Interstitial lung disease (ILD) affects millions of patients globally. The sheer number of ILDs, the varied nature of their presentation and progression, and the fact that many ILDs are idiopathic, make this a fascinating but challenging group of clinical disorders. This is further complicated by the fact that a confident diagnosis often requires careful consideration of clinical presentation, imaging studies, and when available, histology, by a multidisciplinary team of experts.

Insights gained over the past two decades about idiopathic pulmonary fibrosis (IPF) and other ILDs have greatly advanced our understanding of these conditions and have helped facilitate earlier diagnosis and intervention and improvements to patient care. Recently, the concept of progressive fibrosing ILD has emerged, as many patients with fibrosing ILDs show rapid deterioration similar to IPF, thereby requiring close monitoring. This publication explores fibrosing ILDs, in recognition of the need for further education about these conditions.
What are progressive fibrosing ILDs?

Kevin R. Flaherty, MD
Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA.

Interstitial lung diseases (ILDs) are a heterogeneous group of diseases characterized by inflammation and/or fibrosis (scar) of the lung parenchyma.

Some ILDs have a known cause, such as those related to connective tissue diseases (CTDs) or to exposure to organic or inorganic material that leads to an exaggerated immune response. Other ILDs have no identifiable cause (idiopathic).

Some patients with ILD develop fibrosing disease. Pulmonary fibrosis may become self-sustaining and progressive. This results in the progressive loss of lung volume (forced vital capacity or FVC) and of the ability of the lungs to exchange oxygen with the blood (diffusion capacity or DLco). Patients with ILDs typically develop dyspnea, cough and fatigue. Ultimately progressive ILD is fatal.

Idiopathic pulmonary fibrosis (IPF) is, by definition, a progressive fibrosing ILD. In addition, a proportion of patients with other fibrosing ILDs develop a progressive phenotype. Although some studies have identified risk factors for worse outcomes in patients with ILDs, the course of disease for an individual patient remains difficult to predict.

Impaired quality of life

Impact of progressive fibrosing ILDs

Dyspnea

Cough

Impaired independence

Loss of independence

Early mortality

ILDs that may develop a progressive fibrosing phenotype

Progressive fibrosing ILDs

Hypersensitivity pneumonitis

Connective tissue disease-related ILDs

Non-IPF idiopathic ILDs

Exposure-related ILDs

Other ILDs

Sarcoidosis-related ILDs

IPF

IPF: the prototypic progressive fibrosing ILD

Joao A. de Andrade, MD
Vanderbilt University School of Medicine, Nashville, TN, USA.

Idiopathic pulmonary fibrosis (IPF) may be described as the “prototypic” progressive fibrosing ILD because it is always fibrosing and always progressive.

IPF is the most well-studied of the ILDs and has provided important learning about the pathogenesis, course and treatment of progressive fibrosing ILDs.

IPF is characterized by a pattern of fibrosis on HRCT or biopsy known as usual interstitial pneumonia (UIP). Patients with other fibrosing ILDs may also have a UIP pattern on HRCT or biopsy. In general, IPF has a worse prognosis than other fibrosing ILDs, but there are some patients with other progressive fibrosing ILDs whose lung function deteriorates as quickly as in IPF.

Acute deteriorations in lung function, known as acute exacerbations, occur in a proportion of patients with IPF. These usually require hospitalization and are associated with very high mortality. Patients with other fibrosing ILDs may also experience acute exacerbations.

Two antifibrotic drugs have been approved by the FDA for the treatment of IPF: nintedanib and pirfenidone. These reduce the rate of decline in FVC by approximately 50% and there is increasing evidence that they improve life expectancy. Importantly, the INPULSIS trials of nintedanib showed that patients with well-preserved FVC (FVC > 90% predicted) at baseline had the same decline in FVC over the next year, and received the same benefit from treatment, as patients with more advanced disease at baseline, demonstrating that patients whose IPF appears stable are still at risk of progression in the short term.

References


FVA, diffusion capacity of the lung for carbon monoxide.

IMPULSIS = INPULSIS trials.
The IPF-PRO Registry: improving our understanding of IPF

Laurie D. Snyder, MD and Scott M. Palmer, MD
Duke Clinical Research Institute and Duke University Medical Center, Durham, NC, USA.

The IPF-PRO Registry (NCT01915511) is an observational registry that enrolled 1002 patients with IPF at 46 sites across the US between June 2014 and October 2018.

The registry is supported by Boehringer Ingelheim Pharmaceuticals, Inc. and co-ordinated by the Duke Clinical Research Institute. It was set up to improve understanding of the natural history of IPF, its diagnosis and treatment, and the burden that IPF places on patients and healthcare resources. In addition, the collection of biological samples has enabled important research into circulating molecules that may serve as biomarkers for the presence, severity, or progression of IPF.

Patients enrolled in the registry are followed prospectively while receiving usual care, with follow-up visits approximately every six months. Data collected include pulmonary function tests, patient-reported outcomes, and treatments. Regular follow-up from a call center helps to reduce missing data on patients’ vital status and interactions with the healthcare system.

Some of the key learnings from the IPF-PRO Registry so far are depicted in this article. Future analyses will include investigations into trajectories of decline in lung function, hospitalizations and post-hospitalization mortality, associations between treatment practices and outcomes, and factors associated with lung transplant.

Reference
Breaking bad news to patients with IPF

Walter F. Baile, MD
University of Texas MD Anderson Cancer Center, Houston, TX, USA (retired).

Breaking bad news such as a diagnosis of IPF is a complex and challenging communication that is easily affected by emotions (both the patient’s and the clinician’s).

Clinicians may be tempted to try to reduce the patient’s distress by downplaying the serious nature of the disease, deflecting difficult questions, or rushing through the conversation. This rarely works and may leave patients confused and dissatisfied. Evidence-based models can help clinicians to improve their skills in having conversations with patients and their loved ones about topics that are difficult to talk about. The SPIKES (Setting, Perception, Invitation for information, Knowledge, Empathy, Strategy, and Summary) protocol is a skills-based, patient-centered process developed to help clinicians in breaking bad news. Emphasis is given to preparing for the visit, understanding the patient’s perceptions of their illness, providing accurate and understandable information, responding to the patient’s emotions with empathy, and providing a plan for the future. In addition to helping clinicians to communicate a diagnosis of IPF or to discuss the prognosis of the disease, the SPIKES framework may be used to guide other discussions that require an empathetic approach, such as those around disease progression and planning for end of life. At every stage, provision of information should be individualized, taking account of how much information the patient wants to receive at that time.

The six steps of SPIKES for breaking bad news

- **SETTING up the interview**: Consider what you want to say, arrange for privacy, involve significant others, sit down, connect with the patient, manage time constraints and avoid interruptions.
- **Assessing the patient’s PERCEPTION**: Use open-ended questions to create a picture of how the patient perceives their situation; for example, “What have you been told about your medical situation so far?”
- **Obtaining the patient’s INVITATION**: Assess the patient’s readiness to hear the information and determine how much information they want at this time.
- **Giving KNOWLEDGE and information to the patient**: Consider the patient’s level of comprehension and vocabulary, use plain language, avoid being blunt or vague.
- **Addressing the patient’s EMOTIONS with empathic responses**: If the patient becomes upset, respond with empathic, exploratory or validating statements.
- **STRATEGY and SUMMARY**: Summarize the information and check patient understanding; form a plan for the future and provide reassurance about continuity of care.

Examples of empathic, exploratory, and validating statements

- **Empathic**: “I’m sorry to have to tell you this.”
  “I can see how upsetting this is to you.”
  “I can tell you weren’t expecting to hear this.”
- **Exploratory**: “Tell me more about it.”
  “You said it frightened you?”
  “You said you were concerned about your family. Tell me more.”
- **Validating**: “I can understand how you felt that way.”
  “It appears that you’ve thought things through very well.”
  “Many other patients have had similar experiences.”

Important!

Effective, empathetic communication is a skill that clinicians can learn and practice. Improving communication skills doesn’t change a patient’s diagnosis, but can help to lessen the impact that IPF has on the lives of patients and their loved ones.

References


What questions do patients with IPF have?

Russell K. Amling and Bill Vick
PF Warriors

Most patients with IPF have never heard of IPF at the time they are diagnosed. Patients will have many questions about what having IPF means for their lives.

Many patients want to take a proactive approach to managing their IPF and to do this, they need to understand their disease.

Some of the questions that patients with IPF may have shortly after they are diagnosed are shown here. However, it’s important that clinicians do not assume that they know the questions that a patient will have. The questions that a particular patient has may differ from those that the last patient you met had, and from those that their family has. The only way that a clinician can find out the questions that an individual patient has is to ask them.

Patients of older age may be more reluctant to ask questions of their doctor. Encourage them to bring their questions and make time to answer them. Asking patients to write their questions down can be helpful. Patients will have questions immediately on receiving a diagnosis of IPF, but many questions will come to their minds later. Clinicians need to make sure that patients know that the right time for them to ask questions is any time.

- **Have I got IPF because I used to smoke or because I was exposed to asbestos or pesticides?**
- **How long do you think I’ve had this?**
- **How long will I live?**
- **What can I expect my life to be like now and later?**
- **Will IPF affect me mentally?**
- **What is the best treatment for IPF?**
- **How will I know if the treatment is working?**
- **What are the side effects of treatment?**
- **Is exercise good for me?**
- **Would a special diet help?**
- **Does cold weather make my condition worse?**
- **Should I have a flu shot? Or other jabs?**
- **Will I need oxygen?**
- **What about stem cell therapy?**
- **Are there any experimental programs I could try?**
- **Where can I find more information?**
- **I have other things going on with my health, does this change the timelines?**

Russell: As a patient, I was always concerned regarding my health. I have always asked my doctors questions pertaining to what, why, when and how. I am an 87 year-old veteran of the Korean War. In 1944, I acquired paralytic polio from the neck down to the bottom of my feet for five months. I needed many ear surgeries. In 2002, I had a quad bypass. In 2006–2007, I had two spinal fusions; in 2009, a knee replacement; three years ago, Valley fever. At times, the answers that I received from my doctor were basic, but I have tried to ask more in-depth questions. I set up another 30-minute visit with the doctor about a week later just to ask these more important questions.

A patient and caregiver information and resource guide “Living with PF-ILD” is provided on joining the group.

References


A patient and caregiver information and resource guide “Living with PF-ILD” is provided on joining the group.
**Detection, monitoring and management of ILD associated with systemic sclerosis**

Anna Maria Hoffmann-Vold, MD
Department of Rheumatology, Oslo University Hospital, Oslo, Norway.

ILD is a common manifestation of systemic sclerosis (SSc) and is associated with significant morbidity and mortality. Although risk factors for the development of SSc-ILD have been identified, all patients with SSc should be regarded as at risk of ILD.

Expert groups have developed consensus algorithms for the detection, monitoring, and management of SSc-ILD. These recommend that all patients diagnosed with SSc should receive an HRCT scan to screen for ILD and to ascertain its extent. In addition, patients should undergo PFTs (FVC and DLco) to establish baseline measurements. The severity of SSc-ILD at the time of diagnosis is prognostic of long-term outcome. Severity should be determined based on HRCT, PFTs, and other parameters such as exercise-induced oxygen desaturation, symptoms, and HRQL.

Regular monitoring of patients with SSc-ILD is essential to assess progression. Progression of SSc-ILD is associated with poor outcome. Monitoring should include regular PFTs and assessment of symptoms, plus repeat HRCT as deemed appropriate by the clinician.

The decision on when to initiate or escalate pharmacological treatment for SSc-ILD should be made based on assessment of ILD severity and progression, ideally following multidisciplinary discussion, taking the views of the patient into account. There is no established treatment algorithm for SSc-ILD, but cyclophosphamide, mycophenolate, and nintedanib have shown efficacy in slowing the progression of SSc-ILD in randomized clinical trials. Nintedanib has been approved by the FDA for reducing the rate of decline in lung function in patients with SSc-ILD. All the drugs used to treat SSc-ILD have side-effects, which should be proactively assessed and managed by the clinical care team.

Patients with SSc-ILD should be offered supportive care as needed. This may include symptom relief, pulmonary rehabilitation, or supplemental oxygen. Many patients find support groups such as those run by the Scleroderma Foundation (https://www.scleroderma.org) valuable for providing psychological support.

**Algorithm for screening, monitoring and management of SSc-ILD proposed by European consensus group**


1. **Screen all patients with SSc for ILD using HRCT**
2. **Measure FVC and DLco at baseline and regular intervals**
3. **Assess ILD severity using multiple methods**
4. **Continue screening for ILD**
5. **Assess ILD progression using multiple methods**
6. **Inadequate treatment response**
7. **Escalate therapy**

**Important!**

All patients diagnosed with SSc should be screened for ILD at baseline using an HRCT scan. PFTs alone are not sufficient to ascertain whether SSc-ILD is present.

**Reference**


**Understanding the results of the SENSICS trial**

Toby M. Maher, MD
Keck School of Medicine, University of Southern California, Los Angeles, CA, USA.

The SENSICS trial was a randomized, double-blind, placebo-controlled trial of nintedanib in 576 subjects with systemic sclerosis-associated ILD (SSc-ILD).

Subjects had fibrotic SSc-ILD and were at risk of progression, but were not required to have shown recent progression of ILD. Patients who had taken stable therapy with mycophenolate or methotrexate for >6 months were allowed to participate. Subjects received nintedanib or placebo until the last subject enrolled had reached week 52 of treatment.

The primary endpoint was the rate of decline in FVC (mL/year) over 52 weeks. Nintedanib reduced the rate of decline in FVC over 52 weeks by 44% compared with placebo (-62.4 vs. -93.3 mL/year, difference: 41.0 [95% CI 2.3, 79.0]; p=0.04). While the absolute effect of nintedanib versus placebo was lower in patients who were taking mycophenolate at baseline than in those who were not, its relative effect was similar between these subgroups (40% and 46%, respectively).

Nintedanib had no significant effect on skin fibrosis or on HRQL over 52 weeks. The adverse events reported were mainly gastrointestinal events, particularly diarrhea. Adverse events led to treatment discontinuation in 16.0% of subjects treated with nintedanib compared to 8.7% who received placebo.

Decline in FVC in patients with SSc-ILD is associated with mortality. The results of the SENSICS trial show that nintedanib provides a clinically meaningful benefit in slowing the progression of SSc-ILD, both when used as monotherapy and as add-on to mycophenolate.

**Key inclusion criteria**

SSc with onset of first non-Raynaud symptom in past <7 years
Fibrotic ILD of ≥10% extent on HRCT, based on assessment of the whole lung
FVC ≥40% predicted
DLco ≥30–69% predicted

**Reference**

Bendergenginger Pharmaceuticals, Inc. Ofev® (nintedanib) prescribing information. Available at: https://www.bendergenginger.com/PrescribingInfo/32/ABCDEFGHIJKLMNOPQRSTUVWXYZ/PrescribingInfo.pdf


**Taking a quiz**

Test your understanding of the results of the SENSICS trial by taking a quiz at: https://www.usscicomms.com/respiratory/SENSCISquiz

**Reference**


**Figure**

<table>
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<th>Placebo (n=148)</th>
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Impact, monitoring and management of CTD-ILDs

Teng Moua, MD
Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA.

ILD is a common manifestation of CTDs including rheumatoid arthritis (RA), systemic sclerosis (SSc), polymyositis/dermatomyositis, and Sjögren’s syndrome.

Risk factors for the development of CTD-ILDs have been identified, but it remains impossible to predict with accuracy which patients with CTDs will develop ILD. ILD may be present on HRCT even in the absence of impaired lung function or symptoms.

A proportion of patients with CTD-ILDs develops a progressive fibrosing phenotype, characterized by increasing fibrosis on HRCT, decline in lung function, worsening symptoms, and high mortality. Although some risk factors for ILD progression and mortality in patients with CTD-ILDs have been identified, its course remains unpredictable. It is important that patients with CTD-ILDs are closely monitored so that patients whose ILD is progressing can be promptly identified and managed. Monitoring should include PFTs, assessment of symptoms and, where deemed appropriate, a repeat HRCT scan.

Monitoring progression of CTD-ILDs

The management of patients with CTD-ILDs requires a multidisciplinary and individualized approach. The decision to initiate or escalate treatment should consider factors such as the severity of the ILD, evidence of progression, risk factors for progression, the patient’s overall health status and the patient’s preferences, and ideally be based on multidisciplinary discussion including at minimum a pulmonologist and rheumatologist, and perhaps also a radiologist.

There are no established algorithms for the treatment of CTD-ILDs. Immunomodulatory therapies are the mainstream of therapy for CTDs, but other than in patients with SSc-ILD, their efficacy in slowing the progression of ILD has not been established in randomised controlled trials. Nintedanib has been approved by the FDA for reducing decline in lung function in patients with SSc-ILD or chronic fibrosing ILDs with a progressive phenotype. In addition to pharmacological therapy, the care of patients with CTD-ILDs may include pulmonary rehabilitation, treatment of comorbidities, the use of supplemental oxygen, and supportive care. Supportive care should not only be provided as end-of-life care, but as needed by the patient throughout the course of their disease.

Multidisciplinary and individualized approach to management of CTD-ILDs
The INBUILD trial was a randomized, placebo-controlled trial of nintedanib in 663 patients with fibrosing ILDs other than IPF who met criteria for progression of ILD within the two years prior to screening. Patients with a wide range of ILD diagnoses participated in the trial. The most frequent diagnoses were hypersensitivity pneumonitis and autoimmune disease-related ILDs, particularly RA-ILD.

As in previous trials, the adverse events reported in patients treated with nintedanib were mainly gastrointestinal events, particularly diarrhea. Adverse events were managed using symptomatic therapies and dose adjustment. Over 52 weeks, adverse events led to permanent discontinuation of treatment in 19.6% of patients treated with nintedanib compared with placebo (16.9%).

The primary endpoint was the rate of decline in FVC (mL/year) over 52 weeks. In the overall population, nintedanib reduced the rate of decline in FVC over 52 weeks by 57% compared with placebo (80.8 vs 187.8 mL/year; difference: 107.0 [95% CI: 65.4, 148.3]; p<0.001). Findings in the co-primary analysis population of patients with a UIP-like fibrotic pattern on HRCT (n=412) and in patients with other fibrotic patterns on HRCT (n=251) were similar.

Some patients continued in the INBUILD trial for more than 52 weeks. The median duration of follow-up over the whole trial was ~19 months. The trial was not powered to study individual ILDs, subgroup analyses suggested that there was no difference across subgroups by diagnosis in the rate at which FVC declined in the placebo group or in the effect of nintedanib in reducing the rate of FVC decline. These findings support the hypothesis that once progressive fibrosis has developed, it continues to progress, irrespective of the original trigger.

Although the INBUILD trial was not designed to study individual ILDs, subgroup analyses suggested that there was no difference across subgroups by diagnosis in the rate at which FVC declined in the placebo group or in the effect of nintedanib in reducing the rate of FVC decline. These findings support the hypothesis that once progressive fibrosis has developed, it continues to progress, irrespective of the original trigger.

The most frequent diagnoses were hypersensitivity pneumonitis and autoimmune disease-related ILDs, particularly RA-ILD.
Information for patients with fibrosing CTD-ILDs

Patients with fibrosing CTD-ILDs need information on the way that their ILD will be monitored, treatment options, and the various forms of support available to them.

**Important information to communicate to patients with CTD-ILDs**

1. **Monitoring your CTD-ILD**
   - The course of CTD-ILD varies between patients and may vary over time.
   - Regular monitoring is important to check if your CTD-ILD is getting worse and if your treatment needs changing.
   - Symptoms of pulmonary and non-pulmonary disease.
   - Lung function.

2. **Treatment options for your CTD-ILD**
   - Drugs that slow the progression of ILD or relieve symptoms.
   - Supplemental oxygen if you have low levels of oxygen in your blood.
   - Pulmonary rehabilitation to help alleviate your symptoms.
   - Your care team will discuss treatment options with you. These may include:
     - Pulmonary rehabilitation to help alleviate your symptoms.
     - Medications.
     - Patient-reported outcomes.

3. **Sources of support**
   - Your care team can answer any questions you have.
   - Patient support groups (on-line or face to face) can be a valuable source of information and support.
   - Your family and friends: help them understand the support that you need.
   - Beware that not all information you find on-line is accurate or relevant to you.

**Reference**


Towards a better understanding of chronic fibrosing ILDs: the ILD-PRO Registry

Laurie D. Snyder, MD and Scott M. Palmer, MD
Duke Clinical Research Institute and Duke University Medical Center, Durham, NC, USA.

In 2018, the IPF-PRO Registry was expanded to become the IPF-PRO/ILD-PRO Registry (NCT01915511).

The ILD-PRO part of the registry is enrolling patients aged ≥30 years who have chronic fibrosing ILDs other than IPF with reticular abnormality and traction bronchiectasis with or without honeycombing confirmed by HRCT scan and/or lung biopsy, and meet criteria for progression of ILD within the prior two years.

Inclusion criteria for ILD progression used in the ILD-PRO Registry

- Relative decline in DLco ≥10% predicted
- Relative decline in FVC ≥10% predicted
- Relative decline in FVC ≥5–<10% predicted plus worsened respiratory symptoms
- Worsened respiratory symptoms plus increased extent of fibrotic changes on HRCT

**Reference**

Acknowledgements

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