Idiopathic Pulmonary Fibrosis: Diagnose Early to Treat Effectively

Learning Objectives

- Review the key diagnostic challenges of idiopathic pulmonary fibrosis (IPF) and how to overcome them
- Describe recent clinical trial data evaluating IPF-specific treatments and their role in the management of IPF at all stages of disease
- Discuss the impact of acute exacerbations and the role of targeted agents to improve outcomes
Incidence and Prevalence of Idiopathic Pulmonary Fibrosis

- The peak age range for IPF is 75 to 79 years\(^1\)

Projected Incidence of IPF\(^2\)

Prevalence of IPF: 5 to 18/100,000 → ~100,000 patients in the EU\(^3,4\)

http://www.peervoice.com/o1/pvr249
IPF: Worst Case of an ILD

Survival Rates in ILD

- NSIP
- IPF
- Other

Causes of Death in IPF

- Pulmonary Fibrosis: 60%
- Other: 24%
- IHD: 9%
- Lung Cancer: 3%
- Pneumonia: 2%
- CHF: 1%
- CVD: 1%

New therapies that intervene on the process of fibrosis may help to reduce mortality in IPF

http://www.peervoice.com/o1/pvr249
Recognising the Signs and Symptoms of IPF$^{1,2}$

**Patients are likely to report**
- Insidious dyspnoea
- Weakness and lack of energy
- Dry, nonproductive cough
- Persistent URTI
- Weight loss/loss of appetite

**Physical examination findings may include**
- Gradual onset (>6 mo) of dyspnoea and/or nonproductive cough
- Fine bibasilar inspiratory crackles (Velcro crackles)
- Hypoxaemia
- Digital clubbing (seen in 25-50% of patients with IPF)
- Pulmonary hypertension at rest (occurs in 20-40% of patients evaluated/recommended LT)
Diagnosing IPF: The Multidisciplinary Discussion

Collaboration and Communication Across Specialties

- Respirologist
- Thoracic Surgeon
- GP
- Patient
- Pathologist
- Rheumatologist
- Radiologist

Suspected IPF\(^1-3\)

- Referral to an ILD centre should be considered, if possible, for a multidisciplinary evaluation (clinical, radiologic, respiratory function, biologic, pathologic)
- Delay from symptom onset to referral can lead to worse outcomes, particularly survival\(^4\)

\(^a\) Rheumatology consult suggested in cases of abnormal serology and signs of connective tissue disease.

http://www.peervoice.com/o1/pvr249
The Importance of Early Diagnosis and IPF Treatment: Impact on Survival

Survival From the Time of Evaluation at Tertiary Care Centre Adjusted for Age and FVC Across Quartiles of Delay in Referral From Onset Dyspnoea

Time, y

Survival

Delayed diagnosis of IPF and delayed referral can result in lower survival rates, independent of disease severity or associated prognostic factors

P for trend = .03

http://www.peervoice.com/o1/pvr249
In an analysis by Lamas et al, early referral of patients with suspected IPF to a tertiary care centre...

- Increased survival rates
- Decreased survival rates
- Did not affect survival rates

Go online to compare your answer with your peers’ responses.

http://www.peervoice.com/o1/pvr249
Differential Diagnosis Algorithm for IPF

Suspected IPF

- Other identifiable causes of ILD?
  - Yes
  - HRCT
    - UIP
    - Possible UIP Inconsistent with UIP
    - Surgical biopsy
      - UIP Probable/possible UIP Nonclassifiable fibrosis
      - Not UIP
    - MDD
      - IPF
      - IPF/not IPF
      - Not IPF
  - No

Diagnosis of IPF Requires
- Exclusion of other ILD causes
  - Domestic/occupational environmental exposures, connective tissue disease, drug toxicity
- Presence of a definite UIP pattern on HRCT in patients not subjected to surgical lung biopsy
  - If inconsistent, discuss surgical biopsy with healthcare team
- Specific combinations of HRCT and surgical lung biopsy pathology suggesting UIP
  - If nondeterminant, discussion with pathologist is needed

Confirm diagnosis to ensure appropriate treatment and management

http://www.peervoice.com/o1/pvr249
UIP Pattern on HRCT

**Definite UIP Pattern (All 4 Features)**
- Subpleural, basal predominance
- Reticular abnormality
- Honeycombing ± traction bronchiectasis
- Absence of features listed as inconsistent with UIP pattern

**Possible UIP Pattern (All 3 Features)**
- Subpleural, basal predominance
- Reticular abnormality
- Absence of features listed as inconsistent with UIP pattern

Subpleural reticulation/Honeycombing
Traction bronchiectasis

http://www.peervoice.com/o1/pvr249
A 62-year-old male presents with a nonproductive cough, shortness of breath, and Velcro crackles. HRCT pattern shows honeycombing and subpleural reticulations. Based on this, what is the most likely diagnosis?

- Asthma
- Emphysema
- IPF
- Lung cancer

Go online to compare your answer with your peers’ responses.

http://www.peervoice.com/o1/pvr249
Risk of Death Due to IPF Increases With Severity of Disease

**Study Design:** Evaluation of mortality outcomes in three phase 3 global clinical trials (CAPACITY [x2] and INSPIRE) in 622 patients\(^a\) with IPF with mild-to-moderate impairment in baseline measures of physiologic function

---

\(^a\) Patients from the placebo treatment arms of CAPACITY and INSPIRE.

\(^b\) Assessed by clinical investigators who remained blinded to treatment assignment.

---

http://www.peervoice.com/o1/pvr249
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Should Be Used</th>
<th>Strength of Recommendation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nintedanib</td>
<td>Yes</td>
<td>Conditional</td>
</tr>
<tr>
<td>Pirfenidone</td>
<td>Yes</td>
<td>Conditional</td>
</tr>
<tr>
<td>Dual endothelin receptor antagonants (eg, macitentan, bosentan)</td>
<td>No</td>
<td>Conditional</td>
</tr>
<tr>
<td>Phosphodiesterase-5 inhibitor (eg, sildenafil)</td>
<td>No</td>
<td>Conditional</td>
</tr>
<tr>
<td>N-acetylcysteine monotherapy</td>
<td>No</td>
<td>Conditional</td>
</tr>
<tr>
<td>Anticoagulation (eg, warfarin)</td>
<td>No</td>
<td>Strong</td>
</tr>
<tr>
<td>Combination prednisone + azathioprine + N-acetylcysteine</td>
<td>No</td>
<td>Strong</td>
</tr>
<tr>
<td>Selective endothelin receptor agonist (eg, ambrisentan)</td>
<td>No</td>
<td>Strong</td>
</tr>
<tr>
<td>Imatinib</td>
<td>No</td>
<td>Strong</td>
</tr>
</tbody>
</table>
Conclusions

- Early diagnosis of IPF is important
  - Incidence is increasing
  - Most aggressive form of ILD
  - Most patients die within 2 to 3 years
  - Chest auscultations are an important clue when IPF is suspected

- Final diagnosis of IPF by a multidisciplinary team
  - Higher level of certainty of diagnosis
  - Tertiary care centres are better equipped to make a diagnosis

- Nintedanib and pirfenidone have conditional recommendations for treatment of IPF in the ATS/ERS/JRS/ALAT 2015 guideline update
Abbreviations and References

Incidence and Prevalence of Idiopathic Pulmonary Fibrosis

*Abbreviation(s):* EU: European Union; IPF: idiopathic pulmonary fibrosis.


IPF: Worst Case of an ILD

*Abbreviation(s):* CHF: congestive heart failure; CVD: cerebrovascular disease;
IHD: ischaemic heart disease; ILD: interstitial lung disease; NSIP: nonspecific interstitial pneumonia/fibrosis.


Recognising the Signs and Symptoms of IPF\(^1,\(^2\)

*Abbreviation(s):* LT: lung transplantation; URTI: upper respiratory tract infection.

Abbreviations and References (Cont'd)

Diagnosing IPF: The Multidisciplinary Discussion

Abbreviation(s): GP: general practitioner.

The Importance of Early Diagnosis and IPF Treatment: Impact on Survival

Abbreviation(s): FVC: forced vital capacity.

Differential Diagnosis Algorithm for IPF

Abbreviation(s): HRCT: high-resolution computed tomography; MDD: multidisciplinary discussion; UIP: usual interstitial pneumonia.

UIP Pattern on HRCT
Risk of Death Due to IPF Increases With Severity of Disease

ATS/ERS/JRS/ALAT Treatment Guideline for IPF: 2015 Update
IPF: Overall Treatment Goals

- Slowing disease progression
- Reducing the frequency of acute exacerbations
- Reducing mortality
- Improving quality of life
Analysis of FVC and All-Cause Mortality in IPF Trials

- FVC is a surrogate marker for mortality and has emerged as the standard primary endpoint in clinical trials

<table>
<thead>
<tr>
<th></th>
<th>FVC Change From BL, mL</th>
<th>Deaths, n (%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study Drug</td>
<td>Placebo</td>
<td>Treatment Difference (95% CI)</td>
<td>Study Drug</td>
<td>Placebo</td>
</tr>
<tr>
<td>Nintedanib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td>-60</td>
<td>-191</td>
<td>131 (27-235)</td>
<td>7 (8.1)</td>
<td>9 (10.3)</td>
</tr>
<tr>
<td>Study 2</td>
<td>-115</td>
<td>-240</td>
<td>125 (78-173)</td>
<td>13 (4.2)</td>
<td>13 (6.4)</td>
</tr>
<tr>
<td>Study 3</td>
<td>-114</td>
<td>-207</td>
<td>94 (45-143)</td>
<td>22 (6.7)</td>
<td>20 (9.1)</td>
</tr>
<tr>
<td>Pirfenidone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td>-235</td>
<td>-428</td>
<td>193 (96-289)</td>
<td>12 (4.3)</td>
<td>21 (7.6)</td>
</tr>
<tr>
<td>Study 2</td>
<td>-318</td>
<td>-475</td>
<td>157 (3-311)</td>
<td>14 (8.0)</td>
<td>20 (11.5)</td>
</tr>
<tr>
<td>Study 3</td>
<td>-379</td>
<td>-373</td>
<td>-6 (-178-167)</td>
<td>18 (10.5)</td>
<td>17 (9.8)</td>
</tr>
</tbody>
</table>

"Although none of the individual studies were powered to demonstrate a statistically significant reduction in mortality in a vital status analysis, in the five studies that revealed a significant difference in FVC decline, there was a numerical trend toward improvement in mortality (HR <1)" — FDA
INPULSIS-1 and -2: Change in FVC With Nintedanib

- **Study Design:** Two replicate, 52-week, randomised, double-blind, phase 3 trials to evaluate the efficacy and safety of nintedanib 150 mg BID versus placebo in 1,061 patients with IPF and FVC ≥50% predicted
- **Primary Endpoint:** Annual rate of decline in FVC
- **Key Secondary Endpoints:** Time to the first acute exacerbation, change from BL in SGRQ total score

**INPULSIS-1**

<table>
<thead>
<tr>
<th>Group</th>
<th>Adjusted Annual Rate of Change in FVC, mL/y</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nintedanib</td>
<td>-114.7</td>
<td>309</td>
</tr>
<tr>
<td>PBO</td>
<td>-239.9</td>
<td>204</td>
</tr>
</tbody>
</table>

Difference, 125.3 (95% CI: 77.7, 172.8); P < .001

**INPULSIS-2**

<table>
<thead>
<tr>
<th>Group</th>
<th>Adjusted Annual Rate of Change in FVC, mL/y</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nintedanib</td>
<td>-113.6</td>
<td>329</td>
</tr>
<tr>
<td>PBO</td>
<td>-207.3</td>
<td>219</td>
</tr>
</tbody>
</table>

Difference, 93.7 (95% CI: 44.8, 142.7); P < .001

Pooled analysis showed a 49.2% relative reduction in the adjusted annual rate of decline in FVC with nintedanib (P = .001)

http://www.peervoice.com/o1/pvr249
INPULSIS-1 and -2 Subgroup Analysis: Nintedanib in Patients With Moderate Lung Function Impairment

- **FVC ≤90% Predicted**
  - Nintedanib: -121.5 mL/y
  - PBO: -223.6 mL/y
  - Difference: 102.1 mL/y (95% CI: 61.9, 142.3)  
  - P = .53

- **FVC >90% Predicted**
  - Nintedanib: -91.5 mL/y
  - PBO: -224.6 mL/y
  - Difference: 133.1 mL/y (95% CI: 68.0, 198.2)

Treatment effect in each subgroup was consistent with the overall pooled populations.
Challenge Question

Which statement describes the observed relative change in FVC in patients receiving nintedanib?

- Similar FVC changes to placebo
- Less than 30% change in FVC vs placebo
- Highest in patients with a baseline FVC >90%
- Highest in patients with a baseline FVC <90%
- Similar change across baseline FVCs

Go online to compare your answer with your peers' responses.

http://www.peervoice.com/o1/pvr249
ASCEND: Change in FVC With Pirfenidone

- **Study Design**: 52-week, randomised, double-blind, phase 3 trial to evaluate the efficacy and safety of pirfenidone 2,403 mg/d versus placebo in 555 patients with IPF
- **Primary Endpoint**: Change in percent-predicted FVC at week 52
- **Key Secondary Endpoints**: 6MWD and PFS

**Decline in FVC ≥10% or Death**

- **Pirfenidone (n = 278)**
- **Placebo (n = 277)**

At week 52, decline in FVC ≥10% or death reduced by 47.9% ($P < .001$)
ASCEND/CAPACITY Pooled Subgroup Analyses: Efficacy Outcomes With Pirfenidone in Patients With Early or Advanced Disease

**Study Design:** Exploratory analysis of pooled data from the ASCEND and CAPACITY\(^a\) trials (1,247 patients with IPF) to obtain more precise estimates of the magnitude of treatment effect of pirfenidone compared with placebo, and to evaluate the treatment effect in subpopulations of interest. Efficacy outcomes were analysed at 12 months\(^1,2\).

<table>
<thead>
<tr>
<th>Efficacy Outcome</th>
<th>Subgroup</th>
<th>Standardised Treatment Effect(^b)</th>
<th>Treatment Effect P</th>
<th>Interaction P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change From BL in Percent-Predicted FVC</td>
<td>Percent-Predicted FVC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;80%</td>
<td></td>
<td></td>
<td>.3969</td>
</tr>
<tr>
<td></td>
<td>≥80%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GAP Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 or 3</td>
<td></td>
<td>&lt; .0001</td>
<td>.8152</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td></td>
<td>&lt; .0001</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) CAPACITY was two concurrent, multinational, phase 3 trials in 779 patients with IPF randomised to pirfenidone or placebo. The primary endpoint was percent change in predicted FVC at week 72.\(^3\)

\(^b\) Defined as decline in FVC ≥10% or death.

http://www.peervoice.com/o1/pvr249
**INPULSIS-1 and -2: Adverse Events Associated With Nintedanib**

<table>
<thead>
<tr>
<th>Event, %</th>
<th><strong>INPULSIS-1</strong></th>
<th></th>
<th><strong>INPULSIS-2</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nintedanib (n = 309)</td>
<td>Placebo (n = 204)</td>
<td>Nintedanib (n = 329)</td>
<td>Placebo (n = 219)</td>
</tr>
<tr>
<td>Any AE(^a)</td>
<td>95.8</td>
<td>87.7</td>
<td>94.5</td>
<td>90.0</td>
</tr>
<tr>
<td>Serious AE</td>
<td>31.1</td>
<td>27.0</td>
<td>29.8</td>
<td>32.9</td>
</tr>
<tr>
<td>AE leading to DC</td>
<td>21.0</td>
<td>10.8</td>
<td>17.6</td>
<td>15.1</td>
</tr>
<tr>
<td>ALT/AST ≥3x ULN</td>
<td>4.9</td>
<td>0.5</td>
<td>5.2</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Most Frequent AEs (≥10%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>61.5</td>
<td>18.6</td>
<td>63.2</td>
<td>18.3</td>
</tr>
<tr>
<td>Nausea</td>
<td>22.7</td>
<td>5.9</td>
<td>26.1</td>
<td>7.3</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12.6</td>
<td>16.7</td>
<td>14.6</td>
<td>15.5</td>
</tr>
<tr>
<td>Cough</td>
<td>15.2</td>
<td>12.7</td>
<td>11.6</td>
<td>14.2</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>11.7</td>
<td>13.7</td>
<td>9.4</td>
<td>7.8</td>
</tr>
<tr>
<td>URTI</td>
<td>9.1</td>
<td>8.8</td>
<td>9.1</td>
<td>11.0</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>7.1</td>
<td>11.3</td>
<td>8.2</td>
<td>11.4</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>8.4</td>
<td>6.9</td>
<td>12.8</td>
<td>4.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12.9</td>
<td>2.0</td>
<td>10.3</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>Weight Loss</strong></td>
<td>8.1</td>
<td>6.4</td>
<td>11.2</td>
<td>0.9</td>
</tr>
</tbody>
</table>

\(^a\) Excluded progression of IPF.

In the **INPULSIS-ON** extension study, safety and tolerability results were confirmed and no new safety concerns were identified.
Managing Side Effects Associated With Nintedanib

**GI Adverse Events**
- Diarrhoea should be managed with adequate hydration and antidiarrhoeal agents
- If symptoms are severe or persist despite supportive therapy, dose reduction or treatment interruption may be required

**Hepatic Adverse Events**
- Check hepatic transaminase and bilirubin levels prior to the initiation of treatment with nintedanib and periodically thereafter
- If transaminase elevation is >3x ULN, dose reduction or interruption of therapy is recommended
## ASCEND: Adverse Events Associated With Pirfenidone

<table>
<thead>
<tr>
<th>Event, %</th>
<th>Pirfenidone (n = 278)</th>
<th>Placebo (n = 277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious AE*</td>
<td>18.7</td>
<td>20.2</td>
</tr>
<tr>
<td>AE leading to DC</td>
<td>14.4</td>
<td>10.8</td>
</tr>
<tr>
<td>Grade 3 GI AE</td>
<td>5.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Grade 3 skin-related AE</td>
<td>1.8</td>
<td>0.4</td>
</tr>
<tr>
<td>ALT/AST ≥3x ULN</td>
<td>2.9</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Most Frequent AEs (≥10%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>36.0</td>
<td>13.4</td>
</tr>
<tr>
<td>Rash</td>
<td>28.1</td>
<td>8.7</td>
</tr>
<tr>
<td>Headache</td>
<td>25.9</td>
<td>23.1</td>
</tr>
<tr>
<td>Cough</td>
<td>25.2</td>
<td>29.6</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>22.3</td>
<td>21.7</td>
</tr>
<tr>
<td>URTI</td>
<td>21.9</td>
<td>20.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20.9</td>
<td>17.3</td>
</tr>
</tbody>
</table>

The safety and tolerability profile of pirfenidone was confirmed during a long-term prospective follow-up of up to 9.9 years through a comprehensive analysis from 5 clinical trials, including ASCEND and its open-label safety extension²,³

* Excluded worsening of IPF.
Managing Side Effects Associated With Pirfenidone

**Photosensitivity**
- Sun exposure should be avoided for a few hours following medication intake
- Use sunscreen active against both UVA and UVB and protective clothing

**GI Adverse Events**
- Use supportive therapies such as prokinetic agents and proton pump inhibitors\(^a\) to mitigate treatment-related GI AEs
- Taking pirfenidone during or after a meal may reduce the risk of side effects such as nausea and dizziness

---

If treatment-related AEs are not tolerable, dose reductions or temporary treatment discontinuation should be considered

---

\(^a\) Of note, concomitant use of moderate inducers of CYP1A2 (eg, omeprazole) may theoretically result in a lowering of pirfenidone plasma levels.

http://www.peervoice.com/o1/pvr249
Challenge Question

Which statement is TRUE regarding the management of side effects with available pharmacotherapies for IPF?

- Avoiding sun exposure is recommended a few hours following pirfenidone treatment to prevent photosensitivity-related rash
- High-dose, continuous corticosteroids should be used to manage treatment-related dyspnoea
- Liver enzyme elevation is the most common side effect of nintedanib treatment and may require dose modification
- Treatment discontinuation is always required if a patient experiences GI adverse events with nintedanib or pirfenidone treatment

Go online to compare your answer with your peers’ responses.

http://www.peervoice.com/o1/pvr249
Considerations in Treatment Selection

Factors that may impact selection of antifibrotic agent

- Clinical trial outcomes
- Side-effect profiles
- Individual patient's disease characteristics
- Comorbidities and comedications
- Dosage regimens
Conclusions

- IPF inevitably progresses, causing respiratory failure and ultimately, death

- New antifibrotics, nintedanib and pirfenidone, have shown to improve outcomes in patients with IPF

- Adverse events are manageable
  - Nintedanib is frequently associated with diarrhoea
  - Pirfenidone is associated with GI and skin-related adverse events

- It’s important to tailor therapy to the individual patient, based on drug and patient characteristics
Abbreviations and References

IPF: Overall Treatment Goals
Abbreviation(s): IPF: idiopathic pulmonary fibrosis.
Reference(s): Raghu G et al; for ATS, ERS, JRS, and ALAT. Am J Respir Crit Care Med. 2015;192:e3-19.

Analysis of FVC and All-Cause Mortality in IPF Trials
Abbreviation(s): BL: baseline; CI: confidence interval; FDA: US Food and Drug Administration; FVC: forced vital capacity; HR: hazard ratio.

INPULSIS-1 and -2: Change in FVC With Nintedanib
Abbreviation(s): BID: twice daily; PBO: placebo; SGRQ: St George's Respiratory Questionnaire.
Abbreviations and References (Cont'd)

INPULSIS-1 and -2 Subgroup Analysis: Nintedanib in Patients With Moderate Lung Function Impairment


ASCEND: Change in FVC With Pirfenidone

Abbreviation(s): 6MWD: 6-minute walk distance; PFS: progression-free survival.

ASCEND/CAPACITY Pooled Subgroup Analyses: Efficacy Outcomes With Pirfenidone in Patients With Early or Advanced Disease

Abbreviation(s): GAP: Gender Age Physiology.
Abbreviations and References (Cont'd)

INPULSIS-1 and -2: Adverse Events Associated With Nintedanib¹

*Abbreviation(s):* AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; DC: discontinuation; ULN: upper limit of normal; URTI: upper respiratory tract infection.


Managing Side Effects Associated With Nintedanib

*Abbreviation(s):* GI: gastrointestinal.


ASCEND: Adverse Events Associated With Pirfenidone¹


http://www.peervoice.com/o1/pvr249
Abbreviations and References (Cont'd)

Managing Side Effects Associated With Pirfenidone

*Abbreviation(s):* UV: ultraviolet (A and B).

What Is an Acute Exacerbation of IPF?

**Definition:** Acute respiratory worsening characterised by diffuse alveolar damage in a patient with IPF.

- **Diagnostic criteria**
  - IPF diagnosis (previous or concurrent)
  - Clinical presentation consistent with diffuse alveolar damage
  - HRCT with new bilateral ground-glass abnormality with or without consolidation

---

*a Note: Tentative definition provided by Dr. Ryerson; official update to be published in 2016.*
Risk Factors, Incidence, and Consequences of Acute Exacerbations in IPF

Risk Factors\(^1,2\)
- Dyspnoea
- Low FVC at baseline
- Pulmonary hypertension at baseline
- Extent of fibrosis on HRCT
- High BMI
- Absence of smoking history

- Annual incidence: 5-20\(^\%\)^3
- Short-term mortality: Around 50\(^\%\)^3
- Death rate for patients with acute exacerbation: Around 85\(^\%\)^1-3
  - Most common cause of death in patients with IPF\(^1-3\)

http://www.peervoice.com/o1/pvr249
Association Between Acute Exacerbation and Disease Progression

- STEP-IPF (N = 180) analysis assessing suspected acute exacerbation as an outcome measure in clinical trials.

The graph shows the percentage of patients across different measures:
- **10% FVC**
  - Definite/suspected acute exacerbation (n = 17) with P < .001
  - No acute worsening (n = 150) with P = .02
  - Other acute worsening (n = 13) with P = .04

- **15% DLco**
  - Definite/suspected acute exacerbation (n = 17) with P < .001
  - No acute worsening (n = 150) with P = 0.004
  - Other acute worsening (n = 13) with P = .10

- **30 m 6MWD**
  - Definite/suspected acute exacerbation (n = 17) with P < .001
  - No acute worsening (n = 150) with P = .10
  - Other acute worsening (n = 13) with P = .21

- **5u UCSD**
  - Definite/suspected acute exacerbation (n = 17) with P < .001
  - No acute worsening (n = 150) with P = .76
  - Other acute worsening (n = 13) with P = .76

- **5u SGRQ**
  - Definite/suspected acute exacerbation (n = 17) with P < .001
  - No acute worsening (n = 150) with P = .76
  - Other acute worsening (n = 13) with P = .76
Challenge Question

Acute exacerbations of IPF are associated with:

- Increase in FVC
- Decrease in FVC
- No change in FVC
- Increase in 6MWD
- No change in 6MWD

Go online to compare your answer with your peers' responses.

http://www.peervoice.com/o1/pvr249
Identifying an Acute Exacerbation

History and Physical Examination
Basic investigations (eg, lab tests, chest radiography)

Extraparenchymal cause identified?

No

HRCT

Yes

Extraparenchymal diagnosis

New bilateral ground glass ± consolidation?

Yes

Multidisciplinary Evaluation

Not acute exacerbation

No

Presentation consistent with DAD?

Yes

Acute exacerbation of IPF

Search for Trigger

No

Trigger identified?

Yes

Acute exacerbation of known cause

No

Idiopathic acute exacerbation

http://www.peervoice.com/o1/pvr249
HRCT Findings Before, During, and After Acute Exacerbation: A Patient With Acute Exacerbation Triggered by Surgery

- 53-year-old female patient with biopsy-proven UIP

Before Acute Exacerbation

During Acute Exacerbation

After Acute Exacerbation

Baseline
- UIP pattern
- Suspicious nodule (LLL)

Two months later
- UIP pattern worse
- Nodule resected (NSCLC)
- Diffuse GGO (R>L)

Three months later
- UIP pattern significantly worse
- Minimal patchy GGO (L>R)

- Patient died 1 month following last CT scan

http://www.peervoice.com/o1/pvr249
A 68-year-old man with IPF presents with worsening dyspnoea over the past week. He also complains of fatigue and decreased appetite. On HRCT, what changes would confirm an acute exacerbation of IPF?

- Increase in honeycombing
- Increase in ground-glass opacifications
- Increase in traction bronchiectasis
- Increase in fibrosis

Go online to compare your answer with your peers' responses.
Current and Emerging Interventions for Acute Exacerbations

- 2015 Guidelines (unchanged from 2011 recommendations): The majority of patients with acute exacerbation of IPF should be treated with corticosteroids [weak recommendation]\(^1\,2\)

**Emerging Options**

**Haemoperfusion, Polymyxin Fibre\(^3\)**
- Study (N = 31) in patients with acute exacerbations of IPF treated with or without direct haemoperfusion with polymyxin B-immobilised fibre column

**Recombinant Human Thrombomodulin\(^4\)**
- Study (N = 40) in patients with acute exacerbations of IPF treated with or without recombinant human soluble thrombomodulin

![Graphs showing survival probability and rate with different treatments]
## Practical Approach to Acute Exacerbations of IPF

### Expert Clinicians’ Perspective:

<table>
<thead>
<tr>
<th>Practical Questions</th>
<th>Answers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you use empirical antibiotic treatment?</td>
<td>We use broad-spectrum antibiotic therapy.</td>
</tr>
<tr>
<td>Do you treat with antivirals?</td>
<td>No, unless the patient is severely lymphopenic.</td>
</tr>
<tr>
<td>Do you treat for pneumocystis?</td>
<td>Yes, we do.</td>
</tr>
<tr>
<td>Do you use anticoagulation?</td>
<td>No, we do not.</td>
</tr>
<tr>
<td>Do you use CS?</td>
<td>Yes, we pulse the patient with 3 daily doses of methylprednisolone of 1 g each.</td>
</tr>
<tr>
<td>Do you use cyclophosphamide for acute exacerbations of IPF?</td>
<td>No.</td>
</tr>
</tbody>
</table>
Acute Exacerbation of IPF: Effect of Nintedanib

- **INPULSIS-1 and INPULSIS-2**: Replicate, 52-wk, phase 3 RCTs in 1,066 patients with IPF randomised to nintedanib 150 mg BID or PBO
  - **Primary Endpoint**: Annual rate of decline in FVC
  - **Key Secondary Endpoint**: Time to first acute exacerbation
    - Pooled: RR: 36% (HR: 0.64 [95% CI: 0.39-1.05], \( P = .08 \))
    - Pooled, adjudicated: RR: 68% (HR: 0.32 [95% CI: 0.16-0.65], \( P = .001 \))

### Subgroup Analysis: Patients With ≥1 Acute Exacerbation by FVC

<table>
<thead>
<tr>
<th>FVC</th>
<th>Nintedanib, n (%)</th>
<th>PBO, n (%)</th>
<th>HR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤70% Predicted</td>
<td>16 (7.7)</td>
<td>23 (14.9)</td>
<td>0.52 (0.28-0.99)</td>
<td>.1747</td>
</tr>
<tr>
<td>&gt;70% Predicted</td>
<td>15 (3.5)</td>
<td>9 (3.3)</td>
<td>1.00 (0.44-2.30)</td>
<td></td>
</tr>
</tbody>
</table>

- **TOMORROW**: Phase 2 data showed 84% reduction in acute exacerbations with nintedanib (2.3%) vs placebo (13.8%), \( P = .0054 \)

http://www.peervoice.com/o1/pvr249
Acute Exacerbation of IPF: Effect of Pirfenidone

- **2005 Japanese double-blind, randomised, placebo-controlled prospective trial (N = 107)**
  - Evaluated the efficacy of three different doses of pirfenidone
  - Incidence of acute exacerbation:
    » 0 patients in the pirfenidone groups
    » 5 patients in the placebo group

- **2010 Japanese multicentre, double-blind, placebo-controlled, randomised phase 3 clinical trial (N = 267)**
  - Examined the safety and efficacy of two different doses of pirfenidone over 52 weeks
  - Incidence of acute exacerbation:
    » 6 patients in the pirfenidone groups
    » 4 patients in the placebo group

The limited and somewhat conflicting data from these trials make it difficult to draw conclusions about the impact of pirfenidone on preventing or delaying acute exacerbations
Conclusions

Acute exacerbations...

- Are clinically important events with high 6-month mortality
- Occur more often in progressive and advanced IPF

- Are usually treated with pulse steroid IV (per guidelines; weak recommendation)
  - New options are currently under investigation

- May be prevented/delayed with antifibrotic drugs
  - Possibly due to slower disease progression and/or direct effect on the acute exacerbation
Abbreviations and References

IPF: Typical Disease Course
*Abbreviation(s):* IPF: idiopathic pulmonary fibrosis.

What Is an Acute Exacerbation of IPF?
*Abbreviation(s):* HRCT: high-resolution computed tomography.

Risk Factors, Incidence, and Consequences of Acute Exacerbations in IPF
*Abbreviation(s):* BMI: body-mass index; FVC: forced vital capacity.

Association Between Acute Exacerbation and Disease Progression
*Abbreviation(s):* 6MWD: 6-minute walk distance; $D_{LCO}$: diffusing capacity of the lungs for carbon monoxide; SGRQ: Saint George’s Respiratory Questionnaire; UCSD (SOBQ): University of California San Diego Shortness of Breath Questionnaire.
Identifying an Acute Exacerbation

*Abbreviation(s):* DAD: diffuse alveolar damage.


HRCT Findings Before, During, and After Acute Exacerbation: A Patient With Acute Exacerbation Triggered by Surgery

*Abbreviation(s):* CT: computed tomography; GGO: ground glass opacity; LLL: lower left lobe; NSCLC: non–small-cell lung cancer; UIP: usual interstitial pneumonia.


Current and Emerging Interventions for Acute Exacerbations

*Abbreviation(s):* PMX-DHP: polymyxin B–immobilised fibre column; rhTM: recombinant human thrombomodulin.

Abbreviations and References (Cont'd)

Practical Approach to Acute Exacerbations of IPF
*Abbreviation(s):* CS: corticosteroid.

Acute Exacerbation of IPF: Effect of Nintedanib
*Abbreviation(s):* BID: twice daily; CI: confidence interval; HR: hazard ratio; PBO: placebo; RCT: randomised clinical trial; RR: relative reduction.

Acute Exacerbation of IPF: Effect of Pirfenidone
About This PeerVoice Activity

PeerVoice is an independent, professional medical publishing concern focused on identifying the unmet needs of the medical community and filling those needs by reporting information pertaining to clinically relevant advances and developments in the science and practice of medicine.

PeerVoice is responsible for the selection of this activity’s topics, the preparation of editorial content, and the distribution of this activity. The preparation of PeerVoice activities is supported by written agreements that clearly stipulate and enforce the editorial independence of PeerVoice and the faculty presenters.

The faculty may discuss unapproved products or uses of these products in certain jurisdictions. Faculty presenters have been advised to disclose any reference to an unlabelled or unapproved use. No endorsement of unapproved products or uses is made or implied by coverage of these products or uses in our activities. No responsibility is taken for errors or omissions.

For approved prescribing information, please consult the manufacturer's product monograph.

Copyright © 2010-2016, PeerVoice

www.peervoice.com