

Developmental drugs for idiopathic pulmonary fibrosis

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Abstract

Introduction. Idiopathic pulmonary fibrosis (IPF) is an age-related lung disease of unknown cause characterized by relentless scarring of the parenchyma resulting in respiratory failure and death. The progressive and irreversible loss of lung function has a devastating impact on patients' quality of life by causing debilitating dyspnea and cough. Two antifibrotic drugs (pirfenidone and nintedanib) are approved for the treatment of IPF worldwide, but they do not offer a cure and are associated with tolerability issues. Owing to its high unmet medical need, IPF is an area of dynamic research activity for the pharmaceutical industry.

Areas covered. There is a growing portfolio of novel therapies that target different pathways involved in the complex pathogenesis of IPF. In this review, we discuss the mechanisms of action and available data for compounds in the most advanced stages of clinical trial development.

Expert opinion. The approval of pirfenidone and nintedanib has fueled drug discovery and development in IPF, with new drugs likely to reach the clinic in the near future. However, a number of challenges remain, including combination therapy, evaluation of drug efficacy in clinical trials, route of administration (systemic vs. inhaled) and performance of early-phase proof of concept studies.

Keywords: idiopathic pulmonary fibrosis, novel drugs, therapy, clinical trials, treatment.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, age-related fibrotic interstitial lung disease (ILD) of unknown origin limited to the lung and associated with a pattern of fibrosis termed “usual interstitial pneumonia” (UIP) either radiologically on chest high resolution CT (HRCT) or histologically on lung biopsy (Raghu). As scar tissue replaces normal lung parenchyma, lung function is progressively and irreversibly lost leading to respiratory failure and eventually death. Median survival of IPF patients is 4 to 5 years, with older age and male sex being associated with a higher incidence of disease and shorter survival time after diagnosis (Raghu). Conservative estimates of disease incidence range from 3 to 9 cases per 100,000 per year in Europe and North America (Hutchinson), whereas the prevalence among individuals aged 65 years or older is as high as 494 cases per 100,000 (Raghu). Patients with IPF often carry multiple comorbid conditions (Raghu), which contribute to the substantial physical, psycho-social and economic burden of the disease. Accordingly, IPF represents an important public health problem (Diamantopoulos), and its burden is expected to steadily increase in the future with the population aging worldwide.

Following three decades of clinical research, two drugs (pirfenidone and nintedanib) have proven efficacious in slowing disease progression (as assessed by forced vital capacity (FVC), a measure of lung “size”) in patients with IPF (King; Richeldi); however, neither drug reverses lung fibrosis and up to one-quarter of patients may need to discontinue antifibrotic treatment due to tolerability issues (Galli). Lung transplant is available only to a highly selected minority of patients with IPF, and is associated with a 3-year and 5-year survival of only 66% and 53%, respectively (Valapour). Together, these limited treatment options illustrate the importance of developing and testing more efficacious and better tolerated therapies for IPF. In this

review, we highlight promising novel agents for the treatment of IPF, with emphasis on those drugs in more advanced stages of development.

Disease pathogenesis

Our understanding of the mechanisms underlying IPF remains incomplete. This is due to both the lack of animal models of pulmonary fibrosis that translate perfectly to human disease and the multiplicity and complexity of co-activated fibrogenic pathways contributing to disease development. With these limitations, favored concepts of disease pathogenesis involve a complex interplay of genetic and environmental factors, ageing-associated processes and epigenetic reprogramming (Selman). In this scenario, persistent epithelial injury by various triggers activates several interrelated wound-healing pathways to restore homeostasis. Failure to contain or eliminate the inciting factors (i.e., smoking, microaspiration secondary to gastric reflux, occupational exposures, pollutants and occult viral infection, among others) results in continuous tissue damage and perpetuates the wound-healing response, leading to excessive deposition of extracellular matrix (ECM) component, and progressive scarring of the lung parenchyma and distal airways (Spagnolo). IPF is an age-related disease and is common in syndromes characterized by a cellular ageing phenotype (i.e., telomeropathies) (Armanios). In fact, senescent epithelial cells release a plethora of cytokines, chemokines and growth factors, thus promoting persistent activation and differentiation of fibroblasts to apoptosis-resistant myofibroblasts (Abbadie; Mora). Proliferating fibroblasts and myofibroblasts are organized in clusters termed *fibroblastic foci*, which represent microscopic areas of acute lung injury and are the histopathologic hallmark of UIP, the defining pattern of IPF (Katzenstein). The fibrotic remodeling of IPF lung makes it

unlikely even for efficacious drugs to restore normal lung architecture and function.

Therefore, the primary aim of developmental therapies for IPF is stabilization of lung function and prevention of further loss.

Drugs in development

Drugs targeting fibroblasts

GLPG1690. Lysophosphatidic acid (acyl-hydroxy-glycero-3-phosphates; LPA) is a bioactive phospholipid that mediates multiple cellular processes including survival, proliferation, differentiation and migration by signaling through cognate G protein-coupled receptors (Choi). Levels of LPA are increased in bronchoalveolar lavage (BAL) fluid from mice following intratracheal instillation of bleomycin, and genetic deletion of one of LPA receptors, LPA₁, significantly protects animals from fibrosis and mortality in this model (Tager). In addition, pharmacological inhibition of LPA₁ markedly reduces fibroblast migration following exposure to the BAL fluid of patients with IPF, suggesting that LPA-LPA₁ signaling contributes to fibroblast recruitment and thus to fibrogenesis in IPF (Tager). Levels of autotaxin (ATX), the enzyme catalyzes lysophosphatidylcholine into LPA, *in vivo*, are also upregulated in IPF lungs, and inhibition of autotaxin attenuates experimental lung fibrosis (Oikonomou).

GLPG1690 is a potent and selective ATX inhibitor. In a phase I, first-in-human trial that evaluated safety, tolerability pharmacokinetics (PK), and pharmacodynamics (PD) of GLPG1690 in eight male healthy subjects (including two who received placebo), the drug was generally safe and well tolerated (Van Der Aar). In addition, GLPG1690 displayed good oral bioavailability with a PD response indicating target engagement. In a double-blind, placebo-controlled phase IIa study (FLORA), 23 patients with IPF were randomly assigned 1:3 to either oral GLPG1690 600 mg once daily (n=17) or placebo (n=6) for 12 weeks, with 20 patients

completing the study (Maher). The drug was generally well tolerated with 11 patients (65%) experiencing mostly mild-to-moderate treatment-emergent adverse events (mainly infections and infestations). Notably, plasma levels of LPA C18:2, the most abundant LPA species in humans, were consistently reduced in the GLPG1690 group, indicating a biomarker effect. Moreover, as compared with placebo, the drug demonstrated favorable effects on mean change from baseline in FVC at week 12 (25 mL vs. -70 mL, respectively), although the study was not powered to detect between-group differences with regard to efficacy. Two identically designed, randomized, double-blind, placebo-controlled phase III studies (ISABELA 1 and 2) are currently being conducted in parallel to further evaluate the efficacy of GLPG1690 for the treatment of IPF (ClinicalTrial.gov Identifier: NCT03733444 and NCT03711162). In each study, 750 patients will be randomized in a 1:1:1 ratio to receive oral GLPG1690 600 mg, GLPG1690 200 mg or matching placebo once daily in addition to standard of care (i.e., pirfenidone, nintedanib, or neither). The primary endpoint is the rate of decline of FVC over 52 weeks, with all patients receiving randomized treatment until the last patient reaches 52 weeks of treatment. Key secondary endpoints include disease progression, defined as the composite endpoint of first occurrence of $\geq 10\%$ absolute decline in per cent predicted FVC (%FVC) or all-cause mortality at week 52; time to first respiratory-related hospitalization over the entire treatment; or change from baseline in the St George's Respiratory Questionnaire (SGRQ) total score (a measure of respiratory quality of life) at week 52 (Maher).

FG3019/Pamrevlumab. Connective tissue growth factor (CTGF) is a secreted glycoprotein produced by various cell types, including fibroblasts, myofibroblasts and endothelial cells. Despite its name, CTGF does not behave like a typical growth factor, as it does not bind to a unique receptor with high affinity to induce signal transduction. Instead, by interacting with

various regulatory modulators, such as transforming growth factor (TGF)- β , vascular endothelial growth factor (VEGF), and receptors such as integrins, it acts as a key regulator of several cellular responses such as cell adhesion and migration, angiogenesis and vascular permeability, myofibroblast activation, extracellular matrix deposition and tissue remodeling (Lipson). The biology of CTGF is complex and only partially understood; however, it is well established that CTGF plays a central role in the pathogenesis of diseases in which tissue remodeling and fibrosis occur. CTGF mRNA is overexpressed in the lung of patients with IPF and is localized predominantly to proliferating type II alveolar epithelial cells and activated fibroblasts in the interstitium (Pan). In addition, plasma levels of CTGF are significantly higher in patients with IPF than in patients with non-IPF ILD and healthy controls and correlate negatively with 6-month change in FVC (Kono). Pamrevlumab (FG-3019) is a fully human recombinant monoclonal antibody against CTGF. In a radiation-induced mouse model of pulmonary fibrosis, administration of FG-3019 reversed established lung remodeling and restored lung function (Bickelhaupt). In addition, CTGF blockade downregulated radiation-induced expression of genes associated with extracellular matrix remodeling and attenuated TGF- β induced epithelial-to-mesenchymal transition.

In an open-label, single-arm, phase II study, pamrevlumab administered at two doses (15 mg/kg and 30 mg/kg) by intravenous infusion every 3 weeks over a period of 48 weeks in patients with IPF (n=89) was safe and well tolerated (Raghu). In addition, the drug showed promising results in terms of change in lung function (2.7% decline in FVC from baseline to week 48 for the combined cohorts) and change in extent of pulmonary fibrosis by quantitative high-resolution CT (HRCT), with 16/46 (35%) of patients with a baseline FVC >55% predicted displaying stable or improved reticular fibrosis at week 48. The PRAISE study was a phase II, randomized, double-blind, placebo-controlled trial designed to assess the efficacy, safety

and tolerability of pamrevlumab (30 mg/kg every three weeks for a total of 16 infusions over 48 weeks) in patients with IPF (n=103) (Richeldi). The primary efficacy outcome was the change from baseline in FVC % predicted at week 48. As compared with placebo, pamrevlumab significantly reduced both the decline of FVC (-2.9% vs. -7.2%, respectively; p=0.033) and the proportion of patients experiencing disease progression (defined as a decline in FVC % predicted \geq 10% from baseline, or death; 10.0% vs. 31.4%, respectively; p=0.013) at week 48. Moreover, HRCT scores of quantitative lung fibrosis were significantly lower in the pamrevlumab than in the placebo arm at week 24 (24.8 mL vs. 86.4 mL; p=0.009) with a significant difference maintained through week 48 (75.4 mL vs. 151.5 mL; p=0.038). Pamrevlumab was well tolerated, with a safety profile similar to that of placebo. The efficacy and safety of pamrevlumab is being further evaluated in the phase III trial ZEPHYRUS (ClinicalTrial.gov Identifier: NCT03955146) that is currently recruiting.

PBI-4050. PBI-4050 (3-pentylbenzeneacetic acid sodium salt) is an orally active, low molecular weight compound with agonist activity towards the G-protein coupled receptors GPR40 and antagonist activity towards GPR84. By binding to GPR40 and GPR84, PBI-4050 inhibits the differentiation of fibroblasts to myofibroblasts and reduces the expression of pro-fibrotic markers such as CTGF and IL-6, resulting in reduced deposition of extracellular matrix proteins and fibrosis (Gagnon). PBI-4050 attenuates tissue fibrosis in multiple animal models, including the mouse model of bleomycin-induced pulmonary fibrosis wherein it significantly attenuates parenchymal disruption, alveolar wall thickness and fibrosis (Gagnon). A 12-week, phase 2, single-arm, open-label trial conducted at six sites across Canada evaluated the safety, tolerability and pharmacokinetics (PK) of oral PBI-4050 800 mg/daily alone or in combination with nintedanib/pirfenidone in patients with IPF (n=41)

(Khalil). PBI-4050 was well tolerated both when given alone or in combination with nintedanib/pirfenidone. Indeed, while most patients experienced at least one adverse event (mainly diarrhea, nausea and headache), the majority of events were mild or moderate. Notably, the PK profile of the PBI-4050 + pirfenidone arm, which included 16 patients, showed shorter half-life, reduced absorption and lower maximum plasma concentration compared with the other treatment groups, consistent with a drug-drug interaction between PBI-4050 and pirfenidone (Khalil). The PBI-4050 + pirfenidone group displayed also a statistically significant mean decrease in FVC from baseline to week 12 (-102 ml; p=0.01).

TD139. Galectin-3 (Gal-3) is a β -galactoside-binding lectin expressed by a variety of cells, including alveolar macrophages, epithelial cells and lung fibroblasts, which plays a central role in inflammation and fibrosis (Henderson). In mice, genetic deletion of Gal-3 significantly attenuates bleomycin-induced pulmonary fibrosis by reducing TGF- β 1-induced epithelial-to-mesenchymal transition, myofibroblast activation, and collagen production (Mackinnon). Increased levels of Gal-3 are found in the serum (Mackinnon) and BAL fluid (Nishi) from patients with IPF and are associated with interstitial lung abnormalities and impaired pulmonary function in undiagnosed research participants (Ho), suggesting a potential role for Gal-3 in early stages of pulmonary fibrosis. Accordingly, modulation of the Gal-3 pathway has been proposed as a potential therapeutic target in IPF. The safety, tolerability, PK and PD of TD139, an inhaled, dry powder, anti-Gal3 small molecule, has been evaluated in a randomized, double-blind, placebo-controlled, phase IIa trial in 24 IPF patients (ClinicalTrial.gov Identifier: NCT02257177) (Hirani). Three dose cohorts (0.3 mg, 3 mg and 10 mg) of 8 subjects each were evaluated in a 5:3 ratio (TD139:placebo) for 14 days. This study showed that TD139 is safe and well tolerated, and that TD139 administration led to target

suppression as shown by Gal-3 expression on BAL macrophages. A phase IIb study of TD139 in IPF is currently recruiting participants (ClinicalTrial.gov Identifier: NCT03832946).

αvβ6 inhibitors. Integrins are transmembrane proteins that mediate cell attachment and migration by connecting the actin cytoskeleton to the extracellular matrix. Integrins also participate in more complex cellular events, including; survival, proliferation and regulation of gene expression (Werb). The integrin αvβ6, an epithelial restricted molecule, is a major activator of latent TGF-β, and mice lacking the β6 subunit are protected from bleomycin-induced and radiation-induced pulmonary fibrosis (Munger; Puthawala). In addition, αvβ6 is upregulated in the overlaying epithelial areas of fibrosis in patients with IPF (Xu). A phase IIb study evaluating the safety and tolerability of subcutaneously-administered, multiple escalating dose of STX-100/BG00011, a humanized monoclonal antibody directed against αvβ6, in patients with IPF has been terminated early due to safety concerns (NCT03573505; full results pending). Two studies are currently evaluating the safety and tolerability of the αvβ1, β3 and β6 selective inhibitor IDL-2965 in healthy subjects and individuals with IPF (ClinicalTrial.gov Identifier: NCT03949530), and the αvβ6 receptor occupancy (as assessed by PET) by the αvβ1 and β6 selective inhibitor PLN-74809 in patients with IPF (ClinicalTrial.gov Identifier: NCT04072315) (Table 1).

Drugs targeting alveolar macrophages and their mediators

PRM151. Pentraxin 2 (PTX-2), also known as serum amyloid P, is an endogenous plasma protein synthesized by the liver. PTX-2 is closely related to PTX-1 (C-reactive protein) and PTX-3, which is an acute-phase protein with an important modulatory role in tissue repair and remodeling (Doni). Thanks to its unique binding properties, PTX-2 localizes at sites of injury

where it promotes resolution of inflammation and scarring by inhibiting the differentiation of monocytes into pro-inflammatory and pro-fibrotic macrophages and by promoting their differentiation into a regulatory phenotype (Pilling). PTX-2 accumulation and consumption at sites of fibrosis accounts for the low levels of circulating PTX-2 seen in several fibrotic diseases including IPF (Castaño).

PRM-151 is a fully recombinant form of the human PTX-2 protein, which ameliorates fibrosis in the bleomycin model of pulmonary fibrosis in mice (Murray). In an initial randomized, double-blind placebo-controlled, multiple ascending dose trial of 21 patients with IPF, PRM-151 was safe and well tolerated at all tested doses (1, 5, or 10 mg/kg), with no serious adverse reactions reported. In addition, PRM-151 increased PTX-2 levels by two- to eight-fold in a dose-dependent manner (van den Blink). Subsequently, in a phase II, double-blind trial, 117 patients with IPF were randomized to receive either recombinant human PTX-2 (rhPTX-2) 10 mg/kg i.v. (n=77) or placebo (n=39) every 4 weeks for 24 weeks (Raghu). Notably, 61 patients (79%) in the PTX-2 arm and 30 (77%) in the placebo arm were on concurrent IPF therapy (pirfenidone, n=39 (64%) and n=22 (73%), or nintedanib, n=22 (36%) and n=8 (27%), respectively). The study met its primary outcome of change from baseline to week 28 in mean FVC % predicted, which was -2.5 and -4.8 in the rhPTX-2 and placebo groups, respectively (p=0.001). Even more strikingly, the change in 6-minute walk distance (6MWD) was -0.5 m in the rhPTX-2 arm and -31.8 m in the placebo arm (difference, 31.3 m; p <0.001), although this effect was significant only in the subgroup without concurrent IPF therapy. Cough (18% vs. 5%), fatigue (17% vs. 10%), and nasopharyngitis (16% vs. 23%), the most common adverse events, were slightly more common in rhPTX-2-treated than placebo-treated patients (Raghu). In the open-label extension phase of the study, which was conducted to assess the safety and tolerability of PRM-151 up to 76 weeks, patients previously randomized to PRM-

151 continued this treatment while those randomized to placebo crossed over to PRM-151 (Raghu). Long-term treatment with PRM-151 was well tolerated (compliance rate 99% and discontinuation rate 13.5%) with the reported adverse events being mostly symptoms or complications of IPF. In addition, as compared with the slopes for placebo, PRM-151 treatment was associated with favorable effects in terms of rate of decline in FVC % predicted and 6MWD both in patients on continued therapy and in those who crossed over from placebo. These data support further study of the efficacy of PRM-151 in slowing disease progression and improving functional status in larger populations of patients with IPF.

Immunotherapies

IW001. Type V collagen (Col V) is a regulatory fibril-forming collagen of the extracellular matrix that is found primarily within the fibrils of the major lung collagen type I. Col V interacts with matrix collagens and structural proteins to confer and preserve elasticity and structural integrity to the lung parenchyma (Mak). Despite being a native protein, Col V may act as a “foreign antigen” if exposed following lung injury, leading to an autoimmune response as shown in human and rodent studies of lung transplantation (Sumpter). Levels of Col V are increased in lung biopsies of patients with IPF (Parra), and Col V-induced tolerance abrogates fibrogenesis and down-regulates TGF- β -related signalling pathways in the bleomycin model of pulmonary fibrosis (Vittal). A phase 1, open-label study was designed to assess the safety, tolerability, and biological and clinical effects of three different doses (0.1, 0.5 and 1 mg/day) of IW001, a Col V oral immunotherapy, in anti-Col V Ab⁺ patients with IPF (n=30) (Wilkes). The drug was safe and well tolerated, with 100% of the patients completing the 24-week treatment period. In addition, while patients in the lowest-dose cohort experienced a decline in FVC comparable to that observed in placebo arms of previous IPF trials (Ley), the highest-

dose cohort showed a trend toward stabilization of FVC and decreased binding of C1q (a collagen-like component of the complement system) to anti-Col V antibodies consistent with an IW001-induced effect on anti-Col V antibody binding and activity.

VAY736/ianalumab. Several lines of evidence suggest a potential role for humoral response in the development and progression of IPF. B cell-rich lymphocyte aggregates are a common finding in end-stage IPF lung tissue (Todd), and levels of anti-vimentin autoantibodies inversely correlate with lung function parameters (Li). In addition, detection of B-cell-activating factor (BAFF) is enriched in the lungs and blood of patients with IPF (Francois). Furthermore, rituximab, a B-lymphocyte depleting monoclonal antibody, has been used successfully as a rescue therapy in patients with severe ILD progressing despite conventional treatment, although this retrospective study did not include patients with IPF (Keir).

VAY736/ianalumab is an IgG1 monoclonal antibody targeting BAFF-R that is being developed for the treatment of several immune-mediated conditions, including autoimmune hepatitis, rheumatoid arthritis, Sjögren's syndrome and systemic lupus erythematosus. A currently ongoing phase II trial will evaluate the safety and efficacy of *VAY736/ianalumab* administered subcutaneously every 4 weeks for 48 weeks in patients with IPF (ClinicalTrial.gov Identifier: NCT03287414).

GLPG1205. GPR84 is a G-protein-coupled receptor expressed mainly in immune cells and upregulated under inflammatory conditions (Venkataraman). GPR84 has been associated with the induction of fibrosis in mice (Gagnon), and GPR84 mRNA is expressed IPF lung tissue, mainly in infiltrating immune cells and bronchial epithelial cells but absent in healthy human lung specimens (Sanjere). *GLPG1205* is a potent and highly selective GPR84

antagonist. In a bleomycin-model of pulmonary fibrosis in mice, GLPG1205 given orally for 14 days starting 7 days post-challenge significantly reduced the Ashcroft score and improved lung function compared to untreated diseased animals (Saniere). Similar results were observed in the irradiation model of pulmonary fibrosis. A phase II proof of concept study in patients with IPF is currently ongoing (ClinicalTrial.gov Identifier: NCT03725852).

Drugs targeting broad pathways

KD025/SLx-2119. The Rho-associated coiled-coil kinase (ROCK) isoforms 1 and 2 mediate a number of cellular functions, including adhesion, migration and phagocytosis, by regulating actin cytoskeleton dynamics (Olson). In lung fibrosis, ROCKs are activated by both biochemical (i.e., TGF- β , thrombin and LPA) and mechanical (i.e., increased matrix stiffness) stimuli (Knipe), and pharmacological inhibition of ROCK protects mice from experimentally induced lung fibrosis (Zhou). Both ROCK1 and ROCK2 contribute to the development of experimental pulmonary fibrosis by inducing exaggerated alveolar epithelial cell apoptosis, pulmonary vascular permeability, and fibroblast activation, suggesting that partial inhibition of either ROCK isoforms or both together has the potential to be an effective therapeutic strategy for pulmonary fibrosis (Knipe). An open-label phase II study assessed the safety, tolerability and efficacy of the ROCK2 selective inhibitor KD025/SLx-2119 400 mg once daily vs. standard of care (excluding nintedanib or pirfenidone) in 39 patients with IPF (Averill). The drug was safe and well tolerated and was associated with a numerically lower decline in FVC compared to standard of care without antifibrotic therapy.

ND-L02-s0201/BMS-986263. The 47-kDa heat shock protein (HSP47) is a collagen-specific molecular chaperone that plays a major role in the synthesis and assembly of various

collagens (Masuda). HSP47 is strongly expressed in IPF lung tissue and is localized predominantly in α -smooth muscle actin-positive myofibroblasts and surfactant protein-positive type II pneumocytes (Iwashita). In addition, inhibition of HSP47 significantly improves bleomycin-induced pulmonary fibrosis in rats (Hagiwara). ND-L02-s0201/BMS-986263 is a lipid nanoparticle encapsulating a small interfering RNA (siRNA), which inhibits HSP47 expression. In the bleomycin model, ND-L02-s0201/BMS-986263 treatment significantly reduced lung weight, collagen deposition and histology and fibrosis scores (Zabludoff). A phase II, randomized, double-blind, placebo-controlled study is currently evaluating the safety, tolerability, biological activity, and PK of ND-L02-s0201 in patients with IPF (ClinicalTrial.gov Identifier: NCT03538301).

CC-90001. The stress-induced kinase c-Jun-N-terminal kinase (JNK) is an important modulator of cell death and, in some settings, a major driver of apoptosis (Dhanasekaran). JNK1 is a major regulator of TGF- β -induced epithelial-to-mesenchymal transition (Alcorn), and *JNK1*^{-/-} mice are protected from TGF- β 1- and bleomycin-induced profibrotic gene expression and pulmonary fibrosis (Alcorn). Using the mouse models of bleomycin- or adenovirus expressing active TGF- β 1 (AdTGF β 1)-induced fibrosis, van der Velden and colleagues have recently demonstrated prominent activation of JNK in bronchial epithelia, whereas active JNK was observed in various regions of IPF lung tissue, including type I and type II pneumocytes and fibroblasts (van der Velden). In addition, ablation of *JNK1* from airway epithelia strongly protects from bleomycin- or AdTGF β 1-induced fibrosis and attenuates mesenchymal genes and proteins in lung tissue while preserving expression of epithelial genes (van der Velden). CC-90001 is a JNK1-biased inhibitor. In a phase Ib dose escalation safety study that included 100 healthy adults and 16 patients with pulmonary

fibrosis, three dose of CC-90001 (100 mg, 200 mg and 400 mg, all once daily) were administered for 12 weeks (Bennett). The drug was safe and well tolerated, with nausea, the most common adverse event, being reported by 8-15% of subjects. The safety and efficacy of CC-90001 is currently being evaluated in phase II, 24-week, randomized, double-blind, placebo-controlled study (ClinicalTrial.gov Identifier: NCT03142191).

Conclusion

Two drugs are approved worldwide for the treatment of IPF. However, the increasing incidence and poor prognosis of the disease make the search for more efficacious and better tolerated drugs an urgent need. Following promising early-phase data, several compounds targeting fibrogenic pathways potentially involved in disease pathogenesis are currently being developed. These will hopefully increase our portfolio of treatment options for this dreadful disease in the near future.

Expert opinion

The efficacy of pirfenidone and nintedanib in slowing functional deterioration and disease progression in patients with IPF demonstrates that the mechanisms driving progressive pulmonary fibrosis - at least some of them - are targetable and treatable. However, this is only *the end of the beginning* as a number of outstanding challenges in drug development in IPF remain, some of which are listed below.

Identification of individuals at risk. Owing to the relentlessly progressive nature of IPF, the identification of individuals at risk or with subclinical disease is of utmost importance.

Intuitively, the earlier patients with IPF receive treatment, the more lung function remains to be preserved. Despite this rationale, IPF patients with less severe FVC impairment are less likely to receive antifibrotic treatment, potentially due to reimbursement restrictions (Moor). A subgroup analysis of pooled data from the INPULSIS trials has shown that patients with IPF and FVC >90% predicted experience the same rate of FVC decline and receive the same benefit from nintedanib as patients with more impaired lung function, which argues against the “watch and wait” approach in IPF patients with *mild* disease (Kolb).

Route of administration. Only a few clinical trials have investigated inhaled therapies in IPF. This is mainly due to concerns that fibrotic distortion of the airways may prevent drug deposition to the peripheral, subpleural regions of the lung - the optimal target of therapy in IPF. Maher and colleagues have recently demonstrated selective lung uptake of a target specific positron emission tomography (PET) ligand following a nebulized 1000 mcg dose of GSK3008348, a novel $\alpha\beta6$ integrin inhibitor, in 8 patients with IPF (ClinicalTrial.gov Identifier: NCT03069989) (Maher). The galectin-3 inhibitor TD139 is another inhaled antifibrotic that is currently being investigated in a phase IIb trial (ClinicalTrial.gov Identifier: NCT03832946; Table 1). Another concern is that systemically administered drugs may not be suitable for inhaled delivery due to their physico-chemical properties or the necessary dose. A recent trial evaluated the PK and safety/tolerability profile of inhaled pirfenidone in healthy volunteers (n=30), healthy smokers (n=8) and patients with IPF (n=6) (Khoo). Inhaled pirfenidone was safe and well tolerated with mild, transient cough representing the most common drug-related adverse event. Moreover, PK data indicate that aerosolized pirfenidone 100 mg resulted in higher lung concentration and lower systemic exposure than those reported with

oral pirfenidone at the dose approved in IPF (i.e., 2401 mg/daily). Inhaled drug delivery in IPF is feasible and deserves further investigation.

How to judge efficacy. With the approval worldwide of pirfenidone and nintedanib, future clinical trials in IPF will include patients on background antifibrotic treatment in their standard-of-care arms, rather than requiring patients to only be receiving a true placebo. This new standard-of-care will result in a slower rate of lung function decline in both the treatment and placebo arms, limiting the ability to detect a further benefit from a new potential therapy. While FVC remains the most practical to measure efficacy endpoint and a surrogate for mortality in trials testing antifibrotic compounds (Ley), composite endpoints for worsening disease and symptom burden (i.e., patient reported outcomes) should be further explored as clinically meaningful outcomes in IPF clinical trials, whether defined as “acute exacerbation” or “respiratory hospitalization.

Combination therapy. Due to the multitude of profibrotic pathways involved in disease pathogenesis (Wolters), IPF represents an ideal target for combination therapy. So far, three studies have explored the feasibility of combined treatment with nintedanib and pirfenidone in individuals with IPF (Ogura; Vancheri; Flaherty). These studies have shown that combination therapy (either nintedanib with add-on pirfenidone or vice versa) has a manageable safety profile in patients with IPF with no unanticipated adverse events. However, overall, about one-fourth of patients did not tolerate combination therapy, thus questioning its long-term tolerability. In addition, whether combination therapy adds benefit over single-agent therapy is unknown, as in these studies, the assessment of efficacy was

only exploratory. There is a strong rationale for combination therapy in IPF, but this approach needs to be explored further.

How to speed up drug development. A multitude of compounds with promising preclinical profiles are currently being developed for IPF. However, positive effects in preclinical and early-phase studies translate poorly to efficacy in late stage clinical trials. In addition, early-phase studies in IPF have generally been too long, too large, and too dependent on clinical efficacy endpoints, which in this setting are only exploratory. Early-phase proof of concept studies should be faster, smaller, and with biological and mechanistic endpoints ([Collard](#)). This approach, which requires the use of human tissue-based investigations, has already proven successful in IPF ([Maher](#)) and has the potential to bridge the gap between early PK and PD data and the mechanism of action and biological activity of the compound under investigation.

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