**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.

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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.5,7,8 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.\textsuperscript{10–14} Haematopoietic stem cell transplantation and lung transplantation have also proven to be effective, especially in SSc-ILD,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{3,5,23–25} Therefore, despite little evidence from RCTs being currently available for CTD-ILDs,\textsuperscript{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.\textsuperscript{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’, ‘randomised’, ‘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\textsuperscript{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.\textsuperscript{27} The most common adverse effects associated with pirfenidone use include constitutional (fatigue), gastrointestinal (nausea, diarrhea, decreased appetite) and skin (rash and photosensitivity reactions) events.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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))\textsuperscript{22,23} and restores the balance between tissue metalloproteinases with opposing profibrotic (matrix metalloproteinases) and antifibrotic activities (tissue inhibitor of metalloproteinases).\textsuperscript{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.\textsuperscript{32–34} 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.\textsuperscript{22,37} As extensively reviewed by Ruwanpura et al.,\textsuperscript{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).
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, (2) reduction of pro-inflammatory cytokines such as TNFα, IL-6 and IL-1, (3) decrease in oxidative stress-related tissue damage mediated by a reduction of oxygen radical production and (4) inhibition of NLRP3 inflammasome activation.

Nintedanib

Nintedanib, an indolinone derivative with inhibitory activity against tyrosine kinase inhibitor activity (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.

The safety and tolerability profile of Nintedanib in IPF has been explored in three RCTs (TOMORROW and two INPULSIS trials) and in an open-label extension study (INPULSIS-ON study). 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. 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. 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. Similarly, in an ex vivo study, nintedanib reduced the proliferation of lung fibroblasts mediated by PDGF, fibroblast growth factor and vascular endothelial growth factor.

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. 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.

Antifibrotic drugs in IPF

Based on preclinical data and findings from a double-blind phase II and a subsequent phase III RCT, 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). Analysis of the CAPACITY and ASCEND pooled data 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. 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.

Figure 1. Chemical structures of pirfenidone and nintedanib.

Source: LiverTox database. https://www.ncbi.nlm.nih.gov/books/NBK547852/
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 characterised 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.52 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 subgroups65,66 (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 RCTs, the use of nintedanib for the treatment of progressive fibrosing ILD, including CTD-ILDs, was approved by the FDA in March 2020.57

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 pirfenidone68 (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.23 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 promoter75 and short leucocyte telomere length76), pathogenetic pathways77 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 HRCT84 (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   | SENSIC – 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)⁵⁸ | 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)
Table 1. (Continued)

| Drug | Trial | Description | Sample size | Results |
|------|-------|-------------|-------------|---------|
| Pirfenidone | A Study of Pirfenidone in Patients with Unclassifiable Progressive Fibrosing Interstitial Lung Disease (NCT03099187)\(^\text{107}\) | 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)\(^\text{104}\) | 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 | Estimated enrolment: 150 patients with SSc-ILD | Ongoing |
| Pirfenidone | TRAIL-1 – Phase II Study of Pirfenidone in Patients with RA-ILD (NCT02808887)\(^\text{104}\) | 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)\(^\text{101}\) | 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.\(^\text{84}\)

**SSc**

Clinically significant ILD develops in about 30–40% of patients with SSc and preferentially early in the disease.\(^\text{85,86}\) 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%.\(^\text{87}\) Typically, SSc-ILD presents with an NSIP pattern on HRCT, although a UIP pattern has also been described.\(^\text{85}\)

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.\(^\text{88,89}\) 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.\(^\text{17}\)

Apart from case reports,\(^\text{90}\) pirfenidone has first been tested in SSc-ILD in the LOTUSS trial.\(^\text{29}\) This phase II trial assessed the safety profile of pirfenidone in combination with mycophenolate or alone in patients with SSc-ILD.\(^\text{29}\) 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\(^\text{91}\) (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.\(^\text{91}\)

The phase III SENSICIS trial randomized 576 patients with SSc-ILD to nintedanib or placebo in addition to mycophenolate in half of the participants\(^\text{92}\) (Table 1). The primary outcome was the absolute change in annual rate decline in percentage predicted FVC over 52 weeks.\(^\text{92}\) 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.\(^\text{92}\) 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 SENSICIS 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).\(^\text{93}\)

The SLS III study (NCT03221257)\(^\text{94}\) 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.\(^\text{94}\) Secondary endpoints include changes in computer-quantified HRCT measures of SSc-ILD and total lung capacity over 18 months.\(^\text{94}\)

**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).\(^\text{95}\) 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).\(^\text{96,97}\) Patients with IIM-ILD usually show a slowly progressive disease; on the contrary, patients with CADM may present with fulminant disease requiring intensive care.\(^\text{98,99}\) 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\(^\text{100}\) (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.\(^\text{100}\) 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)\(^\text{101}\) (Table 1).

**SS, SLE and IPAF**

SS-ILD usually shows an NSIP pattern on HRCT, whilst UIP and organising pneumonia are less common.\(^\text{102,103}\) 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.\textsuperscript{104} The occurrence of ILD in patients with SLE is not common.\textsuperscript{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.\textsuperscript{106} As previously discussed, IPAF are ILDs presenting with serological and/or clinical features suggestive of an underlying CTD.\textsuperscript{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;\textsuperscript{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.\textsuperscript{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.
2. Kowal-Bielecka O, Fransen J, Avouac J, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis*. 2017;76(8):1327–1339. https://doi.org/10.1136/annrheumdis-2016-209909

3. Collins BF, Raghu G. Antifibrotic therapy for fibrotic lung disease beyond idiopathic pulmonary fibrosis. *Eur Respir Rev*. 2019;28(153). https://doi.org/10.1183/16000617.0022-2019

4. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*. 2011;183(6):788–824. https://doi.org/10.1164/rccm.2009-040GL

5. Richeldi L, Du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370(22):2071–2082. https://doi.org/10.1056/NEJMoa1402584

6. Fischer A, Antoniou KM, Brown KK, et al. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. *Eur Respir J*. 2015;46:976–987. https://doi.org/10.1183/13993003.00150-2015

7. Wells AU, Brown KK, Flaherty KR, Kolb M, Thannickal VJ. What’s in a name? That which we call IPF, by any other name would act the same. *Eur Respir J*. 2018;51(5):1800692. https://doi.org/10.1183/13993003.00692-2018

8. Kelly CA, Saravanan V, Nisar M, et al. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics—a large multicentre UK study. *Rheumatol*. 2014;53(9):1676–1682. https://doi.org/10.1093/rheumatology/keu165

9. Oldham JM, Adegunsoye A, Valenzi E, et al. Characterisation of patients with interstitial pneumonia with autoimmune features. *Eur Respir J*. 2016;47(6):1767–1775. https://doi.org/10.1183/13993003.01565-2015

10. Vecchi C, Manfredi A, Cassone G, Salvarani C, Cerri S, Sebastiani M. Combination therapy with nintedanib and sarilumab for the management of rheumatoid arthritis related interstitial lung disease. *Case Rep Med*. 2020;2020:6390749. https://doi.org/10.1155/2020/6390749

11. Cassone G, Manfredi A, Atzeni F, et al. Safety of abatacept in Italian patients with rheumatoid arthritis and interstitial lung disease: a multicenter retrospective study. *J Clin Med*. 2020;9(1):277. https://doi.org/10.3390/jcm9010277

12. Khanna D, Spino C, Johnson S, et al. Abatacept in early diffuse cutaneous systemic sclerosis: results of a phase II investigator-initiated, multicenter, double-blind, randomized, placebo-controlled trial. *Arthritis Rheumatol*. 2020;72(1):125–136. https://doi.org/10.1002/art.41055

13. Khanna D, Denton CP, Lin CJF, et al. Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of a phase II randomised controlled trial (faSScinate). *Ann Rheum Dis*. 2018;77(2):212–220. https://doi.org/10.1136/annrheumdis-2017-21682

14. Hallowell RW, Amarii D, Danoff SK. Intravenous immunoglobulin as potential adjunct therapy for interstitial lung disease. *Arthritis Rheumatol*. 2016;74(6):976–987. https://doi.org/10.1002/art.40155

15. Hallowell RW, Amarii D, Danoff SK. Intravenous immunoglobulin as potential adjunct therapy for interstitial lung disease. *Arthritis Rheumatol*. 2018;74(6):1760–1769. https://doi.org/10.1002/art.40155

16. Walker UA, Saketkoo LA, Distler O. Haematopoietic stem cell transplantation in systemic sclerosis. *Eur Respir J*. 2018;51(10):1682–1688. https://doi.org/10.1183/13993003.2018-0376PS

17. Khanna D, Denton CP, Lin CJF, et al. Safety of abatacept in Italian patients with rheumatoid arthritis and interstitial lung disease: a multicenter retrospective study. *J Clin Med*. 2020;9(1):277. https://doi.org/10.3390/jcm9010277

18. Khanna D, Spino C, Johnson S, et al. Abatacept in early diffuse cutaneous systemic sclerosis: results of a phase II investigator-initiated, multicenter, double-blind, randomized, placebo-controlled trial. *Arthritis Rheumatol*. 2020;72(1):125–136. https://doi.org/10.1002/art.41055

19. Park JE, Kim SY, Song JH, et al. Comparison of short-term outcomes for connective tissue disease-related interstitial lung disease and idiopathic pulmonary fibrosis after lung transplantation. *J Thorac Dis*. 2018;10(3):1538–1547. https://doi.org/10.21037/jtd.2018.02.50

20. Erre GL, Sebastiani M, Fenu MA, et al. Efficacy, safety, and tolerability of treatments for systemic sclerosis-related interstitial lung disease: a systematic review and network meta-analysis. *J Clin Med*. 2020;9(8):2560. https://doi.org/10.3390/jcm9082560

21. Zheng J-N, Yang Q-R, Zhu G-Q, Pan L, Xia J-X, Wang Q. Comparative efficacy and safety of immunosuppressive therapies for systemic sclerosis related interstitial lung disease: a Bayesian network analysis. *Mod Rheumatol*. 2020;30(4):687–695. https://doi.org/10.1007/s10029-020-01403-4

22. Barnes H, Holland AE, Westall GP, Goh NSL, Glaspole IN. Cyclophosphamide for connective tissue disease-associated interstitial lung disease. *Cochrane Database Syst Rev*. 2018;2018(1). https://doi.org/10.1002/14651858.CD001090.pub2

23. Brodatkova T, Poobalan AS, Jamieson NV, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370(22):2083–2092. https://doi.org/10.1056/NEJMoa1402582

24. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet*. 2011;377(9779):1760–1769. https://doi.org/10.1016/S0140-6736(11)60405-4
25. Richeldi L, Costabel U, Selman M, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med*. 2011;365(12):1079–1087. https://doi.org/10.1056/NEJMoa1103690

26. Fischer A, Distler J. Progressive fibrosing interstitial lung disease associated with systemic autoimmune diseases. *Clin Rheumatol*. 2019;38(10):2673–2681. https://doi.org/10.1007/s10067-019-04720-0

27. Shi S, Wu J, Chen H, Chen H, Wu J, Zeng F. Single- and multiple-dose pharmacokinetics of pirfenidone, an antifibrotic agent, in healthy Chinese volunteers. *J Clin Pharmacol*. 2007;47(10):1268–1276. https://doi.org/10.1177/0091270007304104

28. Cottin V, Koschel D, Günther A, et al. Long-term safety of pirfenidone: results of the prospective, observational PASSPORT study. *Open Res*. 2018;4:84–2018. https://doi.org/10.1186/s41204-018-00084-2018

29. 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(9):1672–1679. https://doi.org/10.3899/jrheum.151322

30. Gurusujalakshmi G, Hollarige MA, Giri SN. Pirfenidone inhibits PDGF isoforms in bleomycin hamster model of lung fibrosis at the translational level. *Am J Physiol Lung Cell Mol Physiol*. 1999;276(2 20–2):311–318. https://doi.org/10.1152/ajplung.1999.276.2.I311

31. Corbel M, Lanchou J, Germain N, Malledant Y, Boichot E, Lagente V. Modulation of airway remodeling-associated mediators by the antifibrotic compound, pirfenidone, and the matrix metalloproteinase inhibitor, batimastat, during acute lung injury in mice. *Eur J Pharmacol*. 2001;426(1–2):113–121. https://doi.org/10.1016/S0022-0717(01)01209-2

32. Iyer SN, Wild JS, Schiedt MJ, Hyde DM, Margolin SB, Giri SN. Dietary intake of pirfenidone ameliorates bleomycin-induced lung fibrosis in hamsters. *J Lab Clin Med*. 1995;125(6):779–785. https://www.ncbi.nlm.nih.gov/pubmed/7539478. Accessed May 17, 2020.

33. Schelegle ES, Mansoor JK, Giri S. Pirfenidone attenuates bleomycin-induced changes in pulmonary functions in hamsters. *Proc Soc Exp Biol Med*. 1997;216(3):392–397. https://doi.org/10.3181/00379727-216-44187

34. Shi Q, Liu X, Bai Y, et al. In vitro effects of pirfenidone on cardiac fibroblasts: proliferation, myofibroblast differentiation, migration and cytokine secretion. *Proc Natl Acad Sci USA*. 2011;6(11). https://doi.org/10.1073/pnas.0909893107

35. Dixon P, Ghosh T, Mondal K, Konar A, Chauhan A, Hazra S. Controlled delivery of pirfenidone through vitamin E-loaded contact lens ameliorates corneal inflammation. *Drug Deliv Transl Res*. 2018;8(5):1114–1126. https://doi.org/10.1007/s13346-018-0541-5

36. Lopez-de-la Mora DA, Sanchez-Roque C, Montoya-Buelna M, et al. Role and new insights of pirfenidone in fibrotic diseases. *Int J Med Sci*. 2015;12(10):840–847. https://doi.org/10.7573/ijms.11579

37. Bergeron A, Soler P, Kambouchner M, et al. Cytokine profiles in idiopathic pulmonary fibrosis suggest an important role for TGF-β and IL-10. *Eur Respir J*. 2003;22(1):69–76. https://doi.org/10.1183/09031936.03.00014703

38. Bizargity P, Liu F, Wang L, Hancock WW, Visner GA. Inhibitory effects of pirfenidone on dendritic cells and lung allograft rejection. *Transplantation*. 2012;94(2):114–122. https://doi.org/10.1097/TP.0b013e3182584879

39. Visner GA, Liu F, Bizargity P, et al. Pirfenidone inhibits T-cell activation, proliferation, cytokine and chemokine production, and host alloresponses. *Transplantation*. 2009;88:330–338. https://doi.org/10.1097/TP.0b013e3181ea3392

40. Grattendick KJ, Nakashima JM, Feng L, Giri SN, Margolin SB. Effects of three anti-TNF-α drugs: etanercept, infliximab and adalimumab on release of TNF-α in medium and TNF-α associated with the cell in vitro. *Int J Med Sci*. 2010;6(11). https://doi.org/10.7573/ijms.11579

41. Liu H, Dre W, Cheng Y, Visner GA. Pirfenidone inhibits inflammatory responses and ameliorates allograft injury in a rat lung transplant model. *J Thorac Cardiovasc Surg*. 2005;130(3):852–858. https://doi.org/10.1016/j.jtcvs.2005.04.012

42. Saito M, Chen-Yoshikawa TF, Suetugru K, et al. Pirfenidone alleviates lung ischemia-reperfusion injury in a rat model. *J Thorac Cardiovasc Surg*. 2019;158(1):289–296. https://doi.org/10.1016/j.jtcvs.2018.08.098

43. Iyer SN, Hyde DM, Giri SN. Anti-inflammatory effect of pirfenidone in the bleomycin-hamster model of lung inflammation. *Inflammation*. 2000;24(5):477–491. https://doi.org/10.1023/A:100708313370

44. Rasooli R, Kamali Y, Mandegary A. Effects of pirfenidone, vitamin E, and pirfenidone–vitamin E combination in paracetamol-induced pulmonary fibrosis. *Comp Clin Path*. 2020;29:667–673. https://doi.org/10.1007/s00580-020-03104-0

45. Li Y, Li H, Liu S, et al. Pirfenidone ameliorates lipopolysaccharide-induced pulmonary inflammation and fibrosis by blocking NLRP3 inflammasome activation. *Mol Immunol*. 2018;99:134–144. https://doi.org/10.1016/j.molimm.2018.05.003

46. Wollin L, Wex E, Pautsch A, et al. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. *Eur Respir J*. 2015;46(5):1434–1445. https://doi.org/10.1183/09031936.00174914

47. Schmid U, Doege C, Dallinger C, Freiwald M. Population pharmacokinetics of nintedanib in patients with idiopathic pulmonary fibrosis. *Pulm Pharmacol Ther*. 2018;48:136–143. https://doi.org/10.1016/j.pupt.2017.11.004

48. Crestani B, Huggins JT, Kaye M, et al. Long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: results from the open-label extension study, INPULSIS-ON. *Lancet Respir Med*. 2019;7(1):60–68. https://doi.org/10.1016/S2213-2600(18)30339-4
49. Hilberg F, Roth GJ, Krssak M, et al. Nintedanib_CanRes2008. Cancer Res. 2008;68(12):4774–4783. https://doi.org/10.1158/0008-5472.CAN-07-6307

50. Wollin L, Distler JHW, Redente EF, et al. Potential of nintedanib in treatment of progressive fibrosing interstitial lung diseases. Eur Respir J. 2019;54(3):1900161. https://doi.org/10.1183/13993003.01901-2019

51. Hostettler KE, Zhong J, Papakonstantinou E, et al. Anti-fibrotic effects of nintedanib in lung fibroblasts derived from patients with idiopathic pulmonary fibrosis. Respir Res. 2014;15(1):157. https://doi.org/10.1186/s12931-014-0157-3

52. Wollin L, Maillot I, Queniaux V, Holweg A, Ryffel B. Anti-fibrotic and anti-inflammatory activity of the Tyrosine Kinase inhibitor nintedanib in experimental models of lung fibrosis. J Pharmacol Exp Ther. 2014;349(2):209–220. https://doi.org/10.1124/jpet.113.208223

53. Wollin L, Ostermann A, Williams C. Nintedanib inhibits pro-fibrotic mediators from T cells with relevance to connective tissue disease-associated interstitial lung disease. Eur Respir J. 2017;50:PA903. https://doi.org/10.1183/13993003.congress-2017.PA903

54. Prasse A, Probst C, Bargagli E, et al. Serum CC-chemokine ligand 18 concentration predicts outcome in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2009;179(8):717–723. https://doi.org/10.1164/rccm.200808-1201OC

55. Bellamri T, Morzadec C, Joannes A, et al. Alteration of human macrophage phenotypes by the anti-fibrotic drug nintedanib. Int Immunopharmacol. 2019;72:112–123. https://doi.org/10.1016/j.intimp.2019.03.061

56. Huang J, Maier C, Zhang Y, et al. Nintedanib inhibits macrophage activation and ameliorates vascular and fibrotic manifestations in the mouse model of systemic sclerosis. Ann Rheum Dis. 2017;76(11):1941–1948. https://doi.org/10.1136/annrheumdis-2016-210823

57. Van Lieshout AWT, Fransen J, Flendrie M, et al. Circulating levels of the chemokine CCL18 but not CXCL16 are elevated and correlate with disease activity in rheumatoid arthritis. Ann Rheum Dis. 2007;66(10):1334–1338. https://doi.org/10.1136/ard.2006.066084

58. Taniguchi H, Ebina M, Kondoh Y, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J. 2010;35(4):821–829. https://doi.org/10.1183/09031936.0005209

59. Azuma A, Nukiwa T, Tsuboi E, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2005;171(9):1040–1047. https://doi.org/10.1164/rccm.200404-571OC

60. Vancheri C, Sebastiani A, Tomassetti S, et al. Pirfenidone in real life: a retrospective observational multicentre study in Italian patients with idiopathic pulmonary fibrosis. Respir Med. 2019;156:78–84. https://doi.org/10.1016/j.rmed.2019.08.006

61. Nathan SD, Costabel U, Albera C, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis and more advanced lung function impairment. Respir Med. 2019;153:44–51. https://doi.org/10.1016/j.rmed.2019.04.016

62. Loehr B, Drakopanagiotakis F, Bandelli GP, et al. Intraindividual response to treatment with pirfenidone in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2015;191(1):110–113. https://doi.org/10.1164/rccm.201406-1106LE

63. Noble PW, Albera C, Bradford WW, et al. Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials. Eur Respir J. 2016;47(1):243–253. https://doi.org/10.1183/13993003.00026-2015

64. Vancheri C, Keuter M, Richeldi L, et al. Nintedanib with add-on pirfenidone in idiopathic pulmonary fibrosis: results of the INJOURNEY trial. Am J Respir Crit Care Med. 2018;197(3):356–363. https://doi.org/10.1164/rccm.201706-1301OC

65. 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. Lancet Respir Med. 2020;2600(20):1–8. https://doi.org/10.1016/s2213-2600(20)30036-9

66. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med. 2019;381(18):1718–1727. https://doi.org/10.1056/NEJMoai1908681

67. FDA News Release. FDA approves first treatment for group of progressive interstitial lung diseases. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-group-progressive-interstitial-lung-diseases

68. Guenther A, Prasse A, Keuter M, et al. Late breaking abstract — exploring efficacy and safety of oral pirfenidone for progressive, non-IPF lung fibrosis (RELIEF). Eur Respir J. 2019;54:RCT1879. https://doi.org/10.1183/13993003.congress-2019.rct1879

69. Raimundo K, Solomon JJ, Olson AL, et al. Rheumatoid arthritis-Interstitial lung disease in the United States: prevalence, incidence, and healthcare costs and mortality. J Rheumatol. 2019;46(4):360–369. https://doi.org/10.3899/jrheum.1713115

70. Bongartz T, Nannini C, Medina-Velasquez YF, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis—a population-based study. Arthritis Rheum. 2010;62(6):1583–1591. https://doi.org/10.1002/art.27405

71. Hyldgaard C, Hilberg O, Pedersen AB, et al. A population-based cohort study of rheumatoid arthritis-associated interstitial lung disease: comorbidity and mortality. Ann Rheum Dis. 2017;76(10):1700–1706. https://doi.org/10.1136/annrheumdis-2017-211338

72. Olson AL, Swigris JJ, Sprunger DB, et al. Rheumatoid arthritis-Interstitial lung disease-associated mortality. Am J Respir Crit Care Med. 2011;183(3):372–378. https://doi.org/10.1164/rccm.201004-0622OC

73. Spagnolo P, Lee J, Sverzellati N, Rossi G, Cottin V. The lung in rheumatoid arthritis. Arthritis Rheumatol. 2018;70(10):1544–1554. https://doi.org/10.1002/art.40574
74. Balbir-Gurman A, Guralnik L, Yigla M, Braun-Moscovici Y, Hardak E. Imaging aspects of interstitial lung disease in patients with rheumatoid arthritis: literature review. *Autoimmun Rev*. 2018;17(2):87–93. https://doi.org/10.1016/j.autrev.2017.09.013

75. Juge P-A, Lee JS, Ebstein E, et al. MUC5B promoter variant and rheumatoid arthritis with interstitial lung disease. *N Engl J Med*. 2018;379(23):2209–2219. https://doi.org/10.1056/NEJMoa1801562

76. Newton CA, Oldham JM, Ley B, et al. Telomere length and genetic variant associations with interstitial lung disease progression and survival. *Eur Respir J*. 2019;53(4):1801641. https://doi.org/10.1183/13993003.01641-2018

77. Paulin F, Doyle TJ, Fletcher EA, Ascherman DP, Rosas IO. Rheumatoid arthritis-associated interstitial lung disease and idiopathic pulmonary fibrosis: shared mechanistic and phenotypic traits suggest overlapping disease mechanisms. *Rev Invest Clin*. 2015;67(5):280–286.

78. Kim EJ, Elicker BM, Maldonado F, et al. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. *Eur Respir J*. 2010;35(6):1322–1328. https://doi.org/10.1183/09031936.00092309

79. Koduri G, Norton S, Young A, et al. Interstitial pulmonary fibrosis has a poor prognosis in rheumatoid arthritis: results from an inception cohort. *Rheumatology*. 2010;49(8):1483–1489. https://doi.org/10.1093/rheumatology/keq035

80. Redente EF, Aguilar MA, Black BP, et al. Nintedanib reduces pulmonary fibrosis in a model of rheumatoid arthritis-associated interstitial lung disease. *Am J Physiol Lung Cell Mol Physiol*. 2018;314(6):L998–L1009. https://doi.org/10.1152/ajplung.00304.2017

81. Bombardieri M, Lewis M, Pitzalis C. Ectopic lymphoid neogenesis in rheumatic autoimmune diseases. *Nat Rev Rheumatol*. 2017;13(3):141–154. https://doi.org/10.1038/nrrheum.2016.217

82. Kakuwa T, Izumi S, Sakamoto K, Suzuki T, Ikura M, Sugiyama H. A successful treatment of rheumatoid arthritis-related interstitial pneumonia with nintedanib. *Respir Med Case Reports*. 2019;26:50–52. https://doi.org/10.1016/j.rmcr.2018.10.026

83. Cassone G, Sebastiani M, Vacchi C, Cerri S, Salvarani C, Manfredi A. Pirfenidone for the treatment of idiopathic pulmonary fibrosis associated to rheumatoid arthritis: a new scenario is coming? *Respir Med Case Reports*. 2020;30:101051. https://doi.org/10.1016/j.rmcr.2020.101051

84. Solomon JJ, Danoff SK, Goldberg HJ, et al. The design and rationale of the trial1 trial: a randomized double-blind phase 2 clinical trial of pirfenidone in rheumatoid arthritis-associated interstitial lung disease. *Adv Ther*. 2019;36(11):3279–3287. https://doi.org/10.1007/s12325-019-01086-2

85. Solomon JJ, Olson AL, Fischer A, Bull T, Brown KK, Raghu G. Scleroderma lung disease. *Eur Respir Rev*. 2013;22(127):6–19. https://doi.org/10.1183/09059180.0005512

86. Denton CP, Khanna D. Systemic sclerosis. *Lancet*. 2017;390(10103):1685–1699. https://doi.org/10.1016/S0140-6736(17)30933-9

87. Perelas A, Silver RM, Arrossi AV, Highland KB. Systemic sclerosis-associated interstitial lung disease. *Lancet Respir Med*. 2020;8(3):304–320. https://doi.org/10.1016/S2213-2600(19)30480-1

88. Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med*. 2006;354(25):2655–2666. https://doi.org/10.1016/j.nephro.2005.12.002

89. Tashkin DP, Roth MD, Clements PJ, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease: scleroderma lung study II (SLS-II), a double-blind, parallel group, randomised controlled trial. *Lancet Respir Med*. 2017;4(9):708–719. https://doi.org/10.1016/S2213-2600(16)30152-7

90. Miura Y, Saito T, Fujita K, et al. Clinical experience with pirfenidone in five patients with scleroderma-related interstitial lung disease. *Sarcoidosis Vasc Diffus Lung Dis*. 2014;31(3):235–238. https://pubmed.ncbi.nlm.nih.gov/25363224/. Accessed August 30, 2020.

91. Acharya N, Sharma SK, Mishra D, Dhooria S, Dhir V, Jain S. Efficacy and safety of pirfenidone in systemic sclerosis-related interstitial lung disease — a randomised controlled trial. *Rheumatol Int*. 2020;40(5):703–710. https://doi.org/10.1007/s12325-020-04565-w

92. Distler O, Highland KB, Gaulemann M, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med*. 2019;380(26):2518–2528. https://doi.org/10.1056/NEJMoa1903076

93. NCT03313180. A trial to evaluate the safety of long term treatment with nintedanib in patients with scleroderma related lung fibrosis. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03313180. Published 2020. Accessed August 30, 2020.

94. NCT03221257. Scleroderma lung study III – combining pirfenidone with mycophenolate. https://clinicaltrials.gov/ct2/show/NCT03221257?term=NCT03221257&draw=2&rank=1. Published 2017. Accessed August 30, 2020.

95. Selva-O’Callaghan A, Pinal-Fernandez I, Trallero-Araguas E, Milisenda JC, Grau-Junyent JM, Mammen AL. Classification and management of adult inflammatory myopathies. *Lancet Neurol*. 2018;17(9):816–828. https://doi.org/10.1016/S1474-4422(18)30254-0

96. Jeganathan N, Sathananthan M. Connective tissue disease-related interstitial lung disease: prevalence, patterns, predictors, prognosis, and treatment. *Lung*. 2020;1:3. https://doi.org/10.1007/s00408-020-00383-w

97. Cavagna L, Trallero-Araguas E, Meloni F, et al. Influence of antisynthetase antibodies specificities on antisynthetase syndrome clinical spectrum time course. *J Clin Med*. 2019;8(11):2013. https://doi.org/10.3390/jcm8112013
98. Ikeda S, Arita M, Morita M, et al. Interstitial lung disease in clinically amyopathic dermatomyositis with and without anti-MDA-5 antibody: to lump or split? *BMC Pulm Med*. 2015;15(1):159. https://doi.org/10.1186/s12890-015-0154-4

99. Meloni F, Cifrian JM, Pesci A, et al. Lung involvement and clinical characteristics in anti-MDA5 positive connective tissue diseases. *Eur Respir J*. 2018;52:OA3818. https://doi.org/10.1183/13993003.congress-2018.0a3818

100. Li T, Guo L, Chen Z, et al. Pirfenidone in patients with rapidly progressive interstitial lung disease associated with clinically amyopathic dermatomyositis. *Sci Rep*. 2016;6:33226. https://doi.org/10.1038/srep33226

101. NCT02821689. Pirfenidone in progressive interstitial lung disease associated with clinically amyopathic dermatomyositis — full text view. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02821689. Accessed August 30, 2020.

102. Roca F, Dominique S, Schmidt J, et al. Interstitial lung disease in primary Sjögren’s syndrome. *Autoimmun Rev*. 2017;16(1):48–54. https://doi.org/10.1016/j.autrev.2016.09.017

103. Manfredi A, Sebastiani M, Cerri S, et al. Prevalence and characterization of non-sicca onset primary Sjögren syndrome with interstitial lung involvement. *Clin Rheumatol*. 2017;36(6):1261–1268. https://doi.org/10.1007/s10067-017-3601-1

104. Enomoto Y, Nakamura Y, Colby TV, Inui N, Suda T. Pirfenidone for primary Sjögren’s syndrome-related fibrotic interstitial pneumonia. *Sarcoidosis Vasc Diffus Lung Dis*. 2017;34(1):91–96. https://doi.org/10.36141/svdld.v34i1.5091

105. Enomoto N, Egashira R, Tabata K, et al. Analysis of systemic lupus erythematosus-related interstitial pneumonia: a retrospective multicentre study. *Sci Rep*. 2019;9(1):7355. https://doi.org/10.1038/s41598-019-43782-7

106. Yang B-B, Man X-Y, Zheng M. Pirfenidone combined with corticosteroids in a patient with systemic lupus erythematosus-associated interstitial lung disease. *J Eur Acad Dermatology Venereol*. 2017;31(9):e388–e389. https://doi.org/10.1111/jdv.14192

107. 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(2):147–157. https://doi.org/10.1016/S2213-2600(19)30341-8