Disease Monitoring of Pulmonary Fibrosis

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Overview

• Current methods of monitoring disease
  – Pulmonary function testing
  – Computed tomography

• Investigational methods of monitoring disease
Pulmonary Function Tests

- A mainstay of ILD evaluation
- Used in diagnosis (restriction)
- Used in monitoring
  - Changes in forced vital capacity (FVC) and DLCO as markers of disease progression
- Used in clinical trials
  - Change in forced vital capacity over 52 weeks
PFTs and ILD Physiology

- Pulmonary Mechanics
  - Lungs have ↓ compliance

PFTs show restrictive defect
- Lung volumes
  - ↓ TLC
  - ↓ RV
- Spirometry
  - ↓ VC
  - FEV₁/FVC normal or even increased
PFTs and ILD Natural History

Figure 2. Decline in FVC in idiopathic pulmonary fibrosis (IPF). Shown are the mean rates of FVC found in the placebo arms of clinical trials in patients with IPF. The FVC declines approximately 150 to 200 ml/yr in patients with IPF. Data from the placebo arms of the following clinical trials: 1Pirfenidone (27), 2Imatinib (29), 3Interferon γ-1b (IFNγ) (25), 4Pirfenidone (30), 5Etanercept (26), 6Bosentan (24), 7N-Acetylcysteine (NAC) (28).

Ley et al, Am J Respir Crit Care Med, 2011; 183: 431-440
It’s change over time that important

<table>
<thead>
<tr>
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<th>Units</th>
<th>Today</th>
<th>History of Previous</th>
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<td>18-Sep-20</td>
<td>05-Mar-20</td>
<td>30-Dec-99</td>
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<tr>
<td>FVC</td>
<td>L</td>
<td>2.39</td>
<td>3.77</td>
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<tr>
<td>FEV₁</td>
<td>L</td>
<td>1.63</td>
<td>3.20</td>
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<tr>
<td>FEV₁ / FVC</td>
<td>%</td>
<td>68</td>
<td>85</td>
</tr>
<tr>
<td>FET</td>
<td>sec</td>
<td>5.93</td>
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<td>L</td>
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<tr>
<td>FRC</td>
<td>L</td>
<td>----</td>
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<tr>
<td>RV</td>
<td>L</td>
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<tr>
<td>VC</td>
<td>L</td>
<td>----</td>
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<td>DLCO [Hb]</td>
<td>mL/min/mmHg</td>
<td>8.28</td>
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</table>
PFTs and Advantages

• Easy to perform

• Reproducible and standardized (can have performed at different locations and still be comparable)

• Low cost

• Changes have clinical significance

• Primary outcome of clinical trials
Nintedanib and FVC

Pirfenidone and FVC

A Decreased FVC or Death

<table>
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<tr>
<th>Week</th>
<th>Pirfenidone (N=278)</th>
<th>Placebo (N=277)</th>
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<tr>
<td>52</td>
<td>52</td>
<td>52</td>
<td>&lt;0.001</td>
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B Change in FVC

C Decreased Walk Distance or Death

<table>
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<tr>
<th>Week</th>
<th>Pirfenidone (N=278)</th>
<th>Placebo (N=277)</th>
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<tr>
<td>52</td>
<td>52</td>
<td>52</td>
<td>0.04</td>
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D Progression-free Survival

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<th>No. at Risk</th>
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<th>Placebo</th>
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Hazard ratio, 0.57 (95% CI, 0.43–0.77)

PFTs and Limitations

- Difficult to predict subsequent progression based on one measurement

Ley et al, Am J Respir Crit Care Med, 2011; 183: 431-440
PFTs and Change over Time

Ley et al, Am J Respir Crit Care Med, 2011; 183: 431-440
Computed Tomography (CT)

- Mainstay of ILD diagnosis
- Used to inform as to ILD pattern type
- Presence of certain findings (UIP pattern) has prognostic significance
- Not used as an outcome measure in clinical trials
IPF Diagnostic Approach

1. Patient suspected to have IPF
2. Potential cause/associated condition
3. Chest HRCT pattern
   - probable UIP, indeterminate for UIP, alternative diagnosis
4. Further evaluation (including HRCT)
5. Specific diagnosis
6. MDD
   - BAL
   - Surgical lung biopsy*
   - Alternative diagnosis
7. IPF per Figure 8
8. Not IPF
CT Pattern Examples

UIP Pattern

Indeterminate for UIP Pattern
CT Patterns and Outcomes

Putman, Am J Respir Crit Care Med, 2019; 200:175-183
Need for a disease activity measure

• Current methods of monitoring (CT and PFTs) measure the end result of scarring and inform as to disease progression over time
  – Do not inform as to disease activity at any one measure

• A measure of disease activity in IPF would:
  – Improve clinical care by enabling treatment plans to be tailored for an individual and enhancing prognostication
  – Advance clinical trials by enabling cohort enrichment strategies and enrolling of patients most likely to have a benefit from treatment
Type I Collagen Imaging

- Accumulation of type I collagen is the hallmark of fibrosis

- Current imaging approaches (e.g. CT) only can visualize the end result of collagen deposition

- $^{68}$Ga-CBP8 is a PET probe that binds type I collagen with high specificity (Désogere et al, Sci Trans Med. 2017)

- $^{68}$Ga-CBP8 can detect treatment response to anti-fibrotic therapy in a mouse model of pulmonary fibrosis (Désogere et al, Sci Trans Med. 2017)

- Pre-clinical data suggest that $^{68}$Ga-CBP8 preferentially binds freshly synthesized as opposed to mature collagen and thus may be ideal imaging marker of disease activity
$^{68}$Ga-CBP8 Detects Increased Collagen in IPF patients and Active Disease

Montesi et al, *Am J Respir Crit Care Med*. 2019
Future Directions

Montesi et al., *J Clin Invest.* 2019
Questions