Antifibrotic therapy for fibrotic lung disease beyond idiopathic pulmonary fibrosis

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Non-IPF progressive fibrotic lung diseases may have similar genetics, pathophysiology and clinical course to IPF. There are multiple clinical trials underway to assess whether antifibrotics may have similar effects on FVC in non-IPF-PF. http://bit.ly/2WKsPH1

Cite this article as: Collins BF, Raghu G. Antifibrotic therapy for fibrotic lung disease beyond idiopathic pulmonary fibrosis. *Eur Respir Rev* 2019; 28: 190022 [https://doi.org/10.1183/16000617.0022-2019].

ABSTRACT Two antifibrotic medications (nintedanib and pirfenidone) were recommended (conditionally) for the treatment of patients with idiopathic pulmonary fibrosis (IPF) in the 2015 IPF evidence-based guidelines. These medications have been shown to reduce the rate of decline in forced vital capacity among patients with IPF over time and are the only two disease-modulating pharmacological agents approved by regulatory agencies and available for clinical use worldwide. With the evolved standard of care for interstitial lung disease evaluation including routine use of high-resolution computed tomography, fibrotic lung diseases other than IPF are increasingly recognised. In addition, it is becoming evident that genetic and pathophysiological mechanisms as well as disease behaviour in patients manifesting other "non-IPF progressive fibrotic interstitial lung diseases" (non-IPF-PF) may be similar to those in patients with IPF. Thus, it is biologically plausible that pharmacological agents with antifibrotic properties may be efficacious in non-IPF-PF. Indeed, studies are underway or planned to assess the safety and efficacy of nintedanib or pirfenidone among patients with several non-IPF fibrotic lung diseases. In this review, we briefly summarise the use of pirfenidone and nintedanib in IPF as well as the rationale and potential for use of these medications in non-IPF-PF that are being investigated in ongoing and upcoming clinical trials.

Introduction

Idiopathic pulmonary fibrosis (IPF) is the best studied of the interstitial lung diseases (ILDs), a family encompassing >200 distinct diseases [1, 2]. IPF is well defined based on evolved knowledge of this disease as a progressive fibrotic lung disorder with poor prognosis [3, 4]. While several pharmacological agents have been developed to target various steps in the pathogenesis of IPF and have been studied in multiple clinical trials, only two drugs, nintedanib and pirfenidone, have been approved by worldwide regulatory agencies for treatment of IPF [5, 6]. Both of these drugs have been shown to reduce the rate of decline in forced vital capacity (FVC) over 1 year among IPF patients with mild to moderate impairment in lung function tests [7–10]. Treatment with an antifibrotic (ninetdanib or pirfenidone) is conditionally recommended in the recently updated evidence-based guidelines for IPF [4, 11].

Other ILDs may also have a progressive fibrosing phenotype [12, 13]. There is known overlap in the pathogenic mechanisms of IPF and other fibrotic lung diseases such as systemic sclerosis (SSc)-associated

Publication of this peer-reviewed article was sponsored by Boehringer Ingelheim, Germany (principal sponsor *European Respiratory Review* issue 153).

Received: 02 Feb 2019 | Accepted after revision: 24 May 2019

ILD, where transforming growth factor (TGF)-β is upregulated and has been shown to instigate a fibrogenic response, similar to that seen in IPF [14–16]. Independent of the specific pathophysiological mechanism of fibrosis, usual interstitial pneumonia (UIP) is a nonspecific pattern of fibrosis and may be a manifestation of advanced fibrosis on high-resolution computed tomography (HRCT) of the chest in several ILDs including IPF, chronic hypersensitivity pneumonitis (cHP), connective tissue disease (CTD)-associated ILD, asbestosis and others. Notably, pattern, extent and severity of lung injury/fibrosis have been shown to primarily affect clinical outcomes, perhaps to a greater extent than the underlying diagnosis, particularly in the case of UIP [17–20]. Given that some of the progressing fibrotic non-IPF fibrotic lung diseases (non-IPF-PF) may have a similar clinical course with relatively poor prognosis, radiographic findings, histopathology and lack of response to immunosuppressive medications as is seen in IPF, it seems plausible that the antifibrotic drugs could exert similar therapeutic effects in these conditions [13, 18, 21–23]. There are few clinical trials focused on treatment for patients with non-IPF fibrotic lung disease other than SSc-associated pulmonary fibrosis. Currently, there is very little published evidence from randomised clinical trials to support antifibrotic use in non-IPF-PF at present, but multiple clinical trials are ongoing and the results are eagerly awaited.

In this review, we provide a brief overview of the antifibrotic medications and their use in IPF, discuss rationale for study of antifibrotic medications in non-IPF-PF and discuss ongoing studies and upcoming clinical trials in this area.

Antifibrotic medications

The concept of "antifibrotic" treatment as a disease-modifying class of medications stemmed from an early, original phase 2 trial of patients with IPF treated with pirfenidone [24]. This was based on preclinical studies and *in vitro* studies that demonstrated decreased pulmonary fibrosis with the use of pirfenidone in experimental models of pulmonary fibrosis. Since pirfenidone decreased 1) morphological and biochemical features of experimental pulmonary fibrosis *in vivo*, and 2) decreased *in vitro* proliferation of lung fibroblasts and collagen synthesis from lung fibroblasts isolated from lung specimens from patients with IPF, the concept of an antifibrotic class of medication was introduced for treatment of IPF [24–26]. Since then, several agents demonstrating "antifibrotic properties" have been developed, but only pirfenidone and nintedanib have proven safe and efficacious for patients with IPF and are thus used as standard of care for IPF in clinical practice worldwide.

Antifibrotic medications in IPF

Table 1 summarises the major existing recent randomised controlled trials of nintedanib and pirfenidone for IPF [7–10, 27]. Both nintedanib and pirfenidone are approved by regulatory agencies worldwide for treatment of IPF and received conditional recommendations in the IPF guidelines [4, 11]. Notably, nintedanib and pirfenidone have been shown to have similar effects on rate of decline in FVC over time, even among patients with normal FVC and among patients with more advanced disease (FVC <50% predicted) [28–34]. Nintedanib has been shown to have similar effects on FVC among patients with definite UIP on HRCT or surgical biopsy in comparison to those with possible UIP and traction bronchiectasis, suggesting that efficacy is independent of IPF phenotype [35]. There is some evidence that IPF patients treated with antifibrotics may have lower rates of acute respiratory decompensation represented by acute exacerbation of IPF (nintedanib) and reduced frequency of respiratory related hospital stays (pirfenidone) [36, 37].

Pirfenidone

The molecular mechanism of pirfenidone has not been fully elucidated, but is thought to involve antifibrotic, anti-inflammatory and antioxidative effects to reduce collagen synthesis, deposition and suppression of TGF-β, among other effects [38–40]. The CAPACITY trials were phase III clinical trials of pirfenidone *versus* placebo for patients with IPF: one of the trials showed a decrease in rate of decline in FVC at 72 weeks in the pirfenidone group compared to the placebo group, while the other did not [9]. Subsequently, the ASCEND trial, also a phase III clinical trial, demonstrated an annual decline in FVC of 235 mL in the pirfenidone group as compared to 428 mL among patients receiving placebo [8]. Common adverse effects of pirfenidone include gastrointestinal symptoms (*i.e.* nausea) as well as skin rash and photosensitivity [8]. In an open-label extension trial (RECAP), the most common adverse drug reactions associated with pirfenidone included nausea, diarrhoea and rash, with ~11% of patients permanently discontinuing the medication due to these and other adverse drug reactions [41]. Similar to nintedanib, pirfenidone has been associated with abnormalities in liver function testing in small proportion of patients (<5%) and regular monitoring of liver function is required [8].

TABLE 1 Major randomised controlled trials of antifibrotics among patients with idiopathic pulmonary fibrosis (IPF)

	Phase	Patients	Intervention	Duration	Primary outcome(s)	Key secondary outcome(s)
Nintedanib						
TOMORROW [25]	II	432	Randomised to 1 of 4 doses nintedanib or placebo	52 weeks	Annual rate of FVC decline 60 mL·year^{-1} in nintedanib 150 mg twice daily group *versus* 190 mL·year^{-1} in placebo group	Lower incidence of AE-IPF, small decrease in SGRQ with nintedanib 150 mg twice daily
INPULSUS I [7]	III	515 IPF patients	Randomised 3:2 ratio to nintedanib 150 mg twice daily or placebo	52 weeks	Annual rate of decline FVC −114.7 mL nintedanib *versus* −239.9 mL placebo (p<0.01)	No significant difference in time to first AE or proportion with AE
INPULSIS II [7]	III	551 IPF patients	Randomised 3:2 ratio to nintedanib 150 mg twice daily or placebo	52 weeks	Annual rate of decline FVC −113.6 mL nintedanib *versus* −207.3 mL placebo (p<0.01)	Increase in time to first AE in nintedanib group and lower proportion with AE in nintedanib group; significant small increase in SGRQ in nintedanib group
Pirfenidone						
CAPACITY I (004) [26]	III	435 IPF patients	Randomised 2:1:2 pirfenidone 2403 mg·day^{-1}, pirfenidone 1197 mg·day^{-1} or placebo	72 weeks	Mean decline FVC −8% pirfenidone *versus* −12.4% placebo (p<0.01)	Decreased proportion of patients with ⩾10% decline in FVC; prolonged PFS
CAPACITY II (006) [26]	III	344 IPF patients	Randomised 1:1 pirfenidone 2403 mg·day^{-1} or placebo	72 weeks	Mean decline FVC −9% pirfenidone *versus* −9.6% placebo (p=0.5)	Reduced decline in 6MWD
ASCEND [8]	III	555 with IPF (surgical biopsy required if possible UIP)	Randomised to pirfenidone 801 mg three times daily or placebo	52 weeks	Proportion of patients with ⩾10% decline in FVC or death reduced by 47.9% pirfenidone *versus* placebo (p<0.01)	Decreased decline in 6MWD, improved PFS
Combination nintedanib and pirfenidone						
Safety and pharmacokinetics of nintedanib and pirfenidone in IPF [27]	II	n=50: 25 patients on pirfenidone ⩾3 months; 25 patients not on antifibrotic	Nintedanib (100 mg twice daily or 150 mg twice daily) or placebo added to pirfenidone	14 days (100 mg), 28 days (150 mg)	Adverse events: 10 out of 21 patients on combination; 9 out of 17 patients on only nintedanib	Nintedanib did not affect pharmacokinetics of pirfenidone

FVC: forced vital capacity; AE: adverse event; SGRQ: St George's Respiratory Questionnaire; PFS: progression-free survival; 6MWD: 6-min walk distance; UIP: usual interstitial pneumonia.

Nintedanib

Nintedanib is an oral intracellular tyrosine kinase inhibitor that inhibits downstream signalling pathways involved in proliferation, migration and maturation of lung fibroblasts by inhibition of activation of platelet-derived growth factor receptor, vascular endothelial growth factor receptor and fibroblast growth factor receptor [42]. Nintedanib has been shown to reduce the rate of annual rate of decline in FVC among patients with IPF, as follows. INPULSIS I: annual decrease in FVC −114.7 mL nintedanib *versus* −239.9 mL placebo; INPULSIS 2: annual decrease in FVC −113.6 mL nintedanib *versus* −207.3 mL with placebo [7]. Nintedanib is relatively well tolerated; the most common side-effect among patients taking nintedanib is diarrhoea, although this can often be managed symptomatically [7]. An open-label extension study following INPULSIS followed IPF patients taking nintedanib for a median of 44.7 months and found that only 5–10% of patients taking nintedanib permanently discontinued the drug due to diarrhoea [43].

Nintedanib is associated with liver function test abnormalities in <5% of patients and regular monitoring of liver function is required [7].

Combination treatment

There has been increasing interest in combination therapy with nintedanib and pirfenidone, particularly as mechanism of antifibrotic action differs between the two drugs. There are no large randomised controlled trials assessing whether combination therapy has increased efficacy compared to treatment with a single antifibrotic. Pharmacokinetically, nintedanib does not seem to affect pirfenidone bioavailability, although in early studies there was a trend toward lower exposure to nintedanib in the presence of pirfenidone [27]. A subsequent study demonstrated that plasma trough levels of nintedanib were unchanged when given with pirfenidone [44]. This same study shows a trend toward less FVC decline over 12 weeks among patients with combination therapy compared to patients treated with nintedanib alone, although this was an exploratory analysis undertaken over a short period of time (12 weeks) and underpowered for this end-point, so findings should be viewed with caution [44]. The combination of pirfenidone and nintedanib has been shown to be relatively well tolerated with adverse medication events similar to that for either treatment alone, and there did not seem to be an increased frequency of liver function test abnormalities [27, 45]. All this suggests that further study of combination therapy may be warranted [46].

Rationale for antifibrotic medications in non-IPF-PF

While IPF is the most often studied fibrotic lung disease, other ILDs have a fibrotic phenotype as well [13]. Some of these diseases may initially be inflammatory in nature (such as acute hypersensitivity pneumonitis) and then progress to a more fibrotic phenotype over time, as is the case with cHP [47, 48]. These other fibrotic lung diseases do have similar pathophysiological, clinical, radiological and histopathological features to IPF. The pattern of UIP is nonspecific, as the UIP or UIP-like pattern is seen in patients with cHP, connective tissue disease (CTD) (especially in rheumatoid arthritis and polymyositis) and drug-induced lung disease, as well as in IPF [48–52]. There is increasing interest in determining features on HRCT of the chest that may distinguish non-IPF causes of UIP (such as CTD-ILD) from IPF, although validation is needed [53]. Rheumatoid arthritis (RA) is of particular interest, as UIP is the most common pattern of ILD among patients with RA-ILD, in contrast to nonspecific interstitial pneumonia (NSIP) in the other CTD-ILDs [54, 55].

Overlap between the progressively fibrotic ILDs has become increasingly apparent with increased study of the genetics of ILD. For instance, the gain of function variant rs35705950 in the mucin 5B (MUC5B) promoter variant observed in ∼50% of patients with IPF and thought to be the strongest identified genetic risk factor for development of IPF has also been found to be associated with hypersensitivity pneumonitis and with RA-ILD, particularly RA-UIP [56, 57]. Mutations in genes that maintain telomeres, resulting in shortened telomeres, have been associated not only with familial and idiopathic pulmonary fibrosis, but also with other ILDs including hypersensitivity pneumonitis, CTD-ILD, unclassifiable lung fibrosis and pleuroparenchymal fibroelastosis [58]. Regardless of ILD phenotype, genetic mutations resulting in shortened telomeres lead to disease that is uniformly progressive: a recent study by Newton *et al.* [58] demonstrated that among 115 patients with familial pulmonary fibrosis and mutations in telomere-related genes that median survival was 2.75 years (95% CI 1.64–4.61 years) for patients with IPF *versus* 3.11 years (95% CI 2.56–4.82 years) for those with a non-IPF diagnosis. This suggests that in some cases, genetics may serve as a stronger predictor of progression of fibrotic lung disease than the presence of UIP on HRCT or histopathology.

It is possible that some patients thought to have IPF and studied in clinical trials actually have other fibrotic lung diseases. Since the diagnosis of IPF in the INPULSIS 1 and 2 trials was not ascertained by histopathology features of UIP in patients who did not have honeycombing (as was recommended in the 2011 guidelines for diagnosis of IPF), it is possible that up to 32% of patients enrolled in these trials may not have had true IPF [35]. However, the therapeutic efficacy and safety profile in this subgroup of patients was similar to patients with diagnosis of IPF ascertained by guideline criteria [35]. A prospective study in Barcelona documented that nearly half of patients who were originally diagnosed with IPF based on 2011 criteria were subsequently diagnosed with cHP after review of exposure history, imaging and histopathology by experienced experts in ILD [59]. Thus, it is conceivable that some patients presumed to have IPF who had a treatment response to nintedanib in the INPULSIS trials may have had non-IPF-PF. This implies that nintedanib may slow disease progression in patients with pulmonary fibrosis in general (*i.e.* non-IPF) and raises the question of whether the same may be true for pirfenidone.

Outside SSc-ILD, there are few randomised controlled trials of medications for non-IPF-PF. Cyclophosphamide and mycophenolate mofetil (MMF) have been associated with stabilisation or

improvement in FVC among patients with SSc-ILD in clinical trials [60, 61]. In other CTD-ILDs, treatment is often based on data from retrospective studies or case series as well as expert opinion, and drugs are often used off-label [62, 63]. This is potentially concerning taken in the context of the PANTHER-IPF study. This study showed that patients randomised to prednisone, azathioprine and N-acetylcysteine had increased mortality compared to those randomised to placebo [64]. There is a dearth of clinical trials to guide treatment in non-IPF fibrotic lung diseases. Often in treating cHP and CTD-ILD clinicians at least trial a course of immunomodulatory therapy such as corticosteroids and steroid-sparing agents (MMF, azathioprine, *etc.*) [47, 48, 62, 63]. However, it is not known whether this is truly beneficial or may be harmful as is the case in IPF, particularly among patients with a UIP pattern of disease. Both nintedanib and pirfenidone have been shown to have some anti-inflammatory effects in addition to antifibrotic effects, which further supports trials for diseases generally thought to initially be more inflammatory, such as connective tissue disease associated ILD [65, 66].

Understanding end-points in clinical trials for non-IPF-PF

Prior to describing currently available data and ongoing clinical trials, it is important to understand what is and is not known about outcome measures in non-IPF-PF. Among patients with IPF, change in FVC is the most commonly used primary outcome in clinical trials. This is based on existing evidence that decline in FVC over time is concordant with disease severity, activity and a surrogate measure for mortality [67–71]. While this may be the most clinically meaningful outcome (*i.e.* extended life) for patients with IPF, randomised controlled trials using mortality as the primary end-point require a large number of patients and long-term follow-up. This is based on a relatively low all-cause mortality rate among patients with IPF who have mild to moderately impaired lung function and who make up the population of interest in most IPF clinical trials [72, 73]. Thus, the feasibility of conducting phase 3 trials using mortality as an end-point in patients with mild to moderate impairment in lung function tests is challenging and not practical [72]. While this topic has been debated widely, to date, only one clinical trial has utilised survival as primary end-point to determine the safety and efficacy of an antifibrotic agent [74]. That said, many question whether end-points such as hospitalisation, or acute exacerbation in addition to mortality would be more meaningful [75, 76]. Since few clinical trials that have focused on non-IPF-PF, there are few studies to assess reliability and validity of FVC as an end-point in such patients. Existing studies are focused on SSc-ILD, where FVC has been shown to be a reasonable surrogate for disease progression, although this is still debated [77–79]. Because it is not yet clear whether FVC is a reliable end-point in non-IPF fibrotic lung disease, it will be particularly important that trials of antifibrotics in non-IPF-PF include multiple secondary outcome measures.

There has been increasing interest in quantitative HRCT imaging as an end-point in clinical trials. This has been studied in SSc-ILD in the Scleroderma Lung Study (SLS) II [80]. Quantitative HRCT imaging in SLS II utilised HRCT at full inspiration at total lung capacity. Quantitative CT texture-based disease extent in lobes and in the whole lung were obtained, then computer-aided diagnostic scores for extent of lung involvement were generated for quantitative lung fibrosis (QLF), quantitative honeycomb (QHC) and quantitative ground glass (QGG). A quantitative ILD score (QILD), made up of the sum of QLF+QHC +QGG was then generated and expressed as percentage of total lung and individual lobar involvement. A change of 4% in QLF or QILD in lobe of maximum involvement or 2% in whole lung were considered significant changes based on prior work [81]. The authors found that treatment with either cyclophosphamide for 1 year followed by placebo or MMF for 2 years was associated with significant improvement in QILD scores at 2 years, while scores tended to worsen among those who did not complete treatment [80]. Changes in QILD were significantly associated with changes in FVC, providing support for QILD score as a potentially useful outcome in clinical trials of patients with SSc-ILD and an outcome that may deserve exploration in non-SSc fibrosing lung disease [80].

Computer quantification of computed tomography (CT) pattern to generate a variable (reticular pattern) was recently combined with mathematical modelling to automatically stratify patients with hypersensitivity pneumonitis into phenotypic groups based on extent of reticular pattern and found that this independently predicted mortality among patients with hypersensitivity pneumonitis, similar to that predicted by the ILD-GAP (gender, age, physiology) model [82]. Studies like this suggest that similar quantitative CT technology and mathematical modelling to stratify patients and generate novel outcome measures may deserve further study in future ILD clinical trials. This could be particularly helpful in some non-IPF-PF, where it can be particularly difficult to visually distinguish ground-glass opacities from fine reticulation. Such technology may be of particular benefit in unclassifiable ILD [83]. Other than the SLS studies, current clinical trials for non-IPF-PF have not yet included change in automated/computer-generated quantitative CT ILD score as outcome measures, although this is likely to change in the future as more information about this technology becomes available, and depending on the findings of the SLS III study.

Currently available reports and ongoing clinical trials of antifibrotic medications for non-IPF-PF

Chronic hypersensitivity pneumonitis

Current data on medication treatment of cHP are sparse and largely based on observational studies and expert opinion. There is one randomised placebo-controlled trial of an 8-week course of prednisone *versus* placebo in acute hypersensitivity pneumonitis (farmer's lung) that demonstrated improvement in pulmonary function in both groups initially, but no differences in pulmonary function between the two groups at 1 year [84]. A retrospective study found that patients who were treated with MMF or azathioprine had a small but significant improvement in diffusing capacity of the lung for carbon monoxide (*D*LCO) after 1 year of treatment and required lower doses of corticosteroids [85]. There are case reports of rituximab to treat refractory cHP with some effect [86]. Experts often suggest a trial of immunosuppression with plan to taper off if the disease progresses [47, 48].

SHIBATA *et al.* [87] reported a series of 23 patients with cHP treated with pirfenidone. Among 16 patients who had pulmonary function data available over 6–12 months, vital capacity decreased by 292±78 mL over the 6 months prior to pirfenidone and decreased by 152±56 mL over the 6 months after pirfenidone was started, suggesting that pirfenidone treatment reduced the rate of decline in FVC, similar to its effect in patients with IPF. Limitations of this study include that it was a case series, and notably the decline in FVC over 6 months pre-pirfenidone is greater than that typically expected over 1 year among patients with IPF (150–200 mL), perhaps indicating a patient population with more rapidly progressive disease [68]. BUENDIA-ROLDAN *et al.* [88] presented an abstract of 29 patients with cHP who had been treated with prednisone and azathioprine without improvement. Patients were randomised to prednisone+azathioprine *versus* prednisone+azathioprine+pirfenidone. Those patients in the group receiving pirfenidone had improvement in 6-min walk distance (6MWD) at 9 months' follow-up.

Limitations to the above studies and clinical trials of hypersensitivity pneumonitis include that there are no evidence-based guidelines to provide a set of standard diagnostic criteria for hypersensitivity pneumonitis [47, 48]. This could lead to the inclusion of some patients who have other fibrotic lung diseases, including IPF. As mentioned earlier, a study in Barcelona by MORELL *et al.* [59] demonstrated that among 46 patients with a diagnosis of IPF, nearly half were diagnosed with hypersensitivity pneumonitis after exposure history and review of imaging and histopathology by experienced experts in ILD. Studies such as this do raise the counterpoint that some IPF clinical trials demonstrating benefit of antifibrotic treatment may have included patients with non-IPF fibrosing lung diseases such as cHP.

There are two ongoing trials assessing pirfenidone in hypersensitivity pneumonitis. One trial will randomise 60 patients with chronic hypersensitivity pneumonitis to an 1800 mg or 1200 mg total daily dose of pirfenidone or placebo as an add-on to what is deemed conventional treatment (prednisone and azathioprine) (NCT02496182) [89]. The primary outcome is mean change in FVC at 26 and 52 weeks. Key secondary outcomes include inflammation and fibrosis grade on chest HRCT using the Kazerooni scale as well as change in 6MWD and St George's Respiratory Questionnaire (SGRQ) score. The other trial is a single-centre study that will randomise 40 patients with fibrotic hypersensitivity pneumonitis to pirfenidone (2403 mg total daily dose) or placebo with primary outcome of change in FVC over 52 weeks (NCT02958917) [90]. Secondary outcomes include progression-free survival, time to acute exacerbation and change in 6MWD. Table 2 summarises ongoing clinical trials in cHP and non-IPF progressive fibrotic lung diseases.

CTD-ILD

Systemic sclerosis

Among the CTD-ILDs, SSc is the disease that is the best studied in clinical trials, although reports of antifibrotic use are scarce. There is a report of five patients with SSc and progressive ILD who experienced improvement in vital capacity after treatment with pirfenidone [102]. An open-label 16-week trial of pirfenidone for SSc was associated with a safety profile similar to that in IPF clinical trials (LOTUSS) [103]. Simultaneous treatment with MMF did not seem to affect tolerability of pirfenidone.

The SLS II study (phase 3) compares nintedanib to placebo for patients with SSc and associated ILD is ongoing [91, 104]. This study aims to enrol 580 patients with SSc and pulmonary fibrosis. SSc is defined by the American College of Rheumatology/European League Against Rheumatism criteria and ILD is diagnosed by HRCT showing >10% fibrosis. FVC must be ⩾40% pred and *D*LCO must be 30–90%. Patients are allowed to be on other medications for SSc-ILD at a stable dose (methotrexate, MMF, prednisone ⩽10 mg daily dose). The primary outcome is annual rate of decline in FVC. Secondary outcomes include time to all-cause mortality, change in modified Rodan skin score, SGRQ score and dyspnoea score. The SLS III study (phase 2) will randomise 150 patients with SSc and pulmonary fibrosis to MMF+placebo *versus* MMF+pirfenidone with a plan to follow-up over 18 months and primary outcome of change in FVC over that time period (NCT03221257) [95]. Important secondary outcomes will include change in

computer-quantified HRCT measures of SSc-ILD over 18 months as well as change in quantified HRCT measures of total lung capacity over 18 months [95].

Rheumatoid arthritis

While NSIP is the most common pattern of ILD in most CTD-ILDs, UIP is the most common pattern in RA-ILD [54, 105]. A recent study demonstrated that a mutation in the MUC5B promoter seen in many patients with IPF is also associated with RA-ILD; RA-UIP in particular [56]. Given shared phenotypic and pathophysiological overlap, antifibrotics may therefore be particularly promising in RA-ILD with a UIP pattern [106]. There is an ongoing phase II clinical trial to assess pirfenidone in RA-ILD (TRAIL1, NCT02808871) [99]. Patients may be on stable background immunosuppressive medication and pirfenidone is added at a total daily dose of 2403 mg [99]. The trial will recruit 270 patients; the primary end-point is a composite end-point of progression-free survival (⩾10% FVC decrease or death) over 52 weeks. Secondary end-points include relative decline in D_{LCO}, FVC, acute exacerbation and change in SGRQ score. A mouse model of RA-ILD demonstrated that treatment with nintedanib was associated with reduced lung collagen levels and, interestingly, with less arthritis, suggesting that nintedanib probably deserves further study among humans with RA-ILD [107].

Myositis

Clinically cutaneous features of dermatomyositis with little to no myopathy characterise clinically amyopathic dermatomyositis (CADM). As many as 65% of patients with CADM may have ILD; ILD in such patients is often rapidly progressive with high associated mortality, particularly among patients with a positive serum MDA5 antibody [108, 109]. Li *et al.* [110] conducted an open-label prospective study of pirfenidone added on to existing immunosuppressive therapy for patients with CADM and ILD (n=30) compared to retrospective matched controls (n=27). They discovered that overall there was not a statistically significant difference in mortality in the pirfenidone group, although subgroup analyses did reveal that among patients with subacute ILD (disease 3–6 months' duration, n=10) 1-year survival was improved (90%) compared to that in controls (n=9; 44%) [110]. The same effect was not seen for patients with acute ILD (duration <3 months) and it could be speculated that this is because those patients perhaps had less fibrotic disease. Limitations include the retrospective nature of the controls, lack of randomisation, small number of patients and single-centre design. As described earlier, serum MDA5 positivity has been associated with rapidly progressive ILD and greater mortality among patients with CADM [108, 109]. Interestingly, 85% of patients in the pirfenidone group were $MDA5^+$ compared to only 57% in the control group, which makes the finding that the pirfenidone group with subacute disease had improved survival more striking. A randomised controlled trial will be needed to draw more robust conclusions. There is an ongoing phase IV clinical trial of pirfenidone or placebo for progressive ILD in 60 CADM patients; 1800 mg daily added on to current treatment and the primary outcome is overall survival over 52 weeks (NCT02821689) [94]. Secondary outcomes include change in HRCT characteristics and change in pulmonary function tests from baseline.

Sarcoidosis

There are no current reports of antifibrotic use among patients with fibrotic sarcoidosis. There is a current trial of pirfenidone or placebo for progressive fibrotic sarcoidosis (NCT03260556) [100]. Patients must have sarcoidosis with >20% fibrosis on HRCT to be included. The trial will aim to recruit 60 patients. Stable immunosuppressive medications and/or prednisone ⩽20 mg daily for 2 months are permitted. Patients will be followed for 24 months; the primary outcome is time to clinical worsening. Secondary outcomes of note are change in FVC and change in composite physiologic index.

Interstitial pneumonia with autoimmune features

There are patients with ILD who have an autoimmune flavour to their disease but do not meet defined criteria for an idiopathic interstitial pneumonia such as IPF or for a specific CTD [111–113]. While many of these patients have UIP, they are often excluded from clinical trials in spite of progressive fibrosing ILD in light of their autoimmune features and positive serologies [20, 113]. Recently, criteria for interstitial pneumonia with autoimmune features (IPAF) have been developed for research purposes, which will hopefully allow further study of such patients, although heterogeneity remains between published IPAF cohorts [112, 114]. There are few existing completed studies or reports of antifibrotic treatment for patients with ILD and autoimmune features, although clinical trials are ongoing that include patients with multiple different types of non-IPF-PF as well as patients with unclassifiable disease [21, 115]. One of these trials has a particular stipulation for patients with IPAF [97]. This is a phase 2 trial of pirfenidone for patients with unclassifiable ILD, meaning patients who cannot be classified with a moderate or high level of confidence to a specific category of fibrosing ILD with multidisciplinary team discussion (NCT03099187) [97]. Patients who are on a stable dose of MMF for

⩾3 months prior to screening may be included (treatment with high-dose steroids or other immunosuppression is an exclusion criterion), allowing the study to further assess pirfenidone with and without ongoing MMF treatment in patients with or without IPAF [97]. This is based on data demonstrating that 7% of patients with ILD are estimated to have IPAF, thereby not meeting criteria for a specific IIP such as IPF or a specific CTD-ILD, which leads to exclusion of such patients from most clinical trials [111, 112, 116, 117]. The primary outcome will be change in FVC over 24 weeks. Secondary end-points of note include change in other PFT measures as well as change in symptom scores, SGRQ score and acute exacerbation.

Non-IPF-PF without a specific diagnosis

Unclassifiable ILD

There are other patients who have fibrotic lung disease that does not meet criteria for a specific diagnosis. Sometimes this is because disease is unclassifiable even after multidisciplinary discussion, often due to high risk associated with surgical lung biopsy for histopathology [118]. This group in particular may make up >20% of patients with ILD, depending on the series [111, 118, 119]. Treatment is typically based on the most likely diagnosis after multidisciplinary discussion [12]. While many would recommend treating such patients according to their clinical behaviour, this is often difficult in the era of high-cost drugs and need for insurance approval in some countries [12, 118, 120]. Some patients may have overlapping features from two different ILDs, thereby not meeting defined/accepted criteria for treatment or entry into disease-specific clinical trials for either disease, for instance patients who we have recently described as having combined sarcoidosis and idiopathic pulmonary fibrosis [121]. Patients with anti-neutrophil cytoplasmic antibodies (ANCA), anti-myeloperoxidase antibody in particular, and pulmonary fibrosis (especially UIP) have been described; it is difficult to know whether to treat these patients with immunosuppressive medications *versus* an antifibrotic and there are no published studies to guide clinicians in this area [122–125].

Progressive fibrotic ILDs other than IPF

Combining fibrotic ILDs other than IPF that are clinically progressive into a category of "progressive fibrotic ILDs" to assess treatment response with currently available antifibrotic agents (nintedanib and pirfenidone) is the strategy taken in two ongoing clinical trials. The INBUILD trial is designed to assess nintedanib among patients with progressive fibrosing ILD other than IPF (NCT02999178) by randomising patients to nintedanib *versus* placebo [92]. Patients with cHP, sarcoidosis, CTD-ILD, idiopathic interstitial pneumonia other than IPF, unclassifiable ILD, *etc*., who have documented progressive disease are eligible to be enrolled in this trial of patients with non-IPF-PF. They must have progressive disease (regardless of underlying disease) as defined by fulfilling one of the following criteria. 1) Clinically significant decline in FVC ⩾10% pred; 2) marginal decline in FVC% (5% to <10%) combined with worsening respiratory symptoms; 3) marginal decline in FVC% (5% to <10%) in combination with increasing extent of fibrotic changes on chest CT; 4) worsening respiratory symptoms and increasing extent of fibrotic changes on chest CT [92, 126]. Patients must have >10% fibrosis on HRCT. Patients must stop any existing immunosuppression prior to enrolling in the trial. The primary end-point for this trial is annual rate of decline in FVC. Key secondary end-points include time to first acute exacerbation or death and time to disease progression (⩾10% decline in FVC or death).

The RELIEF study is a phase II trial randomising patients to 2403 mg total daily dose of pirfenidone or placebo as an add-on to existing treatment for CTD-ILD, fibrotic NSIP, cHP and asbestos-related pulmonary fibrosis with primary end-point of change in FVC over 48 weeks [96]. Secondary end-points include time to disease worsening, change in D_{LCO} and 6MWD, as well as change in SGRQ score.

For patients with pulmonary fibrosis and a positive ANCA, there is an ongoing study of pirfenidone (NCT03385668) [98]. This trial will recruit 15 patients, all of whom will receive pirfenidone. The primary outcome is change in FVC over 52 weeks. Secondary outcomes include adverse events related to treatment, change in FVC and D_{LCO}, as well as progression-free survival (table 2).

Antifibrotics for chronic lung allograft dysfunction as a result of bronchiolitis obliterans syndrome post-lung transplant

Based on progressive luminal fibrosis in bronchioles of the lung allograft in lung transplant recipients manifesting bronchiolitis obliterans syndrome (BOS), antifibrotics have been considered in the context of clinical trials to decrease the decline in lung allograft dysfunction as a result of BOS post-lung transplant [127, 128]. A clinical trial is ongoing of patients with grade 1–2 BOS post-lung transplant receiving nintedanib *versus* placebo (NCT03283007) [93]. In addition, pirfenidone is being studied among patients with grade 1–3 BOS post-lung transplant, with primary outcome of change in FEV1 over 6 months; similar to the nintedanib trial, patients ⩾6 months post-lung transplant with BOS are randomised to drug

TABLE 2 Ongoing clinical trials of antifibrotic medications in non-idiopathic pulmonary fibrosis (IPF) fibrotic interstitial lung diseases (ILDs)

	Name	Phase	Patients	Intervention	Duration	Primary outcome	Key secondary outcomes
Nintedanib							
NCT02597933 [91]	Safety and Efficacy of 150 mg Nintedanib Twice Daily in Systemic Sclerosis (SENSCIS)	III	n=580, SSc-pulmonary fibrosis	Nintedanib 150 mg twice daily or placebo added to exisiting treatment (stable dose methotrexate, MMF and/or prednisone ⩽10 mg daily)	52 weeks	Annual rate of decline FVC (mL)	Time to all-cause mortality, absolute change dyspnoea score, Modified Rodan Skin Score, SGRQ, change in FVC % pred, change *D*LCO
NCT02999178 [92]	Efficacy and Safety of Nintedanib in Patients with Progressive Fibrosing-ILD (INBUILD®)	III	n=663, progressive fibrosing ILD (see text)	Nintedanib 150 mg twice daily or placebo	52 weeks	Annual rate of decline FVC	Change in K-BILD score, time to first AE or death, time to progression (⩾10% decrease FVC or death)
NCT03283007 [93]	Nintedanib in Lung Transplant Recipients with BOS Grade 1–2 (INFINITx-BOS)	III	n=80, ⩾6 months post-lung transplant with BOS	Nintedanib 150 mg twice daily or placebo (patients already on azithromycin)	6 months	Rate of decline in FEV_1 (mL) over 6 months	Change 6MWD, change SGRQ, change in BOS grade, absolute change oxygen saturation
Pirfenidone							
NCT02821689 [94]	Pirfenidone in Progressive ILD Associated with Clinically Amyopathic Dermatomyositis	IV	n=60, CADM with ILD	1800 mg pirfenidone total per day or placebo added on to existing treatment	52 weeks	Overall survival	Change in HRCT score, change in PFT from baseline
NCT03221257 [95]	Scleroderma Lung Study III – Combining Pirfenidone with Mycophenolate (SLSIII)	II	n=150, SSc-pulmonary fibrosis	Pirfenidone (target dose 801 mg three times daily) or placebo+MMF (target dose of 1500 mg twice daily)	18 months	Change in FVC % pred	Change *D*LCO % pred, change modified Rodan Skin Score, SGRQ, dyspnoea assessment score, change from baseline ILD by computer-quantified HRCT
DRKS00009822 [96]	Exploring Efficacy and Safety of Pirfenidone for Progressive, Non-IPF Lung Fibrosis (RELIEF)	II	Collagen vascular disease-associated fibrosis, fibrotic NSIP, cHP, asbestos-related lung fibrosis	Pirfenidone (801 mg three times daily) or placebo	48 weeks	Absolute change in FVC (%) from baseline to week 48	Time to disease worsening, change in *D*LCO, 6MWD, SGRQ and EQ-5D
NCT03099187 [97]	A Study of Pirfenidone in Patients with Unclassifiable Progressive Fibrosing Interstitial Lung Disease	II	n=252, nonclassifiable ILD (cannot be classified to a specific category of ILD with moderate or high level of confidence with MDD)	Pirfenidone (801 mg three times daily) or placebo (stable dose MMF allowed)	24 weeks	Rate of decline in FVC over 24 weeks	Change in FVC (% pred), change in *D*LCO (% pred), change in FVC of >5%, change in FVC of >10%, change in 6MWD, change in symptom scores (dyspnoea, cough), SGRQ score, AE-IPF, PFS

Continued

TABLE 2 Continued

	Name	Phase	Patients	Intervention	Duration	Primary outcome	Key secondary outcomes
NCT03385668 [98]	Pilot Study of Pirfenidone in Pulmonary Fibrosis with Anti-myeloperoxidase Antibodies (PIRFENIVAS)	II	15 patients with +anti-MPO antibody and pulmonary fibrosis (definite or possible UIP or NSIP on HRCT)	Pirfenidone (2403 mg total daily dose) (no placebo group)	52 weeks	Absolute change FVC % pred	Treatment emergent adverse events, change FVC % pred, 6MWD, change % *D*LCO, PFS
NCT02808871 [99]	Phase II Study of Pirfenidone in Patients with RA-ILD (TRAIL1)	II	270 patients with RA-ILD	Pirfenidone 801 mg three times daily or placebo	52 weeks	Composite end-point: ⩾10% decline in FVC or death	Relative decline *D*LCO (⩾15%), relative decline in FVC (⩾10%), acute exacerbation, dyspnoea scores, SGRQ
NCT03260556 [100]	Pirfenidone for Progressive Fibrotic Sarcoidosis (PirFS)	IV	60 patients with sarcoidosis and >20% fibrosis on HRCT (stable immunosuppressive medications and/or ⩽ 20 mg prednisone/ day for 2 months prior allowed)	Pirfenidone 801 mg three times daily or placebo	24 months	Time until clinical worsening	Change in FVC, change in composite physiologic index
NCT02958917 [90]	Study of Efficacy and Safety of Pirfenidone in Patients with Fibrotic Hypersensitivity Pneumonitis	N/A	40 patients with fibrotic hypersensitivity pneumonitis	Pirfenidone 801 mg three times daily or placebo	52 weeks	Mean change in FVC	PFS, ⩾5% mean change FVC, acute exacerbation, 6MWD
NCT02496182 [89]	Pirfenidone in the Chronic Hypersensitivity Pneumonitis Treatment (Picheon)	II/III	n=60, cHP	Pirfenidone (1800 mg or 1200 mg total daily dose) or placebo in addition to conventional therapy (prednisone and azathioprine)	52 weeks	Change in FVC	Inflammation and fibrosis grade on HRCT (Kazerooni scale), 6MWD, SGRQ score
NCT02262299 [101]	European Trial of Pirfenidone in BOS, A European Multi-center Study (EPOS)	II/III	n=80, ⩾6 months post-lung transplant with grade 1–3 BOS	Pirfenidone 801 mg three times daily or placebo (patients already on azithromycin)	26 weeks	Change in FEV_1 (in L) over 26 weeks	% change in FEV_1, % change FVC, change in % pred *D*LCO, change 6MWD, change BOS grade, hospitalisation, survival

SSc: systemic sclerosis; MMF: mycophenolate mofetil; FVC: forced vital capacity; SGRQ: St George's Respiratory Questionnaire; % pred: % predicted; *D*LCO: diffusing capacity of the lung for carbon monoxide; K-BILD: King's Brief Interstitial Lung Disease questionnaire; AE: adverse event; BOS: bronchiolitis obliterans syndrome; FEV_1: forced expiratory volume in 1 s; 6MWD: 6-min walk distance; CADM: clinically amyopathic dermatomyositis; HRCT: high-resolution computed tomography; PFT: pulmonary function test; NSIP: nonspecific interstitial pneumonia; cHP: chronic hypersensitivity pneumonitis; EQ-5D: EuroQuol five-dimensions questionnaire; MDD: multidisciplinary discussion; MPO: myeloperoxidase; UIP: usual interstitial pneumonia; PFS: progression-free survival; RA: rheumatoid arthritis.

or placebo on top of baseline azithromycin (NCT02262299) [101]. There is a phase 2 trial of nintedanib among patients with BOS after haematopoietic stem cell transplant (HSCT) (NCT03805477) as well as a phase 1 trial of pirfenidone for patients with BOS after HSCT (NCT03315741), although these trials are not randomised or placebo controlled [129, 130].

Conclusion

At present, nintedanib and pirfenidone are routinely used to treat IPF based on phase III clinical trials demonstrating a reduced rate of decline in FVC over time among patients with IPF taking either medication. IPF and non-IPF progressive fibrotic ILDs have overlapping genetics, pathophysiological mechanisms and clinical behaviour. There is an unmet clinical need for randomised controlled trials of treatment in non-IPF-PF, particularly to assess treatment with nintedanib or pirfenidone. There are currently multiple clinical trials ongoing to assess use of antifibrotic medications for non-IPF-PF and results are eagerly awaited.

Conflict of interest: B.F. Collins has nothing to disclose. G. Raghu has served as a consultant for Boehringer Ingelheim, Roche and Genentech for work unrelated to the current review article.

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