Idiopathic Pulmonary Fibrosis
Diagnosis & Treatment

Kevin R. Flaherty MD, MS
Professor of Medicine
University of Michigan Health System
Division of Pulmonary/Critical Care Medicine
Disclosure Information

• I have the following financial relationships to disclose:
  Consultant for: Boehringer Ingelheim, Roche/Genentech, Veracyte, Biogen, Gilead, Pharmakea, Aeolus
  Speaker’s Bureau for: None
  Grant/Research Support from: Afferent, Boehringer Ingelheim, Roche/Genentech
  Stockholder in: None
  Honoraria from: None
  Employee of: None

• I will not discuss off label use or investigational use in my presentation.
Outline & Objectives

• Understand the classification and diagnosis of Interstitial Lung Diseases and IPF
• Recognize typical patterns of disease on HRCT
• Discuss the potential benefits and adverse reactions of approved therapies for IPF
Distinguishing Dyspnea: IPF Prevalence

Disease Prevalence, US

- IPF\(^1\): 128,100
- Heart Failure\(^2\): 5.1 million
- COPD\(^3\): 15.7 million

COPD: chronic obstructive pulmonary disease; IPF: idiopathic pulmonary fibrosis.
Interstitial Lung Diseases - Difficulties

- Diverse group of disorders (130+)
- Similar symptoms, physiology, radiology
- Difficult nomenclature
- Limited, often toxic, treatments
Diffuse Parenchymal Lung Disease (DPLD)

- DPLD of known cause, eg, drugs or association, eg, collagen vascular disease
- Idiopathic Interstitial Pneumonias
- Granulomatous DPLD, eg, sarcoidosis
- Other forms of DPLD, eg, LAM, HX, etc

Major

- Idiopathic Pulmonary Fibrosis
- Nonspecific interstitial pneumonia (idiopathic)
- Acute Interstitial Pneumonia
- Respiratory bronchiolitis interstitial lung disease
- Desquamative Interstitial Pneumonia
- Cryptogenic Organizing Pneumonia

Rare

- Lymphoid Interstitial Pneumonia
- Pleuroparenchymal Fibroelastosis

Unclassifiable

Diagnosis Matters!
IPF/UIP confers a poor prognosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPF diagnosis</td>
<td>28.46 (5.5, 147)</td>
</tr>
<tr>
<td>Age</td>
<td>0.99 (0.95, 1.03)</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.31 (0.13, 0.72)</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.30 (0.13, 0.72)</td>
</tr>
<tr>
<td>Physio CRP</td>
<td>1.06 (1.01, 1.11)</td>
</tr>
<tr>
<td>Onset Sx (yrs)</td>
<td>1.02 (0.93, 1.12)</td>
</tr>
<tr>
<td>CTfib score ≥2</td>
<td>0.77 (0.29, 2.04)</td>
</tr>
</tbody>
</table>

Communication among multidisciplinary team members is essential for an accurate diagnosis.
Clinical Tools for Diagnosis

- History and physical
- PFT
- Lab

- Raise suspicion that ILD is present
- Identify the cause of the disease
  - Infection
  - Systemic disorders
  - Exposures (eg, occupational, environment, hobby)
  - Idiopathic
# Radiographic Tools for Diagnosis

**HRCT:** allows detailed evaluation of the lung parenchyma

<table>
<thead>
<tr>
<th><strong>HRCT Features</strong></th>
<th><strong>HRCT Distribution</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Ground glass attenuation</td>
<td>- Upper</td>
</tr>
<tr>
<td>- Honeycombing/cysts</td>
<td>- Lower</td>
</tr>
<tr>
<td>- Lines/reticular thickening</td>
<td>- Central</td>
</tr>
<tr>
<td>- Consolidation</td>
<td>- Peripheral</td>
</tr>
<tr>
<td>- Nodules</td>
<td>- Diffuse/bilateral</td>
</tr>
<tr>
<td>- Decreased lung attenuation</td>
<td></td>
</tr>
</tbody>
</table>
Histologic Tools for Diagnosis

Histology

- Bronchoscopy
- Surgical lung biopsy

**UIP Pattern**

- Marked fibrosis/architectural distortion ± honeycombing, predominantly subpleural/paraseptal
- Patchy fibrosis
- Fibroblastic foci
- Absence of features to suggest alternative diagnosis

1. Images courtesy of Steven Nathan, MD.
Putting the Pattern in Context

**Usual Interstitial Pneumonia (UIP)**
- Idiopathic Pulmonary Fibrosis (IPF)
- Rheumatoid Lung
- Chronic Exposures
  - Hypersensitivity pneumonia
  - Occupational

**Nonspecific Interstitial Pneumonia (NSIP)**
- Idiopathic
- Connective Tissue Disease
- Hypersensitivity Pneumonia

**Organizing Pneumonia**
- Idiopathic COP/BOOP
- OP due to:
  - a very long list….
## Causes of OP

### Table 1. Causes of SOP

<table>
<thead>
<tr>
<th>Associated with connective tissue disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Systemic lupus erythematosus</td>
</tr>
<tr>
<td>- Rheumatoid arthritis</td>
</tr>
<tr>
<td>- Sjogren syndrome</td>
</tr>
<tr>
<td>- Polymyositis-dermatomyositis</td>
</tr>
<tr>
<td>- Polymyalgia rheumatica</td>
</tr>
<tr>
<td>- Systemic sclerosis</td>
</tr>
<tr>
<td>- Behcet's disease</td>
</tr>
<tr>
<td>- Ankylosing spondylitis</td>
</tr>
<tr>
<td>- Mixed connective tissue disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Associated with immunological disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Common variable immunodeficiency syndrome</td>
</tr>
<tr>
<td>- Essential mixed cryoglobulinemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Associated with infectious disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial</strong></td>
</tr>
<tr>
<td>- Streptococcus pneumoniae</td>
</tr>
<tr>
<td>- Legionella pneumophila</td>
</tr>
<tr>
<td>- Mycoplasma pneumoniae</td>
</tr>
<tr>
<td>- Coxiella burnettii</td>
</tr>
<tr>
<td>- Nocardia asteroides</td>
</tr>
<tr>
<td>- Chlamydia pneumoniae</td>
</tr>
<tr>
<td>- Staphylococcus aureus</td>
</tr>
<tr>
<td><strong>Viral</strong></td>
</tr>
<tr>
<td>- Adenovirus</td>
</tr>
<tr>
<td>- Cytomegalovirus</td>
</tr>
<tr>
<td>- Influenza and parainfluenza</td>
</tr>
<tr>
<td>- Human immunodeficiency virus</td>
</tr>
<tr>
<td>- Herpes virus</td>
</tr>
<tr>
<td><strong>Fungal</strong></td>
</tr>
<tr>
<td>- Cryptococcus neoformans</td>
</tr>
<tr>
<td>- Pneumocystis jiroveci</td>
</tr>
<tr>
<td><strong>Parasites</strong></td>
</tr>
<tr>
<td>- Plasmodium vivax</td>
</tr>
</tbody>
</table>

| Associated with aspiration pneumonia       |
| Associated with radiation therapy for breast cancer |
| Associated with organ transplantation      |
| - Bone marrow                               |
| - Lung                                      |
| - Renal                                     |
| - Liver                                    |

**Drug-related (see Table 2)**

**Miscellaneous**
- Inflammatory bowel disease
- Primary biliary cirrhosis
- Polyarteritis nodosa
- Chronic thyroiditis
- Hematological malignancies (myelodysplastic syndrome, T-cell leukemia, lymphoma)
- Coronary artery bypass graft surgery
- Environmental exposure (textile printing dye, house fire, cocaine abuse)
- Sweet's syndrome

---

### Table 2. Drug-Associated OP

**Most common:**
- Amiodarone, bleomycin, carbamazepine, interferon-a, -b, gold salts

**Less common:**
- Acebutolol, doxorubicin, mesalamine, sulphasalazine, nitrofurantoin, sirolimus

**Rare:**
- Amphotericin B, bucillamine, busulfan, chlorambucil, cefradin, erlotinib, fluorastatin, L-tryptophan, minocycline, nilutamide, phenytoin, risedronate, rituximab, tacrolimus, temozolomide, thalidomide, ticlopidine, trastuzumab, vinbarbital

*Adapted from Pneumotox (www.pneumotox.com).*

High Resolution Computed Tomography

- Does NOT use contrast
- Thin collimation
  - HRCT, approximately 1mm slice thickness
  - MDCT (contiguous slices) preferred
    - Close tracking of subtle parenchymal and airway abnormalities
    - Avoids missing small/subtle abnormalities
- Should use Low Dose (~80 mA)
- Reconstruction with specific Windows
- Inspiration, Expiration, and prone images
High Resolution Computed Tomography

- Examines the entire lungs
  - Avoids sampling error (like surgical biopsy)
  - Can visualize mixed disease patterns
- Expiratory images add physiologic element
- Key Limitation is resolution
  - Ground Glass may be inflammation, fibrosis, infection, water, blood, etc.
  - Microscopic honeycomb change
  - Histopathologic features
Impact of Thickness & Algorithm

CT
10-mm standard algorithm

HRCT
1.5-mm high resolution algorithm
HRCT Pitfalls

- Dependent atelectasis mimics ground glass opacity
  - More common in smokers and with increased age
  - Always do prone images
Dependent Opacity: Normal

supine

prone
Normal HRCT

- Clear 1 cm periphery
- Few interlobular septa
- Should see no airways in the peripheral 1/3 of the lungs; bronchioles not visible
- Dependent opacity
Mosaic Attenuation
(aka mosaic perfusion)

- wedge-shaped areas of alternating attenuation
- altered perfusion
  » pulmonary emboli
- altered ventilation
  » air-trapping
  » small airway disease
- patchy ground glass (ILD)
Inspiratory/ Expiratory HRCT

inspiration  expiration
Emphysema vs. Cyst
Ground Glass

- Hazy opacity you can see through
  - Less opaque than consolidation
  - Able to see bronchial & vascular markings
- Partial filling of airspaces
  - Fluid (water, blood)
  - Infection
  - Fibrosis
Honeycombing

- Clustered cystic air spaces
- Well–defined walls
- Usually comparable diameter (3-10mm)
- Usually subpleural
- Can be confused with traction bronchiectasis

Hansell et al., 2008 Radiology 246(3):697-22
Respiratory Bronchiolitis / ILD

Pattern:
- Ill defined centrilobular nodules
- Ground Glass
- Decreased lobular attenuation

Distribution:
- mid/upper lungs
Langerhans Histiocytosis (aka EG)

Pattern:
- Numerous cysts (often bizarre shapes)
- Peribronchiolar nodules
- Interstitial changes/scar

Distribution:
- Upper lobe

Progression:
- Nodules → cavitary nodules → cysts → confluent cysts
Sarcoidosis

**Pattern:**
- Nodules
- Confluent alveolar spaces
- Distortion, fibrosis, cysts

**Distribution:**
- Upper lobe
- Central/bronchovascular
Lymphangioleiomyomatosis

Pattern:
- Numerous thin-walled cysts
- No nodules or fibrosis

Distribution:
- Diffuse, no predominance
Lymphangioleiomyomatosis
Hypersensitivity Pneumonitis

Pattern:
- Ground Glass
- Mosaic attenuation
- Peribronchiolar thickening

Distribution:
- Upper / Diffuse
50 year old male with Hypersensitivity Pneumonia – Treated with removal of doves and immunosuppression

<table>
<thead>
<tr>
<th></th>
<th>06/18/13</th>
<th>06/20/16</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (% pred)</td>
<td>1.95 (50%)</td>
<td>2.93 (78%)</td>
</tr>
<tr>
<td>FVC (% pred)</td>
<td>2.04 (38%)</td>
<td>3.22 (61%)</td>
</tr>
<tr>
<td>DLCO (% pred)</td>
<td>12.25 (38%)</td>
<td>25.22 (81%)</td>
</tr>
</tbody>
</table>

04/05/13

06/20/16
Hypersensitivity Pneumonitis - Chronic

Similar morphology to UIP but... patchy or mosaic distribution & air trapping
Nonspecific interstitial pneumonia

Pattern:
- Reticulation
- Traction Bronchiectasis
- Ground Glass
- Honeycomb rare (5%)

Distribution:
- Lower
- Peripheral / Diffuse
Updated Consensus Statement for Diagnosis of IPF

The diagnosis of IPF requires:

1. Exclusion of other known causes of interstitial lung disease
2. Presence of UIP pattern on HRCT (in patients without surgical biopsy)
3. A HRCT pattern of definite/possible UIP with a Surgical lung biopsy showing Definite/Probable UIP

*The Major and Minor Criteria proposed in the 2000 ATS/ERS Consensus Statement were Eliminated*

Raghu et al., *Am J Respir Crit Care Med* 2011; 183:788-24
## Role of HRCT in Diagnosing UIP

<table>
<thead>
<tr>
<th>UIP Pattern (All 4 Features)</th>
<th>Possible UIP (All 3 Features)</th>
<th>Inconsistent With UIP (Any)</th>
</tr>
</thead>
</table>
| • Subpleural, basal prominence  
• Reticular abnormality  
• Honeycombing with/without traction bronchiectasis  
• Absence of features listed as inconsistent with UIP (column 3) | • Subpleural, basal prominence  
• Reticular abnormality  
• Absence of features listed as inconsistent with UIP (column 3) | • Upper or mid-lung predominance  
• Peribronchovascular predominance  
• Extensive ground glass abnormality (extent > reticular abnormality)  
• Profuse micronodules (bilateral, predominantly upper lobe)  
• Discrete cysts (multiple, bilateral, away from areas of honeycombing)  
• Diffuse mosaic attenuation/air-trapping (bilateral, ≥3 lobes)  
• Consolidation in bronchopulmonary segment(s)/lobe(s) |

Usual Interstitial Pneumonia

Pattern:
• irregular septal lines & honeycombing
• ground glass opacity (not predominant)
• traction bronchiectasis

Distribution:
• lower > upper lung
• subpleural distribution
Radiology (HRCT) Diagnosis of IPF/UIP Versus NSIP

Consecutive patients with UIP or NSIP  
\[ n = 96 \]

HRCT definite/probable UIP  
\[ n = 27 (28\%) \]

HRCT not UIP  
\[ n = 69 (72\%) \]

UIP diagnosis  
\[ n = 27 (100\%) \]

Non-UIP diagnosis  
\[ n = 0 (0\%) \]

UIP diagnosis  
\[ n = 46 (67\%) \]

Non-UIP diagnosis  
\[ n = 23 (33\%) \]

63% of UIP cases

## Emphysema + IPF/UIP

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>3.63 (89%)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>2.74 (102%)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC</td>
<td>115%</td>
</tr>
<tr>
<td>RV</td>
<td>2.67 (113%)</td>
</tr>
<tr>
<td>TLC</td>
<td>6.30 (98%)</td>
</tr>
<tr>
<td>DL&lt;sub&gt;CO&lt;/sub&gt;</td>
<td>11.90 (48%)</td>
</tr>
</tbody>
</table>
UIP: Irregular Reticular Opacities

Courtesy of W. Richard Webb, MD.
Early HRCT Findings in IPF
Histologic Tools for Diagnosis

**Histology**
- Bronchoscopy
- Surgical lung biopsy

**UIP Pattern**
- Marked fibrosis/architectural distortion ± honeycombing, predominantly subpleural/paraseptal
- Patchy fibrosis
- Fibroblastic foci
- Absence of features to suggest alternative diagnosis

1. Images courtesy of Steven Nathan, MD.
Idiopathic Pulmonary Fibrosis

A specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, and limited to the lungs.

It is characterized by progressive worsening of dyspnea and lung function and is associated with a poor prognosis.
Having a Conversation With the Patient Newly Diagnosed With IPF

- Spend adequate time to explain the prognosis and assess patient's preferences and values
- Burden and morbidity of IPF can be emotionally overwhelming and will likely impact family members as well
- Each individual patient with IPF is different; consider physiology, exercise tolerance, radiology, and pathology when choosing a course of treatment
- Patients who are at increased risk of mortality should be referred for lung transplantation early in the course
## 2015 Treatment Recommendations for IPF

<table>
<thead>
<tr>
<th>Strong Recommendation Against Use:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation (warfarin), Pred/Aza/NAC, ambrisentan, Imatinib</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conditional Recommendation for Use:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nintedanib, pirfenidone, GERD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conditional Recommendation Against Use:</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAC, macitentan, bosentan, sildenafil</td>
</tr>
</tbody>
</table>

High Dose Acetylcysteine in Idiopathic Pulmonary Fibrosis

Mortality
NAC = 9%
Placebo = 11%
p=0.69

Demedts et al; NEJM 2005;353:2229-42
PANTHER
Prednisone-Azathioprine-N-acetyl cysteine: A Trial That Evaluates Responses in IPF

Diagnosis of IPF with FVC > 50%, DLCO > 30% predicted

Three arms
  - Placebo
  - N-acetyl cysteine
  - Pred/aza/NAC

Primary Endpoint – Change in FVC over 60wks
Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

- Interim Analysis with 50% data
  - Combination n = 77, Placebo n= 78
  - Increased Death 8 vs 1, p=0.01
  - Increased Hosp 23 v 7, p<0.001
  - No physio/clinical benefit

- Termination of combination therapy at mean of 32 weeks
- Recommendation against use of pred/azathioprine/N-acetyl cysteine

NAC Does Not Reduce FVC Decline

### 2015 Treatment Recommendations for IPF

<table>
<thead>
<tr>
<th>Strong Recommendation Against Use:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation (warfarin), Pred/Aza/NAC, ambrisentan, Imatinib</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conditional Recommendation for Use:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nintedanib, pirfenidone, GERD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conditional Recommendation Against Use:</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAC, macitentan, bosentan, sildenafil</td>
</tr>
</tbody>
</table>
Nintedanib: INPULSIS-1 and INPULSIS-2 Trial Design

Inclusion Criteria
- Age ≥40
- IPF ≤5 y
- ≥50% FVC pred
- 30%-79% DLCO pred
- HRCT within 1 y

Endpoints
1. Δ FVC
2. Time to first AE
   Δ SGRQ

1,066 Patients

52 Weeks

INPULSIS Primary Endpoint: Adjusted Annual Rate of Decline in FVC

INPULSIS: Time to First Investigator-Reported Acute Exacerbation

**INPULSIS-1**

- Cumulative Incidence of First Investigator-Reported Acute Exacerbation, %
  - Nintedanib, 150 mg Twice Daily
  - Placebo
  - HR 1.15 (95% CI, 0.54-2.42)
  - \(P = .67\)

**INPULSIS-2**

- Cumulative Incidence of First Investigator-Reported Acute Exacerbation, %
  - Placebo
  - Nintedanib, 150 mg Twice Daily
  - HR 0.38 (95% CI, 0.19-0.77)
  - \(P = .005\)

Nintedanib – Time to First Exacerbation Statified by FVC +/- 70% predicted
# Nintedanib – Safety & Tolerability

<table>
<thead>
<tr>
<th></th>
<th>Nintedanib (n=638)</th>
<th>Placebo (n=423)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Reduction*</td>
<td>178 (28%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td>Treatment Interruptions*</td>
<td>151 (24%)</td>
<td>42 (10%)</td>
</tr>
<tr>
<td>Incidence/Discontinue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>63% / 4.4%</td>
<td>18% / 0.2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>25% / 2.0%</td>
<td>7% / 0%</td>
</tr>
<tr>
<td>Mild/Mod/Severe (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>57 / 38 / 5</td>
<td>77 / 20 / 3</td>
</tr>
<tr>
<td>Nausea</td>
<td>74 / 24 / 2</td>
<td>93 / 7 / 0</td>
</tr>
</tbody>
</table>

* No particular time

FDA Approval of Nintedanib

Approved October 15, 2014, for the treatment of IPF

Liver function tests required prior to treatment and should be evaluated every 3 months in first year

Dosage and administration

150 mg twice daily with food
Take each dose approximately 12 h apart

Adverse reactions? Consider temporary dose reduction to 100 mg, temporary interruption, or discontinuation
Pirfenidone: ASCEND Trial Design

**Inclusion Criteria**
- Age 40-80 y
- Confirmed IPF
- 50%-90% FVC pred
- 30%-90% DLCO pred
- FEV₁/FVC ≥0.80
- 6MWD ≥150 m

**Endpoints**
1\(^0\): Δ FVC or death
2\(^0\): 6MWD
  PFS
  Dyspnea
  Death

**555 Patients**

ASCEND: Primary Efficacy Analysis

**Patients With ≥10% Decline in FVC or Death, %**

- **Week 13**: Pirfenidone (n = 278) vs. Placebo (n = 277)
- **Week 26**: Pirfenidone (n = 278) vs. Placebo (n = 277)
- **Week 39**: Pirfenidone (n = 278) vs. Placebo (n = 277)
- **Week 52**: Pirfenidone (n = 278) vs. Placebo (n = 277)

<table>
<thead>
<tr>
<th>Week</th>
<th>Absolute difference</th>
<th>Relative difference</th>
<th>Rank ANCOVA P</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>2.5%</td>
<td>54.0%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>26</td>
<td>7.9%</td>
<td>58.0%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>39</td>
<td>12.3%</td>
<td>57.8%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>52</td>
<td>15.3%</td>
<td>47.9%</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

**Primary endpoint**: 48% Relative Reduction

**ANCova**: analysis of covariance.

## Table 2. Summary of finding form Pirfenidone for idiopathic pulmonary fibrosis.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipate absolute effects (Study population) (95% CI)</th>
<th>Relative Effect</th>
<th>NO of participants</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with placebo</td>
<td>Risk with Pirfenidone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause-mortality</td>
<td>67 per 1000</td>
<td>36 per 1000 (22 to 59)</td>
<td>RR 0.53 (0.32 to 0.88)</td>
<td>1247 (3 RCTs)</td>
</tr>
<tr>
<td>Progression free-survival</td>
<td>442 per 1000</td>
<td>372 per 1000 (332 to 416)</td>
<td>RR 0.83 (0.75 to 0.94)</td>
<td>728 (3 RCTs)</td>
</tr>
<tr>
<td>Acute exacerbation</td>
<td>26 per 1000</td>
<td>15 per 1000 (5 to 47)</td>
<td>RR 0.59 (0.19 to 1.84)</td>
<td>235 (2 RCTs)</td>
</tr>
<tr>
<td>Worsening of IPF</td>
<td>168 per 1000</td>
<td>107 per 1000 (84 to 139)</td>
<td>RR 0.64 (0.50 to 0.83)</td>
<td>1615 (5 RCTs)</td>
</tr>
<tr>
<td>Change on 6MWT</td>
<td>417 per 1000</td>
<td>308 per 1000 (267 to 358)</td>
<td>RR 0.74 (0.64 to 0.86)</td>
<td>1236 (3 RCTs)</td>
</tr>
<tr>
<td>Change on aminotransferases</td>
<td>30 per 1000</td>
<td>68 per 1000 (40 to 115)</td>
<td>RR 2.26 (1.33 to 3.83)</td>
<td>764 (5 RCTs)</td>
</tr>
</tbody>
</table>

1: Non primary outcome from RCTs, 2: High heterogeneity; 6MWT: Six minutes walk test; RCT: Randomized controlled trial; RR: Risk ratio; CI: confidence interval.
ASCEND: Treatment-Emergent Adverse Events more common in pirfenidone group

• Nausea (36% vs 13%)
• Rash (28% vs 9%)

• Adverse events (AEs) generally mild to moderate severity, reversible, and without clinically significant sequelae

FDA Approval of Pirfenidone

Approved October 15, 2014, for the treatment of IPF

Liver function tests required prior to treatment and should be evaluated every 3 months in first year

Dosage and administration

- 801 mg 3x daily with food (three 267-mg capsules per dose)
- Take each dose at the same time each day
- Initiate with titration
  - Days 1-7: one capsule 3x daily
  - Days 8-14: two capsules 3x daily
  - Days 15 onward: three capsules 3x daily

Adverse reactions? Consider temporary dosage reduction, treatment interruption, or discontinuation
Gastroesophageal reflux (GERD) in IPF

- GER is highly prevalent in patients with IPF
- Observational study (n = 204); 47% received GER medical therapy, and 5% surgical

Engaging in a Shared Decision-Making Process

- Discuss the efficacy and safety of FDA-approved therapies
- Listen to patient’s preferences and concerns
- Focus on symptom control and management of comorbidities
- Set treatment expectations
- Look at the option of lung transplantation
IPF - Acute Exacerbations

- Incidence of 4-24% / 100 IPF person years
- Triggers – Infections, Mechanical, GERD, other
- Prognosis
  - 46% of IPF mortality due to AE-IPF
  - Median survival after AE-IPF 3-4 months
- Risk Factors
  - Advanced disease (primarily FVC)
  - Younger age
  - Co-morbid Coronary Artery Disease
  - Increased BMI

IPF - Acute Exacerbations (overlap with ALI)

IPF - Acute Exacerbation Definition

Acute respiratory deterioration in IPF (typically < 1 month duration)

Extra-parenchymal cause identified?

Yes

Not acute exacerbation
Alternative diagnosis (e.g., pneumothorax, pleural effusion, pulmonary embolism)

No

New, bilateral GGO/consolidation on CT?
(not fully explained by cardiac failure or fluid overload)

Yes

Acute exacerbation of IPF
Triggered Acute Exacerbation
(e.g., infection, post-procedural/post-operative, drug toxicity, aspiration)

No

Not acute exacerbation
Alternative diagnosis (e.g., infection, aspiration, drug toxicity, congestive heart failure)

Idiopathic Acute Exacerbation
No trigger identified

IPF - Acute Exacerbation Treatment

- **No proven effective therapy**
- Weak recommendation for use of steroids
  - High value on anecdotal reports
- Supportive Care – Oxygen, palliation of symptoms
- Recommendation against mechanical ventilation
- Case reports / series of numerous agents
  - Cyclosporin / Tacrolimus
  - Cyclophosphamide
  - Rituximab + Plasma Exchange + IVIG
  - IV Thrombomodulin
  - Polymyxin-B hemoperfusion
Members of the IPF Care Team

- Multidisciplinary Team of Physicians
  - Pulmonary, Radiology, Pathology, Rheumatology, Cardiology, Thoracic Surgery, Lung Transplant
- Social Work
- Clinical Nurse Specialist
- Palliative Care
- Students/Residents/Fellows
- Research Coordinator
- Support Group
Supportive Care for Patients With IPF

- Educate patients
  - Refer to reliable sources
- Prescribe $O_2$
  - Screen for resting/nocturnal/exertional requirement
- Supportive Care Options
  - Close monitoring of symptoms and pulmonary function
  - Exercise
    - Pulmonary rehabilitation
  - Treatment of comorbid illness
    - GERD, OSA, CAD

OSA: obstructive sleep apnea.
Lung Transplantation for Pulmonary Fibrosis: Referral and Listing Guidelines

Referral

- Diagnosis of IPF (histologic or radiographic)
- Diagnosis of fibrotic NSIP (histologic)

Transplantation

- $DL_{CO} < 39\%$ predicted
- Decline in FVC by $\geq 10\%$ over 6 months
- Oxyhemoglobin saturation $< 88\%$ with 6MWT
- Honeycombing on HRCT
- Histologic evidence of NSIP and
  - $DL_{CO} < 35\%$ predicted
  - Decline in FVC of $\geq 10\%$ over 6 months
  - Decline in $DL_{CO}$ of $\geq 15\%$ over 6 months
