A NEW ERA in Idiopathic Pulmonary Fibrosis

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Educational Activity
Learning Objectives

• Describe the differential diagnosis of IPF utilizing clinical features, imaging studies, and surgical biopsy.
• Implement evidence-based strategies for measuring disease progression and treatment response.
• Identify opportunities for interdisciplinary collaboration, consultation, and referral that can facilitate early and accurate IPF diagnosis and therapy.

Outline

• What is Idiopathic Pulmonary Fibrosis (IPF)?
  – Presentation
  – Incidence/Prevalence
• Diagnosing IPF
• Breakthroughs in Treating Patients with IPF
  – Pirfenidone (Esbriet)
  – Nintedanib (OFEV)
• Stem Cell Treatments for IPF?

Disclosures

Faculty Disclosures
• Steering Committee, PIPF-016 InterMune
• Lead Investigator, Nintedanib EAP, Boehringer Ingelheim

Activity Staff Disclosures
• The planners, reviewers, editors, staff, or other members at The France Foundation who control content have no relevant financial relationships to disclose

Educational Support
• ???
**What Is IPF?**

- Idiopathic fibrotic disease of the lungs
  - As opposed to MANY other known causes of fibrosis of the lungs
- Men > Women
- Typically presents after age 60
- Progressive, debilitating, with median survival of 3-5 years

**Diagnosing IPF**

**2011 ATS/ERS Diagnostic Criteria for IPF**

- UIP pattern on HRCT without surgical biopsy
- Definite/possible UIP pattern on HRCT with a surgical lung biopsy showing definite/probable UIP

Exclusion of known causes of Interstitial Lung Disease

**High Resolution CT Scan**

- Inspiratory supine and expiratory supine
- ≤1.25mm axial reconstruction
- High spatial frequency reconstruction ("bone") algorithm
- Prone imaging in select cases
- No IV contrast

**HRCT Criteria for UIP**

<table>
<thead>
<tr>
<th>UIP Pattern</th>
<th>Possible UIP Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subpleural, basal predominance</td>
<td>+</td>
</tr>
<tr>
<td>Reticular abnormality</td>
<td>+</td>
</tr>
<tr>
<td>Honeycombing (+/- traction bronchiectasis)</td>
<td>+</td>
</tr>
<tr>
<td>Absence of &quot;inconsistent&quot; features</td>
<td>+</td>
</tr>
</tbody>
</table>

**HRCT Features Inconsistent with IPF**

- Inconsistent Features
  - Upper lobe predominant
  - Peribronchovascular predominance
  - Ground-glass > extent of reticular abnormality
  - Profuse micronodules
  - Discrete cysts
  - Diffuse mosaic attenuation/gas-trapping
  - Consolidation

**Diagnosing IPF**

- Appropriate History
  - No suggestion of other etiology
- Consistent Physical Exam
  - No Evidence of other processes
- CT Scan evidence of UIP
- Serological evaluation
  - Should be performed before a biopsy
Before You Get a Biopsy…

- Referral to an ILD Center
- Is a lung biopsy safe and necessary for diagnosis?
  - No: if meets all HRCT criteria
  - No: if there is extensive disease
  - No: if there is pulmonary hypertension
  - No: if there are high oxygen requirements
- Avoid a “diagnostic trial” of steroids: no evidence now (Panther trial)

Diagnosing IPF: Putting It All Together

- History
- Exam
- Physiology
  - Full PFTs
  - Gas exchange
  - 6MWT
- Radiology
  - HRCT
- Labs
- Pathology

Predictors of Disease Severity and Progression in IPF

<table>
<thead>
<tr>
<th>Tests/Clinical Factors</th>
<th>Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>Initial value and change over time correlate with mortality</td>
</tr>
<tr>
<td>DLCO</td>
<td>&lt; 35% predicted → lower survival</td>
</tr>
<tr>
<td>6MWT</td>
<td>O₂ sat ≤ 88% → increased mortality risk for IPF &amp; NSIP</td>
</tr>
<tr>
<td></td>
<td>Walk distance correlates with mortality</td>
</tr>
<tr>
<td></td>
<td>Heart rate recovery correlates with mortality</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>Associated with higher mortality</td>
</tr>
<tr>
<td>Dyspnea score</td>
<td>Correlates with survival</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>Predicts worse survival</td>
</tr>
</tbody>
</table>

6MWT Parameters Predict Survival in IPF

Which 6MWT parameter best predicts survival in IPF?

Monitoring for Disease Progression

- Every 3 to 6 months:
  - PFTs
  - 6MWT (distance/nadir saturation)
  - O₂ requirement
  - Comorbidities
  - Consider dyspnea questionnaire (UCSD)
- HRCT
  - Annually or when suspicion for clinical worsening

Breakthroughs in Treating IPF

Three Recent Clinical Trials
American Thoracic Society 2014

- PANTHER N-acetylcysteine (NAC)
- ASCEND Pirfenidone
- INPULSIS Nintedanib (BIBF1120)
Cumulative Distribution of Patients by Change in Percent Predicted FVC from Baseline to Week 52

- Figure presents the cumulative distribution of all cut-offs for the change from baseline %FVC at Week 52.
- The dashed lines indicate ≥10% decline or ≥0% decline.
- For all categorical declines in lung function, the proportion of patients declining was lower on Esbriet than on placebo. Study 2 showed similar results.

ASCEND Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Pirfenidone (%) (N = 278)</th>
<th>Placebo (%) (N = 277)</th>
<th>∆ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>36</td>
<td>13.4</td>
<td>22.6</td>
</tr>
<tr>
<td>Rash</td>
<td>28.1</td>
<td>8.7</td>
<td>19.4</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>31.2</td>
<td>6.1</td>
<td>25.1</td>
</tr>
<tr>
<td>Anorexia</td>
<td>15.8</td>
<td>6.5</td>
<td>9.3</td>
</tr>
<tr>
<td>GERD</td>
<td>11.9</td>
<td>6.5</td>
<td>5.4</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>12.6</td>
<td>7.9</td>
<td>4.7</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11.2</td>
<td>6.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12.9</td>
<td>8.7</td>
<td>4.2</td>
</tr>
<tr>
<td>Cough</td>
<td>14.7</td>
<td>17.7</td>
<td>-3</td>
</tr>
<tr>
<td>IPF</td>
<td>9.4</td>
<td>18.1</td>
<td>-8.7</td>
</tr>
</tbody>
</table>

Mean (SEM) Observed FVC Change from Baseline (mL) over Time in Study 2 (INPULSISTM-1)1-3

- When the mean observed FVC change from baseline was plotted over time, the curves diverged at all timepoints through Week 52 in Study 2 (INPULSISTM-1).
- Similar plots were seen for Studies 1 (TOMORROW) and 3 (INPULSISTM-2).

FDA Approval of Pirfenidone

- Approved October 15, 2014
- Indicated for the treatment of IPF
- Dosage and administration
  - 801 mg (three 267 mg capsules) three times daily with food
  - Doses should be taken at the same time each day
  - Initiate with titration
    - Days 1 through 7: 1 capsule 3x per day
    - Days 8 through 14: 2 capsules 3x per day
    - Days 15 onward: 3 capsules 3x per day
  - Consider temporary dosage reduction, treatment interruption, or discontinuation for management of adverse reactions
- Prior to treatment, conduct liver function tests

Common Nintedanib Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>INPULSIS-1 Nintedanib (n = 309)</th>
<th>Placebo (n = 204)</th>
<th>INPULSIS-2 Nintedanib (n = 329)</th>
<th>Placebo (n = 219)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any (%)</td>
<td>96</td>
<td>89</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>Diarrhea (%)</td>
<td>62</td>
<td>19</td>
<td>63</td>
<td>18</td>
</tr>
<tr>
<td>Nausea (%)</td>
<td>23</td>
<td>6</td>
<td>26</td>
<td>7</td>
</tr>
</tbody>
</table>

FDA Approval of Nintedanib

- Approved October 15, 2014
- Indicated for the treatment of IPF
- Dosage and administration
  - 150 mg twice daily approximately 12 hours apart taken with food
  - Consider temporary dose reduction to 100 mg, temporary interruption, or discontinuation for management of adverse reactions
- Prior to treatment, conduct liver function tests

Important Safety Information throughout. Full Prescribing Information is available at the presentation.

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Current Phase 2 Trials for IPF
Next Generation Therapy?

<table>
<thead>
<tr>
<th>Trial</th>
<th>Target</th>
<th>N</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-trimoxazole (Ph 3)</td>
<td>Pneumocystis jiroveci</td>
<td>56</td>
<td>Change in FVC or resp. Hospitalization</td>
</tr>
<tr>
<td>FG-3019</td>
<td>Anti-CTGF</td>
<td>90</td>
<td>Change in FVC from baseline</td>
</tr>
<tr>
<td>Rituximab</td>
<td>CD-20</td>
<td>58</td>
<td>Titers of anti-HEp-2 autoantibodies</td>
</tr>
<tr>
<td>Simtuzumab</td>
<td>Anti-LOXL2</td>
<td>500</td>
<td>PFS</td>
</tr>
<tr>
<td>GC-1008</td>
<td>TGF-β</td>
<td>25</td>
<td>Safety, tolerability, PK</td>
</tr>
<tr>
<td>QAX976</td>
<td>Anti-IL-13</td>
<td>40</td>
<td>Safety, tolerability, FVC</td>
</tr>
<tr>
<td>Tralokinumab</td>
<td>Anti-IL-13</td>
<td>302</td>
<td>Change in FVC from baseline</td>
</tr>
<tr>
<td>STX-100</td>
<td>αvβ6</td>
<td>32</td>
<td>Adverse events</td>
</tr>
<tr>
<td>BMS-986620</td>
<td>LPA Receptor</td>
<td>300</td>
<td>Rate of change in FVC</td>
</tr>
</tbody>
</table>

Resources

- National Support Groups
  - https://www.inspire.com/conditions/pulmonary-fibrosis/
- Pulmonary Fibrosis Physician Blogs
  - Jeff Swigris: www.pulmonaryfibrosisresearch.org/blog
  - David Lederer: PFDoc.org
- On-line Resources
  - www.patientslikeme.com
  - www.coalitionforpf.org
  - www.pulmonaryfibrosis.org
  - www.lungsandyou.com
  - www.knowipfnow.com

Why Refer Early to an ILD Center?

- Diagnostic expertise
  - Standardized assessment
  - Confirmation of diagnosis
- Management expertise
  - Choice of an appropriate therapy
  - Oxygen prescription
  - Pulmonary rehabilitation
  - Attention to obesity and sarcopenia/frailty
  - Potential enrollment in a clinical trial
  - Transplant evaluation

Lung Transplantation Is Increasing


Lung Transplantation for IPF: 2014 Referral Guidelines

- Age limits
- Histopathologic or radiographic evidence of usual interstitial pneumonitis (UIP)
- Abnormal lung function: FVC <80% predicted or DLCO <40% predicted
- Any dyspnea or functional limitation attributable to lung disease
- Any oxygen requirement, even if only during exertion

Conclusions

- Pirfenidone and nintedanib are FDA approved for treatment of IPF.
- Diagnosis of IPF requires multidisciplinary approach.
- Patients should be referred early
  - Pulmonary rehabilitation
  - ILD center
  - Lung transplantation evaluation

Stem Cell Treatments for IPF?

- Mesenchymal Stem Cells (MSCs)
- Isolated from adult tissues
- Multipotent
- Immuno-privileged
- Multiple effects
  - Anti-proliferative
  - Anti-inflammatory
  - Immunomodulatory


A Phase I Randomized, Placebo-controlled Trial to Evaluate the Safety, Tolerability, and Potential Efficacy of Human Mesenchymal Stem Cell Infusion in patients with Idiopathic Pulmonary Fibrosis


Hypothetical Patient Profile: 63-year-old Mr. Smith with Definitive IPF

Pulmonary function testing (PFT) at diagnosis

<table>
<thead>
<tr>
<th>PFT</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>FVC</td>
<td>2.80 L (79.5%)</td>
</tr>
<tr>
<td>FEV₁</td>
<td>2.27 L</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>0.81</td>
</tr>
<tr>
<td>DLCO</td>
<td>47.7%</td>
</tr>
</tbody>
</table>

Testing for ANA, antinuclear antibody; CCP, cyclic citrullinated peptide; RF, rheumatoid factor; SCL-70, scleroderma antibody; SS-A/SS-B, Sjogren’s antibodies; HP panel, hypersensitivity were negative

FVC Predicts Survival in IPF

<table>
<thead>
<tr>
<th>Months</th>
<th>Baseline 2.80 L (79.5%)</th>
<th>Month 3 2.75 L</th>
<th>Month 6 2.74 L</th>
<th>Month 9 2.73 L</th>
<th>Month 12 2.68 L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent Survival</td>
<td></td>
<td>100%</td>
<td>90%</td>
<td>80%</td>
<td>70%</td>
</tr>
</tbody>
</table>


Mr. Smith's Mean Observed Change from Baseline in FVC after Treatment

<table>
<thead>
<tr>
<th>FVC ≥70%</th>
<th>FVC 55-69%</th>
<th>FVC &lt;55%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.80 L (79.5%)</td>
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<td>Month 9</td>
<td>2.73 L</td>
<td></td>
</tr>
<tr>
<td>Month 12</td>
<td>2.68 L</td>
<td></td>
</tr>
</tbody>
</table>

p = 0.0053

Two Drugs and New Choices for Patients with IPF

- Not a cure
- Big step forward
- More research needs to be done to find a cure