Management of Co-morbidities in Idiopathic Pulmonary Fibrosis

Joyce S. Lee, MD MAS
Director, Interstitial Lung Disease Clinic
University of California, San Francisco

Disclosures

• Intermune, advisory board member and steering committee member
Overview

• Comprehensive care of patients with interstitial lung disease
• Why it’s important to identify and treat co-morbidities
• Discussion on select co-morbidities in IPF

Comprehensive Care of ILD Patients

- Accurate MDD diagnosis
- Disease Targeted Therapy
- Lung Transplant Evaluation
- Hospice & Palliative Care
- Pulmonary Rehabilitation & Oxygen Therapy
- Education & Self-Management
Pharmacologic Therapy

Prevention

Clinical Trials

Symptom Management

Co-morbidities

DISEASE TARGETED THERAPY

Why diagnose and treat co-morbidities?

Pulmonary Fibrosis

Co-morbidities

Morbidity, Mortality & QOL
Mechanism of Co-morbidities

Pulmonary Fibrosis ↔ Co-morbidities

Shared Risk Factors

Co-morbidity: Overview

<table>
<thead>
<tr>
<th>Co-morbidity in IPF</th>
<th>Reported Prevalence</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary hypertension</td>
<td>2.7%</td>
<td>15.56</td>
</tr>
<tr>
<td>Emphysema</td>
<td>8.0%</td>
<td>7.11</td>
</tr>
<tr>
<td>Venous thromboembolism/PE</td>
<td>0.5%/2.7%</td>
<td>1.72/6.97</td>
</tr>
<tr>
<td>Heart failure</td>
<td>20.2%</td>
<td>3.83</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>5.9%</td>
<td>3.65</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>3.0%</td>
<td>2.83</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>7.2%</td>
<td>2.42</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3.2%</td>
<td>2.13</td>
</tr>
<tr>
<td>Depression</td>
<td>3.4%</td>
<td>1.40</td>
</tr>
</tbody>
</table>

Collard et al. J Med Econ 2012
Select Co-Morbidities

**Pulmonary**
- Emphysema
- Pulmonary HTN
- Lung Cancer

**Extra-pulmonary**
- CAD
- Heart failure
- GERD
- Sleep apnea
- VTE
- Depression

DATA

GAPS IN KNOWLEDGE

IN-PRACTICE
Emphysema

• Referred to as combined pulmonary fibrosis and emphysema (CPFE)
• Male, smokers
• PFTs with preserved lung volumes and severely reduced DLCO
• Increased prevalence of pulmonary hypertension

Cottin et al, ERJ 2005
CPFE and Mortality in IPF?

- Mejia et al, Chest 2009
- Ryerson et al, Chest 2013

Current Gaps: Emphysema

- Is it a distinct clinical syndrome or coincidental combination of two separate lung diseases?
- What defines CPFE?
- How to monitor disease progression in those with CPFE?

- Ryerson et al, Chest 2013
In Practice: CPFE

- No specific treatment
- Still important to define the etiology of the underlying pulmonary fibrosis
- Smoking cessation
- Lower threshold to look for pulmonary hypertension
- Consider inhalers for COPD component

GERD
GERD and hiatal hernia are common in IPF

<table>
<thead>
<tr>
<th>First Author</th>
<th>Study Location</th>
<th>Time of Publication</th>
<th>Primary Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belcher</td>
<td>London, UK</td>
<td>1949</td>
<td>Case reports of pulmonary fibrosis in patients with dysphagia</td>
</tr>
<tr>
<td>Pearson</td>
<td>Bristol, UK</td>
<td>1971</td>
<td>4% of people with hiatal hernias had diffuse pulmonary fibrosis</td>
</tr>
<tr>
<td>Mays</td>
<td>San Francisco</td>
<td>1976</td>
<td>73% prevalence of hiatal hernia and 44% prevalence of reflux in pulmonary fibrosis</td>
</tr>
<tr>
<td>Tobin</td>
<td>Seattle</td>
<td>1998</td>
<td>94% prevalence of GERD in IPF</td>
</tr>
<tr>
<td>Patti</td>
<td>San Francisco</td>
<td>2005</td>
<td>66% prevalence of GERD in IPF</td>
</tr>
<tr>
<td>Raghu</td>
<td>Seattle</td>
<td>2006</td>
<td>87% prevalence of GERD in IPF</td>
</tr>
<tr>
<td>Salvioli</td>
<td>Bologna, Italy</td>
<td>2006</td>
<td>67% prevalence of GERD in IPF</td>
</tr>
<tr>
<td>Sweet</td>
<td>San Francisco</td>
<td>2007</td>
<td>67% prevalence of GERD in IPF</td>
</tr>
<tr>
<td>Noth</td>
<td>Chicago</td>
<td>2012</td>
<td>39% prevalence of CT hiatal hernia in IPF</td>
</tr>
<tr>
<td>Savarino</td>
<td>Padua, Italy</td>
<td>2013</td>
<td>83% prevalence of GERD in IPF</td>
</tr>
</tbody>
</table>

Treatment of GER may slow decline in FVC

Raghu et al. Chest 2006;129:794

Lee et al, Lancet Resp Med 2013
Current Gaps: GERD

- What is the role of GERD in IPF pathogenesis?
  - Why are there so many people with GERD and so few with IPF?
  - What is causing the injury?
- GERD ≠ Microaspiration
  - So, how do we test for microaspiration?
- How should we treat GERD in IPF?
  - Medical vs. surgical therapy?
In Practice: GERD

• Symptomatic
  – Treat with PPI and lifestyle modifications
  – Consider surgery if symptomatic on medical therapy

• Asymptomatic
  – Screen with 24 ph/manometry
  – Treat if positive, as above

Obstructive Sleep Apnea (OSA)
OSA is common in IPF

- 50 patients with IPF
  - Prospective PSG in patients without a prior diagnosis of OSA
  - Age 64.9 years
- 88% with OSA
  - Mostly with hypopneas, rather than apneas

Predictors of OSA in IPF

<table>
<thead>
<tr>
<th>Variable</th>
<th>No OSA (AHI &lt; 5) n = 6</th>
<th>Mild OSA (AHI 5-15) n = 10</th>
<th>Severe OSA (AHI &gt; 15) n = 34</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>69</td>
<td>64</td>
<td>64</td>
<td>0.5</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>50</td>
<td>60</td>
<td>73</td>
<td>0.4</td>
</tr>
<tr>
<td>BMI</td>
<td>26</td>
<td>33</td>
<td>33</td>
<td>0.05</td>
</tr>
<tr>
<td>Neck circ, inches</td>
<td>15</td>
<td>17</td>
<td>17</td>
<td>0.1</td>
</tr>
<tr>
<td>Prednisone use, %</td>
<td>0%</td>
<td>20%</td>
<td>24%</td>
<td>0.4</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>58</td>
<td>63</td>
<td>73</td>
<td>0.03</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>43</td>
<td>38</td>
<td>48</td>
<td>0.1</td>
</tr>
<tr>
<td>ESS</td>
<td>8.2</td>
<td>5.8</td>
<td>8.3</td>
<td>0.6</td>
</tr>
<tr>
<td>SA-SDQ</td>
<td>28</td>
<td>30</td>
<td>37</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Lancaster et al, Chest 2009
Treatment of OSA in IPF

• 92 treatment-naïve, newly diagnosed consecutive IPF patients had PSG
• In those with AHI ≥ 15, CPAP was started
• 1 year of follow-up
• Good compliance group (n=37)
  – improvement in QOL and sleep instruments
• Poor compliance group (n=18)
  – Smaller effect in some of the metrics

Mermigkis et al, Sleep Breath. 2014

Current Gaps: OSA

• What is the best method of screening for OSA in IPF?
• What are the risk factors for OSA in IPF?
• Does treatment of OSA in IPF impact clinical outcomes?
• Is there a causal link between OSA and IPF? Or is it explained by the co-existence of GERD?
In Practice: OSA

- No clear guidelines
- Symptomatic patients – diagnose with PSG and treat if positive
- Asymptomatic patients, but high risk (e.g. BMI and SA-SDQ) – test with PSG and treat if positive
- Treatment: CPAP, weight loss, avoidance of sedatives, etc

Pulmonary Hypertension
PHTN in IPF

- PHTN = mean PAP ≥ 25 mmHg
- WHO Group 3
- Wide prevalence in IPF
  - Initial evaluation: 8-15%
  - Advanced IPF: 30-50%
  - End-stage IPF: over 60%
- Associated with mortality

Kimura et al, Respiration 2013

How to Diagnose PH in IPF

Echocardiogram:
RVSP able to be estimated in only 55%
32% without RVSP had pHTN
[Nathan et al Respir Med 2008]

PA Diameter on CT scan:
Main PA measured at widest diameter
No correlation with mPAP by RHC
[Zisman et al Chest 2007]

BNP:
N=39 ILD with no LV dysfunction
Sensitive and Specific for mod-severe PHTN
[Leuchte AJRCCM 2004]

Severely reduced DLCO:
N=79 pre-transplant IPF
DLCO <40% + LTOT is specific but not sensitive
[Lettieri Chest 2006]

Gold Standard = RHC
Should we treat PH in IPF?

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Agent</th>
<th>Data</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelin Receptor Antagonists</td>
<td>Bosenten</td>
<td>No benefit (PVR, Sx) No harm</td>
<td>RHC confirmed PH in IIP</td>
</tr>
<tr>
<td></td>
<td>(2) Bosenten</td>
<td>No benefit (6MWD, time to IPF worsening)</td>
<td>Not designed as a PH study</td>
</tr>
<tr>
<td>Ambrisentan</td>
<td>No benefit</td>
<td>(time to disease progression)</td>
<td>Terminated early</td>
</tr>
<tr>
<td></td>
<td>(27% vs. 17%)</td>
<td></td>
<td>Stratified based on RHC evidence of PH</td>
</tr>
<tr>
<td>Macitentan</td>
<td>No benefit</td>
<td>(FVC)</td>
<td>Not designed as PH study</td>
</tr>
<tr>
<td>Prostenoid Therapy</td>
<td>Inhaled iloprost</td>
<td>Minimal harm</td>
<td>Abstract only</td>
</tr>
<tr>
<td>Phosphodiesterase Inhibitors</td>
<td>Sildenafil</td>
<td>No benefit (6MWD)</td>
<td>Improved O2, dyspnea, QOL*</td>
</tr>
</tbody>
</table>

Sildenafil in IPF

- Secondary data analysis of original IPFNet study
- 119 of 180 had echocardiograms
  - RVH (12.8%)
  - RVSD (18.6%)
  - RVSP measurable (60%)
- In subgroup with RVSD: more preserved 6MWD

Han et al. Chest 2013
Current Gaps: PHTN

- No evidence that PAH therapies should be used in IPF
  - Unclear if 6MWD is the right primary end-point
  - Differences in behavior between mild PHTN and severe PHTN – should we stratify?
  - Differences in lung disease severity – should we stratify?
- What exactly defines dis-proportionate PH?
- Distinguishing the anti-fibrotic effect to the vasodilatory effect

In Practice: PHTN

- No recommendation for routine screening
- Diagnose PHTN for clinically suspected cases and lung transplant evaluation
- Further diagnostic testing if PHTN is found
  - Rule out OSA, chronic VTE, CHF
- Treatment
  - Oxygen therapy, if needed
  - Clinical trial, if available
  - Consider sildenafil in advanced IPF with evidence of RVSD
Depression

Depression is common in ILD

• 52 subjects with ILD, 40% with IPF (n=21)
• Predictors of depression:
  – Dyspnea severity, pain severity, sleep quality, FVC
• Only 2 patients on anti-depressants at baseline

Depression measured with the Center For Epidemiologic Studies Depression Scale

Ryerson et al, Respirology 2011
Does the underlying ILD make a difference?

• IPF (n=102, dark grey) vs. HP (n=69 light grey)
• SF-36
• Higher score = better QOL
• HRQL is worse in HP compared to IPF
  – Dyspnea, gender, fatigue

Lubin et al Chest 2014

Effect of Pulmonary Rehab

• Prospective study looking at the short and long term effect of pulmonary rehab in ILD
• Pre-rehab, post-rehab, and 6-months post-rehab surveys and functional assessments
• N=54, 22 with IPF
• 93% completed the rehab program
• 72% returned for 6-month follow-up

Ryerson et al Resp Med 2014
Current Gaps: Depression

- Complex interaction between breathlessness, deconditioning, and depression
  - Does treating one improve the other?
- What is the best treatment for depression in IPF?
- How should we screen for depression in IPF?
In Practice: Depression

• Screen all patients for depression
• Treat depression if found
  – Pharmacologic
    • Anti-depressants
  – Non-pharmacologic
    • Pulmonary rehabilitation
    • Cognitive behavioral therapy
    • Support group participation

Key Points

• The comprehensive care of patients with IPF is complex
• Co-morbidities contribute to morbidity, mortality, and QOL in IPF
• Low threshold to assess for co-morbidities as they may effect outcome in IPF
Thanks!