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REVIEW

Antifibrotic drugs in connective tissue disease-related interstitial lung disease (CTD-ILD): from mechanistic insights to therapeutic applications

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Abstract

Fibrosing interstitial lung disease (ILD) is one of the most important causes of morbidity and mortality in patients with connective tissue diseases (CTDs), which include systemic sclerosis, rheumatoid arthritis, Sjögren's syndrome, idiopathic inflammatory myositis and systemic lupus erythematosus. The treatment of CTD-ILDs is challenging due to the paucity of proven effective treatments. Recently, two antifibrotic drugs conditionally approved for use in patients with idiopathic pulmonary fibrosis, nintedanib and pirfenidone, have been trialled in CTD-ILDs based on overlapping pathological and clinical features between the two diseases. In this narrative review, we discuss the experimental evidence and clinical trials investigating the efficacy and safety of antifibrotic drugs in patients with CTD-ILDs and the potential mechanisms of action involved. Results from clinical trials suggest that nintedanib use retards lung function decline in progressive fibrotic CTD-ILDs. By contrast, the evidence for the efficacy of pirfenidone in these groups is not equally compelling. Further, well-designed randomized clinical trials are needed to evaluate the efficacy and safety of individual antifibrotic drugs in specific CTD-ILD subgroups.

Keywords: connective tissue diseases, idiopathic inflammatory myopathies, interstitial lung disease, pirfenidone, nintedanib, rheumatoid arthritis, Sjögren's syndrome, systemic sclerosis.

Citation

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Introduction

Interstitial lung disease (ILD) is an umbrella term encompassing over 200 distinct diseases of the lung parenchyma.[1,2] Idiopathic pulmonary fibrosis (IPF), the most prevalent ILD, has been widely studied in terms of evolution and treatment.[3] IPF typically presents with histological features of usual interstitial pneumonia (UIP), rapid lung functional decline and early mortality, with a median survival of 3–5 years.[4] Recently published randomized controlled trials (RCTs) in patients with IPF reported the efficacy of two antifibrotic drugs, nintedanib and pirfenidone, in reducing the rate of lung functional decline.[5]

ILD can also complicate the course of connective tissue diseases (CTDs), such as systemic sclerosis (SSc), rheumatoid arthritis (RA), idiopathic inflammatory myopathies (IIM), Sjögren's syndrome and systemic lupus erythematosus (SLE). Moreover, the American Thoracic Society and the European Respiratory Society suggest using the term 'interstitial pneumonia with autoimmune features' (IPAF) to describe ILD with autoimmune features in patients not meeting the classification criteria for CTDs.[6]

From a histological point of view, ILDs related to CTD (CTD-ILDs) are characterized by a variety of subtypes in addition to UIP, including non-specific interstitial pneumonia (NSIP), organising pneumonia, lymphoid interstitial pneumonia and diffuse alveolar damage. Of note, CTD-ILDs with a UIP pattern typically share a progressive fibrotic phenotype with IPF that is characterized by common radiographic and histopathological features, severe clinical course, lack of response to immunosuppressants and poor prognosis.[3,7,8] On the other hand, CTD-ILDs associated with non-UIP patterns typically show slow progression and improved survival.[9]

Due to the paucity of RCTs, with the best available evidence limited to SSc-related ILD (SSc-ILD), the management of CTD-ILDs remains challenging. Current therapeutic strategies include immunosuppressant agents such as glucocorticoids, cyclophosphamide, mycophenolate mofetil and rituximab. Monoclonal antibodies (e.g. anti-IL-6), modulators of immune response (e.g. abatacept) and intravenous immunoglobulins have also been tested in CTD-ILDs, with conflicting results.[10–14] Haematopoietic stem cell transplantation and lung transplantation have also proven to be effective, especially in SSc-ILD,[15,16] but should be reserved to selected patients with progressive refractory disease in the context of clinical trials conducted in centres with high expertise.

Despite an increasing number of RCTs, in particular in the context of SSc, direct comparisons of treatments in high-quality studies are not yet available for CTD-ILD. The comparative efficacy and harms of different immunosuppressive treatments in SSc-ILD and CTD-ILDs have been assessed in recent systematic reviews and meta-analyses.[17–21] However, due to the inherent limitations of RCTs included in these meta-analyses (low number of RCTs, small sample sizes, high risk of bias), the evidence generated is generally moderate-to-low quality.[17–21]

Experimental evidence from *in vitro* models of pulmonary fibrosis suggests that the use of antifibrotic molecules is associated with impaired lung fibroblast proliferation and *in loco* collagen synthesis.[22] These preliminary observations paved the way to the development of several compounds with antifibrotic properties for the management of IPF.

Two antifibrotic drugs, pirfenidone and nintedanib, have emerged as the gold standard treatment for patients with IPF worldwide based on the results of multiple RCTs.[3,5,23–25] Therefore, despite little evidence from RCTs being currently available for CTD-ILDs,[26] it seems plausible that antifibrotic drugs may also be effective in patients with CTD-ILD exhibiting a progressive fibrotic phenotype refractory to immunosuppressive medications.[3,7]

The objective of this narrative review is to outline the rationale for the use of pirfenidone and nintedanib in CTD-ILDs and discuss the available evidence from completed RCTs and the expected results from ongoing trials in this patient group.

Methods

We searched Scopus, Web of Science, ClinicalTrials.gov and EU Clinical Trials Registry, from inception to 15 July 2020, for papers in English language containing the following terms alone or in combination: 'nintedanib', 'pirfenidone', 'antifibrotics', 'lung', 'interstitial lung disease', 'idiopathic pulmonary fibrosis', 'pulmonary fibrosis', 'connective tissue diseases', 'rheumatoid arthritis', 'Sjogren's syndrome', 'systemic sclerosis', 'scleroderma', 'systemic lupus erythematosus', 'myositis', 'mixed connective tissue disease', 'randomized', 'randomised', 'trial', 'controlled' and 'placebo'. Reference lists were also manually reviewed.

Pharmacology and mechanisms of action

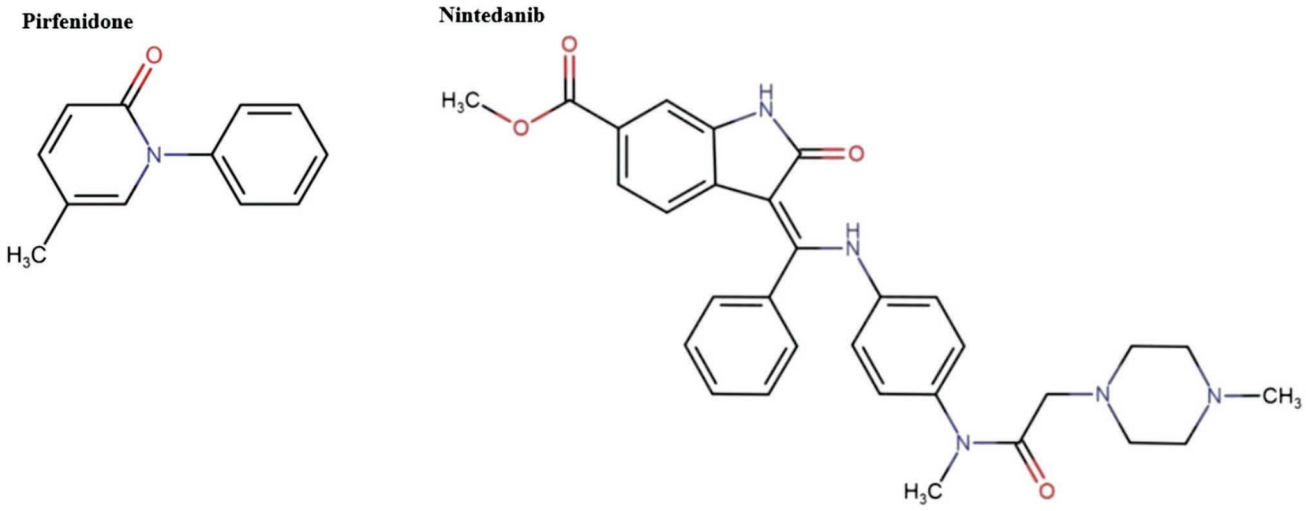
Pirfenidone

Pirfenidone (5-methyl-1-phenyl-2(1H)-pyridone), a pyridone derivative[27] (Figure 1), is absorbed from the gastrointestinal tract (peak concentration in plasma at 1–2 hours), metabolized by the liver and excreted in the urine approximately 6 hours after ingestion.[27] The most common adverse effects associated with pirfenidone use include constitutional (fatigue), gastrointestinal (nausea, diarrhoea, decreased appetite) and skin (rash and photosensitivity reactions) events.[28] Pirfenidone use can also cause liver abnormalities that, even if infrequent (<5% of patients), may be serious and need regular evaluation and close follow-up. At the dose of 2403 mg/day, used in RCTs of IPF, adverse events are generally mild or moderate and rapidly responsive to dose reduction or treatment withdrawal.[29] In a real-world, prospective, post-authorisation study (the PASSPORT study) promoted by the European Medical Association, the discontinuation rate of pirfenidone for any single gastrointestinal and skin event, even if higher than that reported in RCTs, was relatively low (<5% of patients).[28]

Despite a large number of mechanistic studies, the exact molecular activities behind the antifibrotic effect of pirfenidone remain largely unknown. Pirfenidone shows inhibitory activity against profibrotic growth factors signalling (platelet-derived growth factor (PDGF) and transforming growth factor-β1 (TGFβ1)[22,30]) and restores the balance between tissue metalloproteinases with opposing profibrotic (matrix metalloproteinases) and antifibrotic activities (tissue inhibitor of metalloproteinases).[31]

Starting from the early 1990s, an increasing number of studies have demonstrated the antifibrotic effect of pirfenidone in animal models of fibrosis involving the lung, heart and liver. In these studies, the antifibrotic properties of pirfenidone were mainly attributed to the inhibition of the fibrogenic signal cascade orchestrated by TGFβ1.[32–36] In the respiratory tract, TGFβ1, produced by several resident activated and inflammatory cells (including hyperplastic alveolar epithelial cells, endothelial cells, fibroblasts, macrophages and neutrophils), is a pivotal mediator of lung repair processes both in fibrotic and chronic inflammatory lung disease.[22,37] As extensively reviewed by Ruwanpura et al.,[22] pirfenidone may suppress TGFβ1-mediated fibrogenic signalling throughout a broad range of actions, including (1) inhibition of the synthesis of TGFβ1 and TGFβ1-downstream signalling mediators, (2) downregulation of the synthesis of TGFβ1-related proteins involved in extracellular matrix deposition such as fibronectin and collagen, (3) inhibition of the heat shock protein 47 (a chaperone specific for collagen, engaged in procollagen deposition during fibrotic processes), (4) inhibition of fibroblast proliferation and differentiation into myofibroblasts mediated by α-smooth muscle actin and (5) containment of the epithelial–mesenchymal transition (a process playing a fundamental role in excessive tissue repair).

Figure 1. Chemical structures of pirfenidone and nintedanib.



Source: *LiverTox* database. https://www.ncbi.nlm.nih.gov/books/NBK547852/

Besides its antifibrotic properties, pirfenidone has been shown to exert a significant anti-inflammatory effect based on the (1) inhibition of dendritic cell-mediated T cell activation,[38] (2) reduction of pro-inflammatory cytokines such as TNFα, IL-6 and IL-1,[22,39–42] (3) decrease in oxidative stress-related tissue damage mediated by a reduction of oxygen radical production[43,44] and (4) inhibition of NLRP3 inflammasome activation.[45]

Nintedanib

Nintedanib, an indolinone derivative with inhibitory activity against tyrosine kinase inhibitor activity[46] (Figure 1), is absorbed relatively quickly from the gastrointestinal tract (peak concentration in plasma at 2–4 hours), metabolized by the liver to form a glucuronidated metabolite and excreted in the faeces.[47]

The safety and tolerability profile of Nintedanib in IPF has been explored in three RCTs (TOMORROW[25] and two INPULSIS trials[5]) and in an open-label extension study (INPULSIS-ON study[48]). In these trials, nausea, bronchitis and pharyngitis, generally of mild-to-moderate intensity, were the most common adverse events.

Nintedanib was first tested as an anticancer agent due to its ability to inhibit three different proangiogenic receptor tyrosine kinases: fibroblast growth factor receptors, vascular endothelial growth factor receptor and PDGF.[49] In addition, nintedanib has been demonstrated to block the colony-stimulating factor-1 receptor, the Src family kinase lymphocyte-specific tyrosine protein kinase and a broad range of other kinases.[50] However, the intracellular effects of nintedanib on kinases have not been clearly defined.

Nintedanib was also shown to reduce the proliferation and migration of lung fibrocytes, a key cell type involved in the fibrotic process, in a model of bleomycin-induced lung fibrosis.[50] Similarly, in an *ex vivo* study, nintedanib reduced the proliferation of lung fibroblasts mediated by PDGF, fibroblast growth factor and vascular endothelial growth factor.[51,52]

Nintedanib also exerts a number of inhibitory effects against a broad range of inflammatory cytokines that are likely to be involved in the profibrotic signalling pathways such as lymphocyte-specific tyrosine protein kinase, IL-2, IL-4, IL-5, IL-10, IL-12 p70, IL-13 and interferon-γ.[49,52,53] Nintedanib also significantly inhibits the release of CCL18, a chemokine involved in the polarisation of macrophages in the lung fibrotic process of IPF and CTDs.[54–57]

Antifibrotic drugs in IPF

Based on preclinical data and findings from a double-blind phase II and a subsequent phase III RCT,[58,59] pirfenidone was licensed for the treatment of patients with IPF in Japan in 2008. The positive effects of pirfenidone in IPF were then replicated in two trials conducted in North America, Australia and Europe (the CAPACITY-004 and CAPACITY-006 trials).[24] Analysis of the CAPACITY and ASCEND pooled data[23] demonstrated the efficacy of pirfenidone in retarding lung functional decline and prolonging progression-free survival. This led to the approval of pirfenidone for the treatment of IPF by the US FDA in 2014. *Post-hoc* analysis of the CAPACITY and ASCEND trials and further real-world use in clinical practice have also provided convincing evidence that pirfenidone use retards the decline of lung function and reduces the risk of hospitalisation and all-cause mortality, especially in more advanced disease.[60–63] The TOMORROW, INPULSIS I and INPULSIS II trials demonstrated that the use of nintedanib is associated with significant retardation in the deterioration of lung function.[5,25]

Based on the different putative mechanisms of action of nintedanib and pirfenidone, it is plausible that combination therapy may be superior, in terms of efficacy, to each individual drug in patients with IPF. The INJOURNEY trial, a 12-week exploratory study in patients with IPF, demonstrated a trend towards a slower lung functional decline in the group receiving nintedanib and pirfenidone in combination compared to the group receiving nintedanib alone, without a significant increase in drug-related adverse events.[64]

Antifibrotic drugs in CTD-ILDs

As previously discussed, CTD-ILDs may show a progressive behaviour characterized by refractoriness to immunosuppressants and rapid deterioration of lung function, a so-called 'progressive fibrotic phenotype'. Besides IPF and fibrotic CTD-ILDs, the category of progressive fibrotic ILDs includes chronic hypersensitivity pneumonitis, idiopathic NSIP, unclassifiable idiopathic interstitial pneumonia and sarcoidosis[7]. Regardless of the underlying disease, these patients need prompt and effective treatment to slow lung deterioration, improve symptoms and increase survival. Based on the results of RCTs in IPF, the currently available antifibrotic drugs represent promising candidate drugs for the management of non-IPF progressive fibrotic ILDs such as CTD-ILDs.

The INBUILD trial assessed the efficacy and harms of nintedanib in non-IPF progressive fibrosing ILDs, grouping all progressive fibrotic ILDs into a single clinical category irrespective of underlying subgroups[7,65,66] (Table 1). In this trial, 633 patients with progressive fibrotic disease, characterized by different combinations of clinically significant decline, worsening symptoms and increasing lung fibrotic involvement on imaging, were randomized to nintedanib or placebo.[66] In patients receiving immunosuppressants, as in the case of patients with CTD-ILDs, these drugs were stopped prior to enrolment in the trial.[66]

The annual rate change in forced vital capacity (FVC) was the primary endpoint of the INBUILD trial. This trial showed that, compared to placebo, the use of nintedanib was associated with retarded lung functional decline in patients with progressive fibrotic ILDs.[66] Of note, the gain in reduced annual rate of decline of FVC with the use of nintedanib in progressive fibrotic ILDs in the INBUILD trial was comparable in magnitude to that obtained in IPF in the INPULSIS trial.[25] This observation suggests that, regardless of the underlying aetiology, disease with fibrotic progressive ILD may benefit from treatment with nintedanib. This proposition is further confirmed by the exploratory *post-hoc* analysis of the INBUILD trial that demonstrated non-significant differences in the efficacy of nintedanib either across ILD subgroups (p=0.4), in the whole sample or in the UIP-like subgroup.[65] Therefore, based on preclinical data and findings from RTCs, the use of nintedanib for the treatment of progressive fibrosing ILD, including CTD-ILDs, was approved by the FDA in March 2020.[67]

Using a similar 'basket approach', the RELIEF study, a phase II trial, randomized 127 patients with ILD and a progressive fibrotic phenotype (37 CTD-ILD, 27 fibrotic NSIP, 57 chronic hypersensitivity pneumonia and 6 asbestos-related lung fibrosis) to receive, in addition to conventional anti-inflammatory therapy, placebo or pirfenidone[68] (Table 1). The primary aim of the RELIEF study was to assess the absolute change in percentage predicted FVC over 48 weeks. Although based on a small sample size, the RELIEF trial showed that the use of pirfenidone in progressive fibrotic ILDs significantly, albeit modestly, retarded the decline in the predicted FVC.[68]

RA

A variable prevalence of ILD, ranging from 5% to 10%,[69–72] has been reported in patients with RA mainly due to between-study differences in diagnosis and case definitions. Patients with RA may develop overt ILD at any point in the course of disease, including the preclinical phase.[73] The occurrence of ILD is associated with reduced survival in RA (mean survival of 5–8 years).[69–72] RA-ILD has a common histological appearance of UIP and NSIP, with UIP being the most prevalent pattern.[74]

RA-ILD, especially the subset with a high resolution computed tomography (HRCT) UIP pattern and IPF share a number of overlapping features, including genetic susceptibility (e.g. rs5705950 of MUC5B promoter[75] and short leukocyte telomere length[76]), pathogenetic pathways[77] and a progressive disease trajectory characterized by severe prognosis and reduced survival.[78,79] Moreover, in a mouse model that replicates the characteristics of RA-ILD, treatment with nintedanib was associated with reduced progression of both articular and lung involvement.[80]

Therefore, based on the available evidence, the use of antifibrotics in patients with RA-ILD is likely to be associated with retarded lung disease progression, improved functional outcomes and, ultimately, in increased survival. In addition, given the systemic inflammatory burden and the presence of organized ectopic lymphoneogenesis in lung tissue of patients with RA-ILD,[81] combination therapy with antifibrotic drugs and immunosuppressants is likely to be effective in patients with RA-ILD[10]. Accordingly, remission of symptoms related to articular involvement together with stabilisation of lung functional decline have been reported in the UIP subgroup of patients with RA-ILD receiving antifibrotic drugs, alone or in combination with immunosuppressants.[10,82,83]

As previously discussed, the results of the INBUILD trial that enrolled 633 patients of whom 89 (13%) had RA-ILD, suggest that patients with RA and progressive fibrotic-ILD may benefit the most from treatment with nintedanib.[66]

The TRAIL-1 is an ongoing phase II trial evaluating the efficacy, safety and tolerability of pirfenidone in 270 patients with RA-ILD at high risk of progression, defined as lung fibrotic disease involvement >10% on HRCT[84] (Table 1). The primary outcome is a composite endpoint of decline in percentage predicted

Table 1. Completed and ongoing clinical trials of antifibrotic drugs in CTD-ILD.

Drug	Trial	Description	Sample size	Results
Nintedanib	SENSCIS – Safety and Efficacy of 150 mg Nintedanib Twice Daily in Systemic Sclerosis (NCT02597933)[92]	A phase III, randomized placebo-controlled, double-blind, parallel-group trial comparing nintedanib to placebo over a 52-week treatment period Primary endpoint: annual rate of decline in FVC	576 patients with systemic sclerosis; 288 received nintedanib and 288 received placebo	Adjusted annual rate of FVC decline: −52.4 mL in the nintedanib group *versus* −93.3 mL in the placebo group (p=0.04)
Nintedanib	INBUILD – Efficacy and Safety of Nintedanib in Patients with Progressive Fibrosing-ILD (NCT02999178)[66]	A phase III, randomized, placebo-controlled, double-blind, parallel-group trial comparing nintedanib to placebo over a 52-week treatment period Primary endpoint: annual rate of decline in FVC	633 progressive fibrosing ILDs (25.6% autoimmune ILDs); 332 received nintedanib and 331 received placebo	Adjusted annual rate of FVC decline: −80.8 mL in the nintedanib group *versus* −187.8 mL in the placebo group (p<0.001)
Pirfenidone	Pirfenidone in Progressive ILD Associated with Clinically Amyopathic Dermatomyositis (NCT02821689)[100]	Open-label, prospective study with matched retrospective controls Primary endpoint: 12-month survival from the onset of ILD	30 rapidly progressive ILD-related to clinically amyopathic dermatomyositis; 27 matched, retrospectively selected controls	No significant difference in survival rate between groups In the subgroup with subacute disease (disease duration 3–6 months), patients receiving pirfenidone had a significantly higher survival rate compared with patients receiving standard treatment (p=0.045)
Pirfenidone	Efficacy and Safety of Pirfenidone in Systemic Sclerosis-Related Interstitial Lung Disease—a Randomised Controlled Trial (CTRI/2018/01/011449)[91]	A phase III, randomized placebo-controlled, double-blind, parallel-group trial comparing pirfenidone to placebo over a 6-month treatment period Primary endpoint: proportion of patients reaching stabilisation/improvement in FVC Key secondary outcome: absolute change in the percentage predicted FVC	34 patients with systemic sclerosis; 17 received pirfenidone and 17 received placebo	There was no difference in the proportion of stabilisation/improvement in FVC between groups: 16 (94.1%) in the pirfenidone group *versus* 13 (76.5%) in the placebo group (p=0.33) Median (range) absolute change in percentage predicted FVC −0.55 (−9% to 7%) in the pirfenidone group *versus* 1.0 (−42% to 11.5%) in the placebo group (p=0.51)
Pirfenidone	RELIEF – Exploring Efficacy and Safety of Pirfenidone for Progressive, Non-IPF Lung Fibrosis (DRKS00009822)[68]	A phase II, randomized, placebo-controlled, double-blind, parallel-group trial comparing pirfenidone to placebo over a 48-week treatment period Primary endpoint: absolute change in percentage predicted FVC	127 patients with progressive fibrosing ILDs (37 patients with collagen vascular diseases)	Primary endpoint was not calculated due to significant variability in home spirometry Significantly lower decline in the median predicted change in FVC in the group receiving pirfenidone

(Continued)

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Table 1. (*Continued*)

Drug	Trial	Description	Sample size	Results
Pirfenidone	A Study of Pirfenidone in Patients with Unclassifiable Progressive Fibrosing Interstitial Lung Disease (NCT03099187)[107]	A phase II, randomized placebo-controlled, double-blind, parallel-group trial comparing pirfenidone to placebo over a 24-week treatment period Primary endpoint: mean predicted change in FVC from baseline over 24 weeks, measured by daily home spirometry Key secondary endpoints: predicted change in FVC from baseline over 24 weeks, measured by site spirometry	253 patients with progressive unclassifiable fibrotic ILDs; 127 received pirfenidone and 126 received placebo	Analysis of the primary outcome was not performed due to significant intra-individual variability in recorded home spirometry The predicted mean change in FVC measured by site spirometry was significantly lower in the pirfenidone group compared to the placebo group (p=0.02)
Pirfenidone	Scleroderma Lung Study III – Combining Pirfenidone with Mycophenolate (NCT03221257)[94]	A phase II, randomized placebo-controlled, double-blind, parallel-group trial comparing pirfenidone plus mycophenolate mofetil to placebo plus mycophenolate mofetil over an 18-month treatment period Primary endpoint: change from baseline in percentage predicted FVC	Estimated enrolment: 150 patients with SSc-ILD	Ongoing
Pirfenidone	TRAIL-1 – Phase II Study of Pirfenidone in Patients with RA-ILD (NCT02808871)[84]	A phase II, randomized placebo-controlled, double-blind, parallel-group trial comparing pirfenidone to placebo over a 52-week treatment period Primary endpoint: incidence of the composite endpoint of decline in percentage predicted FVC of 10% or greater, or death	Estimated enrolment: 270 patients with RA-ILD	Ongoing
Pirfenidone	Pirfenidone in Progressive Interstitial Lung Disease Associated with Clinically Amyopathic Dermatomyositis (NCT02821689)[101]	A phase IV, randomized, placebo-controlled, double-blind, parallel-group trial comparing pirfenidone to placebo over a 12-month treatment period Primary endpoint: changes of 12-month survival from the onset of ILD	Estimated enrolment: 57 patients with clinically amyopathic dermatomyositis	Ongoing

CTD-ILD, connective tissue disease-related interstitial lung disease; FVC, forced vital capacity; SSc-ILD, systemic sclerosis related-ILD; RA-ILD, rheumatoid arthritis-related ILD.

FVC of 10 or greater or death over 52 weeks. Secondary and exploratory outcomes include safety measures, candidate biomarkers, effect on extra-pulmonary RA-specific efficacy measures and patient-reported outcomes.[84]

SSc

Clinically significant ILD develops in about 30–40% of patients with SSc and preferentially early in the disease.[85,86] The presence of ILD is linked to significant morbidity, an increased rate of hospitalisation and reduced survival in patients with SSc, with an estimated 10-year mortality of about 10%.[87] Typically, SSc-ILD presents with an NSIP pattern on HRCT, although a UIP pattern has also been described.[85]

Despite the available RCTs, the treatment of SSc-ILD remains challenging due to the lack of head-to-head comparisons of available treatments. Cyclophosphamide and mycophenolate are considered the standard of care in SSc-ILD based on the findings of the SLS-I (cyclophosphamide against placebo) and the SLS-II (cyclophosphamide against mycophenolate) trials.[88,89] Observational studies, two small RCTs and a meta-analysis also support the efficacy of rituximab in reducing lung functional deterioration in patients with SSc-ILD.[17]

Apart from case reports,[90] pirfenidone has first been tested in SSc-ILD in the LOTUSS trial.[29] This phase II trial assessed the safety profile of pirfenidone in combination with mycophenolate or alone in patients with SSc-ILD.[29] Of note, the safety and tolerability of pirfenidone in the LOTUSS study were not affected by the simultaneous treatment with mycophenolate and was consistent with those reported in RCTs conducted in IPF.

In a recent RCT, 34 patients with SSc-ILD were randomized to pirfenidone or placebo[91] (Table 1). The primary endpoint was the proportion of patients with either stabilisation or improvement in FVC over 6 months. In the context of a small sample size, this trial did not find a significant effect of pirfenidone compared to placebo in stabilising or improving functional lung decline in SSc-ILD.[91]

The phase III SENSCIS trial randomized 576 patients with SSc-ILD to nintedanib or placebo in addition to mycophenolate in half of the participants[92] (Table 1). The primary outcome was the absolute change in annual rate decline in percentage predicted FVC over 52 weeks.[92] When compared to placebo, the use of nintedanib was associated with a significantly slower lung functional decline as measured by FVC (−52.4 mL in the nintedanib group *versus* −93.3 mL in the placebo group), yet it did not affect the deterioration in the diffusing capacity for carbon monoxide.[92] Lung decline in the group of participants receiving mycophenolate was similar to that reported in the whole population (−40.2 mL in the nintedanib group *versus* −66.5 mL for placebo group). The most common reported adverse event was diarrhoea (75.7% in the nintedanib group *versus* 31.6% in the placebo group). Based on the results of the SENSCIS trial, nintedanib was licensed for use in patients with SSc-ILD by the FDA (September 2019) and the European Medical Agency (April 2020). The long-term safety profile of nintedanib in patients with SSc-ILD is under evaluation in an open label extension study (NCT03313180).[93]

The SLS III study (NCT03221257)[94] is another ongoing study randomising 150 patients with SSc-ILD to receive the combination of pirfenidone and mycophenolate or mycophenolate alone (Table 1). The primary endpoint is the absolute change in FVC over 18 months.[94] Secondary endpoints include changes in computer-quantified HRCT measures of SSc-ILD and total lung capacity over 18 months.[94]

IIM

The term IIM encompasses a broad range of conditions characterized by distinctive histological, serological and clinical features, including polymyositis, dermatomyositis (DM), overlap myositis and anti-synthetase syndrome (ASS).[95] The occurrence of ILD complicates the course of polymyositis, DM and ASS in 20–80% of patients, with higher frequencies reported in patients with ASS and anti-melanoma differentiation-associated protein 5-positive clinically amyopathic DM (CADM).[96,97] Patients with IIM-ILD usually show a slowly progressive disease; on the contrary, patients with CADM may present with fulminant disease requiring intensive care.[98,99] Although immunosuppressants are widely considered as first-line treatment, no evidence-based guidelines are available on their efficacy and harms in IIM-ILD.

In a small prospective open label study, the rate of 1-year mortality in 30 patients with CADM receiving pirfenidone plus standard immunosuppressive therapy was compared with that of 27 retrospectively identified matched controls that received immunosuppressants alone[100] (Table 1). Although there was no difference in mortality between the two groups, subgroup analysis demonstrated a significant reduction of mortality in patients with subacute CADM receiving pirfenidone. The authors speculated that patients with subacute disease, having a more fibrotic disease than patients with an acute course, were more likely to benefit from pirfenidone treatment.[100] Overall survival over 52 weeks is the primary outcome of an ongoing clinical trial planning to randomize 60 patients with CADM to receive pirfenidone/blank add-on (NCT02821689)[101] (Table 1).

SS, SLE and IPAF

SS-ILD usually shows an NSIP pattern on HRTC, whilst UIP and organising pneumonia are less common.[102,103] Although rare, lymphocytic interstitial pneumonia is thought to be a specific pattern of SS-ILD. Evidence-based guidelines regarding the treatment of SS-ILD are still lacking and current recommendations on the use of immunosuppressants, including steroids, mycophenolate, cyclophosphamide and rituximab, are based on case reports, expert opinion and data deriving from the treatment of non-pulmonary extra-glandular manifestations of SS. To date, there is only anecdotal evidence

regarding the efficacy of pirfenidone in SS-ILD with a UIP pattern on HRCT.[104]

The occurrence of ILD in patients with SLE is not common.[105] Consequently, evidence-based recommendations regarding its treatment are still lacking. A review of the literature identified only one case report of a Chinese woman with SLE-ILD showing a good response, in terms of disease activity and lung function, to pirfenidone in combination with glucocorticoids.[106]

As previously discussed, IPAF are ILDs presenting with serological and/or clinical features suggestive of an underlying CTD.[6] In a recent phase II open label trial, 253 patients with unclassifiable ILD were randomized to pirfenidone or placebo (Table 1). The primary outcome was the predicted mean change in FVC from baseline over 24 weeks as measured by daily home spirometry, whereas the change in FVC from baseline, measured by spirometry during clinic visits, was a secondary endpoint;[107] analysis of the primary outcome was prevented by significant variability in recorded home spirometry. However, the analysis of secondary outcomes suggested that the use of pirfenidone may be effective in unclassifiable progressive fibrotic ILDs, including IPAF.[107]

Conclusions

Based on available experimental data, preclinical evidence and commonalities with IPF, nintedanib and pirfenidone are likely to be effective in CTD-ILDs, especially in those exhibiting a progressive fibrotic phenotype. However, whilst data from clinical trials support the use of nintedanib in this patient group, evidence for pirfenidone is lacking. Therefore, further RCTs are urgently needed that comparatively assess the efficacy and safety of pirfenidone and nintedanib in patients with CTD-ILDs as a whole and according to underlying disease subgroups. Results of ongoing clinical trials expected to inform evidence-based treatment regimens in CTD-ILDs are therefore eagerly awaited.

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