INTERSTITIAL LUNG DISEASES: FOCUS ON IDIOPATHIC PULMONARY FIBROSIS (IPF)

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DISCLOSURES

- Advisory Boards: Boehringer Ingelheim, Genentech, Mesoblast

- Research Grants: Genentech; Lester and Sue Smith Foundation, Marcus Foundation; NIH
74-YEAR-OLD MALE EX-SMOKER WITH COUGH & DYSPNEA

- **History:** 12 months ago developed productive cough and shortness of breath
- Referred to pulmonologist with abnormal CXR and had HRCT of chest
- Hospitalized 14 months later with increased dyspnea and hypoxemia—treated with antibiotics and steroids
- Dyspnea with ADLs
- Since discharge, requires continuous oxygen therapy
- Frequent heartburn
- Reports poor sleep, snoring and daytime fatigue

- **Past Medical/Family/Social History**
  - +HTN, Hyperlipidemia
  - Family history of CAD,
  - Former 30 pack year smoker

- **Exam**
  - 140/66, 86, 22, SpO2 90% at rest on RA; BMI 27
  - Bibasilar inspiratory crackles, no wheeze
  - No peripheral edema or signs of CHF
# 74-Year-Old Male Ex-Smoker with Cough & Dyspnea

<table>
<thead>
<tr>
<th>Date</th>
<th>FEV₁</th>
<th>FVC</th>
<th>FEV₁/FVC</th>
<th>DL&lt;sub&gt;CO&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>February 15</td>
<td>2.42</td>
<td>2.80</td>
<td>0.86</td>
<td>8.75</td>
</tr>
</tbody>
</table>

FEV₁: Forced Expiratory Volume in 1 second  
FVC: Forced Vital Capacity  
FEV₁/FVC: Ratio of FEV₁ to FVC  
DL<sub>CO</sub>: Diffusing Capacity for CO
HRCT 14 MONTHS LATER
IDIOPATHIC PULMONARY FIBROSIS

Normal Lung

Usual Interstitial Pneumonia
WHERE DOES IPF FIT IN THE CONTEXT OF THE ILDS?

- The most common ILD: 42,000 new cases per year
- Definition of IPF:
  - Specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause
  - Occurring primarily in males above the age of 55
  - Limited to the lungs
  - 80% are ex-smokers

HISTORICAL CLASSIFICATION OF INTERSTITIAL LUNG DISEASES

Adapted from ATS/ERS. Am J Respir Crit Care Med. 2013;188: 733-748.

**1970s**

- **Idiopathic IPs**
  - Heterogeneous group that included a number of diseases
- **Asbestosis**
- **LAM**
- **BML**
- **LG**

**2016**

- **IPF**
- **DIP**
- **RB-ILD**
- **AIP**
- **NSIP**
- **COP**
- **Cellular**
- **Fibrotic**
- **Unclassifiable IIPs**
- **Rare IIPs**
  - Pleuroparenchymal Fibroelastosis

**Idiopathic IPs**

- **Sarcoidosis**
- **Hypersensitivity Pneumonitis (EAA)**
IPF IS THE MOST COMMON IDIOPATHIC INTERSTITIAL PNEUMONIA

Interstitial lung disease (ILD)

- ILD of known cause
- Idiopathic interstitial pneumonias
- Granulomatous ILD
- Other forms of ILD

Idiopathic interstitial pneumonias

- Major idiopathic interstitial pneumonias
  - Desquamative interstitial pneumonia
  - Cryptogenic organizing pneumonia
  - Acute interstitial pneumonia
- Rare idiopathic interstitial pneumonias
- Unclassifiable idiopathic interstitial pneumonias
- Idiopathic pulmonary fibrosis (IPF)
- Idiopathic nonspecific interstitial pneumonia
- Respiratory bronchiolitis-interstitial lung disease
- Idiopathic lymphoid interstitial pneumonia
- Idiopathic pleuroparenchymal fibroelastosis

DISTINGUISHING DYSPNEA

Disease Prevalence, United States

- **IPF**
  - 136,170

- **Heart failure**
  - 5.1 million

- **COPD**
  - 15.7 million

THE INCIDENCE OF IPF INCREASES WITH AGE

RISK FACTORS/LOCATION OF IPF IN US

- Age
- Male sex
- Hispanic ethnicity
- Geography

SURVIVAL IN IPF IS WORSE THAN MOST CANCERS

IPF survival is comparable to that of lung cancer.
PATIENTS WITH IPF ARE OFTEN MISDIAGNOSED

Patients are often misdiagnosed with bronchitis, asthma, COPD, emphysema, or heart disease.
PROGRESSION OF IPF

Normal

Progressive destruction of lung architecture

5-year survival rate from diagnosis = 20 to 40%
Age of onset: 2/3 over age 60
IPF: A DISEASE WITH AN UNPREDICTABLE CLINICAL COURSE

DIFFUSING CAPACITY PREDICTS SURVIVAL IN IPF

FVC PREDICTS SURVIVAL IN IPF


P = 0.0053
6MWT: PARAMETERS PREDICT SURVIVAL IN IPF

Baseline 6MWT distance

Δ 6MWT distance at 24 weeks

GERD TREATMENT AND SURVIVAL

Survival

Time to Event (days)

HR = 0.51, p value < 0.01

Taking GER Medications
Not taking GER Medications

OBSTRUCTIVE SLEEP APNEA IS COMMON IN IPF

55 subjects with IPF

Sleep apnea evaluation
- Epworth Sleepiness Scale
- Sleep Apnea Scale of Sleep Disorders
- Nocturnal polysomnography

Findings that did not correlate with OSA
- Spirometry
- Lung volume
- DLCO
- ESS

AHI: apnea-hypopnea index

No OSA
AHI ≤ 5/h

12%

Mild
AHI 5–15/h

20%

Moderate/Severe
AHI > 15 events/h

68%

Clinical presentation:
- Typically affects adults >50 years of age
- Chronic exertional dyspnea
- Dry, nonproductive cough
- Crackles or rales on auscultation
- Digital clubbing

Patient presents with suspected ILD
- Detailed history
- Physical exam
- PFT

Adapted from Raghu G et al. 1 CTD, connective tissue disorder; MDD, multidisciplinary discussion; PFT, pulmonary function testing.
Diagnostic Algorithm for IPF

1. Patient presents with suspected ILD
   • Detailed history
   • Physical exam
   • PFT

2. Identifiable cause of ILD?
   Yes
   - Serologic testing to exclude CTD
   No

3. Exposures (environmental, occupational, pets)¹
   - Skin, joint, or muscle findings including arthritis, pleurisy, skin thickening, and Raynaud’s phenomenon may indicate a connective tissue disorder¹

Not IPF

Adapted from Raghu G et al.¹ CTD, connective tissue disorder; MDD, multidisciplinary discussion; PFT, pulmonary function testing.
Patient presents with suspected ILD

- Detailed history
- Physical exam
- PFT

Identifiable cause of ILD?

Yes

Identifiable cause of ILD?  

No

Serologic testing to exclude CTD

Not IPF

Diagnostic Algorithm for IPF

HRCT is critical to making an accurate diagnosis of IPF
• UIP
• Possible UIP
• Inconsistent with UIP

Patient presents with suspected ILD
• Detailed history
• Physical exam
• PFT

Identifiable cause of ILD?
Yes
• Positive
  Serologic testing to exclude CTD
  Negative

No
HRCT

Identifiable cause of ILD?
Yes
Positive

Not IPF

Adapted from Raghu G et al. CTD, connective tissue disorder; MDD, multidisciplinary discussion; PFT, pulmonary function testing.
HRCT is critical to making an accurate diagnosis of IPF.

1. UIP
2. Possible UIP
3. Inconsistent with UIP
4. Not IPF
5. IPF

Patient presents with suspected ILD

- Detailed history
- Physical exam
- PFT

Identifiable cause of ILD?

- No

Serologic testing to exclude CTD

- Negative

HRCT

Definite UIP

Image courtesy of and used with permission from Jonathan Goldin, MD, PhD.

Adapted from Raghu G et al. 1 CTD, connective tissue disorder; MDD, multidisciplinary discussion; PFT, pulmonary function testing.

Patient presents with suspected ILD

- Detailed history
- Physical exam
- PFT

If no identifiable cause of ILD:

Serologic testing to exclude CTD

If negative:

HRCT – Definite UIP

If positive:

Identifiable cause of ILD?

Yes

No

Not UIP

Not IPF

IPF

Adapted from Raghu G et al.¹ CTD, connective tissue disorder; MDD, multidisciplinary discussion; PFT, pulmonary function testing.
Patient presents with suspected ILD

- Detailed history
- Physical exam
- PFT

Yes

Identifiable cause of ILD?

Positive

Serologic testing to exclude CTD

Negative

HRCT

Possible UIP

Surgical lung biopsy

Not UIP

Not IPF

Possible UIP

IPF

Definite UIP

Adapted from Raghu G et al. 1 CTD, connective tissue disorder; MDD, multidisciplinary discussion; PFT, pulmonary function testing.
Diagnostic Algorithm for IPF

Patient presents with suspected ILD

- Detailed history
- Physical exam
- PFT

Yes

Identifiable cause of ILD?

Positive

Serologic testing to exclude CTD

Negative

HRCT

Not UIP

Possible UIP

Surgical lung biopsy

Not UIP

Not IPF

Definite UIP

IPF

Adapted from Raghu G et al. 1 CTD, connective tissue disorder; MDD, multidisciplinary discussion; PFT, pulmonary function testing.
Diagnostic Algorithm for IPF

Patient presents with suspected ILD

- Detailed history
- Physical exam
- PFT

Identifiable cause of ILD?

Yes

Identifiable cause of ILD?

No

Serologic testing to exclude CTD

Positive

Not UIP

HRCT

Possible UIP

Not UIP

Surgical lung biopsy

MDD

UIP/Probable UIP

Not UIP

IPF

Definite UIP

Adapted from Raghu G et al. CTD, connective tissue disorder; MDD, multidisciplinary discussion; PFT, pulmonary function testing.
PATHOGENESIS OF IPF

- Epithelial cell injury and activation
- Wound clot
- Angiogenesis
- Baseline membrane disruption
- Myofibroblast accumulation
- Progressive fibrosis and impaired reepithelialization

# Past Negative Clinical Trials in IPF 2000-Present

<table>
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<tr>
<th>Trial</th>
<th>n</th>
<th>Primary Endpoint</th>
<th>Result</th>
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<tbody>
<tr>
<td>Interferon-beta (1999)</td>
<td>167</td>
<td>Progression-free survival time</td>
<td>Negative</td>
</tr>
<tr>
<td>Interferon-gamma (GIPF-001)</td>
<td>330</td>
<td>Progression-free survival</td>
<td>Negative</td>
</tr>
<tr>
<td>Interferon-gamma (Inspire)</td>
<td>826</td>
<td>Survival time</td>
<td>Negative</td>
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<tr>
<td>Pirfenidone (CAPACITY 1)</td>
<td>344</td>
<td>Change in FVC</td>
<td>Negative</td>
</tr>
<tr>
<td>Etanercept</td>
<td>100</td>
<td>Change in DLco, FVC</td>
<td>Negative</td>
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<tr>
<td>Imatinib Mesylate</td>
<td>120</td>
<td>Progression-free survival</td>
<td>Negative</td>
</tr>
<tr>
<td>Bosentan (BUILD 1 and 2)</td>
<td>132</td>
<td>Change in 6MW</td>
<td>Negative</td>
</tr>
<tr>
<td>Bosentan (BUILD 3)</td>
<td>390</td>
<td>Progression-free survival time</td>
<td>Negative</td>
</tr>
<tr>
<td>Sildenafil (STEP)</td>
<td>29</td>
<td>Change in 6MWD, Borg dyspnea index</td>
<td>Negative</td>
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<tr>
<td>Ambrisentan (Artemis-IPF)</td>
<td>478</td>
<td>Progression-free survival</td>
<td>Stopped –</td>
</tr>
<tr>
<td>Ambrisentan (Artemis-PH)</td>
<td>50</td>
<td>6MWD</td>
<td>Stopped –</td>
</tr>
<tr>
<td>Everolimus</td>
<td>89</td>
<td>Progression</td>
<td>Negative</td>
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Two drugs: Nintedanib and Pirfenidone

Effective in slowing functional decline and disease progression

Current evidence supports timely diagnosis and administration of treatment

Neither drug cures IPF
MSCS: A UNIQUE IMMUNOPRIVILEGED CELL

YOUNG MSCS PREVENT LUNG FIBROSIS

Saline

Bleomycin

Bleomycin + yASC

No infusion related adverse events

Most common adverse event was bronchitis

Promising exploratory endpoints:
- Walk test distance
- Lung Function
- Oxygen usage
KEY POINTS:
WORK-UP SHORTNESS OF BREATH
WWW.BREATHLESSIPF.COM
REFER EARLY TO SPECIALIST