



# Pharmacological treatment of idiopathic pulmonary fibrosis and fibrosing interstitial lung diseases: current trends and future directions

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## ABSTRACT

Idiopathic pulmonary fibrosis (IPF) was considered untreatable until the development of therapeutic drugs and diagnostic technology that made it possible to slow the progression of IPF. In 2014, pirfenidone and nintedanib were approved simultaneously as therapeutic drugs for patients with IPF. These drugs have proven effective in reducing further progression of pulmonary fibrosis, acute exacerbation, and mortality and have consistent effects regardless of the severity of IPF. The indications of nintedanib and pirfenidone are gradually expanding for various other diseases that cause pulmonary fibrosis. Currently, IPF pathogenesis is associated with the type 2 alveolar epithelium and repeated or persistent damage to its cells. Such damage may induce an abnormal wound healing response, causing fibrosis rather than repair. Several promising drugs have been developed for reducing or reversing fibrosis, each with a different molecular target implicated in pulmonary fibrosis. Due to the heterogeneous mechanisms underlying pulmonary fibrosis, future disease management is likely to comprise combinations of therapies targeting a range of disease mechanisms.

**Keywords:** Idiopathic pulmonary fibrosis; Nintedanib; Pirfenidone

## INTRODUCTION

Usual interstitial pneumonia (UIP) refers to cases where lung biopsy in a patient with diffuse pneumonia of unknown cause reveals temporal and spatial heterogeneity of fibrosis in the lung tissue. In diffuse parenchymal lung disease with suspected pulmonary fibrosis, UIP is the most common pathologic finding after a lung biopsy. Cases in which pathologic findings indicate UIP and with no clinically identified causative factors—such as rheumatic disease or environmental disease—are referred to as idiopathic pulmonary fibrosis (IPF) [1,2].

The etiology of IPF involves alveolar collapse and the resulting hardening of the alveoli. The major mechanisms of pathogenesis include the abnormal production of surfactant proteins and damage to the type 2 alveolar cells that also function as stem cells [3], which induces an abnormal wound healing response and causes fibrosis rather than repair [4]. The role of mac-

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rophages in the fibrosis process is also considered important [5]. Drug candidates evaluated in recently completed or ongoing phase 2 and 3 clinical trials of IPF are known to be primarily involved in the pre-fibrotic process. In IPF, fibrosis appears to begin primarily in the interstitium and then expand elsewhere. However, the abnormal repair process that leads to IPF progression and the resulting fibrosis can occur both in the interstitium and inside the alveoli [6]. Connective tissue disorders are commonly associated with interstitial lung disease (ILD), and research suggests that inflammatory pathways are also related to lung fibrosis [7].

With improvements in the resolution of chest computed tomography (CT) scans, high-resolution computed tomography (HRCT) can be used to predict the pathological outcomes of IPF. Accordingly, the diagnostic focus for pulmonary fibrosis has gradually shifted from lung biopsy to chest CT [8]. In cases where HRCT scans indicate reticular opacity, traction bronchiectasis, and honeycombing in the subpleural region, there is a high rate of agreement with the pathologic findings of UIP [9]. In contrast to IPF, common findings in nonspecific interstitial pneumonia (NSIP) include bilateral reticular opacities, traction bronchiectasis, reduced volume of the lobes, and ground-glass opacity in the lower lungs [10]. Chest HRCT has largely replaced lung biopsy for the diagnosis of IPF, and the IPF treatment regime has changed substantially since the publication of this guideline in 2011 [1].

Pulmonary fibrosis is regarded as an irreversible lesion. The goal of the current treatment is to slow the progression of further pulmonary fibrosis rather than clearing fibrosis from the lesions [11]. Since the primary endpoint shifted from patient survival to the reduction of forced vital capacity (FVC) decline [12-17], there has been remarkable growth in clinical studies of IPF.

It has been reported that drugs effective against IPF also reduce fibrosis in pulmonary diseases other than IPF [18-20]. In systemic sclerosis-associated ILD, nintedanib—not an immunosuppressant—has been successful in suppressing the progression of pulmonary fibrosis [21,22].

The effectiveness of various drugs has been well-proven through many studies. In this review, the focus is on the use of pirfenidone and nintedanib in the current treatment of IPF, followed by a discussion on the treatment effects according to the severity of pulmonary fibrosis and side effects of each drug.

## THE CURRENT PHARMACOLOGICAL TREATMENT OF IPF AND FIBROSING INTERSTITIAL LUNG DISEASES

### Pirfenidone

#### *The effects of pirfenidone on IPF*

Many studies have shown that pirfenidone is effective it was finally approved as a treatment for IPF in the United States, after the results of the ASCEND study were published in 2014 [23]. In the ASCEND study, UIP diagnosis was mainly based on HRCT findings. Among the participants in this study, 95% showed indications of UIP on HRCT, and the rest were classified as possible UIP. Men accounted for 80% of the participants, and the average age was approximately 68 years. The severity of the IPF was classed by a pulmonary function test. The FVC was approximately 67% of the predicted value, the forced expiratory volume in 1 second (FEV1)/FVC ratio was on average 84%, and the diffusing capacity of the lung for carbon monoxide (DLco) was 43% of the predicted value [23]. Subsequent studies have analyzed the effect of pirfenidone treatment in patients with mild (% predicted FVC 90%) and severe (percent predicted FVC <50%) IPF [24,25]. Both studies showed the effectiveness of pirfenidone in IPF regardless of FVC impairment.

Among patients with recent unclassifiable idiopathic interstitial disease, more than 10% fibrosis on HRCT, percent predicted FVC 45%, and percent predicted DLco 30%. The treatment effect of pirfenidone has also been studied in patients with progressive ILD using HRCT [19].

Among patients with moderate IPF (percent predicted FVC  $\geq$  50%), those treated with pirfenidone (2,403 mg for 52 weeks) had significantly lower FVC decline and mortality compared to those in the placebo group. In addition, an effect of reducing exercise distance decline was also observed [23]. However, pirfenidone had little effect on reducing cough or dyspnea [26]. The reduction in FVC decline was also comparable among pirfenidone-treated patients with severe (percent predicted FVC <50% or percent predicted DLco <35%) and mild IPF [25,27,28]. The lesser the FVC decline, the greater the decrease in mortality [29], and pirfenidone treatment improved life expectancy by 2.5 years in patients with IPF [30].

#### *The effects of pirfenidone non-IPF ILD*

In patients with unclassifiable idiopathic interstitial disease, reduction in spirometry values as measured using a home spirometer—the primary endpoint of this study—was not sig-

nificant between the pirfenidone-treated and placebo groups [29]. However, the FVC measured at the hospital decreased by 95.3 mL less in the pirfenidone group than in the placebo group. Other secondary endpoints, such as changes in percent predicted DLco, were also reached [19]. Current research is focused on examining the effect of pirfenidone on chronic hypersensitivity pneumonia, a common form of idiopathic interstitial pneumonia (IIP) [31].

#### *The side effects of pirfenidone*

Pirfenidone doses are scheduled as follows: a starting dose of 267 mg (one capsule) taken thrice daily; after 1 week, two capsules (534 mg) taken thrice daily; and after 2 weeks, three capsules (801 mg) taken thrice daily. Unlike clinical trials conducted in the West, a Japanese randomized controlled study of patients with IPF administered a dose of 1,800 mg to patients in the pirfenidone treatment group [32]; these patients showed a significantly increased exercise capacity and significantly lower FVC decline than those in the control group. In a subsequent Japanese study in patients with IPF, patients administered either 1,800 or 1,200 mg doses of pirfenidone showed less reduction in FVC compared to the placebo control group [33]. In Korea, the dose of pirfenidone in IPF may follow the Japanese studies.

In the ASCEND study, the most common side effects in patients treated with pirfenidone (compared to the placebo group) were nausea and indigestion. The frequencies of them were 36% and 19%, respectively [23]. Side effects such as gastrointestinal symptoms and skin rash usually improved gradually with medication. Recommended techniques to reduce side effects include using an intestinal motility agent, a proton pump inhibitor, and a sunblock lotion, as well as reducing exposure to sunlight. In addition, if the side effects are considered serious, the dose can be reduced or treatment can be temporarily halted. If the clinician judges that continuous treatment with pirfenidone is impossible due to its side effects, a replacement with nintedanib may also be considered.

#### **Nintedanib**

##### *The effects of nintedanib on IPF*

In the INPULSIS randomized controlled study conducted to determine the effect of nintedanib, a lung biopsy was performed in approximately 20% of patients with IPF and the FEV1/FVC ratio was above 80% on average [34]. The INPULSIS study included not only patients with UIP pattern in the HRCT scan but also those diagnosed with possible UIP (with-

out honeycombing patterns in the HRCT scan). If the HRCT shows the form of UIP but not a honeycomb pattern, it is considered to be a disease other than UIP [1] or an early lesion of UIP [35]. A previous study has compared the efficacy of nintedanib therapy in reducing FVC between patients with UIP patterns in the HRCT scan and those with possible UIP [36]. An observational study has also studied the effect of nintedanib on FVC reduction in patients with very severe IPF (percent predicted FVC <50% or percent predicted DLco <30%) [37].

In patients with IPF, the FVC of the group treated with nintedanib for 52 weeks decreased less by approximately 100 mL compared to the placebo group [34]. A further analysis of the INPULSIS study found no difference in the effect of nintedanib regardless of the presence of honeycombing in HRCT scans (patients with UIP and possible UIP, respectively) [36]. Several studies have shown that the effects of nintedanib remain consistent from mild to severe IPF [38]. When acute exacerbation occurs in patients with IPF, the prognosis is poor and the mortality rate exceeds 40% [39,40]. However, nintedanib treatment is likely to significantly increase the time to onset of acute exacerbation in patients with IPF and reduce its frequency [34]. Similar to the effects of pirfenidone, the lesser the FVC decline, the greater the decrease in mortality [29].

##### *The effects of nintedanib on non-IPF ILD*

The therapeutic effect of nintedanib in progressive fibrosing ILDs has also been studied [18]. Patients with progressive fibrosing ILDs are characterized by >10% pulmonary fibrosis in HRCT and confirmed progression of ILD, a relative decline in the FVC of at least 10% of the predicted value during the preceding 24 months, and include patients with chronic hypersensitivity pneumonitis, NSIP, and unclassifiable IIPs [18]. In patients (>10% pulmonary fibrosis), with chronic hypersensitivity pneumonitis, NSIP, unclassifiable IIPs, administration of nintedanib for 52 weeks reduced the decline in FVC by 75 mL compared to the control group after disease progression for 24 months [18]. Nintedanib is effective in reducing the rate of decline of FVC regardless of the UIP pattern in HRCT scans; therefore, its efficacy appears to be similar for pulmonary fibrosis lesions even in different diseases [18].

##### *Doses and side effects of nintedanib*

Unlike pirfenidone, nintedanib is taken twice daily with food, and its dosage does not require adjustment. The digestive side effects generally improve gradually with time, and anti-

diarrheal and antiemetic drugs can be used to control the side effects. If serious side effects occur, the dose can be reduced or sometimes temporarily halted. The ideal dosage of nintedanib is 150 mg taken twice daily; however, if severe diarrhea occurs and cannot be controlled by other methods, dosage can be reduced to 100 mg taken twice a day. If nintedanib treatment is difficult to continue even with this method, clinicians may consider replacing it with pirfenidone. In cases liver dysfunction, nintedanib is contraindicated. Therefore, liver function tests and a history of liver disease should be reviewed before administration of this drug. Even after treatment, liver function tests should be conducted every month for the first 3 months. When liver profiles become stable, liver function tests are recommended every 3 months. In the INPULSIS study, the occurrence of diarrhea was 60% higher in the nintedanib treatment group than in the control group, and the frequency of nausea was 22.7% (3.5 times that of the control group). There was no difference in the frequency of cough between the nintedanib treatment group and the control group; however, the frequency of dyspnea was lower in the treatment group. Drug treatment was terminated due to serious side effects in 17% to 21% of patients in the nintedanib treatment group and 10% to 15% in the control group [34].

### Sildenafil

Sildenafil is a phosphodiesterase inhibitor that inhibits cyclic guanosine monophosphate (cGMP) degradation, increases the concentration of cGMP, and expands the pulmonary artery. This effect can be used for primary pulmonary arterial hypertension (PAH) [41]. PAH is more often seen in patients with IPF [42]. Among patients with severe IPF (percent predicted DLco <35%), studies have shown that sildenafil treatment improves exercise capacity and quality of life in those with right heart failure or hypertrophy of the right heart [43], and administration of sildenafil (20 mg, thrice daily) and nintedanib (150 mg, twice daily) reduces FVC decline and improves quality of life [38]. It should be noted that in the latter study, when the two drugs were administered simultaneously in patients with severe IPF, the side effects did not increase further, and a stable outcome was achieved with the combined treatments. However, STEP-IPF [44] and INSTAGE [45] trials did not meet the primary endpoint. If sildenafil is to be used in patients with IPF, it is necessary to be aware of the limitations of its effectiveness.

## THE FUTURE PHARMACOLOGICAL TREATMENT OF IPF

Several drugs are being developed to treat the aberrant wound healing of fibrosis in IPF. In the following paragraphs, I will discuss the following treatment regimens: nintedanib and pirfenidone combination therapy, pentraxin-2 (purified serum amyloid P), pamrevlumab, GLPG1690 (autotaxin inhibitor), omipalisib, and TD139 (galectin-3 inhibitor).

### Nintedanib and pirfenidone combination therapy

Due to the pleiotropic nature of disease pathogenesis in IPF, combination treatment regimens are now being implemented. Pirfenidone has pleiotropic effects, including antifibrotic, anti-inflammatory, and antioxidant properties. Although it attenuates fibrosis in many animal models—including fibrosis of the lungs and other organs [46]—its antifibrotic molecular targets have not been identified [47]. Nintedanib is a multi-target inhibitor of tyrosine kinase. Targeted kinases include vascular endothelial growth factor (VEGF) receptors 1, 2, and 3; platelet-derived growth factor (PDGF)  $R\alpha$  and PDGFR $\beta$ ; fibroblast growth factor (FGF) receptors 1, 2, and 3; lymphocyte-specific protein tyrosine kinase; Lyn; and Src [48]. Several fibrotic mediators—e.g., transforming growth factor  $\beta$  (TGF $\beta$ ), interleukin 1, tumor necrosis factor  $\alpha$ , and basic FGF—exhibit PDGF-dependent fibrosis activity or stimulate PDGF expression in animal models [49]. FGFs and their receptors have various functions that regulate cell proliferation, survival, migration, and differentiation, which may be involved in profibrotic processes [50]. VEGF, FGF, and PDGF are also involved in the abnormal angiogenesis that is a feature of IPF [51].

Researchers have studied the safety, tolerability, and pharmacokinetic and exploratory efficacy endpoints in patients treated with nintedanib and add-on pirfenidone versus those treated with nintedanib alone [52]. Patients with IPF and percent predicted FVC > 50% were enrolled in this study. Gastrointestinal side effects were reported in 37 of 53 (69.8%) patients treated with nintedanib with additional pirfenidone and in 27 of 51 (52.9%) patients treated with nintedanib alone. Plasma trough concentrations prior to the administration of nintedanib were similar when administered alone or with additional pirfenidone. This study concluded that nintedanib treatment with add-on pirfenidone had manageable levels of safety and tolerability (Table 1) [52].

Table 1. Recent representative studies on emerging antifibrotic drugs in IPF

Study <sup>a)</sup>	Study type	Treatment	No. of patients	Primary outcomes	Efficacy	Duration (phase)
NCT02579603 [52]	Open-label nintedanib with add-on pirfenidone in IPF	Nintedanib with pirfenidone or nintedanib alone	104	Percentage of patients with on-treatment gastrointestinal adverse events from baseline to week 12	GI adverse events: 69.8% in patients treated with nintedanib with add-on pirfenidone, and 52.9% in those treated with nintedanib alone.	12 weeks (Phase IV)
NCT02550873 [58]	Randomized, double-blind, placebo-controlled trial	Recombinant human pentraxin-2 (10 mg/kg), taken intravenously every 4 weeks or placebo	116	The least-squares mean change in decline of FVC percentage of predicted values from baseline to week 28	The least-squares mean change in decline of percent predicted FVC values from baseline to week 28 in patients treated with recombinant human pentraxin-2 was -2.5, compared to -4.8 in the placebo group (difference, 2.3; 90% CI, 1.1 to 3.5; P=0.001).	28 weeks (Phase II)
NCT01890265 [64]	Randomized, double-blind, placebo-controlled trial	Intravenous infusion of pamrevlumab (30 mg/kg) or placebo, taken every 3 weeks over 48 weeks (16 infusions)	103	Change from baseline in percentage of predicted FVC at week 48	Pamrevlumab reduced the decline in percentage of predicted FVC by 60.3% at week 48 (mean change from baseline -0.9% with pamrevlumab, compared to -7.2% with placebo, P=0.013).	48 weeks (Phase II)
NCT02738801 [69]	Randomized, double-blind, placebo-controlled trial	Placebo or 600 mg oral GLPG1690 taken once daily	23	Safety (adverse events), tolerability, pharmacokinetics, and pharmacodynamics	Four (67%) patients in the placebo group and 11 (65%) in the GLPG1690 group had treatment-emergent adverse events, most of which were mild to moderate. The most frequent events in the GLPG1690 group were infections.	12 weeks (Phase IIa)
NCT01725139 [74]	Randomized, placebo-controlled, double-blind study	Omipalisib or placebo	17	Safety, tolerability, pharmacokinetics, and pharmacodynamics	The most common adverse event was diarrhea, reported by four participants. Dose-related increases in insulin and glucose were observed.	8-32 days (Phase I)
NCT02257177 [78]	Randomized, double-blind, placebo-controlled study	Inhaled TD139 or placebo	60	Safety, tolerability, pharmacokinetics, and pharmacodynamics	Inhaled TD139 was well tolerated, with no significant treatment-related side effects. TD139 was rapidly absorbed, with mean T <sub>max</sub> values ranging from 0.6 to 3 hours and a T <sub>1/2</sub> of 8 hours. The concentration of TD139 in the lung was >567-fold higher than that in the blood, with systemic exposure predicting exposure in the target compartment.	14 days (Phase I/IIa)

IPF, idiopathic pulmonary fibrosis; GI, gastrointestinal; FVC, forced vital capacity; CI, confidence interval.

<sup>a)</sup>ClinicalTrials.gov identifier.

### Pentraxin-2

Pentraxin-2, also known as serum amyloid P, is a circulating protein and a soluble pattern recognition receptor in the innate immune system [53-55]. Its unique binding activity can be specifically localized to the site of damage and aids in the removal of damaged tissue. In mice, genetic mutations in the pentraxin-2 gene lead to enhanced fibrosis [56,57]. In a randomized clinical trial of 117 patients with IPF where participants received every 4 weeks treatments with recombinant human pentraxin-2 over 28 weeks, the change in percent predicted FVC values were -2.5% and -4.8% in the treatment and placebo groups, respectively—a statistically significant difference. Recombinant human pentraxin-2 injections were tolerated well (Table 1) [58]. This study also reported that the 6-minute walk test was improved in patients treated with pentraxin-2 who had not been receiving concurrent nintedanib or pirfenidone during treatment [58]. Currently, antifibrotic therapy is reported to be ineffective in reversing fibrosis, only slowing the progression of the disease. However, the ability of pentraxin to reverse fibrosis is under investigation, and further research is needed on this subject.

### Connective tissue growth factor inhibitor

Connective tissue growth factor (CTGF) plays a central role in diseases that involve tissue remodeling. CTGF expression is driven by a number of cytokines and conditions associated with pathophysiology [59]. Its presence leads to differentiation to other cell types, including epithelial to mesenchymal transition [60] or fibroblast proliferation and differentiation [61]. CTGF also activates myofibroblasts and stimulates the deposition and remodeling of extracellular matrix proteins, which leads to tissue remodeling and fibrosis. Gene expression and plasma levels of CTGF are also elevated in patients with IPF [62,63]. Pamrevlumab is a fully human monoclonal antibody that inhibits the activity of CTGF and may be capable of reversing lung fibrosis. A recently published randomized, double-blind, placebo-controlled trial of pamrevlumab enrolled patients with IPF and a percent predicted FVC of  $\geq 55\%$ . The treatment arm was assigned an intravenous infusion of pamrevlumab, with doses of 30 mg/kg every 3 weeks for over 48 weeks (16 infusions). The primary efficacy outcome was achieved by the approximately 60% reduction of decline in percent predicted FVC values at week 48 compared to that at baseline (Table 1) [64].

### Autotaxin inhibitor

Previously, there has been great interest in the bioactive lipid

mediator lysophosphatidic acid (LPA) in the pathogenesis of fibrotic diseases. Researchers have demonstrated an important role of LPA signaling through one of the receptors, LPA1, in animal models of fibrosis in several organs, including the lungs [65,66]. Genetic deletion or pharmacological inhibition of autotaxin—the enzyme responsible for generating most extracellular LPA—limits the development of lung fibrosis in the bleomycin model [67]. The expression of autotaxin increases both IPF and fibrotic NSIP [67]. GLPG1690 is a powerful and selective inhibitor of autotaxin and is associated with a reduced concentration of LPA after oral administration [68]. A randomized, double-blind, placebo-controlled phase 2a study was performed to test the safety of GLPG1690 (Table 1) [69]. The results showed that over 12 weeks of treatment, mean FVC values were maintained at even higher values than at baseline in the autotaxin inhibitor group, whereas the values decreased in the placebo group. This drug is currently undergoing a phase III clinical trial [70] that is scheduled to end on December 31, 2021.

### PI3K/mTOR inhibitor

A recent meta-analysis of genome-wide association studies found three novel association signals near KIF15, MAD1L1, and the DEP domain-containing mammalian target of rapamycin (mTOR)-interacting protein (DEPTOR) [71]. The sentinel variant, rs28513081, was found to be located in an intron of DEPTOR, and the IPF risk allele was associated with decreased expression of DEPTOR in the lung. The DEPTOR-related gene was also associated with reduced FVC, but not FEV1. Another study has reported that the fibrogenic effects of TGF $\beta$ 1 are mediated via the cooperation between canonical Smad3 and rapamycin-insensitive mTORC1/4E-BP1 [72]. This study also showed that ATP-competitive mTOR inhibition halts collagen synthesis in IPF lung slices, which may be a potential novel antifibrotic strategy. An *in vivo* study has provided a strong scientific rationale for progressing the potent pan-phosphoinositide 3-kinase (PI3K)/mTOR inhibitor omipalisib (GSK2126458) as a novel antifibrotic agent [73]. Omipalisib exhibits broad target specificity and may overcome functional redundancy between PI3K isoforms and compensatory feedback loops in this pathway. Finally, a randomized, placebo-controlled, double-blind, repeat dose escalation, experimental medicine study of omipalisib treatment has been conducted in patients with IPF (Table 1) [74]. In this study,  $^{18}\text{F}$ -2-fluoro-2-deoxy-d-glucose (FDG)-positron emission tomography/CT scans were performed, revealing that omipalisib treatment reduced FDG uptake in fibrotic ar-

eas of the lung (apparent as honeycombing patterns on HRCT scans) compared to that at baseline [74].

### Galectin-3 inhibitor

Galectin-3 can regulate a variety of cellular functions, such as the proliferation, compartmentalization, and endocytosis of proteins and glycolipids of the plasma membrane, and the functioning of membrane receptors [75]. Studies in several organ fibrosis models have demonstrated that galectin-3 regulates the activity of fibroblasts and macrophages in chronically inflamed organs, including the lungs [76]. Increased galectin-3 expression also activates myofibroblasts, causing scarring, thus affecting the general fibrosis pathway that leads to fibrosis in several organs. Galectin-3 is also known to mediate fibrosis through pathways related to inflammation and infection [75]. In addition, galectin-3 may play a key role in the pathogenesis of IPF exacerbation [76, 77]. A randomized, double-blind, placebo-controlled, phase I/IIa study was conducted to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of inhaled TD139, a galectin-3 inhibitor (Table 1) [78]. This study showed that inhibition of galectin-3 expression in the lung was associated with reduction in the levels of plasma biomarkers relevant to IPF pathobiology, including galectin-3. Currently, an ongoing clinical trial is investigating the efficacy of inhaled TD139 in patients with IPF planned treatment duration is over 52 weeks (NCT03832946).

### CONCLUSION

Pirfenidone and nintedanib are effective in patients with moderate severity IPF. However, the efficacy of pirfenidone in patients with mild and severe severity IPF is comparable to that in patients with moderate severity. Pirfenidone and nintedanib have been proven effective in patients with forms of pulmonary fibrosis other than IPF, and the indications for pirfenidone and nintedanib continue to expand with ongoing studies.

The current paradigm of IPF etiology is related to problems with the type 2 alveolar epithelium and repeated or persistent damage to type 2 alveolar epithelial cells. IPF may induce an abnormal wound healing response, leading to fibrosis rather than repair. Several promising drugs are emerging for the treatment of fibrotic lung diseases including IPF. Future disease management is likely to comprise combinations of therapies targeting a range of disease mechanisms.

### CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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### AUTHOR CONTRIBUTIONS

Conception or design: WIC.

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Drafting the work or revising: WIC.

Final approval of the manuscript: WIC.

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