Monitoring and management of fibrosing interstitial lung diseases: a narrative review for practicing clinicians

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Abstract: Close monitoring of patients with fibrosing interstitial lung diseases (ILDs) is important to enable prompt identification and management of progressive disease. Monitoring should involve regular assessment of physiology (including pulmonary function tests), symptoms, and, when appropriate, high-resolution computed tomography. The management of patients with fibrosing ILDs requires a multidisciplinary approach and should be individualized based on factors such as disease severity, evidence of progression, risk factors for progression, comorbidities, and the preferences of the patient. In this narrative review, we discuss how patients with fibrosing ILDs can be effectively monitored and managed in clinical practice.

Keywords: connective tissue diseases, pulmonary fibrosis, pulmonary function tests, treatment outcome

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Introduction

Interstitial lung diseases (ILDs) are a large and heterogeneous group of disorders, which in some cases become fibrotic and progressive. Idiopathic pulmonary fibrosis (IPF) is relentlessly progressive and may be regarded as the ‘prototypic’ progressive fibrosing ILD. Other ILDs, such as fibrotic hypersensitivity pneumonitis (HP) and those associated with autoimmune diseases, may also develop progressive fibrosing disease behavior characterized by worsening respiratory symptoms and hypoxemia, decline in lung function, increasing fibrotic abnormalities on high-resolution computed tomography (HRCT), and early mortality.

Diagnosis of fibrosing ILDs

A differential diagnosis of ILD is made based on a comprehensive medical history, clinical examination, serologies, HRCT, and, if needed, bronchoalveolar lavage or lung biopsy. Multidisciplinary discussion, involving a pulmonologist, a radiologist, and, where appropriate, a rheumatologist and pathologist, is regarded as the gold standard for differential diagnosis of ILD. This approach may be particularly valuable in the diagnosis of autoimmune disease-related ILDs. Some patients do not fulfill the criteria for a specific ILD diagnosis even after multidisciplinary discussion; in such cases, a ‘working diagnosis’ may be appropriate but should be re-assessed regularly. Patients with interstitial lung abnormalities (ILAs) that do not meet criteria for diagnosis of ILD and who have risk factors for progression to ILD such as smoking or other inhalational exposures, or evidence of fibrosis, should be monitored closely to ensure that progression to ILD is detected promptly.

Diagnostic criteria for IPF developed by the Fleischner Society and jointly by the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society proposed similar categories to interpret HRCT scans in patients suspected of having ILD. The categories proposed by the Fleischner Society are: typical usual interstitial pneumonia (UIP) CT pattern; probable UIP CT pattern; CT pattern indeterminate for UIP; CT features most consistent with a non-IPF diagnosis. A typical UIP pattern is defined by a peripheral and basal distribution of reticulation,
architectural distortion, traction bronchiectasis, and subpleural honeycombing (Figure 1). A probable UIP pattern has similar features but without honeycombing. Typical and probable UIP patterns usually preclude biopsy in patients suspected of having IPF. A pattern indeterminate for UIP has some inconspicuous features suggestive of a non-UIP pattern such as a lack of an apical-basilar gradient or scattered mosaic attenuation. Features most consistent with a non-IPF diagnosis include atypical distributions such as mid- or upper-lung zone predominant fibrosis or peribronchovascular predominance with subpleural sparing. Additional features that suggest an alternative diagnosis include extensive ground-glass opacities (without acute exacerbation), extensive mosaic attenuation with sharply defined lobular air trapping on expiration involving three or more lobes, diffuse nodules or cysts. Certain patterns of fibrosis on HRCT are suggestive of specific diagnoses. Non-specific interstitial pneumonia (NSIP) typically manifests with peripheral ground-glass opacities that often demonstrate subpleural sparing (Figure 2(a)). Certain myositis syndromes such as the anti-synthetase syndrome often manifest with a combined NSIP/organizing pneumonia (OP) pattern (Figure 2(b)). The fibrotic form of HP should be considered with the ‘three-density pattern’ (i.e. normal lung, hyperlucent lung and ground-glass opacities), mid- and upper-lung zone distribution of fibrosis with ground-glass opacities, mosaic lung attenuation and expiratory air trapping (Figure 2(c) and (d)).

**Progression of fibrosing ILDs**

IPF is always progressive, but its rate of progression varies among individuals and acute exacerbations of the disease are unpredictable and often fatal.\(^1,10\) Progressive disease behavior is also observed in a subgroup of patients with other fibrosing ILDs including fibrotic HP\(^5,11\) ILDs associated with autoimmune diseases such as systemic sclerosis\(^12,13\), rheumatoid arthritis\(^4,11\) and anti-synthetase myositis;\(^16\) sarcoidosis-related ILD;\(^17\) exposure-related ILDs;\(^18\) and unclassifiable ILD.\(^19\)

When a typical UIP-fibrotic pattern is present on HRCT, decline in lung function in patients with other ILDs may be as rapid as in patients with IPF.\(^3,19–24\) As well as decline in lung function, progression of ILD may manifest as an increase in the extent of fibrotic abnormalities on HRCT\(^12,25,26\) or as deterioration in symptoms, exercise capacity, or oxygen saturation during exercise, and quality of life.\(^27–30\)

Although the course of fibrosing ILD is difficult to predict, observational studies have identified a number of factors associated with mortality. A greater extent of fibrosis on HRCT has been associated with mortality in studies across ILDs.\(^12,21,26,31–35\) In an analysis of 519 patients with systemic sclerosis from a nationwide Norwegian cohort, the standardized mortality ratio over a mean observation period of 10 years increased from approximately 2 in patients with no fibrosis on HRCT to 5 in patients with an extent of fibrosis > 10% and 8 in those with an extent of fibrosis > 25%.\(^12\) In an analysis of data from 159 patients with RA-ILD, patients with an
extent of fibrosis $\geq 20\%$ on HRCT had over twice the risk of dying during a 14-year follow-up period than patients with a lesser extent of fibrosis.\textsuperscript{31} In patients with HP, the predominant presence of fibrosis on HRCT or lung biopsy or both is the strongest predictor of mortality and led to the re-categorization of HP into fibrotic and non-fibrotic subtypes in the latest international diagnostic guidelines.\textsuperscript{5} A decline in forced vital capacity (FVC) of $\geq 10\%$ of the predicted value has consistently been associated with mortality in patients with ILDs.\textsuperscript{3,24,34,36–38} Among 331 patients with progressive fibrosing ILDs who received placebo in the INBUILD trial, a relative decline in FVC $\geq 10\%$ predicted was associated with a more than three-fold increase in the risk of death over 52 weeks.\textsuperscript{24} Among 137 patients with RA-ILD at a US center, patients with an absolute decline in FVC $\geq 10\%$ predicted at any time over a median follow-up of 4.8 years had a 2.5-fold greater death rate than patients without such a decline.\textsuperscript{36} An analysis of 112 patients with chronic HP found that median survival was 53 months in patients who had an absolute decline in FVC $\geq 10\%$ predicted 6–12 months after diagnosis, compared with 139 months among those who did not.\textsuperscript{38} Factors specific to particular ILDs should also be considered. In patients with HP, lower lymphocyte count in bronchoalveolar lavage fluid\textsuperscript{39} and continued exposure to an inciting antigen\textsuperscript{40} are associated with worse outcome. In patients with autoimmune disease-related ILDs, several autoantibodies have been associated with a greater risk of progression of ILD; for example, anti-topoisomerase I (Scl-70) antibody in patients
with early systemic sclerosis and anti-cyclic citrullinated peptide antibody in patients with rheumatoid arthritis. In patients with antisyntetase myositis-ILD, negativity for anti-Jo-1 antibodies is associated with higher mortality.

**Monitoring of fibrosing ILDs**

Close monitoring of patients with ILDs is important to assess disease progression and inform patient care, such as initiation of pharmacotherapy and counseling. Monitoring should involve regular assessment of symptoms, physiology (e.g. pulmonary function and six-minute walk testing) and, where appropriate, HRCT. International guidelines suggest that patients with IPF should have FVC and diffusing capacity of the lung for carbon monoxide (DLco) measured every 3 to 6 months (or sooner if clinically indicated). The 6-minute walk test can be a useful tool to assess disease progression in patients with IPF, but may be more challenging to perform in patients with rheumatic diseases due to the impact of extra-pulmonary problems affecting ambulation such as joint pain and fatigue. In addition, evaluation for oxygen desaturation and need for supplemental oxygen during a walk test in patients with Raynaud’s phenomenon may be confounded by falsely low peripheral oxygen saturation readings (SpO2) due to reduced digital perfusion. In such patients, it may be useful to perform 6MWTs using both ear and finger pulse oximetry. Monitoring changes in symptoms may be based on a simple overall assessment, but questionnaires can also be used to provide a more objective measure of disease progression. When interpreting patient-reported outcomes in patients with ILDs, it should be considered that deterioration in symptoms, exercise capacity, or quality of life may reflect deterioration in manifestations of disease other than ILD, or new or worsening comorbidities such as pulmonary hypertension. Experts in the management of patients with SSc-ILD have proposed that patients should be monitored for disease progression every 3–6 months using multiple methods, including symptom assessment, pulmonary function tests, exercise-induced blood oxygen desaturation and, where appropriate, HRCT. However, for most ILDs, there are no guidelines for how patients should be monitored. An individualized approach is essential, taking into account factors such as disease severity, evidence of progression, risk factors for progression, comorbidities, quality of life, and the patient’s preferences (Figure 3). Regular monitoring of patients with ILDs also provides an opportunity to screen for onset or deterioration of other disease manifestations and comorbidities. Imaging of patients with ILD and deteriorating respiratory symptoms may reveal problems other than progression of ILD such as lung carcinoma (Figure 4).

There are no consensus recommendations regarding imaging follow-up for patients with progressive fibrosing ILDs. Many providers will obtain an HRCT at the patient’s initial presentation and then every 12–18 months to assess for progression. There are no data to support the use of chest

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**Figure 3.** Proposed approach to monitoring and management of non-IPF fibrosing ILDs.
radiography over HRCT for follow-up of patients with confirmed ILD. More frequent imaging is often obtained when patients present with acute or worsening symptoms or declining pulmonary function tests.

Management of fibrosing ILDs
IPF is an inexorably progressive disease. As such, barring any contraindications, patients with IPF should be offered prompt treatment with an approved antifibrotic therapy (nintedanib or pirfenidone) to slow the progression of their disease. Immunosuppression should not be used for chronic treatment of IPF and there is evidence that it may be harmful. As IPF progresses, action should be taken to optimize symptom relief and preserve quality of life, including referral for palliative care as appropriate. For fibrosing ILDs other than IPF, the optimal sequence, combination and timing of use of immunosuppressants, nintedanib, and supportive therapies has not been established. Management of these diseases requires a multidisciplinary and individualized approach that takes into account the severity of ILD, evidence of progression, other disease manifestations and comorbidities, as well as the patient’s preferences (Figure 3). For exposure-related ILDs, such as HP, drug-induced ILD, and occupational ILDs/pneumoconioses, it is essential to identify, eliminate, and avoid culprit exposures.

Based on data from the INPULSIS, SENSCIS and INBUILD trials (Table 1), nintedanib 150 mg twice daily (or 100 mg twice daily for patients with mild hepatic impairment) has been approved by regulatory authorities including the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of IPF, for slowing decline in FVC in patients with ILD associated with systemic sclerosis, and for the treatment of chronic fibrosing ILDs with a progressive phenotype. Although the INBUILD trial was not designed or powered to evaluate individual ILDs, subgroup analyses suggested that there was no heterogeneity in the rate of decline in FVC in the placebo group or in the treatment effect of nintedanib across subgroups by ILD diagnosis (Figure 5). Further, a comparison of data from the placebo groups of the INPULSIS and INBUILD trials showed that the rate of decline in FVC over 52 weeks was similar in patients with IPF as in patients with other fibrosing ILDs and a UIP-like fibrotic pattern on HRCT (mean −223.2 versus −214.6 mL/year). Across all clinical trials, the adverse events associated with nintedanib were predominantly gastrointestinal events, particularly diarrhea. Diarrhea should be managed promptly with adequate hydration and antidiarrheal agent (e.g. loperamide), and with dose reduction from 150 mg twice daily to 100 mg twice daily or treatment interruption if symptoms persist. Liver enzymes and bilirubin should be monitored prior to the

Figure 4. High-resolution computed tomography scans of the chest from a 68-year-old man with idiopathic pulmonary fibrosis and a right upper lobe lung cancer. Coronal images obtained in 2015 (left), 2018 (middle) and 2020 (right) show an enlarging subpleural nodule (arrow) in the right upper lobe proven to represent a primary lung cancer. Note peripheral right lower lobe reticulation and honeycombing in keeping with a usual interstitial pneumonia (UIP) pattern of fibrosis.
| Trial | Patient population/key inclusion criteria | Drug investigated | Number of patients treated | Primary endpoint results |
|-------|------------------------------------------|------------------|---------------------------|-------------------------|
| INPULSIS trials⁵⁷ | Patients with IPF, FVC ⩾ 50% predicted, DLco 30% to 79% predicted | Nintedanib | 1061 | INPULSIS-1: Rate of decline in FVC (mL/year) over 52 weeks: −114.7 mL/year in nintedanib group and −239.9 mL/year in placebo group (p < 0.001 for difference) INPULSIS-2: Rate of decline in FVC (mL/year) over 52 weeks: −113.6 mL/year in nintedanib group and −207.3 mL/year in placebo group (p < 0.001 for difference) |
| SENSIC trial⁵⁸ | • Patients with SSc-ILD and > 10% extent of fibrotic ILD on HRCT (based on assessment of the whole lung), FVC ⩾ 40% predicted, DLco 30 to 89% predicted  
• No requirement for evidence of recent ILD progression  
• Patients taking prednisone ⩽ 10 mg/day and/or stable therapy with mycophenolate or methotrexate for ⩾ 6 months prior to randomization were eligible to participate | Nintedanib | 576 | Rate of decline in FVC (mL/year) over 52 weeks: −52.4 mL/year in nintedanib group and −93.3 mL/year in placebo group (p = 0.04 for difference) |
| INBUILD trial⁵⁹ | • Patients with chronic fibrosing ILDs other than IPF with FVC ⩾ 45% predicted, DLco 30 to 79% predicted, who met ⩾ 1 of the following criteria for ILD progression within the 24 months before screening, despite management deemed appropriate in clinical practice:  
  - Relative decline in FVC ⩾ 10% predicted  
  - Relative decline in FVC ⩾ 5 to <10% predicted and worsened respiratory symptoms  
  - Relative decline in FVC ⩾ 5 to <10% predicted and increased extent of fibrosis on HRCT  
  - Worsened respiratory symptoms and increased extent of fibrosis on HRCT | Nintedanib | 663 | Rate of decline in FVC (mL/year) over 52 weeks: −80.8 mL/year in the nintedanib group and −187.8 mL/year in the placebo group (p < 0.001 for difference) |
| CAPACITY trials⁶⁰ | Patients with IPF, FVC ⩾ 50% predicted, DLco ⩾ 35% predicted, FVC ⩾ 90% predicted and/or DLco ⩽ 90% predicted, 6MWT ⩾ 150m | Pirfenidone | 779 | CAPACITY 1: Change from baseline in FVC % predicted at week 72: −9.0% in pirfenidone group and −9.6% in placebo group (p = 0.501)  
CAPACITY 2: Change from baseline in FVC % predicted at week 72: −8.0% in pirfenidone groups and −12.4% in placebo group (p = 0.001) |
| ASCEND trial⁶¹ | Patients with IPF, FVC 50 to 90% predicted, DLco 30 to 90% predicted | Pirfenidone | 555 | Change from baseline in FVC % predicted at week 52 was significantly lower with pirfenidone versus placebo (p < 0.001) |

FDA, US Food and Drug Administration; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung diseases; IPF, idiopathic pulmonary fibrosis; 6MWT, 6-minute walk test distance; SSc, systemic sclerosis.
initiation of nintedanib, at regular intervals during the first 3 months of treatment, and then periodically or as clinically indicated.65

Pirfenidone 801 mg three times daily has been approved for the treatment of IPF, based on demonstration of a reduced rate of decline in FVC compared with placebo in the ASCEND trial61 (Table 1). A randomized, placebo-controlled trial of pirfenidone in 253 patients with progressive fibrosing unclassifiable ILD failed to meet its primary endpoint of change in FVC % predicted over 24 weeks measured by daily home spirometry, but in-clinic spirometry suggested that pirfenidone reduced the rate of decline in FVC, with a mean decline of −17.8 mL in the pirfenidone group compared to −113.0 mL in the placebo group.19 Commonly reportedly side-effects associated with pirfenidone included gastrointestinal disorders, photosensitivity and rash.19,61,60 Patients are advised to avoid exposure to sunlight and to wear protective clothing and sunscreen. Adverse events can be managed by dose reductions or treatment interruptions.66 Liver enzymes and bilirubin should be monitored prior to the initiation of pirfenidone, monthly for the first 6 months, and every 3 months thereafter.66 No clinical trials assessing the efficacy of pirfenidone in treating ILDs other than IPF and unclassifiable ILD have been completed but several are in progress (NCT03260556, NCT02808871, NCT03856853).

In patients with IPF, treatment with nintedanib plus add-on pirfenidone or pirfenidone plus add-on nintedanib over 24 weeks demonstrated a safety and tolerability profile in line with the adverse event profiles of each drug.67,68 Few data are available on switching between antifibrotic therapies. Among 782 patients in a large US registry, most patients taking an antifibrotic therapy at enrollment were still taking the same therapy approximately 6 months later.69

Most patients with autoimmune diseases are receiving immunosuppressant therapy to treat their systemic disease irrespective of whether they have ILD. There is evidence from randomized, double-blind, controlled trials to support the use of mycophenolate mofetil and cyclophosphamide in the treatment of SSc-ILD70–72 and the use of these therapies has been recommended by experts in the field.46–48 No other randomized, double-blind controlled trials have demonstrated a benefit of immunosuppressant therapy in the treatment of autoimmune disease-associated ILDs, but they are widely used,73 likely based on extrapolation.
from findings in patients with SSc-ILD and the findings of uncontrolled studies. High RA disease activity has been associated with increased risk of developing RA-ILD, suggesting that treatment of underlying rheumatic disease may also influence ILD risk. Immunosuppressants are also frequently used to treat fibrotic HP, but in the absence of well-designed prospective randomized controlled trials, it remains unclear whether they are effective in slowing its progression.

At present, neither expert consensus nor clinical practice guidelines exist for specific pharmacologic treatment of progressive fibrosing ILDs. If the decision is made to start treatment, we believe that an initial ILD diagnosis established by a multidisciplinary discussion should inform the initial treatment choice (e.g. antifibrotics for IPF, immunosuppression for CTD-ILDs and non-fibrotic HP). If immunosuppression is contraindicated, not tolerated, or declined due to patient preference, nintedanib (the only antifibrotic drug currently approved for non-IPF ILD indications) should be considered. Of note, high-quality data are lacking regarding optimal first-line treatment for various non-IPF ILDs. For patients with progressive fibrosing ILD, as defined by the INBUILD trial criteria, despite or in lieu of immunosuppression (e.g. due to recurrent infection), nintedanib may be a reasonable choice as monotherapy or as add-on combination therapy with immunosuppressive agents.

Patients with fibrosing ILDs may benefit from non-pharmacological therapies such as smoking cessation, pulmonary rehabilitation, exercise training, and attendance at patient support groups (Figure 6). An official clinical practice guideline recently published by the ATS provided strong recommendations for long-term oxygen use in patients with ILD and severe chronic resting hypoxemia and conditional recommendations for oxygen use in patients with ILD and severe exertional hypoxemia, while recognizing that patients and their caregivers need education on how to use oxygen equipment.
The treatment of patients with fibrosing ILDs should be re-assessed if symptoms or lung function deteriorate, ideally based on multidisciplinary discussion. Select patients with rapidly progressive SSC at risk of organ failure may be considered for autologous hematopoietic stem cell transplantation at specialized centers, based on a careful assessment of the potential risks-benefits for the individual. A consensus statement from the International Society for Heart and Lung Transplantation (ISHLT) specified that referral for lung transplantation should be based on predictors of poor prognosis such as histopathologic or radiographic evidence of UIP or fibrosing NSIP, impaired lung function (FVC < 80% predicted, DLco < 40% predicted), or supplemental oxygen use. The timing of listing for transplantation should be based on factors indicating physiological decline such as a decline in FVC > 10% predicted, a decline in DLco ≥ 15% predicted over 6 months, or hospitalization due to respiratory decline. Similar guidance was provided for patients with autoimmune disease-associated ILD who have not responded to treatment and do not have extrapulmonary contraindications to transplantation. Survival rates after lung transplant appear to be similar between patients with IPF and patients with autoimmune disease-associated ILDs or sarcoidosis. Survival rates after lung transplant among patients with HP may be greater but more data are needed.

**Conclusions**

Fibrosing ILDs have an unpredictable clinical course. A proportion of patients with fibrosing ILDs develop a progressive phenotype characterized by worsening symptoms, declining exercise capacity, increasing hypoxemia, decline in lung function, increasing fibrotic abnormalities on HRCT, and early mortality. Patients with fibrosing ILDs require close monitoring to ensure that disease progression is identified promptly. The management of patients with fibrosing ILDs requires a multidisciplinary and individualized approach.

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References
1. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018; 198: e44–e68.

2. Wells AU, Brown KK, Flaherty KR, et al. What’s in a name? That which we call IPF, by any other name would act the same. *Eur Respir J* 2018; 51: 1800692.

3. Cottin V, Wollin L, Fischer A, et al. Fibrosing interstitial lung diseases: knowns and unknowns. *Eur Respir Rev* 2019; 28: 180100.

4. Lynch DA, Sverzellati N, Travis WD, et al. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society white paper. *Lancet Respir Med* 2018; 6: 138–153.

5. Raghu G, Remy-Jardin M, Ryerson CJ, et al. Diagnosis of hypersensitivity pneumonitis in adults. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2020; 202: e36–e69.

6. Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013; 188: 733–748.

7. Furini F, Carnevale A, Casoni GL, et al. The role of the multidisciplinary evaluation of interstitial lung diseases: systematic literature review of the current evidence and future perspectives. *Front Med* 2019; 6: 246.

8. Ageeley G, Souza C, De Boer K, et al. The impact of multidisciplinary discussion (MDD) in the diagnosis and management of fibrotic interstitial lung diseases. *Can Respir J* 2020; 2020: 9026171.

9. Hatabu H, Hunninghake GM, Richeldi L, et al. Interstitial lung abnormalities detected incidentally on CT: a position paper from the Fleischner Society. *Lancet Respir Med* 2020; 8: 726–737.

10. Collard HR, Ryerson CJ, Corte TJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. *Am J Respir Crit Care Med* 2016; 194: 265–275.

11. Salisbury ML, Gu T, Murray S, et al. Hypersensitivity pneumonitis: radiologic phenotypes are associated with distinct survival time and pulmonary function trajectory. *Chest* 2019; 155: 699–711.

12. Hoffmann-Vold AM, Fretheim H, Halse AK, et al. Tracking impact of interstitial lung disease in systemic sclerosis in a complete nationwide cohort. *Am J Respir Crit Care Med* 2019; 200: 1258–1266.

13. Hoffmann-Vold AM, Allanore Y, Alves M, et al. Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database. *Ann Rheum Dis* 2021; 80: 219–227.

14. Zamora-Legoff JA, Krause ML, Crowson CS, et al. Progressive decline of lung function in rheumatoid arthritis-associated interstitial lung disease. *Arthritis Rheumatol* 2017; 69: 542–549.

15. Kawano-Dourado L, Doyle TJ and Bonfiglioli K. Baseline characteristics and progression of a spectrum of interstitial lung abnormalities and disease in rheumatoid arthritis. *Chest* 2020; 158: 1546–1554.

16. Zamora AC, Hoskote SS, Abascal-Bolado B, et al. Clinical features and outcomes of interstitial lung disease in anti-Jo-1 positive antisyntetase syndrome. *Respir Med* 2016; 118: 39–45.

17. Kirkil G, Lower EE and Baughman RP. Predictors of mortality in pulmonary sarcoidosis. *Chest* 2018; 153: 105–113.

18. Khalil N, Churg A, Muller N, et al. Environmental, inhaled and ingested causes of pulmonary fibrosis. *Toxicol Pathol* 2007; 35: 86–96.

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

20. Kim EJ, Elicker BM, Maldonado F, et al. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. *Eur Respir J* 2010; 35: 1322–1328.

21. Jacob J, Hirani N, van Moorsel CHM, et al. Predicting outcomes in rheumatoid arthritis related interstitial lung disease. *Eur Respir J* 2019; 53: 1800869.

22. Singh N, Varghese J, England BR, et al. Impact of the pattern of interstitial lung disease on mortality in rheumatoid arthritis: a systematic literature review and meta-analysis. *Semin Arthritis Rheum* 2019; 49: 358–365.

23. Alberti ML, Malet Ruiz JM, Fernández ME, et al. Comparative survival analysis between idiopathic pulmonary fibrosis and chronic hypersensitivity pneumonitis. *Pulmonology* 2020; 26: 3–9.

24. Brown KK, Martinez FJ, Walsh SLF, et al. The natural history of progressive fibrosing interstitial lung diseases. *Eur Respir J* 2020; 55: 200085.
25. Lee HY, Lee KS, Jeong YJ, et al. High-resolution CT findings in fibrotic idiopathic interstitial pneumonias with little honeycombing: serial changes and prognostic implications. *Am J Roentgenol* 2012; 199: 982–989.

26. Walsh SL, Sverzellati N, Devaraj A, et al. Chronic hypersensitivity pneumonitis: high resolution computed tomography patterns and pulmonary function indices as prognostic determinants. *Eur Radiol* 2012; 22: 1672–1679.

27. Lama VN, Flaherty KR, Toews GB, et al. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003; 168: 1084–1090.

28. Baron M, Sutton E, Hudson M, et al. The relationship of dyspnoea to function and quality of life in systemic sclerosis. *Ann Rheum Dis* 2008; 67: 644–650.

29. Khadawardi H and Mura M. A simple dyspnoea scale as part of the assessment to predict outcome across chronic interstitial lung disease. *Respirology* 2017; 22: 501–507.

30. Kreuter M, Swigris J, Pittrow D, et al. The clinical course of idiopathic pulmonary fibrosis and its association to quality of life over time: longitudinal data from the INSIGHTS-IPF registry. *Respir Res* 2019; 20: 59.

31. Kelly CA, Saravanan V, Nisar M, et al. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics —a large multicenter UK study. *Rheumatology* 2014; 53: 1676–1682.

32. Walsh SL, Sverzellati N, Devaraj A, et al. Connective tissue disease related fibrotic lung disease: high resolution computed tomographic and pulmonary function indices as prognostic determinants. *Thorax* 2014; 69: 216–222.

33. Jacob J, Bartholmai BJ, Rajagopalan S, et al. Automated computer-based CT stratification as a predictor of outcome in hypersensitivity pneumonitis. *Eur Radiol* 2017; 27: 3635–3646.

34. Doubková M, Svancara J, Svoboda M, et al. EMPIRE Registry, Czech part: impact of demographics, pulmonary function and HRCT on survival and clinical course in idiopathic pulmonary fibrosis. *Clin Respir J* 2018; 12: 1526–1535.

35. Fu Q, Wang L, Li L, et al. Risk factors for progression and prognosis of rheumatoid arthritis-associated interstitial lung disease: single center study with a large sample of Chinese population. *Clin Rheumatol* 2019; 38: 1109–1116.

36. Solomon JJ, Chung JH, Cosgrove GP, et al. Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. *Eur Respir J* 2016; 47: 588–596.

37. Goh NS, Hoyles RK, Denton CP, et al. Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. *Arthritis Rheumatol* 2017; 69: 1670–1678.

38. Gimenez A, Storrer K, Kuranishi L, et al. Change in FVC and survival in chronic fibrotic hypersensitivity pneumonitis. *Thorax* 2017; 73: 391–392.

39. De Sadeleer LJ, Hermans F, De Dycker E, et al. Impact of BAL lymphocytosis and presence of honeycombing on corticosteroid treatment effect in fibrotic hypersensitivity pneumonitis: a retrospective cohort study. *Eur Respir J* 2020; 55: 1901983.

40. Fernández Pérez ER, Swigris JJ, Forssen AV, et al. Identifying an inciting antigen is associated with improved survival in patients with chronic hypersensitivity pneumonitis. *Chest* 2013; 144: 1644–1651.

41. Assassi S, Sharif R, Lasky RE, et al. Predictors of interstitial lung disease in early systemic sclerosis: a prospective longitudinal study of the GENISOS cohort. *Arthritis Res Ther* 2010; 12: R166.

42. Rojas-Serrano J, Herrera-Bringas D, Mejía M, et al. Prognostic factors in a cohort of antisyntetase syndrome (ASS): serologic profile is associated with mortality in patients with interstitial lung disease (ILD). *Clin Rheumatol* 2015; 34: 1563–1569.

43. 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: 788–824.

44. Lancaster LH. Utility of the six-minute walk test in patients with idiopathic pulmonary fibrosis. *Multidiscip Respir Med* 2018; 13: 45.

45. Swigris JJ, Brown KK, Abdulqawi R, et al. Patients’ perceptions and patient-reported outcomes in progressive-fibrosing interstitial lung diseases. *Eur Respir Rev* 2018; 27: 180075.

46. Hoffmann-Vold AM, Maher TM, Philpot EE, et al. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. *Lancet Rheumatol* 2020; 2: E71–E83.

47. Roofeh D, Distler O, Allanore Y, et al. Treatment of systemic sclerosis–associated interstitial lung disease.
disease: lessons from clinical trials. J Scleroderma Relat Disord 2020; 5: 61–71.
48. Perelas A, Silver RM, Arrossi AV, et al. Systemic sclerosis-associated interstitial lung disease. Lancet Respir Med 2020; 8: 304–320.
49. Elicker BM, Kallianos KG and Henry TS. The role of high-resolution computed tomography in the follow-up of diffuse lung disease. Eur Respir Rev 2017; 26: 170008.
50. Maher TM and Strek ME. Antifibrotic therapy for idiopathic pulmonary fibrosis: time to treat. Respir Res 2019; 20: 205.
51. Raghu G, Rochwer B, Zhang Y, et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. Am J Respir Crit Care Med 2015; 192: e3–e19.
52. Raghu G, Anstrom KJ, King TE, et al. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med 2012; 366: 1968–1977.
53. Wuyts WA, Wijsenbeek M, Bondue B, et al. Idiopathic pulmonary fibrosis: best practice in monitoring and managing a relentless fibrotic disease. Respiration 2020; 99: 73–82.
54. George PM, Spagnolo P, Kreuter M, et al. Progressive fibrosing interstitial lung disease: clinical uncertainties, consensus recommendations, and research priorities. Lancet Respir Med 2020; 8: 925–934.
55. Varone F, Sgalla G, Iovene B, et al. Progressive fibrosing interstitial lung disease: a proposed integrated algorithm for management. Ann Am Thorac Soc 2020; 17: 1199–1203.
56. Wijsenbeek M and Cottin V. Spectrum of fibrotic lung diseases. N Engl J Med 2020; 383: 958–968.
57. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014; 370: 2071–2082.
58. Distler O, Highland KB, Gahlemann M, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med 2019; 380: 2518–2528.
59. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med 2019; 381: 1718–1727.
60. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 2011; 377: 1760–1769.
61. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014; 370: 2083–2092.
62. Wells AU, Flaherty KR, Brown KK, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet Respir Med 2020; 8: 453–460.
63. Lancaster L, Crestani B, Hernandez P, et al. Safety and survival data in patients with idiopathic pulmonary fibrosis treated with nintedanib: pooled data from six clinical trials. BMJ Open Respir Res 2019; 6: e000397.
64. Seibold JR, Maher TM, Highland KB, et al. Safety and tolerability of nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from the SENSCIS trial. Ann Rheum Dis 2020; 79: 1478–1484.
65. Boehringer Ingelheim. OFEV (nintedanib) prescribing information, 2020, https://docs.boehringer-ingelheim.com/Prescribing%20Information/Pis/Ofev/ofev.pdf
66. Genentech. ESBRJET (pirfenidone) prescribing information, 2019, https://www.gene.com/download/pdf/esbriet_prescribing.pdf
67. Flaherty KR, Fell CD, Huggins JT, et al. Safety of nintedanib added to pirfenidone treatment for idiopathic pulmonary fibrosis. Eur Respir J 2018; 52: 1800230.
68. Vancheri C, Kreuter 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: 356–363.
69. Salisbury ML, Conoscenti CS, Culver DA, et al. Antifibrotic drug use in patients with idiopathic pulmonary fibrosis. Data from the IPF-PRO Registry. Ann Am Thorac Soc 2020; 17: 1413–1423.
70. Hoyles RK, Ellis RW, Wellsbury J, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. Arthritis Rheum 2006; 54: 3962–3970.
71. Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006; 354: 2655–2666.
72. Tashkin DP, Roth MD, Clements PJ, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. *Lancet Respir Med* 2016; 4: 708–719.

73. Wijsenbeek M, Kreuter M, Olson A, et al. Progressive fibrosing interstitial lung diseases: current practice in diagnosis and management. *Curr Med Res Opin* 2019; 35: 2015–2024.

74. Huang S, Kronzer VL, Dellaripa PF, et al. Rheumatoid arthritis–associated interstitial lung disease: current update on prevalence, risk factors, and pharmacologic treatment. *Curr Treatm Opt Rheumatol* 2020; 6: 337–353.

75. Morisset J, Johansson KA, Vittinghoff E, et al. Use of mycophenolate mofetil or azathioprine for the management of chronic hypersensitivity pneumonitis. *Chest* 2017; 151: 619–625.

76. De Sadeleer LJ, Hermans F, De Dycker E, et al. Effects of corticosteroid treatment and antigen avoidance in a large hypersensitivity pneumonitis cohort: a single-centre cohort study. *J Clin Med* 2018; 8: 14.

77. Ryerson CJ, Cayou C, Topp F, et al. Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: a prospective cohort study. *Respir Med* 2014; 108: 203–210.

78. Holland AE, Dowman LM and Hill CJ. Principles of rehabilitation and reactivation: interstitial lung disease, sarcoidosis and rheumatoid disease with respiratory involvement. *Respiration* 2015; 89: 89–99.

79. Jacobs SS, Krishnan JA, Lederer DJ, et al. Home oxygen therapy for adults with chronic lung disease: an official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med* 2020; 202: e121–e141.

80. Kowal-Bielecka O, Fransen J, Avouac J, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis* 2017; 76: 1327–1339.

81. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014—an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2015; 34: 1–15.

82. Yazdani A, Singer LG, Strand V, et al. Survival and quality of life in rheumatoid arthritis-associated interstitial lung disease after lung transplantation. *J Heart Lung Transplant* 2014; 33: 514–520.

83. 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: 1538–1547.

84. Wille KM, Gaggar A, Hajari AS, et al. Bronchiolitis obliterans syndrome and survival following lung transplantation for patients with sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2008; 25: 117–124.

85. Kern RM, Singer JP, Koth L, et al. Lung transplantation for hypersensitivity pneumonitis. *Chest* 2015; 147: 1558–1565.