from a Japanese phase III clinical trial [20]. They evaluated pirfenidone-treated IPF patients for 3 months and categorized them into 2 groups: a "worsening" group with a relative VC decline of ≥ 5% and a "no worsening" group with no such decline. For 71.7% of the pirfenidone-treated cases in the "no worsening" group, no deterioration occurred 1 year posttreatment, while 87.1% of the pirfenidone-treated cases in the "worsening" group deteriorated 1 year posttreatment. In our examination, 5 of the 6 short-term improvement cases remained on pirfenidone for >1 year, and 4 of the 5 cases were evaluated as stable (data not shown). Although our investigation of the long-term effects was not sufficient, evaluation of the short-term effects may be useful for predicting long-term responsiveness.

Pirfenidone is a promising drug for IPF; however, adverse effects (photosensitivity and anorexia and/or nausea) frequently occurred in several clinical trials [5–7,9]. Gastrointestinal adverse effects are the most important dose-limiting and withdrawal-determining factors of pirfenidone. Our investigation showed the possible preventive effects of PPIs and H2RA against nausea, anorexia, or both.

The pathophysiology of anorexia and nausea with pirfenidone administration has not been fully elucidated; however, it might be associated with the suppression of gastrointestinal motility [21]. Although gastroscopy was not performed on any of our cases, we do not believe anorexia occurred from gastroduodenal ulcers, as it spontaneously resolved after pirfenidone discontinuation. PPIs and H2RAs do not directly activate gastric motility; however, they are known to improve postprandial fullness and early satiation observed in functional dyspepsia without organic disease [22] through attenuating duodenal hypersensitivity to acids [23]. It is reported that PPI monotherapy improves dysmotility-like symptoms significantly better than that of H2RAs plus mosapride in functional dyspepsia [24].

The effect of PPIs on the pharmacokinetics of pirfenidone is an important problem. Although neutralizing acid does not affect pirfenidone absorption or its plasma concentration [25], drug interactions between PPIs and pirfenidone should be considered. *In vitro* metabolism studies revealed that approximately 48% of pirfenidone is metabolized via cytochrome P450 (CYP) 1A2, while <13% is done so by each of CYP2C9, 2C19, 2D6, and 2E1 [26]. PPIs inhibit some CYP reactions; however, all the CYPs associated with pirfenidone metabolism are not simultaneously inhibited [27], and we postulate that the inhibitory effects of pirfenidone may be clinically limited.

In vitro evaluations using hepatoma cell-lines showed that CYP1A2, the most important metabolizer of pirfenidone, was induced by omeprazole and lansoprazole, but not by rabeprazole [28]. Thus, omeprazole and lansoprazole may accelerate pirfenidone metabolism and theoretically decrease its serum concentration and clinical effects; however, *in vitro* studies are not always consistent with *in vivo* studies. *In vivo* interactions of theophylline and caffeine, which are metabolized by CYP1A2, with omeprazole could be clinically negligible in accordance to pharmacokinetic studies [29]. Although the coadministration of pirfenidone and PPIs might not affect the *in vivo* clinical effects, rabeprazole is better than omeprazole and lansoprazole from the standpoint of CYP1A2 induction. Rabeprazole was administered to 2 of the 6 improved cases in our examination (data not shown). Esomeprazole may be another important PPI, as it does not interact with drugs metabolized by CYP1A2 [30].

As for H2RAs, cimetidine is known to interfere with the metabolism of many drugs by inhibiting CYP3A4, CYP1A2, and CYP2D6 [31]. Thus, cimetidine and pirfenidone coadministration might lead to elevated serum pirfenidone levels and deteriorating gastrointestinal symptoms in some cases. Interactions of ranitidine and famotidine with CYP isoenzymes are weak and negligible [32,33].

Our study had several limitations. First, this was not a randomized trial, and PPIs were used for comorbidities. Second, the number of patients was small. Future randomized, controlled trials are necessary to assess the effects of PPIs on nausea, anorexia, or both caused by pirfenidone.

5. Conclusion

IPF patients with a mild disease, diagnosis by SLB, or both showed indications of a good response to pirfenidone. In addition, acid-secretion inhibitors may reduce the frequency of nausea, anorexia, or both from pirfenidone.

Conflict of interest

The authors have no conflicts of interest.

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Appendix A. Supplementary materials

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.resinv.2013.09.002.

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