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Practical management of idiopathic pulmonary fibrosis

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Abstract. Idiopathic Pulmonary Fibrosis (IPF) is relentless progressive interstitial lung disease (ILD) of unknown etiology. Main pathogenesis is aberrant recovery of epithelial injury and collagen deposition. Majority of IPF patients have been elderly men with smokers. However, there are important differential diagnosis such as fibrotic non-specific interstitial pneumonia (NSIP), Connective Tissue Disease (CTD) associated ILD, chronic hypersensitivity pneumonia (CHP). Clinical point of view, non-productive cough and progressive exertional dyspnea are main symptoms. In addition, scalene muscle hypertrophy, fine crackles and finger clubbing are key findings. Serum marker such as lactate deydrogenase (LDH), Krebs von den Lungeng-6 (KL-6) are sensitive for ILD detection and activity. Pulmonary function test and 6 minute walk test (6MWT) are quite meaningful physiological examination. Serial change of forced vital capacity 6MWT distance predict mortality of IPF. International IPF guideline published recently and highlighted on the importance of high resolution computed tomography (HRCT) findings. Key findings of IPF are honeycombing, traction bronchiectasis and subpleural reticular opacity. IPF is chronic progressive disease. Therefore, tracing disease behavior is crucial and unifying clinical, physiological, imaging information over time provide useful information for physicians.In management, many candidate agent failed to have positive result. Pirfenidone which is anti-fibrotic agent showed to slow the decline of vital capacity and prevent of acute exacerbation. Molecular agent such as nintedanib is promising agent for prevention of progression of IPF. In this review, we review the clinical information of IPF and IPF guideline. Lastly, we show the clinical algorithm of this devastated disease.*(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 90-98)*

Key words: clinical disease behavior, forced vital capacity, high resolution computed tomography, idiopathic pulmonary fibrosis, management

Introduction

Idiopathic pulmonary fibrosis (IPF) is relentless progressive interstitial lung disease of unknown etiology (1,2). IPF occurs usually elderly people over 50 with smoking history. For diagnosis, chronic non-productive cough and progressive exertional dyspnea with typical high resolution CT findings (HRCT) and pathological usual interstitial pneumonia (UIP) are essential (3,4). International guideline especially insist on the importance of HRCT findings such as sub pleural distribution and honeycombing recently (3,5). Pathological point of view, UIP is associated with many clinical conditions (1,6). Therefore, multi-disciplinary discussion including clinicians, radiologists and pathologists is important for diagnosis of IPF. In this review, we describe clinical approach and unresolving issue for diagnosis and management of IPF.

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History taking

Non-productive cough and progressive exertional dyspnea are key symptom in IPF. Cough sometimes worse both on exercise and at night. Understanding triggering situation is important. In addition, cough predict disease progression (OR 4.97, 95% CI: 1.25-19.80, P = 0.02) independent of disease severity, and may predict time to death or lung transplantation (HR 1.78, 95% CI: 0.94-3.35, P = 0.08) (7), Cough is associated with quality of life in IPF (8). When patient report more cough and heart burn on supine, we suspect gastroesophageal reflux and IPF (9). Regarding dyspnea, we should evaluate modified Medical Research Council dyspnea scale (10). Tracing the grade of dyspnea over time is quite important for understanding health status of IPF patients. Sensation of change of dyspnea grade is associated with forced vital capacity (FVC) (11).

Physical findings

General appearance is important for evaluation of nutritional status and body mass index (BMI) is associated with breathing work load. Neck is treasure house of chronic lung disease. Patients with rmoderate to severe restrictive disorder such as IPF have often hypertrophy of scalene muscle and use this when develop acute exacerbation. Typical auscultation is bilateral fine crackles (12,13). Fine crackles are early findings of interstitial lung disease(ILD) including IPF before apparent fibrotic changes are detected by CT scan (14,15), If IPF progress, crackles are heard from base to upper zones (16). Extent of fine crackles have often have positive correlation with area of fibrosis in HRCT findings. Compared with granulomatous lung diseases such as sarcoidosis, IPF have many crackles. Squawk is short phase high-pitched mixed sound including musical and non-musical sound. It is often heard chronic hypersensitivity pneumonitis (CHP) (17) and combined pulmonary fibrosis and emphysema (CPFE). Finger clubbing signify chronicity of disease process. Approximately half of IPF patients have clubbing. For ruling out important differential diagnosis, such as connective tissue disease (CTD), we should check arthralgia, myalgia and specific rash including heliotrope rash and Gottron sign.

Serum biomarker

Classically, serum LDH is usefulmarker for activity of IPF and helpful parameter of severity of acute exacerbation (AE) of IPF (19). During acute phase, LDH is more sensitive for treatment response. KL-6 is reported to be a sensitive marker for ILD activity recently. KL-6 is associated with fibrotic area of HRCT findings and future exacerbation of IPF (20,21). Other epithelial or macrophage-related proteins such as surfactant protein-A(SP-A), SP-D, chemokine ligand-18 (CCL18) and matrix metalloproteinase-7(MMP-7) are associated with reduced survival (22-25). SP-D often have positive associated with extent of ground glass opacity (GGO) and negative association with percent FVC.

Pulmonary function test

FVC is robust parameter for prediction of mortality of IPF and is used as primary endpoint of many clinical trials in IPF (11). FVC is reliable, reproducible important indicator of patient clinical status and future prediction in IPF. Reduction of FVC over 6 months predicts 1-year mortality. Minimal clinically important difference (MCID) of FVC absolute change is 2-6%. (Table 1).

In the meantime, absolute change of FVC is used. However, if we identify over 10% decline in FVC patients, choosing relative change is not different (26). Diffusing capacity for carbon monoxide (DLco) is another important physiological parameter for IPF. However, if patient's vital capacity under 1500 ml, the value is not reliable with single breath method. In addition, it is affected by respiratory infection, anemia and reprodcuctivity is not enough. Therefore, it is not robust marker compared with FVC.

6 minute walk test

It is classic physiological test for chronic lung disease. it is simple test and reliability for IPF patients is good. It is weakly correlated with physiological function. In addition, 24-week decline of greater than 50 m in 6 miniute walk test (MWT)distance predict mortality (27). The estimated MCID of 6 MWT distance is 24-45 m.

Table 1. Patient 's sense of dyspnea with FVC change per year (Reference 11)

	N	Change in Percent-predicted FVC*	
		Unadjusted Mean (SD)	Adjusted Mean (SD)†
Global change in health status‡			
Much better	25	2.3 (7.3)	5.1 (7.3)
Somewhat better	55	−2.1 (6.4)	0.7 (6.4)
Same	96	−2.8 (5.8)	0 (5.8)
Somewhat worse	59	−6.5 (6.6)	−3.7 (6.6)
Much worse	14	−6.1 (9.5)	−3.3 (9.5)
Somewhat better or worse	114	2.3 (7.7)	2.2 (6.6)

FVC: forced vital capacity

Chest radiogragh

It is useful for evaluation of disease distribution and serial change of volume loss especially in lower lung field. Therefore, comparison of previous film is important for decision to start aggressive treatment. In addition, IPF patients often have pulmonary hypertension (PH) in advanced stage. In these clinical condition, change of cardio-thoracic ratio and prominence of bilateral hilum are important information.

HRCT findings

HRCT provide useful information about anatomical location of disease process and key findings of IPF such as reticular opacity, traction bronchiectasis and honeycombing (5,28). (Table 2) Honeycombing is manifested on HRCT as clustered cystic airspaces, typically of comparable diameters on the order of 3-10 mm. It is usually located subpleural and characterized by well-defined walls (29). Recently, the concept of not only multi-layered clustered cysts but also sub-pleural single layered ones should be diagnosed as honeycombing is proposed (30). In this occasion, clinician's role for collecting information about IPF possibility is quite important for diagnosis and management.

When we see atypical findings , we consider alternative diagnosis. Both micronodules and air trapping suggest CHP. Extensive GGO, peribronchuvascular predominant distribution suggest non specific interstitial pneumonia (NSIP) and CTD-associated ILD. Significant pleural plaques and subpleural curvilinear opacity with definite occupational exposure suggest asbestosis. And multi-focal peripheral consolidation is associated with organizing pneumonia(OP) (31). If we see undetermined pattern, HRCT provide adequate site for surgical lung biopsy fro definitive diagnosis. Integration of clinical and imaging information contribute to definite diagnosis.

Table 2. HRCT features of IPF/UIP pattern (Reference 3)

UIP Pattern (All Four Features)	Possible UIP Pattern (All Three Features)	Inconsistent with UIP Pattern (Any of the Seven Features)
• Subpleural, basal predominance • Reticular abnormality • Honeycombing with or without traction bronchiectasis • Absence of features listed as inconsistent with UIP pattern (*see* third column)	• Subpleural, basal predominance • Reticular abnormality • Absence of features listed as inconsistent with UIP pattern (*see* third column)	• Upper or mid-lung predominance • Peribronchovascular predominance • Extensive ground glass abnormality (extent > reticular abnormality) • Profuse micronodules (bilateral, predominantly upper lobes) • Discrete cysts (multiple, bilateral, away from areas of honeycombing) • Diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes) • Consolidation in bronchopulmonary segment(s)/lobe(s)

HRCT: High resolution computed tomography, IPF: Idiopathic pulmonary fibrosis, UIP: Usual interstitial pneumonia

Bronchoalveolar lavage (BAL)

BAL is helpful for ruling out infection, diagnosis of granulomatous lung disease and prediction of treatment response. It is quite useful especially in AE of IPF. Because advanced stage patients, it is very difficult for distinction of infection and AE clinical information only. Bronchoalbeolar lavage fluid (BALF) cellular analysis provide additive information for evaluation of ILD. In smokers, alveolar macrophages are predominant. In typical IPF patients, cell populations are usually normal or neutrophil is predominant. When we see BALF lymphocytosis over 30% with similar presentation of IPF, we consider the possibility of CHP and NSIP (32). And other possibility is sarcoidosis (33). Regarding CD4/CD8 ratio, acute HP is usually decreased. On the other hand, that is elevated for CHP and sarcoidosis (34). In BALF eosinophilia, eosinophilic pneumonia or drug associated ILD is possible (Table 3) (35). Utility of BALF have some limitations. However, when we see ILD patients, BALF biomarkers such as KL-6, thrombomodulin in AE of IPF have potentials to predict mortality and treatment response (36).

Surgical lung biopsy

Among the IPF patients, approximately one-third of patients have atypical presentation both clinical symptom and HRCT findings (36). In these cases, we think surgical lung biopsy for definite diagnosis (3,37). When we perform video-assisted thoracic surgery, we should take at least two or three specimens from different lobes. Especially choosing less intense area is very crucial for prediction of disease activity. However, some patients have contraindication for surgery such as pulmonary hypertension, severe heart failure and advanced age. Or patient reject this procedure. Without surgical procedure with undetermined cases, clinicians should decide whether or not to do aggressive treatment based on disease behavior (38).

Pathology

International guideline showed main histological IPF/UIP pattern. These findings are as follows: honeycombing in a predominantly subpleural or paraseptal distribution, patchy involvement of lung parenchyma by fibrosis, presence of fibroblastic foci and absence of features against a diagnosis of UIP (38). When we see UIP pattern with lymphoid aggregates with germinal centers,extensive pleuritis, prominent plasmacytic infiltration and dense perivascular collagen, lung dominant CTD is possible (39). In short, we carefully follow future development of CTD. If we see centrilobular fibrosis, bridging fibrosis, bronchiolitis with granuloma, we should think about CHP (40). In NSIP usually show diffuse homogeneous fibrosis with temporal uniformity and preserve architecture and honeycombing is absent or scant, After obtained pathological information, multi disciplinary discussion is able to compensate for the weakness of each diagnostic process and lead to practical diagnosis with sharing key information (41).

Table 3. Differential diagnosis with BALF cell population (Reference 35)

a. Disorders associated with increased percentage of specific BAL cell types

Lymphocytic cellular pattern	Eosinophilic cellular pattern	Neutrophilic cellular pattern
>15% lymphocytes	>1% eosinophils	>3% neutrophils
Sarcoidosis	Eosinophilic pneumonias	Collagen vascular diseases
Nonspecific interstitial pneumonia (NSIP)	Drug-induced pneumonitis	Idiopathic pulmonary fibrosis
Hypersensitivity pneumonitis	Bone marrow transplant	Aspiration pneumonia
Drug-induced pneumonitis	Asthma, bronchitis	Infection: bacterial, fungal
Collagen vascular diseases	Churg-Strauss syndrome	Bronchitis
Radiation pneumonitis	Allergic bronchopulmonary aspergillosis	Asbestosis
Cryptogenic organizing pneumonia (COP)	Bacterial, fungal, helminthic, *Pneumocystis* infection	Acute respiratory distress syndrome (ARDS)
Lymphoproliferative disorders	Hodgkin's disease	Diffuse alveolar damage (DAD)

b. Abnormal BAL differential cell patterns that suggest specific types of ILD

BALF: Bronchoalveolar lavage fluid

Clinical disease behavior

Disease behavior of diffuse lung disorders are proposed in 2013 international guidelines. And clinical courses of IPF patients are heterogeneous (42). Among IPF patients, we subdivide into four groups including progressive deteriorating, later acceleration, slowly progressive, stable based on clinical symptom trend and physiological tendency.

Clinical trials

Many clinical trials of IPF patients failed to have treatment effect in terms of survival. In pharmacological treatment, interferon(IFN)-γ- b trials did not improve progression-free survival and survival benefit (43). Anticoagulation therapy trial ACE-IPF(AntiCoagulant Effectiveness in Idiopathic Pulmonary Fibrosis) was associated with an increased mortality risk in IPF patients (44). PANTHER-IPF (Prednisone, Azathioprine, and N-Acetylcysteine: A Study That Evaluates Response in Idiopathic Pulmonary Fibrosis) reported that triple therapy group is associated with hospitalization and death (45). However, this study have limitations. Tapering of steroid dose was quite rapid and management and prevention of infection were not sufficient. Pirfenidone showed a significant effect on decline of forced vital capacity (FVC) and PFS in 267 patients treated with pirfenidone compared with placebo in Japanese phase II study (46). The ASCEND study is a Phase III multinational randomized, double-blind, placebo controlled study which demonstrated that pirfenidone reduce the decline in %FVC at Week 52 compared with placebo ($p<0.000001$). Both key secondary endpoints were achieved: pirfenidone improved PFS (HR 0.57; 95% CI 0.43-0.77; $p=0.0001$) and reduced the decline in 6MWD ($p=0.036$). In addition pirfenidone showed reduction of mild to moderate severity of IPF-related mortality [HR 0.32; 95% CI 0.14-0.76; $p=0.0061$]) (47). N-acetylcysteine (NAC) mono therapy study showed that preservation of FVC in IPF patients with mild-to-moderate physiological abnormalities is accomplished with NAC (48). Nintedanib is molecular agent which is tyrosine kinase inhibitor and targets are fibroblast growth factor, platelet-derived growth factor and vascular endothelial growth factor receptors. Based on the positive result of phase II study, phase III study was conducted and demonstrated that the primary endpoint, the annual rate of decline in FVC, was significantly reduced in the nintedanib group compared to placebo. Both key secondary endpoints such as reduction of deterioration Saint George Repiratory Question (SGRQ) total score and AE were met (49).

According to these results, inhibition of one-pathway do not stop the progression of IPF. We should stratify which patients response pirfenidone, NAC or Nintedanib. For this strategy, we must collect serial clinical, physiological, radiological change properly.

Management

We had the result of three crucial clinical trials recently. First, phase 3 trial of pirfenidone showed there was a relative reduction of 47.9% in the proportion of patients who had an absolute decline of 10 percentage points or more in the percentage of the predicted FVC or who died over 52 weeks ($P<0.001$) (50). In addition, pirfenidone had significant effect on reduction for death from any cause ($P=0.01$) and from idiopathic pulmonary fibrosis ($P=0.006$) (Figure 1). And all patients met the criteria a ratio of the forced expiratory volume in 1 second (FEV_1) to the FVC of 0.80 or more, and a 6-minute walk distance of 150 m or more in this study. So, obstructive component was strictly excluded and target population were mild to moderate restrictive disorder. In terms of adverse effect, nausea and rash were common. Proton pump inhibitor and smoking are possible to promote pirfenidone metabolism (51). Therefore, stomach protection such as Histamine-2 antagonist may be better. In addition, both UV exposure and smoking should be avoided.

Second, the result of phase 3 two trial of nintedanib which is named INPULSIS-1 and INPULSIS-2 are available. In this study, the adjusted annual rate of change in FVC was −114.7 ml with nintedanib versus −239.9 ml with placebo (difference, 125.3 ml; 95% confidence interval [CI], 77.7 to 172.8; $P<0.001$) in INPULSIS-1 and −113.6 ml with nintedanib versus −207.3 ml with placebo (difference, 93.7 ml per year; 95% CI, 44.8 to 142.7; $P<0.001$) in INPULSIS-2. And INPULSIS-2,

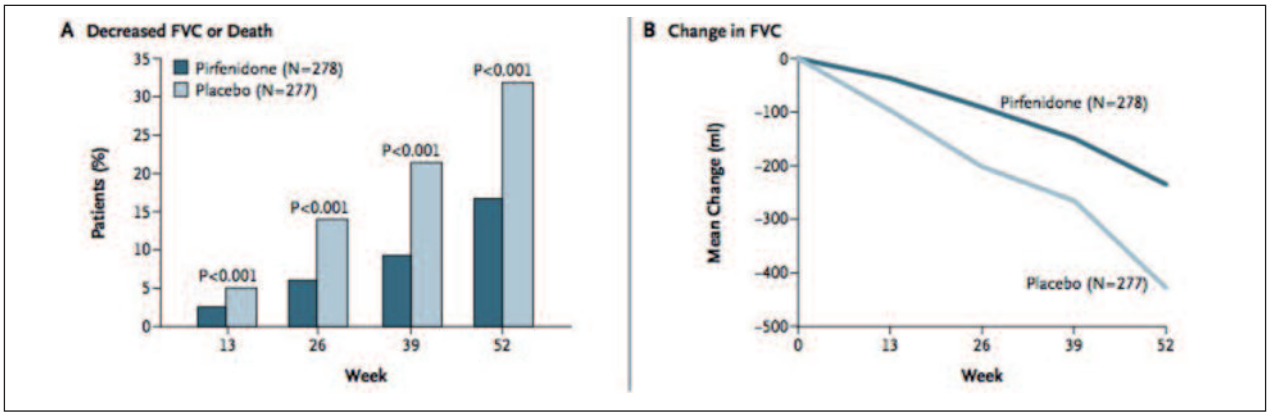

Fig. 1. Change in FVC or Death with Pirfenidone (50).
FVC: forced vital capacity

there was a significant benefit with nintedanib versus placebo (hazard ratio, 0.38; 95% CI, 0.19 to 0.77; P=0.005) (Figure 2) (52). The most frequent adverse effect of nintedanib was diarrhea. However, majority of patients were controllable with anti-diarrhea drug or dose reduction.

Third, Acetylcysteine treatment of IPF patients showed no significant difference in the change in FVC between the acetylcysteine group and the placebo group (–0.18 liters and –0.19 liters, respectively over 60 weeks; P=0.77) (53) (Figure 3). In addition, there were no significant differences between

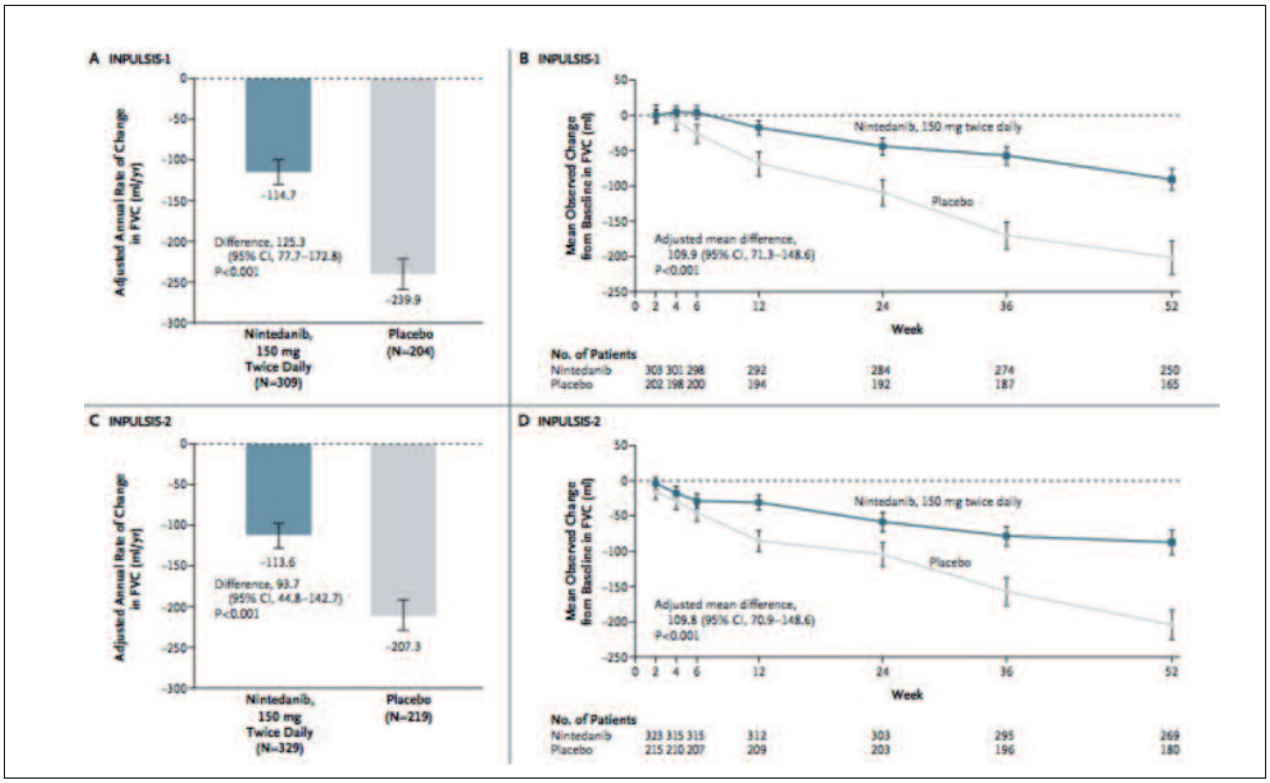

Fig. 2. Annual Rate of Decline and Change from Baseline in FVC with Nintedanib (52)
FVC: forced vital capacity

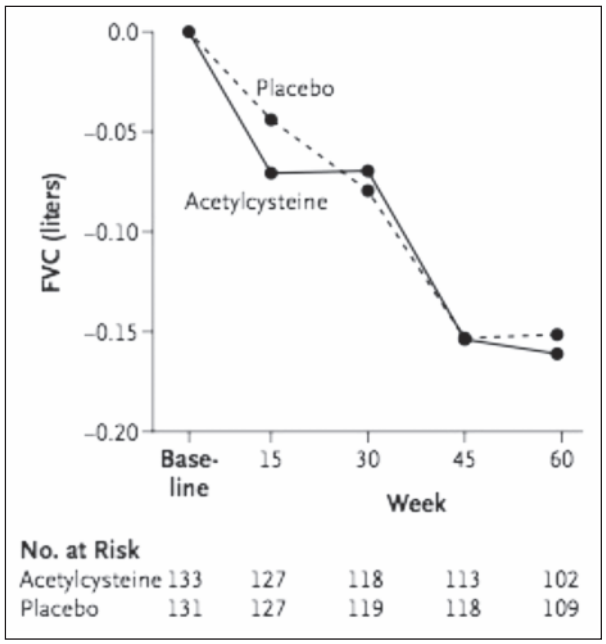

Fig. 3. Change from Baseline in FVC with NAC (53)
FVC: forced vial capacity, NAC: N-acetylcysteine

the acetylcysteine group and the placebo group in the rates of death (4.9% vs. 2.5%, P=0.30 by the log-rank test) or acute exacerbation (2.3% in each group, P>0.99). Therefoe, acetylcysteine is not routinely recommended. However, if both pirfenidone and nintedanib cannot be used due to adverse effect, acetylcysteine may have play a role for IPF.

Non-pharmacological option are rehabilitation and oxygen for quality of life (3). For physician, we monitor trend and change of cough frequency, dyspnea grade carefully. In progressive deteriorating group, first three months trend of vital capacity is predictive of mortality (54). When we see decreased vital capacity over 5% within three months, we recommend pirfenidone and nintedanib for prevention of AE. In later acceleration group, serial monitoring of FVC and dyspnea is crucial. Decrease of FVC over 10% within six months or elevation of mMRC dyspnea scale leads to commence pirfenidone or nintedanib for slow reduction of FVC and prevention of AE. In slowly progressive group, starting pirfenidone or nintedanib initially. If clinical symptom worse or progression of imaging findings and decreased FVC are definite, we recommend combination therapy such as pirfenidone with nintedanib. In stable disease, pulmonary function have been steady. Therefore, conservative management is warranted. However, if patient notice more cough or dyspnea, we should consider NAC or NAC with pirfenidone for prevention of disease worsening. In case of acute exacerbation, we recommend systemic steroid. (Table 4) Finally, we check treatable comorbidity such as obstructive sleep apnea(OSA), pulmonary arterial hypertension(PAH) and left heart failure. Both OSA and heart failure is controllable with nasal continuous positive airway pressure (n-CPAP) or diuretics. Secondary PAH is challenging issue. Currently, PAH-specific drugs are not approved for IPF with PAH. In advanced stage IPF patients have high incidence of PAH. Therefore, we think lung transplantation in case of young age or PAH-specific drug such as sildenafil or bosentan is an option for elderly patients.

Table 4. Clinical disease behavior and treatment option

	Clinical goal	Treatment option	Quality of evidence
Progressive deteriorating	Prevention of AE	Pirfenidone If pirfenidone fails, Consider Pirfenidone with Nintedanib	Very low
Later acceleration	Support QOL and prevention of AE	Pirfenidone or Nintedanib	Low
Slowly progressive	Slow reduction of FVC and support QOL	Pirfenidone, Nintedanib If mono therapy fails, combination therapy for disease progression	Mono therapy is high, combination therapy is very low
Stable	Symptom management	NAC If iNAC fails, consider add on Pirfenidone	Low
Acute exacerbation	Control of disease activity	Systemic steroid	Moderate

AE: Acute exacerbation, QOL: Quality of life, FVC: forced vital capacity, NAC: N-Acetylcysteine

In conclusion, IPF consists of heterogeneous patients. Clinicians should monitor trend of clinical parameters, imaging findings, physiological items carefully. We decide to treat depend on clinical behavior.

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