A new era in the treatment of progressive fibrosing interstitial lung diseases

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Idiopathic pulmonary fibrosis and progressive pulmonary fibrosis are characterised by progressive fibrosis and share common pathophysiological pathways that have led to the study of promising new therapeutic targets. https://bit.ly/3RdJRqA

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Abstract

Idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF) are characterised by an irreversible progression of pulmonary fibrosis and functional lung decline. Current antifibrotic therapies (nintedanib and pirfenidone for IPF and nintedanib for PPF) can reduce disease progression but not halt or reverse it. PPF and IPF share common pathophysiological pathways that need to be further elucidated for the development of novel therapeutic strategies. The educational aim of this review is to explain the pathogenic pathways that have led to the discovery of new therapeutic agents and their favourable implementation in phase 2 and 3 studies. This includes phosphodiesterase 4 inhibitors, αvβ6 and αvβ1 integrin inhibitors, lymphosphatidic acid antagonists, inhaled treprostinil, hedgehog inhibitors, tyrosine kinase inhibitors and angiotensin type 2 receptor agonists. The aim is also to better understand current therapeutic challenges and future perspectives, including cellular therapies, exosomes and their cargoes, as well as the integration of transcriptomics and proteomics, plus gene therapy.

Introduction

Idiopathic pulmonary fibrosis (IPF) is the hallmark of pulmonary fibrosis with a progressive evolution. Similarly, progressive pulmonary fibrosis (PPF) represents a subtype of patients suffering from interstitial lung diseases (ILDs) of various origins but sharing a common feature with IPF – pulmonary fibrosis progression. It is subsequently assumed that some pathological pathways of fibrosis development are shared between IPF and PPF, leading to common therapeutic targets.

IPF is a chronic, lethal, ILD of unknown origin with radiological and histological features of usual interstitial pneumonia (UIP) characterised by progressive worsening of lung function even under anti-fibrotic therapies [1]. It displays low prevalence, estimated globally at about four cases per 10 000 persons, and poor prognosis, with a median survival of five to seven years from diagnosis, following implementation of current antifibrotics [2, 3]. PPF was defined by the official American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Asociación Latinoamericana de Tórax Clinical Practice Guideline 2022 as a subtype of patients with ILD having radiological evidence of pulmonary fibrosis other than IPF and at least two of the following occurring within the last year: worsening of respiratory symptoms (without alternative explanation), physiological or radiological evidence of disease progression [1].

Current guidelines on PPF and IPF are based on the use of two antifibrotics (pirfenidone and nintedanib in IPF, and nintedanib with a conditional recommendation in PPF) [1, 4]. Although these drugs represent a significant advance in the treatment of pulmonary fibrosis by slowing down the progression of the disease, they are not curative, thus leaving patients with major functional disability. Given the important medical and socioeconomic burden associated with IPF and PPF, a thorough understanding of the pathophysiological pathways underlying fibrosis is necessary for the development of new therapies.

Nintedanib and pirfenidone

The use of nintedanib and pirfenidone have both been approved in IPF by the US Food and Drug Administration (FDA) and European Medicines Agency in 2014 following positive results in phase 3 randomised-controlled trials (RCTs). Nintedanib is an intracellular inhibitor of tyrosine kinase targeting among others vascular endothelial growth factor, fibroblast growth factor and platelet-derived growth factor [5]. It displays antifibrotic effects by interfering with fibroblast proliferation, differentiation and migration and extracellular matrix (ECM) secretion, but also anti-vascular remodelling effects. Pirfenidone displays antifibrotic and anti-inflammatory effects through transforming growth factor β (TGF-β) and tumour necrosis factor inhibition.

Nintedanib was studied in IPF in INPULSIS-1 and INPULSIS-2, showing attenuation of forced vital capacity (FVC) decline which was confirmed subsequently in a meta-analysis, while pirfenidone was evaluated in CAPACITY I, CAPACITY II and ASCEND demonstrating reduced FVC decline and improvement in progression-free-survival [6–9]. A meta-analysis demonstrated a consistent reduction of acute exacerbation risk for nintedanib but not for pirfenidone while all-cause mortality was reduced for both antifibrotics [10]. Moreover, a phase 4 clinical trial in France evaluates the feasibility, safety and efficacy of the combination pirfenidone and nintedanib *versus* a "switch monotherapy" in patients presenting chronic worsening IPF despite receiving either pirfenidone or nintedanib (https://clinicaltrials.gov/ identifier: NCT03939520).

Concerning patients with non-IPF progressive fibrosis, the INBUILD trial reported a slower decline in FVC over one year compared to placebo in patients with progressive fibrosis under nintedanib, while effectiveness, albeit less marked, was also shown in the SENSCIS trial on patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) [11, 12]. An INBUILD subgroup analysis revealed that nintedanib decreases the rate of FVC decline and has a beneficial effect on disease progression, irrespective of the underlying ILD subtypes and radiological patterns [13]. Its use in PPF patients has therefore also been approved by the FDA and European Medicines Agency. Its efficacy in PPF was subsequently confirmed in real-world multicentre observational study [14]. Furthermore, two prospective observational studies are currently aiming to investigate the potential benefit in quality of life in patients with PPF under nintedanib treatment by assessing the correlation between changes from baseline to 52 weeks in FVC percentage of predicted value and changes in dyspnoea scale and cough score tests, respectively (NCT04702893, NCT05151640).

On the other hand, the available data regarding the use of pirfenidone in PPF are limited, but they provide a positive therapeutic signal towards disease progression and lung function, as indicated by FVC, diffusing capacity of the lungs for carbon monoxide (D_{LCO}) and 6-min walk test changes, particularly in patients with a radiological UIP pattern [15]. For instance, the RELIEF trial, comparing pirfenidone to placebo in PPF, was terminated early because of futility triggered by slow recruitment, but imputation for missing data concluded towards a lower FVC decline in the treatment group [16]. In addition, a phase 2 clinical trial evaluating pirfenidone in unclassifiable ILD demonstrated a slower decline in FVC compared to placebo, further supporting its potential role in fibrosing ILDs [17]. Considering the frequency of adverse effects of oral pirfenidone, inhaled pirfenidone was studied in IPF patients and showed a more favourable safety profile [18]. A randomised, double-blind, placebo-controlled clinical study (NCT06329401) is therefore currently being conducted in order to assess the efficacy of two doses of inhaled pirfenidone *versus* placebo in addition to standard of care in patients with PPF over 52 weeks. Furthermore, two structural analogues of pirfenidone, SC101 (sufenidone) and HEC585 (yfenidone) are under investigation in phase 2/3 trials (NCT06125327) in IPF and phase 2 RCTs (NCT05060822) in IPF and PPF (NCT05139719).

Despite enthusiasm arising from the above therapeutic data, there remains a necessity for the development and implementation of more effective and tolerable therapeutic agents, targeting fibrotic mechanisms in both IPF and PPF. In the past few years a breakthrough in our understanding on the underlying disease mechanisms has unravelled novel therapeutic pathways, herein discussed.

Pathophysiological mechanisms leading to new therapeutic targets with recent or ongoing phase 2b/3/4 clinical trials in IPF and PPF

Pulmonary fibrosis results from alveolar epithelial damage due to age, cigarette exposure, occupational exposure, viral and microbial particles, oesophageal reflux and oxidative stress, which represent recurrent inflammation for epithelial cells [19, 20]. In addition, genetic factors have been described, such as mutations in the MUC5B and SFPTC genes, as well as genes responsible for telomere length maintenance [21]. In non-IPF ILDs, the presence of UIP pattern, lower body mass index and desaturation on the 6-min

walk test are known risk factors for fibrotic progression, irrespective of the aetiology of the underlying interstitial pathology [22].

Following alveolar epithelium damage, normal lung tissue is replaced by disorganised ECM within lung interstitium through aberrant collagen production by fibroblasts and myofibroblasts. Upon injury and stress, alveolar epithelial cells, macrophages and endothelial cells secrete numerous profibrotic signalling molecules including TGF-β [23]. TGF-β promotes fibroblast recruitment, proliferation and survival, epithelial-to-mesenchymal transition, fibroblast-to-myofibroblast conversion and secretion of other profibrotic signals, leading to excess of collagen production and deposition [24].

TGF-β is secreted in its latent form and activated through binding to $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins which are heterodimeric transmembrane receptors, expressed by lung epithelial cells, fibroblasts and myofibroblasts, capable of transducing mechanical force between cells and ECM [25, 26]. Blocking $\alpha_v\beta_6$ and $\alpha_v\beta_1$ therefore represents an interesting therapeutic target. Bexotegrast (PLN-74809) is an oral $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrin inhibitor preventing TGF-β activation [25, 26]. Its effect was validated on an *in vivo* mouse model by showing dose-dependent reduction of pulmonary collagen deposition and more potent collagen gene inhibition than clinically relevant pirfenidone and nintedanib doses [26]. Based on the above, bexotegrast was investigated in a phase 2a multicentre trial (INTEGRIS-IPF) including 119 IPF patients randomised to receive bexotegrast at different doses or placebo and displayed encouraging results, recently published [25]. The primary endpoint was the emergence of treatment-emergent adverse events (TEAEs). Bexotegrast, compared to placebo, was well tolerated, with the incidence of TEAEs being similar between the bexotegrast (69.7%) and placebo groups (67.7%). Diarrhoea was the most common TEAE, but most participants with diarrhoea also received nintedanib. Furthermore, exploratory efficacy endpoints showed FVC decline reduction, quantitative lung fibrosis extent reduction, and changes from baseline in fibrosis-related biomarkers. BEACON-IPF (NCT06097260), a phase 2b/3 randomised, double-blind, dose-ranging, placebo-controlled study, is currently recruiting patients to evaluate the efficacy and safety of bexotegrast in IPF.

Phosphodiesterase 4 (PDE4) inhibition, already approved for inflammatory diseases such as chronic obstructive pulmonary disease and psoriasis, also holds promising results for its antifibrotic effects. It prevents the degradation of cyclic adenosine monophosphate (cAMP), enhancing the action of antifibrotic mediators that signal through G-protein-coupled receptors, such as prostaglandin E2 (PGE2), prostacyclin and adenosine. PGE2 has several antifibrotic actions, including blocking fibroblast activation, making fibroblasts more prone to apoptosis, and preserving the integrity of alveolar epithelial cells [27, 28].

Preclinical data have shown the anti-inflammatory and antifibrotic potential of nerandomilast (BI 1015550), a specific PDE4B inhibitor, in both *in vitro* and *in vivo* models of lung fibrosis and its synergy with nintedanib regarding fibroblast proliferation [29, 30]. It was investigated in a phase 2 trial including 147 IPF patients treated with or without another antifibrotic agent, showing superiority compared to placebo in preventing FVC decrease on 12 weeks [31]. The most frequent adverse event was diarrhoea but the percentages of patients with serious adverse events were similar in the two trial groups and only 13 patients discontinued treatment due to them.

Consecutively, two phase 3 double-blinded RCTs investigating nerandomilast, FIBRONEER-IPF (NCT05321069), including IPF patients, and FIBRONEER-ILD (NCT05321082), including PPF patients, were conducted. The primary endpoint was met for FIBRONEER-IPF with encouraging results related to changes in FVC from baseline at week 52 anticipated to be published [32, 33]. Based on this, a new drug application for nerandomilast for the treatment of IPF will be submitted to the US FDA and other health authorities worldwide. An open-label extension trial of the long-term safety and efficacy of nerandomilast in IPF and PPF is currently recruiting patients who completed those trials (FIBRONEER-ON, NCT06238622).

A different pathway studied in pulmonary fibrosis involves lysophosphatidic acid (LPA). LPA is a phospholipid activating a family of six G protein-coupled receptors, $LPA_{1\text{-}6}$ [34]. It is produced by hydrolysis of lysophosphatidylcholine by the enzymatic action of autotaxin [35]. LPA1 signalling specifically contributes to lung fibrosis *via* promoting apoptosis of epithelial cells, increasing vascular permeability resulting in increased intra-alveolar coagulation, recruiting fibroblasts *via* chemotaxis to the injured sites and increasing fibroblast resistance to apoptosis [36]. In mice models with bleomycin-induced fibrosis, bronchoalveolar lung fluid showed increased levels of LPA, while LPA1 receptor knockout protected them from fibrosis by reducing fibroblast recruitment and vascular leak [37]. In patients with IPF, LPA levels were also upregulated in bronchoalveolar lung fluid and in exhaled breath condensates [37, 38]. LPA1 antagonism may therefore represent a valuable therapeutic target for IPF and PPF. Unfortunately,

ziritaxestat (GLPG-1960), an autotaxin inhibitor, recently showed no beneficial effect in FVC change compared to placebo in the phase 3 trials ISABELA 1 and 2, which included IPF patients, and the trials were stopped early because all-cause mortality was higher in the ziritaxestat group [39]. On the other hand, a phase 2 double-blind RCT (NCT04308681) evaluating admilparant (BMS-986278), a LPA1 antagonist, in IPF and PPF patients demonstrated efficacy irrespective of background antifibrotic therapy by showing lower FVC changes over 26 weeks compared to placebo. An acceptable safety and tolerability profile have been also demonstrated [40]. Decrease in transient post-dose blood pressure on the first day of administration was more important in treatment groups. Currently, the efficacy of BMS-986278 is under further evaluation in IPF and PPF in several phase 3 RCTs (NCT06003426 for IPF and NCT06025578 for PPF). Other autotaxin inhibitors are being developed, including BBT-877 and BLD040 undergoing phase 2 trials in IPF (NCT05483907 and NCT05373914 respectively).

Another drug being investigated in phase 3 trials, TETON I and II for IPF (NCT04708782 and NCT05255991) and TETON-PPF for PPF patients (NCT05943535) is inhaled treprostinil, a prostacyclin receptor agonist that exhibits high affinity for PGE2, prostaglandin D1 (PGD1) receptors and peroxisome proliferator-activated receptor β (PPARβ). The primary endpoint is absolute FVC change at 52 weeks. TETON-OLE (NCT04905693) is an open-label extension for IPF patients evaluating long-term safety and tolerability. Interestingly, activation of the PGE2 and PGD1 inhibits fibroblast proliferation and differentiation into myofibroblasts, as well as collagen and ECM production through a G protein-coupled pathway resulting in the elevation of protein kinase A levels [41]. Several studies have shown that treprostinil exerts its antifibrotic effects *via* suppression of fibroblast proliferation and PPARβ activation [42]. Furthermore, treprostinil attenuates bleomycin-induced lung injury and vascular muscularisation preserving lung architecture and function [43]. A large RCT (INCREASE) investigated treprostinil efficacy in 326 patients with PH-ILD [44]. Patients were assigned in a 1:1 ratio to receive inhaled treprostinil, administered by an ultrasonic, pulsed-delivery nebuliser in up to 12 breaths (total, 72 μg) four times daily, or placebo and were followed for 16 weeks. A statistically significant improvement in peak 6-min walk test, reduction in clinical worsening and N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels has been shown, leading to drug FDA approval in 2021. Post-hoc analysis of FVC difference in IPF subgroup showed a 168.5 mL improvement in the drug arm compared to the placebo (standard error 64.5, 95% CI 40.1 to 297.0; p=0.011) at week 16 [45].

New data in lung fibrosis show interest towards the hedgehog cell signalling pathway which is active during embryonic formation controlling cell specification and proliferation, survival factors and tissue patterning formation [46]. Later in life, it is responsible for normal tissue repair by taking part in mesenchymal and epithelial quiescence and proliferation. Hedgehog cell signalling pathway is over-activated in some diseases displaying tissue injuries, like pulmonary fibrosis where it shows aberrant, high and chronic expression in epithelial cells [47]. It regulates growth factors and paracrine signals secretion leading to ECM overproduction by myofibroblasts, crosstalk between fibroblasts and epithelial–mesenchymal transition, M2 macrophage polarisation and myofibroblast resistance to apoptosis leading to an uncontrolled collagen deposition.

Taladegib (ENV-101) is a selective oral inhibitor of Smoothened, a crucial transmembrane protein in the hedgehog signalling pathway [46]. ENV-101 was evaluated in a phase 2a, 12-week RCT including 41 IPF patients [47]. Participants were randomised in a 1:1 ratio to receive 200 mg of taladegib or placebo once daily. Most common TEAEs were dysgeusia (57%), alopecia (52%) and muscle spasm (43%). While the study initially reported an acceptable safety profile, taladegib was poorly tolerated, with a notable incidence of strong muscle spasms and alopecia. Despite demonstrating statistically significant FVC improvement and quantitative lung fibrosis reduction, concerns regarding its tolerability remain. The WHISTLE-PF trial (NCT06422884) is a phase 2b, 6-month, randomised, double-blind, controlled, dose-ranging study of taladegib (ENV-101) that is not yet recruiting. It involves two parallel cohorts targeting patients with IPF and PPF.

Moreover, anlotinib, already approved for the treatment of advanced non-small-cell lung cancer, represents a novel, multitarget small molecule tyrosine kinase inhibitor, with similar targets to nintedanib, such as vascular endothelial growth factor, fibroblast growth factor and platelet-derived growth factor receptors [48]. A recent study has shown that anlotinib could remarkably attenuate bleomycin-induced pulmonary fibrosis in mouse lungs through suppression of TGF-β1 signalling pathway, inhibition of epithelial–mesenchymal transition in alveolar epithelial cells and promotion of fibroblast apoptosis [49]. The administration of anlotinib capsules for the treatment of patients with IPF/PPF is therefore investigated through a phase 3, multicentre, randomised, double-blind, placebo-controlled clinical trial with FVC as a primary endpoint (NCT05828953). Notably, this study is currently being conducted in China, highlighting the ongoing efforts to evaluate the potential of anlotinib in fibrotic lung diseases.

Finally, angiotensin type 2 receptor (AT2R) agonism has recently gained increased interest as therapeutic target for the treatment of lung fibrosis. Compelling evidence supports the profibrotic role of enhanced production of angiotensinogen by apoptotic alveolar epithelial cells, myofibroblasts and macrophages leading to angiotensin II binding to angiotensin type 1 receptor (AT1R) and AT2R in experimental models of lung fibrosis [50]. AT1R expression is pro-fibrotic and pro-inflammatory while AT2R is anti-fibrotic and anti-inflammatory. Both are upregulated in fibrosis but AT1R is predominant. Buloxibutid (C21) is an oral, selective AT2 receptor agonist with potential anti-fibrotic properties. It recently underwent a phase 2, multicentre, open-label, 36 weeks, single-armed trial, called AIR, proving safety and tolerance of the drug [51]. The study enrolled 52 patients with confirmed IPF who received oral buloxibutid at 100 mg twice daily for 24 weeks, with an optional extension to 36 weeks. Buloxibutid was well tolerated with no serious adverse events reported. 10 participants experienced reversible, mild to moderate hair loss. ASPIRE (NCT06588686), a global 52-week phase 2b evaluating the safety and efficacy of buloxibutid as a treatment of IPF is currently recruiting patients and results of this study are greatly anticipated.

A summary of current therapeutic targets and relevant clinical trials including IPF and PPF patients is shown in table 1. Given the large number of ongoing studies in IPF, only phase 3 and 4 studies have been listed. Figure 1 represents specific molecular pathways involved in the pathogenesis of fibrosis and therapeutic targets. Moreover, ongoing research continues to expand the list of potential treatments. Among them, the Src pathway, the Rho kinase pathway, yes–associated protein and transcriptional coactivator with PDZ–binding motif, the NOX2 pathway, TGF-β receptors, and transient receptor potential cation A1 channels have emerged as promising areas of investigation, further underscoring the complexity of fibrotic lung disease and the need for innovative treatment strategies.

Other therapeutic targets in non-IPF inflammatory ILDs

As mentioned above, PPF is characterised by a progressive course of fibrosis similar to IPF, leading to shared treatment strategies described previously. The paragraph below provides a non-exhaustive list of therapies under investigation for four inflammatory ILDs which may (but do not always) present a progressive course: systemic sclerosis, rheumatoid arthritis, idiopathic inflammatory myopathies and sarcoidosis. The most promising therapeutic targets for those inflammatory ILDs are presented in table 2.

Systemic sclerosis

According to 2023 American College of Rheumatology/American College of Chest Physician guidelines about ILD treatment in case of auto-immune systemic rheumatoid diseases, mycophenolate mofetil (MMF) is the preferred initiation therapy in SSc-ILD but other options include tocilizumab, rituximab, cyclophosphamide and nintedanib (conditional recommendations). In case of disease progression on first ILD therapy, nintedanib has a conditional recommendation depending on pace of progression, amount of fibrotic disease or presence of UIP on high-resolution computed tomography. Other options in case of progression include MMF, rituximab, tocilizumab and cyclophosphamide, and some patients could be evaluated for lung transplant or autologous haemopoietic stem-cell transplantation [52].

LOTUSS, an open-label 16-week study evaluating the benefit safety of pirfenidone in SSc-ILD showed an acceptable tolerability profile [53]. A scleroderma lung study III trial aiming to compare MMF plus placebo *versus* MMF plus pirfenidone assessing changes in FVC % pred did not show any improvement in the pirfenidone arm at 18 months but was believed to be underpowered [54].

Emerging evidence supports the cardinal role of the abnormal B-cell function in SSc-ILD pathogenesis. The effectiveness of belimumab, a monoclonal antibody that targets and blocks B-lymphocyte stimulator, which is essential for the survival of B cells, is being tested in a phase 3 clinical trial (NCT05878717, BLISSc-ILD). This treatment aims to reduce the activity of B cells, which play a key role in autoimmune diseases [55].

Efzofitimod targets neuropilin-2 (NRP2), a membrane protein mainly expressed in areas of inflammation, particularly on myeloid cells, which are involved in diseases like sarcoidosis and SSc-ILD. Previous studies have shown that NRP2 levels are elevated in skin macrophages of SSc patients resulting in excessive inflammatory signals and abnormal reaction to stimuli compared to healthy individuals. Efzofitimod has been found to reduce these inflammatory responses by decreasing cytokine production and inhibiting the activity of receptors like CD14, which is coined to SSc progression [56]. Because of these similarities in inflammation patterns between sarcoidosis and SSc-ILD, and its proven anti-inflammatory and anti-fibrotic effects in animal studies and sarcoidosis patients, efzofitimod is a promising treatment for SSc-ILD (NCT05892614). Tulisokibart (MK-7240/PRA023), a tumour necrosis factor-like cytokine 1A monoclonal antibody, is investigated in the ATHENA-SSc-ILD (NCT05270668) clinical trial, as it enhances the production of anti-inflammatory cytokines.

TABLE 1 Main recent randomised controlled trials (RCTs) with encouraging results and ongoing phase 2/3/4 RTCs in idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF)

Treatment	Molecule	Disease	Trial name/ clinicaltrials.gov identifier	Status	Phase/Type	Duration/ Number of patients	Primary endpoints	Adverse events
Antifibrotic	Combination: nintedanib plus pirfenidone	IPF	PROGRESSION NCT03939520	Recruiting	4 Open label Randomised	24 weeks 378 patients	Slope of the decline in FVC	
	Inhaled pirfenidone	PPF	NS NCT06329401	Recruiting	2b Double-blind, placebo-controlled, randomised	52 weeks 300 patients	Change from baseline in FVC	
	HEC585	PPF	NS NCT05139719	Recruiting	2b Double-blind, placebo-controlled, randomised	24 weeks 110 patients	Change from baseline in FVC	
Pirfenidone analogue	Sufenidone	IPF	NS NCT06125327	Recruiting	2–3 Double-blind, placebo-controlled, randomised	52 weeks 210 patients	Annual rate of decline in FVC	
Integrin inhibitor	Bexotegrast	IPF	INTEGRIS-IPF NCT04396756	Published 2024	2a Double-blind, placebo-controlled, randomised	12 weeks 119 patients	Incidence of treatment-emergent adverse events	Diarrhoea
PDE4 inhibitor	Nerandomilast	IPF	NS NCT04419506	Published 2022	2 Double-blind, placebo-controlled, randomised	12 weeks 147 patients	Change in absolute FVC	Diarrhoea
		IPF	FIBRONEER-IPF NCT05321069	Completed	3 Double-blind, placebo-controlled, randomised	52 weeks 1177 patients	Absolute change in FVC	
		PPF	FIBRONEER-ILD NCT05321082	Active, not recruiting	3 Double-blind, placebo-controlled, randomised	52 weeks 1178 patients	Absolute change from baseline in FVC	
		IPF/PPF	FIBRONEER-ON NCT06238622	Recruiting	3 Open-label extension	Up to 99 weeks and 3 days 1700 patients	Occurrence of any adverse event over the course of the extension trial	

Continued

TABLE 1 Continued

Treatment	Molecule	Disease	Trial name/ clinicaltrials.gov identifier	Status	Phase/Type	Duration/ Number of patients	Primary endpoints	Adverse events
LPA1 antagonist	BMS-986020	PPF	NS NCT01766817	Published 2018	2 Double-blind, placebo-controlled, randomised	26 weeks 143 patients	Change in absolute FVC	Cholecystitis, dose-dependent hepatic enzymes elevation
	Admilparant	PPF	NS NCT04308681	Published 2024	2 Double-blind, placebo-controlled, randomised	26 weeks 278 patients	Change in % pred FVC	Day 1 post-dose blood pressure reduction
		PPF	NS NCT06003426	Recruiting	3 Double-blind, placebo-controlled, randomised	52 weeks 1185 patients	Spontaneous syncopal events at 4 weeks Absolute change from baseline in FVC	
		PPF	ALOFT NCT06025578	Recruiting	3 Double-blind, placebo-controlled, randomised	52 weeks 1092 patients	Spontaneous syncopal events at 4 weeks Absolute change from baseline in FVC	
Prostacyclin vasodilator	Inhaled treprostinil	IPF	INCREASE NCT02630316 Waxman *et al.* [44]	Published 2021	3 Double-blind, placebo-controlled, randomised	16 weeks 326 patients (with ILD +PH)	Change in 6MWD	Cough, headache, dyspnoea, dizziness, nausea, fatigue, diarrhoea
		IPF	TETON I NCT04708782	Recruiting	3 Double-blind, placebo-controlled, randomised	52 weeks 576 patients	Absolute change from baseline in FVC	
		IPF	TETON II NCT05255991	Active, not recruiting	3 Double-blind, placebo-controlled, randomised	52 weeks 597 patients	Absolute change from baseline in FVC	
		IPF	TETON-OLE NCT04905693	Enrolling by invitation	3 Open-label extension	Up to 6 years 792 patients	Long-term safety and tolerability	
		PPF	TETON-PPF NCT05943535	Recruiting	3 Double-blind, placebo-controlled, randomised	52 weeks 698 patients	Absolute change from baseline in FVC	
Hedgehog inhibition	Taladegib	IPF	NS NCT04968574	Published 2024	2 Double-blind, placebo-controlled, randomised	12 weeks 41 patients	Safety and tolerability	Dysgeusia, alopecia, muscle cramps
		IPF/PPF	WHISTLE-PF NCT06422884	Not yet recruiting	2 Double-blind, placebo-controlled, randomised	24 weeks 320 patients	Safety	

Continued

TABLE 1 Continued

Treatment	Molecule	Disease	Trial name/ clinicaltrials.gov identifier	Status	Phase/Type	Duration/ Number of patients	Primary endpoints	Adverse events
Tyrosine kinase inhibitor	Anlotinib	IPF/PPF	NS NCT05828953	Recruiting	2–3 Double-blind, placebo-controlled, randomised	52 weeks 30 patients	Absolute change from baseline in FVC	
Angiotensin 2 receptor agonist	Buloxibutid	IPF	AIR NCT04533022	Completed 2024	2 Open-label Single-arm	36 weeks 52 patients	Change in absolute FVC	Hair loss

Given the large number of ongoing studies in IPF, only phase 3 and 4 studies have been listed, while phase 2 studies have been listed for PPF. FVC: forced vital capacity; LPA1: lysophosphatidic acid receptor 1; NS: not specified; PDE4: phosphodiesterase 4; ILD: interstitial lung disease; PH: pulmonary hypertension; % pred: percentage of predicted value; 6MWD: 6-min walk distance.

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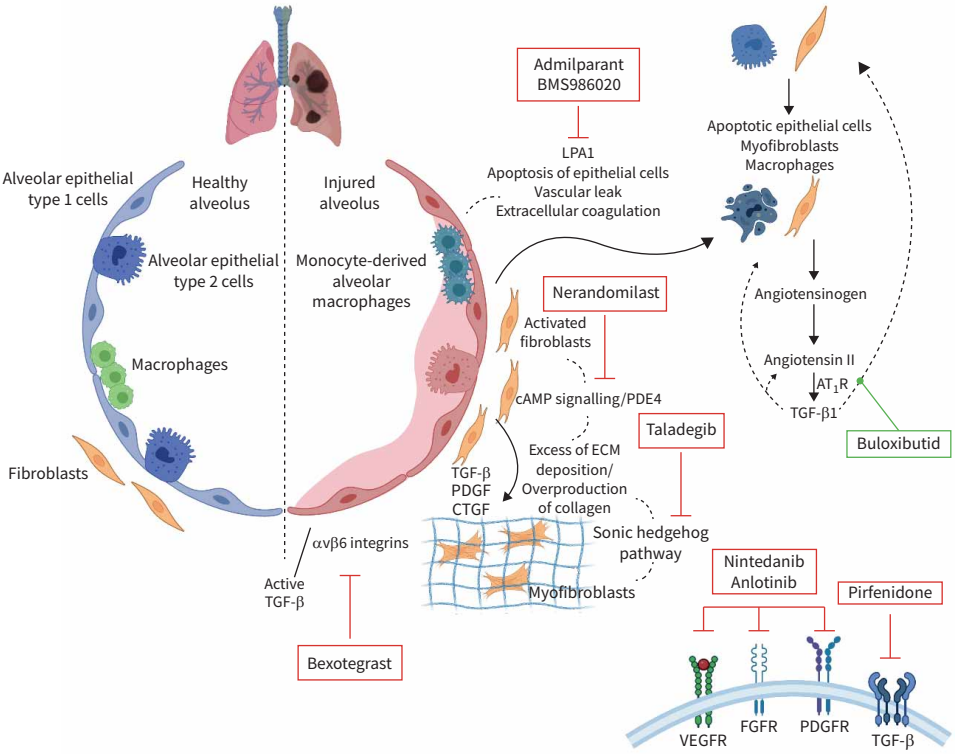

FIGURE 1 Specific molecular pathways involved in the pathogenesis of fibrosis and novel therapeutic targets. AT_1R: angiotensin type 1 receptor; cAMP: cyclic adenosine monophosphate; CTGF: connective tissue growth factor; ECM: extracellular matrix; FGFR: fibroblast growth factor receptor; LPA1: lymphosphatidic acid 1; PDE4: phosphodiesterase 4; PDGF: platelet-derived growth factor; PDGFR: platelet-derived growth factor receptor; TGF-β: transforming growth factor β; VEGFR: vascular endothelial growth factor receptor. Figure created with BioRender.com.

Rheumatoid arthritis

A substantial proportion of rheumatoid arthritis (RA) patients manifest ILD features. Different risk factors have been identified, including MUC5B promoter region mutation, older age at RA onset, masculine sex and rheumatoid disease activity [57–59].

The management of rheumatoid arthritis-associated ILD (RA-ILD) remains a matter of debate, as there are no RCTs comparing treatments. Concerning antifibrotics, nintedanib has demonstrated its ability to reduce disease progression in connective tissue disease-associated ILDs including RA-ILD, while TRIAL 1, aiming to assess safety and efficacy of pirfenidone in RA-ILD, was terminated early and results should be interpreted with caution [60].

Similarly, PULMORA study (NCT04311567) comparing the effectiveness of tofacitinib *versus* methotrexate was prematurely stopped due to low recruitment during pandemic and high screening failure rates. Results are still awaited concerning a phase 2 open-label study investigating the safety of abatacept among patients with RA-ILD (NCT03084419, APRIL).

Idiopathic inflammatory myopathies

ILD characteristics may appear in up to 80% of idiopathic inflammatory myopathies, often preceding muscular signs. Occasionally, idiopathic inflammatory myopathies-associated ILDs (IIM-ILDs) are linked to rapid progression and respiratory failure presenting high mortality rates, particularly among patients with positive MDA5 autoantibody [61]. Given the rapid onset of action and easy accessibility, corticosteroids are the cornerstone of treatment of IIM-ILDs, followed by steroid-sparing agents to minimise the adverse effects of long-term steroid therapy. Rituximab and cyclophosphamide are used as second-line treatment for refractory disease, while maintenance therapy over time seems to be indispensable [62]. To date, no prospective studies have directly compared the effectiveness of different immunosuppressive drugs for

TABLE 2 Ongoing randomised controlled trials in non-idiopathic pulmonary fibrosis inflammatory interstitial lung diseases (ILDs)

Treatment	Trial name/ clinicaltrials.gov identifier	Study cohort	Current status	Phase/Type	Molecule	Duration/Number of patients (estimated)	Primary endpoint
BlyS inhibitor	BLISSc-ILD NCT05878717	SSc-ILD	Recruiting	2–3 Double-blind Placebo-controlled Randomised	Belimumab *versus* placebo	52 weeks 300 patients	Absolute change in FVC
NRP2	NS NCT05892614	SSc-ILD	Recruiting	2 Double-blind Placebo-controlled Randomised	Efzofitimod *versus* placebo	24 weeks 25 patients	Changes in FVC and HRCT fibrosis score
TL1A mAb	ATHENA-SSc-ILD NCT05270668	SSc-ILD	Recruiting	2 Double-blind Placebo-controlled Randomised	Tulisokibart *versus* placebo	Up to 50 weeks 152 patients	Number of patients with one AE/with serious AE/who discontinue due to AE/changes in FVC
CTLA-4 analogue	APRIL NCT03084419	RA-ILD	Unknown status	2 Feasibility trial	Abadacept	28 weeks 30 (estimated)	FVC
Immunosuppression	CATR-PAT NCT03770663	Antisynthetase syndrome-related-ILD	Unknown status	3 Comparative Randomised Controlled Open-labelled	Cyclophosphamide+ azathioprine *versus* tacrolimus	12 months 76 patients	Progression-free survival
Antifibrotic	MINT NCT05799755	Myositis-ILD	Recruiting	4 Double-blind Randomised Exploratory	Nintedanib *versus* placebo	12 weeks 134 patients	Change in living symptoms and impact questionnaire dyspnoea score
Antifibrotic	NS NCT03857854	DM-ILD	Unknown Status	3 Double-blind Placebo-controlled Randomised	Pirfenidone *versus* placebo	52 weeks 152 patients	Changes in FVC
Anti-GMCSF	RESOLVE-LUNG	Sarcoidosis	Active, not recruiting	2 Double-blind Placebo-controlled Randomised With open label extension	Namilumab *versus* placebo	26 weeks 107 patients	Proportion of subjects with a rescue event during the double-blind period
Antifibrotic	NINSARC NCT06479603	Sarcoidosis	Recruiting	4 Open label trial	Nintedanib *versus* standard of care	12 months 120 patients	Difference in the mean change in FVC between the study groups
Antifibrotic	PirFS NCT03260556	Sarcoidosis	Unknown Status	4 Double-blind Placebo-controlled Randomised	Pirfenidone *versus* placebo	2 years 60 patients	Time until clinical worsening

Continued

TABLE 2 Continued

Treatment	Trial name/ clinicaltrials.gov identifier	Study cohort	Current status	Phase/Type	Molecule	Duration/Number of patients (estimated)	Primary endpoint
Immunomodulator	NS NCT05415137	Sarcoidosis	Active, not recruiting	3 Randomised Double-blind Placebo-controlled	Efzofitimod *versus* placebo	48 weeks 268 patients	Change from baseline in mean daily OCS dose post-taper
TNFα mAb	NS NCT05890729	Sarcoidosis	Recruiting	1b/2 Randomised Sequential assignment	XTMAB-16 or placebo	20 weeks 94 patients	Rate of AEs, dose-limiting toxicities, and AEs of special interest
Oral inhibitor of chitinase-1	NS NCT06205121	Sarcoidosis	Recruiting	2 Randomised Double-blind Placebo-controlled	OATD-01 or placebo	12 weeks 98 patients	Response to treatment

AE: adverse event; BlyS: B-lymphocyte stimulator; CTLA4: cytotoxic T-lymphocyte-associated protein-4; DM-ILD: dermatomyositis ILD; FVC: forced vital capacity; GMCSF: granulocyte–macrophage colony-stimulating factor; HRCT: high-resolution computed tomography; NRP2: neuropilin 2; NS: not specified; RA-ILD: rheumatoid arthritis-associated ILD; SSc-ILD: systemic sclerosis-associated ILD; OCS: oral corticosteroid; TL1A mAb: tumour necrosis factor-like cytokine 1A monoclonal antibody; TNFα mAb: tumour necrosis factor monoclonal antibody.

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IIM-ILD treatment. Based on the limited available research in the field, it seems that the commonly used drugs in this category might have similar effects and could be used interchangeably. A recent multicentric, randomised phase 3 trial (NCT03770663, CATR-PAT) has already enrolled 76 patients with anti-synthetase syndrome-related-ILD and compares the effects of cyclophosphamide and azathioprine *versus* tacrolimus both followed by pulses of methylprednisolone with gradual tapering. The primary endpoint is progression-free survival from baseline over 12 months, while the secondary endpoints include 6-min walk test, FVC and D_{LCO} changes. In the context of antifibrotics, nintedanib (NCT05799755, MINT) and pirfenidone (NCT03857854) are under investigation in myositis and dermatomyositis associated ILD, respectively.

Sarcoidosis

Sarcoidosis is typically treated with immune-modulatory agents, specifically oral corticosteroids, and in some cases, methotrexate or azathioprine are administrated as steroid-sparing agents [63]. Approximately 5% of sarcoidosis patients will develop pulmonary fibrosis [64]; yet with more favourable progression than that observed in IPF. More studies are sorely needed to assess the impact of antifibrotics on this small proportion of sarcoidosis-associated pulmonary fibrosis. A stage 4 RCT (NCT06479603, NINSARC) is trying to evaluate the efficacy of nintedanib on mean change in FVC at 12 months in patients presenting with sarcoidosis-associated fibrotic ILD. Regarding pirfenidone, a current trial (NCT03260556, PirFS) is conducted in patients with sarcoidosis showing >20% fibrosis on high-resolution computed tomography and time to clinical worsening as primary outcome.

Beyond nintedanib and pirfenidone, additional therapeutic compounds are under investigation. Efzofitimod has shown potential in reducing inflammation and fibrosis in sarcoidosis by targeting dysregulated immune responses. A phase 2b study (NCT05415137) is currently evaluating its efficacy in chronic pulmonary sarcoidosis. Interestingly, efzofitimod at therapeutic doses, as compared with a subtherapeutic dose or placebo, was associated with lower rates of relapse as corticosteroids were tapered, suggesting a potential role in reducing steroid dependency [65]. XTMAB-16, a monoclonal antibody targeting tumour necrosis factor-like ligand 1A (TL1A), is also being explored for its immunomodulatory effects in sarcoidosis. TL1A has been implicated in granuloma formation and persistent inflammation in sarcoidosis. A phase 2 clinical trial (NCT05890729) is underway to assess the safety and efficacy of XTMAB-16 in patients with pulmonary sarcoidosis.

Another promising agent, OATD-01, is a first-in-class chitotriosidase inhibitor designed to modulate macrophage-driven inflammation and fibrosis in sarcoidosis. Chitotriosidase is thought to play a role in the persistence of granulomatous inflammation. A phase 2 trial (NCT06205121) is currently recruiting patients to evaluate OATD-01 as a potential therapeutic option for pulmonary sarcoidosis.

Granulocyte–macrophage colony-stimulating factor (GMCSF) is thought to play a key role in the granulomatous response associated with sarcoidosis. A phase 2 RCT (NCT05314517) was conducted to investigate namilumab, an anti-GMCSF monoclonal antibody, in subjects with chronic pulmonary sarcoidosis. However, recent results from the RESOLVE-LUNG study indicated that namilumab failed to demonstrate significant efficacy in this patient population. This highlights the need for further research into alternative therapeutic approaches for sarcoidosis.

Future perspectives

The future of therapeutic management in progressive fibrosing ILDs hinges on a profound understanding of the molecular mechanisms regulating wound healing responses. Ongoing research is focused on identifying new targets that can either prevent fibrosis or halt disease progression more effectively than current anti-fibrotics and target mechanisms at stake in both PFF and IPF.

Emerging regenerative approaches aim to repair damaged tissue and preserve lung function. The pluripotency of mesenchymal stem cells (MSCs) and their capacity for immune modulation, inhibition of inflammation and epithelial tissue repair highlight the potential of MSC as a promising therapy for fibrosing ILDs [66]. However, optimal clinical trials are still inadequate for multi-parameter selection in MSC therapy. Early-phase clinical trials try to assess the safety and efficacy of MSC therapy in PPF (NCT02594839). Moreover, recent advancements in molecular biology discovered exosomes and their cargos, such as miRNAs, as a novel direction in the field of therapeutics of ILDs. Their ability to promote epithelial to mesenchymal transition, regulate the differentiation of bone marrow MSCs into myofibroblasts and promote their proliferation, identify them as a less invasive alternative to stem cell therapy [67]. By integrating transcriptomic and proteomic data from blood and tissue samples, specific molecular subtypes of pulmonary fibrosis with clinical significance could be pinpointed. Therefore, patients more likely to experience disease progression could be identified and categorised into endotypes enhancing clinical

outcomes (NCT01915511). Furthermore, ongoing research holds promise to identify viable gene therapy targets for fibrotic lung diseases, focusing on correcting mutations in genes involved in TGF-β signalling pathway, immune regulation and fibroblast activation. Although its progression is in early stages, gene therapy such as CRISPR-Cas9 technology could revolutionise therapeutic management and may be elucidated as a long-term solution for pulmonary fibrosis [68]. The role of immune checkpoint inhibitors in fibrotic lung diseases remains controversial. While studies have suggested that agents targeting the programmed cell death protein 1 and ligand (PD-1/PD-L1) axis, such as pembrolizumab, may have antifibrotic potential based on preclinical murine models [69], their use in patients with IPF and fibrosing ILDs should be approached with caution. Immune checkpoint inhibitors have been associated with acute exacerbations and increased mortality in patients with lung cancer and underlying IPF. Therefore, further research is warranted to evaluate their safety profile and potential therapeutic benefit in this patient population.

Challenges in progressive fibrosing ILDs treatment and concluding remarks

The management of progressive fibrosing ILDs remains challenging due to disease heterogeneity, the complexity of its underlying pathogenetic mechanisms and the limitations of current therapeutic options. Although significant advances have been made, many hurdles must be overcome to improve clinical trial outcomes and patients' quality of life.

One of the key challenges is the lack of personalised approaches that account for individual differences in disease pathogenesis and progression. Future research should focus on elucidating molecular and genetic biomarkers that can guide treatment decisions. By stratifying patients based on their biomarker profile, clinicians could tailor the most appropriate therapy improving efficacy and limiting adverse effects [70]. Given the multifactorial nature of the ILDs and the potential synergistic effects of antifibrotics with immunomodulated drugs, combination therapies targeting various pathways may provide more effectiveness than monotherapy.

Key points

- IPF and PPF are characterised by progressive fibrosis and share common pathophysiological pathways.
- Current guidelines are based on the use of antifibrotic agents such as nintedanib and pirfenidone, but these can only slow functional decline, making the implementation of novel therapies an absolute necessity.
- Drugs with recent encouraging phase 2 or 3 results include pirfenidone analogues, pirfenidone and nintedanib combination, phosphodiesterase 4 inhibitors, αvβ6 and αvβ1 integrin inhibitors, lymphosphatidic acid antagonists, inhaled treprostinil, hedgehog inhibitors, tyrosine kinase inhibitors and angiotensin type 2 receptor agonists.

Self-evaluation questions

1. Which of the statements is true concerning PPF therapy?
    a) Nintedanib has been shown to reduce the rate of FVC decline across various ILD subtypes.
    b) Pirfenidone is currently approved for use as a first-line treatment for PPF.
    c) Both nintedanib and pirfenidone have been approved as effective monotherapies for PPF, with no ongoing trials assessing combination therapies.
    d) Inhaled pirfenidone has been already approved for both IPF and PPF treatment.
2. What is the principal mechanism by which bexotegrast exerts its therapeutic action in IPF patients?
    a) It enhances the production of TGF-β.
    b) It inhibits TGF-β activation by blocking its binding to αvβ6 and αvβ1 integrins.
    c) It decreases the collagen production and ECM deposition.
    d) It promotes PDE4 inhibition.
3. What is the main mechanism by which PDE4 inhibitors can potentially be used in patients with ILD?
    a) They promote the degradation of cAMP, resulting in reduced inflammation.
    b) They inhibit the degradation of cAMP, enhancing the action of antifibrotic mediators.
    c) They directly inhibit the collagen production in fibrotic lung tissue.
    d) They activate TGF-β signalling pathways, promoting fibrosis.
4. Which is the main mechanism of action of taladegib in pulmonary fibrosis?
    a) Enhancing the hedgehog signalling pathway to promote cell survival.
    b) Inhibiting the transmembrane protein Smoothened, disrupting the hedgehog signalling pathway.
    c) Promoting the differentiation of fibroblasts into myofibroblasts.
    d) Increasing the expression of ECM components and collagen production.

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References

1 Raghu G, Remy-Jardin M, Richeldi L, *et al.* Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med* 2022; 205: e18–e47.

2 Maher TM, Bendstrup E, Dron L, *et al.* Global incidence and prevalence of idiopathic pulmonary fibrosis. *Respir Res* 2021; 22: 197.

3 Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; 183: 431–440.

4 Raghu G, Rochwerg B, Zhang Y, *et al.* An official ATS/ERS/JRS/ALAT Clinical Practice Guideline: treatment of idiopathic pulmonary fibrosis. An Update of the 2011 Clinical Practice Guideline. *Am J Respir Crit Care Med* 2015; 192: e3–e19.

5 Chianese M, Screm G, Salton F, *et al.* Pirfenidone and nintedanib in pulmonary fibrosis: lights and shadows. *Pharmaceuticals* 2024; 17: 709.

6 Richeldi L, du Bois RM, Raghu G, *et al.* Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2071–2082.

7 Noble PW, Albera C, Bradford WZ, *et al.* Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011; 377: 1760–1769.

8 King TE Jr, Bradford WZ, Castro-Bernardini S, *et al.* A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2083–2092.

9 Bonella F, Cottin V, Valenzuela C, *et al.* Meta-analysis of effect of nintedanib on reducing FVC decline across interstitial lung diseases. *Adv Ther* 2022; 39: 3392–3402.

10 Petnak T, Lertjitbanjong P, Thongprayoon C, *et al.* Impact of antifibrotic therapy on mortality and acute exacerbation in idiopathic pulmonary fibrosis: a systematic review and meta-analysis. *Chest* 2021; 160: 1751–1763.

11 Flaherty KR, Wells AU, Cottin V, *et al.* Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019; 381: 1718–1727.

12 Distler O, Highland KB, Gahlemann M, *et al.* Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med* 2019; 380: 2518–2528.

13 Wells AU, Flaherty KR, Brown KK, *et al.* Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet Respir Med* 2020; 8: 453–460.

14 Raman L, Stewart I, Barratt SL, *et al.* Nintedanib for non-IPF progressive pulmonary fibrosis: 12-month outcome data from a real-world multicentre observational study. *ERJ Open Res* 2023; 9: 00423-2022.

15 Ghazipura M, Mammen MJ, Bissell BD, *et al.* Pirfenidone in progressive pulmonary fibrosis: a systematic review and meta-analysis. *Ann Am Thorac Soc* 2022; 19: 1030–1039.

16 Behr J, Prasse A, Kreuter M, *et al.* Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase (2b). trial. *Lancet Respir Med* 2021; 9: 476–486.

17 Maher TM, Corte TJ, Fischer A, *et al.* Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet Respir Med* 2020; 8: 147–157.

18 West A, Chaudhuri N, Barczyk A, *et al.* Inhaled pirfenidone solution (AP01) for IPF: a randomised, open-label, dose-response trial. *Thorax* 2023; 78: 882–889.

19 Spagnolo P, Cottin V. Genetics of idiopathic pulmonary fibrosis: from mechanistic pathways to personalised medicine. *J Med Genet* 2017; 54: 93–99.

20 Saha P, Talwar P. Idiopathic pulmonary fibrosis (IPF): disease pathophysiology, targets, and potential therapeutic interventions. *Mol Cell Biochem* 2024; 479: 2181–2194.

21 Adegunsoye A, Kropski JA, Behr J, *et al.* Genetics and genomics of pulmonary fibrosis: charting the molecular landscape and shaping precision medicine. *Am J Respir Crit Care Med* 2024; 210: 401–423.

22 Rajan SK, Cottin V, Dhar R, *et al.* Progressive pulmonary fibrosis: an expert group consensus statement. *Eur Respir J* 2023; 61: 2103187.
23 Zaman T, Lee JS. Risk factors for the development of idiopathic pulmonary fibrosis: a review. *Curr Pulmonol Rep* 2018; 7: 118–125.
24 Frangogiannis N. Transforming growth factor-β in tissue fibrosis. *J Exp Med* 2020; 217: e20190103.
25 Lancaster L, Cottin V, Ramaswamy M, *et al.* Bexotegrast in patients with idiopathic pulmonary fibrosis: the INTEGRIS-IPF clinical trial. *Am J Respir Crit Care Med* 2024; 210: 424–434.
26 Decaris ML, Schaub JR, Chen C, *et al.* Dual inhibition of α(v)β(6) and α(v)β(1) reduces fibrogenesis in lung tissue explants from patients with IPF. *Respir Res* 2021; 22: 265.
27 Essayan DM. Cyclic nucleotide phosphodiesterase (PDE) inhibitors and immunomodulation. *Biochem Pharmacol* 1999; 57: 965–973.
28 Maher TM, Evans IC, Bottoms SE, *et al.* Diminished prostaglandin E2 contributes to the apoptosis paradox in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2010; 182: 73–82.
29 Selige J, Hatzelmann A, Dunkern T. The differential impact of PDE4 subtypes in human lung fibroblasts on cytokine-induced proliferation and myofibroblast conversion. *J Cell Physiol* 2011; 226: 1970–1980.
30 Matsuhira T, Nishiyama O, Tabata Y, *et al.* A novel phosphodiesterase 4 inhibitor, AA6216, reduces macrophage activity and fibrosis in the lung. *Eur J Pharmacol* 2020; 885: 173508.
31 Richeldi L, Azuma A, Cottin V, *et al.* Trial of a preferential phosphodiesterase 4B inhibitor for idiopathic pulmonary fibrosis. *N Engl J Med* 2022; 386: 2178–2187.
32 Richeldi L, Azuma A, Cottin V, *et al.* Design of a phase III, double-blind, randomised, placebo-controlled trial of BI 1015550 in patients with idiopathic pulmonary fibrosis (FIBRONEER-IPF). *BMJ Open Respir Res* 2023; 10: e001563.
33 Maher TM, Assassi S, Azuma A, *et al.* Design of a phase III, double-blind, randomised, placebo-controlled trial of BI 1015550 in patients with progressive pulmonary fibrosis (FIBRONEER-ILD). *BMJ Open Respir Res* 2023; 10: e001580.
34 Chun J, Hla T, Lynch KR, *et al.* International Union of Basic and Clinical Pharmacology. LXXVIII. Lysophospholipid receptor nomenclature. *Pharmacol Rev* 2010; 62: 579–587.
35 Oikonomou N, Mouratis MA, Tzouvelekis A, *et al.* Pulmonary autotaxin expression contributes to the pathogenesis of pulmonary fibrosis. *Am J Respir Cell Mol Biol* 2012; 47: 566–574.
36 Shea BS, Tager AM. Role of the lysophospholipid mediators lysophosphatidic acid and sphingosine 1-phosphate in lung fibrosis. *Proc Am Thorac Soc* 2012; 9: 102–110.
37 Tager AM, LaCamera P, Shea BS, *et al.* The lysophosphatidic acid receptor LPA1 links pulmonary fibrosis to lung injury by mediating fibroblast recruitment and vascular leak. *Nat Med* 2008; 14: 45–54.
38 Montesi SB, Mathai SK, Brenner LN, *et al.* Docosatetraenoyl LPA is elevated in exhaled breath condensate in idiopathic pulmonary fibrosis. *BMC Pulm Med* 2014; 14: 5.
39 Maher TM, Ford P, Brown KK, *et al.* Ziritaxestat, a novel autotaxin inhibitor, and lung function in idiopathic pulmonary fibrosis: the ISABELA 1 and 2 randomized clinical trials. *JAMA* 2023; 329: 1567–1578.
40 Corte TJ, Behr J, Cottin V, *et al.* Efficacy and safety of admilparant, an LPA(1) antagonist in pulmonary fibrosis: a phase 2 randomized clinical trial. *Am J Respir Crit Care Med* 2024; 211: 230–238.
41 Kolb M, Orfanos SE, Lambers C, *et al.* The antifibrotic effects of inhaled treprostinil: an emerging option for ILD. *Adv Ther* 2022; 39: 3881–3895.
42 Ali FY, Egan K, FitzGerald GA, *et al.* Role of prostacyclin versus peroxisome proliferator-activated receptor beta receptors in prostacyclin sensing by lung fibroblasts. *Am J Respir Cell Mol Biol* 2006; 34: 242–246.
43 Nikitopoulou I, Manitsopoulos N, Kotanidou A, *et al.* Orotracheal treprostinil administration attenuates bleomycin-induced lung injury, vascular remodeling, and fibrosis in mice. *Pulm Circ* 2019; 9: 2045894019881954.
44 Waxman A, Restrepo-Jaramillo R, Thenappan T, *et al.* Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *N Engl J Med* 2021; 384: 325–334.
45 Nathan SD, Waxman A, Rajagopal S, *et al.* Inhaled treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonary hypertension: a post-hoc analysis of the INCREASE study. *Lancet Respir Med* 2021; 9: 1266–1274.
46 Effendi WI, Nagano T. The Hedgehog signaling pathway in idiopathic pulmonary fibrosis: resurrection time. *Int J Mol Sci* 2021; 23: 171.
47 Maher TM, Goldin JG, DiFrancesco A, *et al.* ENV-101, a novel hedgehog inhibitor, increases lung function, and reduces lung fibrosis in patients with idiopathic pulmonary fibrosis: results from a randomized, double-blind, placebo-controlled phase 2 trial. *Am J Respir Crit Care Med* 2024; 209: A1056.
48 Shen G, Zheng F, Ren D, *et al.* Anlotinib: a novel multi-targeting tyrosine kinase inhibitor in clinical development. *J Hematol Oncol* 2018; 11: 120.
49 Ruan H, Lv Z, Liu S, *et al.* Anlotinib attenuated bleomycin-induced pulmonary fibrosis via the TGF-β1 signalling pathway. *J Pharm Pharmacol* 2020; 72: 44–55.
50 Young ON, Bourke JE, Widdop RE. Catch your breath: The protective role of the angiotensin AT_2 receptor for the treatment of idiopathic pulmonary fibrosis. *Biochem Pharmacol* 2023; 217: 115839.

51 Ganslandt C, Maher TM, Molyneaux PL, *et al.* Buloxibutid, a novel angiotensin ii type 2 receptor agonist, stabilized and improved lung function in individuals with idiopathic pulmonary fibrosis in the 36-week phase 2 AIR trial. *Am J Respir Crit Care Med* 2024; 209: A1055.

52 Johnson SR, Bernstein EJ, Bolster MB, *et al.* 2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) guideline for the treatment of interstitial lung disease in people with systemic autoimmune rheumatic diseases. *Arthritis Rheumatol* 2024; 76: 1182–1200.

53 Khanna D, Albera C, Fischer A, *et al.* An open-label, phase II study of the safety and tolerability of pirfenidone in patients with scleroderma-associated interstitial lung disease: the LOTUSS trial. *J Rheumatol* 2016; 43: 1672–1679.

54 Khanna D, Spino C, Bernstein E, *et al.* Combination therapy of mycophenolate mofetil and pirfenidone vs. mycophenolate alone: results from the Scleroderma Lung Study III [abstract]. *Arthritis Rheumatol* 2022; 74: Suppl. 9, 0520.

55 Gordon JK, Martyanov V, Franks JM, *et al.* Belimumab for the treatment of early diffuse systemic sclerosis: results of a randomized, double-blind, placebo-controlled, pilot trial. *Arthritis Rheumatol* 2018; 70: 308–316.

56 Siefker D, Xu Z, Ferrer M, *et al.* Efzofitimod: a novel therapeutic candidate for SSc-ILD. *Eur Respir J* 2023; 62: Suppl. 67, PA419.

57 Myasoedova E, Matteson EL. Updates on interstitial lung disease and other selected extra-articular manifestations of rheumatoid arthritis. *Curr Opin Rheumatol* 2024; 36: 203–208.

58 Guiot J, Miedema J, Cordeiro A, *et al.* Practical guidance for the early recognition and follow-up of patients with connective tissue disease-related interstitial lung disease. *Autoimmun Rev* 2024; 23: 103582.

59 Juge PA, Granger B, Debray MP, *et al.* A risk score to detect subclinical rheumatoid arthritis-associated interstitial lung disease. *Arthritis Rheumatol* 2022; 74: 1755–1765.

60 Solomon JJ, Danoff SK, Woodhead FA, *et al.*. Safety, tolerability, and efficacy of pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease: a randomised, double-blind, placebo-controlled, phase 2 study. *Lancet Respir Med* 2023; 11: 87–96. .

61 Karampitsakos T, Tzilas V, Papaioannou O, *et al.* Clinical features and outcomes of patients with myositis associated-interstitial lung disease. *Front Med* 2022; 9: 1096203.

62 Morisset J, Johnson C, Rich E, *et al.* Management of myositis-related interstitial lung disease. *Chest* 2016; 150: 1118–1128.

63 Bączek K, Piotrowski WJ. Lung fibrosis in sarcoidosis. Is there a place for antifibrotics? *Front Pharmacol* 2024; 15: 1445923.

64 Bonham CA, Strek ME, Patterson KC. From granuloma to fibrosis: sarcoidosis associated pulmonary fibrosis. *Curr Opin Pulm Med* 2016; 22: 484–491.

65 Obi ON, Baughman RP, Crouser ED, *et al.* Therapeutic doses of efzofitimod demonstrate efficacy in pulmonary sarcoidosis. *ERJ Open Res* 2025; 11: 00536-2024.

66 Yang S, Liu P, Jiang Y, *et al.* Therapeutic applications of mesenchymal stem cells in idiopathic pulmonary fibrosis. *Front Cell Dev Biol* 2021; 9: 639657.

67 Ruan P, Todd JL, Zhao H, *et al.* Integrative multi-omics analysis reveals novel idiopathic pulmonary fibrosis endotypes associated with disease progression. *Respir Res* 2023; 24: 141.

68 Hussen BM, Najmadden ZB, Abdullah SR, *et al.* CRISPR/Cas9 gene editing: a novel strategy for fighting drug resistance in respiratory disorders. *Cell Commun Signal* 2024; 22: 329.

69 Karampitsakos T, Galaris A, Chrysikos S, *et al.* Expression of PD-1/PD-L1 axis in mediastinal lymph nodes and lung tissue of human and experimental lung fibrosis indicates a potential therapeutic target for idiopathic pulmonary fibrosis. *Respir Res* 2023; 24: 279.

70 Karampitsakos T, Juan-Guardela BM, Tzouvelekis A, *et al.* Precision medicine advances in idiopathic pulmonary fibrosis. *EBioMedicine* 2023; 95: 104766.

Suggested answers

1. a.
2. b.
3. b.
4. b.