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Acute exacerbation of Idiopathic Pulmonary Fibrosis

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Abstract

Idiopathic Pulmonary Fibrosis (IPF) is most common idiopathic interstitial pneumonias. IIPF is often seen in elderly smoker man. Diagnosis of IPF is integration of detailed clinical history, specific physical examination, laboratory findings, pulmonary function test, chest high-resolution computed tomography (HRCT) and pathology. IPF have heterogeneous clinical course from asymptomatic stable state to progressive respiratory failure or acute exacerbation (AE). AE of IPF have several important differential diagnosis such as heart failure and volume overload. International working project proposed new criteria of AE of IPF in 2016. They divided into triggered and idiopathic AE. On the basis of this criteria, physician can capture AE of IPF more easily. Recent international IPF guideline emphasized the utility of chest HRCT. In addition, two anti-fibrotic agents have been available. We should pay attention to not only management of AE, but also prevention it. I review diagnostic process, laboratory findings, typical chest imaging, management and prognosis of AE.

Keywords: Acute exacerbation; consolidation: GGO; HRCT; Idiopathic; IPF; LDH; Nintedanib; Pirfenidone; Triggered

Introduction

Idiopathic Pulmonary Fibrosis (IPF) is chronic parenchymal lung disease of unknown etiology and most common fibrotic lung disease of Idiopathic Interstitial Pneumonias [1]. Majority of IPF patients are over 60's men and smokers [1,2]. Familial cluster is sometimes identified around 3% [3]. Genetic background such as MUC5B is associated with development of IPF [4,5]. Natural history of IPF is quite heterogeneous from chronic stable to progressive respiratory failure or acute exacerbation (AE)[6]. Incidence of AE of IPF is 5-10% per year [7].

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However, there is variable incidence depend on ethnicity. Japanese is more susceptible to AE of IPF [8]. Therefore, some genetic regulatory factor may be related with AE [9]. In this review, I describe clinical pictures, laboratory findings, chest imaging especially high resolution computed tomography(HRCT) findings, management and prognosis in AE of IPF.

Diagnosis process

There have been reported that reduced pulmonary function especially forced vital capacity (FVC) ,never smoker and baseline serum Krebs von den Lungen-6 (KL-6) are crucial risk factors of AE of IPF [10-13]. Reduced FVC patients often have decreased normal area due to extensive fibrosis. Therefore, these patients is easy to develop severe lung injury consistent with gefitinib-associated interstitial lung disease(ILD)[14].In never smoker IPF patients, baseline dyspnea grade and serial progression of dyspnea can predict near-future development of AE [15]. So, once we diagnose IPF, physiological evaluation and impairment of activity if daily living due to exertional dyspnea are main task for physician.

International working group report proposed revised criteria of AE of IPF in 2016 [16]. Important situation is previous diagnosis of IPF and acute worsening or development of progressive dyspnea less than 1 month duration. And important change is bronchoalveolar lavage does not necessarily require for diagnosis of AE compared with 2007 criteria [17](Table 1). Therefore, AE of IPF can be diagnosed in general hospital. This criteria is rather broad coverage compared to original criteria in 2007 [7,16].

New criteria divided into two groups comprising of triggered and idiopathic. Triggered consists of infection, post-procedural, post-operative, drug toxicity and aspiration. (Figure 1) In medical interview, disease duration is less than 1 month, next we should exclude pneumothorax, pleural effusion by chest radiography and pulmonary embolism is excluded by combination of clinical history and contrast enhanced chest CT. Furthermore, if we see bilateral shadow by chest radiograph, chest CT will be required for evaluation of bilateral ground glass opacity (GGO) and consolidation with chronic fibrotic findings such as honeycombing, traction bronchiectasis/bronchioloectasis or reticular opacity.

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Before, we arrive at diagnosis of AE of IPF, we should exclude heart failure or volume overload clinically.

In terms of physical findings, patients always show acute respiratory distresss, neck shows marked use of respiratory ancillary muscle especially scalene muscle. Lung auscultation reveals bilateral diffuse fine crackles.

Biomarker

In laboratory findings, classic inflammation marker such as white blood cell and C-reactive protein are usually elevated [1]. In chemistry panel, lactate dehydrogenase (LDH) is simple and sensitive marker of prediction of short-term prognosis of AE of IPF patients. Kishaba,et al. reported that serial trend of serum LDH is associated with 90-day mortality of AE [18]. In addition, Enomoto,et al showed that serum Ferritin over 500 ng/ml will predict poor prognosis of AE of IPF[19].Recently, serum periostin have been pay attention to attractive biomarker of IPF. Serum periostin is elevated both acute phase and chronic stable phase in IPF patients [20,21]. Further multi-center study will be required for further validation.

Both serum KL-6 and surfactant protein-D (SP-D) are useful marker of IPF [22,23]. However, KL-6 is high-molecular weight protein. Therefore, response of KL-6 is rather slow than LDH and elevation of serum KL-6 is seen after acute phase of AE. Regarding serum SP-D, which reflects inflammation process [24]. So, severe pneumonia patients often show elevation of SP-D. On the basis of these findings, distinction AE of IPF from severe pneumonia is quite difficult by serum SP-D alone. On the basis of 2016 new criteria proposal, we reported that triggered group showed more extensive new shadow than idiopathic group [18](Table 2). Multivariate analysis showed that serum LDH and serial trend of LDH predict 90-day mortality [18](Table 3). Kaplan-Meier survival curve showed that over 80 IU/L of serum LDH within 2 weeks was associated with poor survival (p=0.046) [18](Figure 2).

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Imaging

In chest radiogragh, new bilateral diffuse shadow superimposed lower lobe reticular shadow is typical findings of AE of IPF patients. Comparison with previous film is a first step of diagnosis.

2018 latest international IPF guideline strongly insists on the importance of chest HRCT for AE of IPF [1]. We should look for existence of usual interstitial pneumonia (UIP) pattern such as subpleural and basal predominant opacity, peripheral dominant and heterogeneous distribution, architectural distortion consist of traction bronchiectasis and honeycombing [25]. Regarding CT findings of AE of IPF, Akira,et al proposed that they divided into three patterns consist of peripheral, multifocal and diffuse [26](Figure 3). New parenchyma shadow extent was significantly higher than other two patterns. They evaluated several follow-up CT scans. In peripheral type survivors, majority of GGO and consolidation regressed to baseline abnormalities. In multifocal survivors, GGO and consolidation disappeared with corticosteroid therapy. On the contrary, diffuse pattern demonstrated significant extension of GGO and consolidation. Kaplan-Meier survival curve showed significant difference based on CT pattern [26](Figure 3). In multivariate analysis, CT patterns such as diffuse was the strongest predictor of mortality (Table 4). Another study, Kishaba,et al showed that staging of AE of IPF is useful for prediction of prognosis. They identified four important parameters such as serum LDH, KL-6, ratio of partial pressure of oxygen and fraction of inspiratory oxygen concentration and GGO score plus consolidation score. They assigned point for each parameter [27] (Table 5) and divided into two stage groups comprising of limited and extensive [27](Table 6). In addition, extensive group showed poor prognosis compared to limited group [27](Figure 4). According to these studies, detail assessment of chest HRCT findings for AE of IPF will provide quite informative information for physician.

Management

In AE of IPF patients, 2018 Japanese IPF treatment guideline suggested corticosteroid including pulse therapy [28]. Steroid pulse therapy have usually

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been done for consecutive three days and sometimes weekly pulse therapy be repeated two times and multiple pulse therapy often have association with opportunistic infection such as pneumocystis pneumonia and viral infection. Therefore, meticulous titration of prednisolone dosage will be needed during maintenance phase. IPF itself is fibrotic lung disease. However, there are component of inflammation in AE of IPF [2]. Therefore, some patients show response to corticosteroid. In addition, when we see partial response with prednisolone, we commence immunosuppressants such as intravenous cyclophosphamide [29]. But these treatment strategy is not supported by robust evidence. Recently, two novel therapy have been reported to be possible effect for AE of IPF. First, some report showed that direct hemoperfusion with polymyxin B-immobilized fiber column (PMX-DHP) is effective for AE and prolongs survival of AE of IPF patients [30-32]. PMX-DHP is originally introduced to manage for sepsis or septic shock because of neutrophil removal by column. In addition, early introduction of PMX-DHP within 3 days after disease on set is effective especially for dermatomyositis [33]. Based on these reports, we see severe inflammation with AE of IPF patients, we may consider PMX-DHP as possible choice. Second is recombinant human soluble thrombomodulin (rhTM) which is anti-inflammatory effect and mitigate coagulation cascade. rhTM is also developed as anti-sepsis agent. In acute lung injury,there is intensive procoagulant activity in lung parenchyma [34]. Therefore, rhTM is a promising agent with mechanism of action for AE of IPF. Several reports showed intravenous rhTM for consecutive six days improved survival of AE of IPF patients [35-39]. Medical insurance does not cover these two therapy for AE of IPF. Therefore, we should discuss about use of such novel therapy with patient and their family thoroughly. And Tomioka,et al. reported that a case of AE of IPF improved by nintedanib alone [40]. When we see mild AE of IPF patients, anti-fibrotic agent may play a role during acute and chronic phase. In addition, high-flow nasal cannula (HFNC) is sometimes introduced for IPF recently. Breathing rate and minute ventilation are decreased with HFNC [41]. In AE of IPF patients, pharrmacological treatment with HFNC can provide relief of dyspnea [42]. HFNC Future multi-center study will be anticipated.

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Prognosis

AE of IPF is usually associated with poor prognosis. Natsuizaka,et al reported that AE accounts for 40% of IPF death [43](Figure 5). Mean survival of AE of IPF is less than 1-year and 90-day mortality is around 50%. Therefore, prevention of AE is crucial issue. Recent anti0fibrotic agent especially nintedanib showed to prevent AE of IPF in international clinical trial about half. And pirfenidone showed long-term tolerance and preservation of FVC. Therefore, sensible use of these anti-fibrotic agents will provide good prognosis and prevention of AE of IPF patients [44](Table 7).

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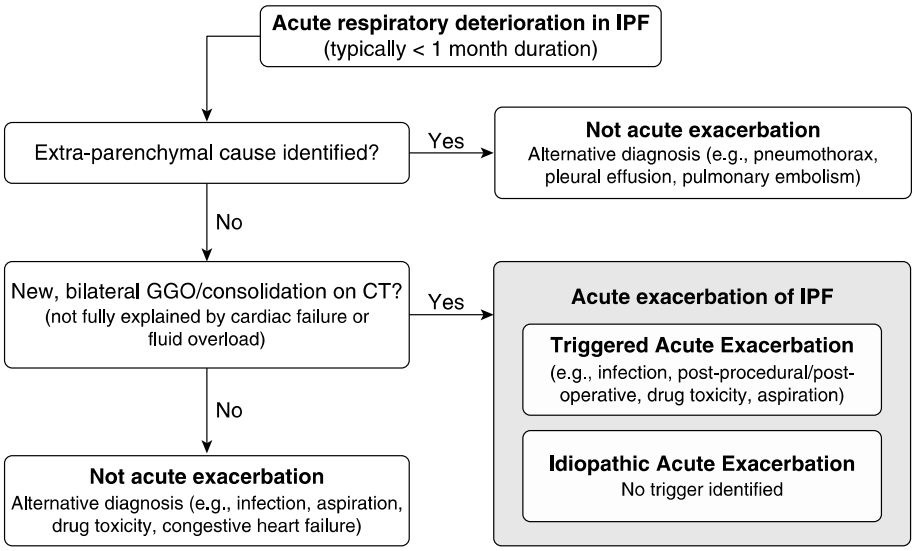
Figure 1. Proposed algorithm for AE of IPF



Reference 16)

Table 1 Comparison of 2007 and 2016 criteria for AE of IPF

Table 1. Comparison between 2007 and 2016 criteria of AE of IPF

	IPF diagnosis	Course	HRCT findings	Exclusion
2007 guideline	Previous or concurrent diagnosis	Less than 1 month	New bilateral GGO and/or consolidation on a background pattern of UIP pattern	Exclusion of alternative etiologies, such as infection, heart failure, and pulmonary embolism; BAL is required
2016 guideline	Previous or concurrent diagnosis	Typically less than 1 month	New bilateral GGO and/or consolidation on a background pattern of UIP pattern	Deterioration not fully explained by heart failure or fluid overload

AE: acute exacerbation; IPF: idiopathic pulmonary fibrosis; HRCT: high resolution computed tomography; GGO: ground-glass opacity; UIP: usual interstitial pneumonia; BAL: broncho-alveolar lavage

Reference 17)

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Table 2 Clinical characteristics of triggered and idiopathic AE of IPF patients

Table 2. Clinical characteristics of patients with idiopathic pulmonary fibrosis with acute exacerbation according to the ATS criteria

Parameters	Triggered (n=12) Mean±SD	Idiopathic (n=53) Mean±SD	P-value
Age (years)	77.1±8.4	74.2±11.8	0.214
Gender (male/female)	8/4	32/21	0.654
Pack-year (years)	49.3±51.3	28.5±37.3	0.056
mMRC	3.2±1.1	2.7±0.9	0.075
Dyspnea duration (days)	4.4±3.7	7.0±6.1	0.918
Clubbing (%)	42	26	0.151
WBC (mm3)	11,008±5116	11.450±5468	0.601
CRP (mg/dl)	8.2±6.5	8.2±7.5	0.504
LDH (IU/l)	410±153	389±144	0.332
KL-6 (IU/l)	2825±2354	1700±1502	0.024
Survival time (months)	1.4±0.4	11.4±3.6	0.094
Imaging findings			
Traction bronchiectasis	2.3±0.7	2.3±0.1	0.395
Honeycombing	1.4±0.5	1.7±0.7	0.858
GGO+consolidation	7.3±6.7	4.2±3.3	0.010
Total extent	11.1±10.7	8.5±5.2	0.005

mMRC: modified Medical Research Council; WBC: white blood cell; CRP: C-reactive protein; LDH: lactate dehydrogenase; KL-6: Krebs von den Lungen-6; ATS: American Thoracic Society; GGO: ground-glass opacity

Reference 18)

Table 3 Univariate and multivariable analysis of predictors with 90-day mortality

Table 3. Univariate and multivariable associations of predictors with 90-day mortality

	Univariate		Multivariable	
Variable	HR (95% CI)	p	HR (95% CI)	p
New criteria	2.275 (0.874, 5.926)	0.009	0.618 (0.312, 1.227)	0.169
LDH	1.002 (1.000, 1.005)	0.002	1.003 (1.001, 1.005)	0.004
ΔLDH	1.009 (1.002, 1.016)	0.013	1.004 (1.001, 1.008)	0.017
ΔKL-6	1.001 (1.000, 1.002)	0.023	1.000 (0.999, 1.001)	0.197
P/F ratio	1.001 (0.520, 1.728)	0.080	0.994 (0.990, 0.999)	0.010

HR: hazard ratio; LDH: lactate dehydrogenase; KL-6: Krebs von den Lungen-6; P/F: ratio of partial pressure of oxygen to the fraction of inspiratory oxygen

Reference 18)

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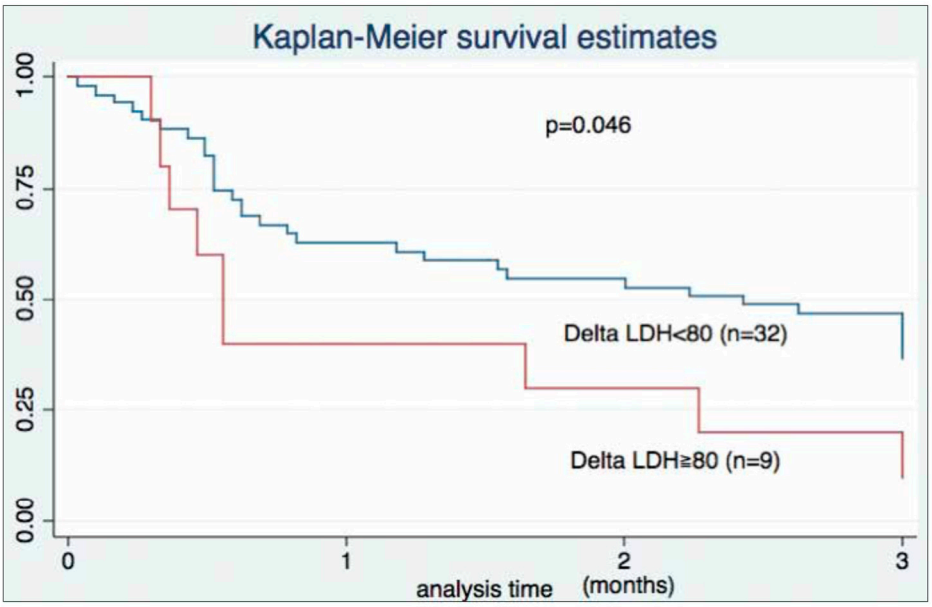
Figure 2 Survival curve based on serial trend of LDH



Reference 18)

Figure 3 CT patterns of AE of IPF

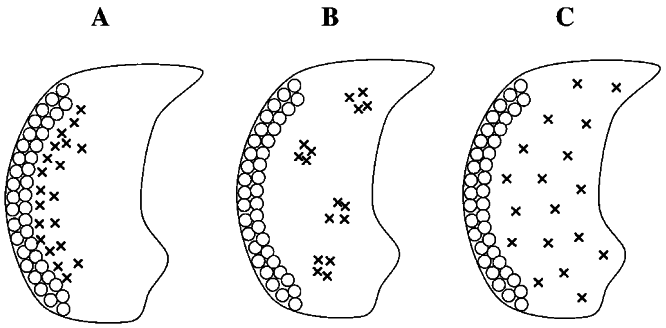


Figure 1. Scheme of computed tomography (CT) patterns. (A) Peripheral pattern; (B) multifocal pattern; (C) diffuse pattern.

Reference 26)

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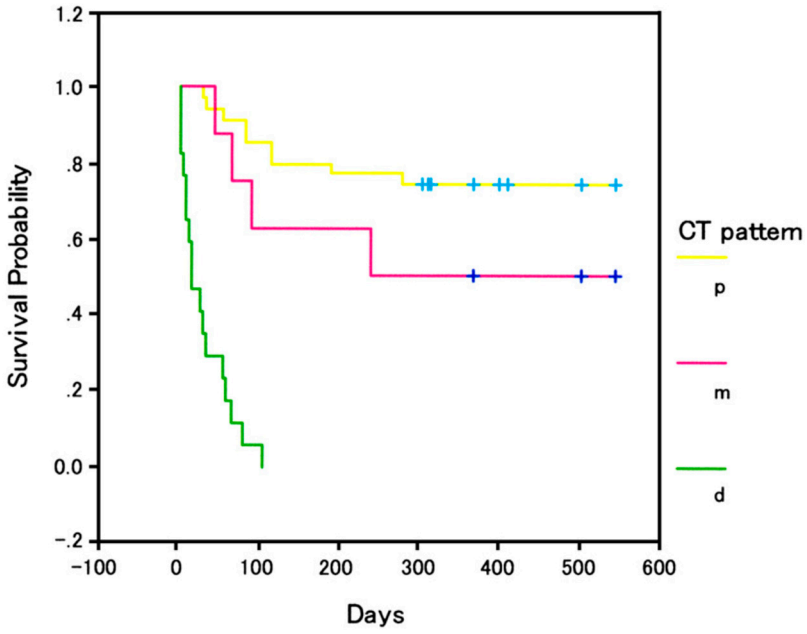
Figure 3 Survival curve based on HRCT pattern



Reference 26)

Table 4 Multivariate analysis of AE of IPF

TABLE 5. MULTIVARIATE ANALYSIS OF SURVIVAL IN PATIENTS WITH USUAL INTERSTITIAL PNEUMONIA WITH ACUTE EXACERBATION

Parameter	Hazard Ratio	95% Confidence Interval	*P* Value
Age, yr	0.999	(0.955, 1.044)	0.952
Male sex	0.913	(0.343, 2.427)	0.855
Positive smoking history	2.473	(0.913, 6.701)	0.075
Baseline FVC	0.984	(0.961, 1.008)	0.185
Baseline D_{LCO}	1.016	(0.996, 1.037)	0.124
CT Patterns	4.629*	(1.900, 11,278)	0.001
CT extent	1.068	(1.022, 1.115)	0.003
Extent of alveolar opacity	0.984	(0.950, 1.019)	0.361
LDH	1.002	(1.000, 1.004)	0.011

Reference 26)

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Table 5　Point assignment of staging of AE of IPF

Table 6 Point assignment for AE staging

Definition	Point
LDH	
\ 280	0
] 280	1
KL-6	
\ 1,000	0
] 1,000	1
P/F ratio	
] 100	0
\ 100	1
Ground-glass opacity ? consolidation score	
\ 20	0
] 20	1

Reference 27)

Table 6　Staging of AE of IPF

Table 8 Staging system for patients with AE of IPF patients

	Points
Limited exacerbation (n = 22)	0-2
Extensive exacerbation (n = 36)	] 3

Reference 27)

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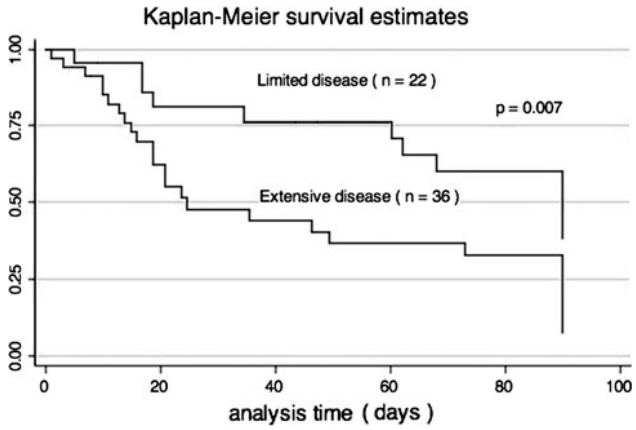
Figure 4 Survival curve based on staging of AE of IPF



Reference 27)

Figure 5 Cause of death of IPF

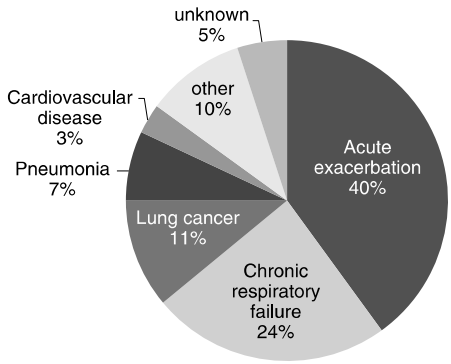


Figure 4. Causes of death in patients with idiopathic pulmonary fibrosis.

Reference 43)

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Table 7 Characteristics of Anti-fibrotic agent

Table 3. Pharmacologic Management of IPF.*

Variable	Nintedanib	Pirfenidone
Mechanism of action	Tyrosine kinase inhibition	Inhibition of TGF-β production and downstream signaling, collagen synthesis, and fibroblast proliferation (selected list)
Efficacy	Slows FVC decline by 50%	Slows FVC decline by 50%
FDA-approved dose	150 mg by mouth twice daily	801 mg by mouth thrice daily
Common side effects	Diarrhea	Anorexia, nausea, photosensitivity
Enzyme metabolism	Ester cleavage (major), CYP 3A4 (minor)	CYP 1A2 (major), other CYP enzymes (minor)
Cautions	Risks of both bleeding and arterial thrombosis; risk of gastrointestinal perforation (rare); anticoagulant and prothrombotic drugs should be avoided	CYP 1A2 inhibitors (e.g., fluvoxamine and ciprofloxacin) can raise pirfenidone levels; CYP 1A2 inducers (e.g., omeprazole and smoking) can lower pirfenidone levels
Need for liver-function monitoring	Yes†	Yes‡
Clinical strategies to minimize side effects	Use of antidiarrheal agents, temporary dose reduction to 100 mg twice daily	Slow dose increase over 14-day period, medication to be taken with food, use of antacids, use of antiemetic agents, sun avoidance

Reference 44)