The Appointment: Patient Perspective

- Wait time
  - 2-3 months
- Travel to IPF center
  - Up to 11-hour drive
  - Must too sick or hypoxic to fly
  - Park and walk into office or medical center
- Time for testing and appointment
  - Pulmonary function test, 6-minute walk test
  - Plan to spend the day
- Anxiety and fear
  - Uncertain expectations for the plan of the day
  - Uncertain expectations of prognosis and recommendations
Causes of an Interstitial Radiologic Pattern

- Infections
  - Fungal (pneumocystis, coccidi, crypto, histo)
  - Atypical bacteria
  - Viral
- Occupational / Environmental toxins
  - Hypersensitivity pneumonitis
  - Asbestos
  - Silica
  - Beryllium
- Drug induced
  - www.pneumotox.com
- Radiation induced
- Malignancy
  - Lung
  - Lymphangitic carcinomatosis
- Connective tissue disease / autoimmune
  - RA
  - SLE
  - Sjögren’s
  - Inflammatory bowel disease
  - Vasculitis
  - GPA
- Idiopathic
  - IPF
  - CTD-ILD
  - Silicosis

Most Challenging Mimickers of IPF

- Fibrosing nonspecific interstitial pneumonitis
- Chronic hypersensitivity pneumonitis
- Connective tissue disease ILD

History

- Obtain a complete history!
  - Environmental exposures
  - Work history
  - Animal exposures / Organic exposures
  - Medications / Substance use
  - GERD / dysphagia / aspiration
  - Sleep history
  - Full review of symptoms
  - Thorough rheumatologic review of symptoms
Environmental History

- Jobs?
  - Protective gear?
- Spouse’s jobs?
- Pets?
- Hot tubs / humidifiers / AC?
- Water damage / standing water?

Smoking Association

- Smokers
  - Pulmonary LCH
  - DIP / RBILD
  - IPF
- Never smokers
  - HP
  - Sarcoidosis

Symptoms/Signs

- Hemoptysis
  - DAH
  - LAM
  - TS
  - PVOD / PCH
  - Mitral valve disease
  - Granulomatous vasculitis
- Wheezing
  - Chronic eosinophilic pneumonia
  - Bronchitis
  - Lymphangitic sarcoidosis
- Chest pain
  - Pleurisy – connective tissue disease
  - Subternal discomfort – sarcoidosis
- Extrapulmonary
  - Connective tissue disease
  - Inflammatory bowel disease
- Pneumothorax
  - Pulmonary LCH / TS
  - LAM
  - Neurofibromatosis
Assess for Comorbidities of IPF

- Gastroesophageal reflux disease
- Obstructive sleep apnea
- Pulmonary arterial hypertension
- Cardiac disease

Physical Exam

- Velcro crackles
- RV lift / augmented P2 / right-sided gallop
- Extra pulmonary signs
- Signs of autoimmune disease
- Clubbing

Laboratory

- Hepatic function
  - Cirrhosis?
- Renal function
  - Connective tissue disease? Vasculitis?
- Bone marrow function
  - MDS? DKC?
- UA
  - Vasculitis?
- Cardiac
  - ECG, echo, BNP

- Serologies
  - ANA, RF, anti-cop, anti scl 70, CPK, anti Jo, anti ds-DNA, anti-extractable nuclear ag (anti-Sm, Anti-ribonucleoprotein), ANCA
- Pulmonary Function Tests
  - Spirometry, lung volumes, DLCO
Clinical Perspectives on the Diagnosis and Treatment of Idiopathic Pulmonary Fibrosis

**Pulmonary Function Testing**

- Restriction
- Reduction in diffusing capacity
- May see preserved lung volumes when emphysema is present

**Walk Studies**

- Assist with determination of oxygen needs and disease progression
  - 6-minute walk study
    - Desats to 88% or less is correlated with a median survival of 3.21 years
  - Exertional walk study

**High-resolution Computed Tomography Criteria for UIP Pattern**

<table>
<thead>
<tr>
<th>UIP Pattern (All Four Features)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Subpleural, basal predominance</td>
</tr>
<tr>
<td>- Linear or reticular opacity</td>
</tr>
<tr>
<td>- Honeycombing with or without traction bronchiectasis</td>
</tr>
<tr>
<td>- Presence of features listed as inconsistent with UIP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Possible UIP Pattern (All Three Features)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Subpleural, basal predominance</td>
</tr>
<tr>
<td>- Focal reticular abnormality</td>
</tr>
<tr>
<td>- Absence of features listed as consistent with UIP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inconsistent with UIP Pattern (Any of the Seven Features)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Upper or mid-lung predominance</td>
</tr>
<tr>
<td>- Peribronchovascular predominance</td>
</tr>
<tr>
<td>- Extensive ground-glass abnormality (without vascular abnormality)</td>
</tr>
<tr>
<td>- Peribronchovascular fibrosis (predominantly upper lobes)</td>
</tr>
<tr>
<td>- Diffuse micronodules (bilateral, away from areas of honeycombing)</td>
</tr>
<tr>
<td>- Subpleural honeycombing (subpleural, predominantly upper lobes)</td>
</tr>
<tr>
<td>- Consolidation in bronchopulmonary segment(s) (with or without traction bronchiectasis)</td>
</tr>
<tr>
<td>- Diffuse ground-glass abnormality (bilateral in three or more lobes)</td>
</tr>
</tbody>
</table>

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## Difficult Discussions

- 2 new FDA approved drugs
- Limited clinical trials
  - Some with a placebo group / some with background therapy
- Supportive care
  - Oxygen
  - Vaccinations
  - Treat Comorbidities
    - Diagnose and treat obstructive sleep apnea
    - Diagnose and treat gastrointestinal reflux
    - Consider treatment of PAH
  - Pulmonary rehab
    - Must have moderate restriction and reduction in DLCO to meet insurance criteria
    - Under-reimbursed
    - Maximize treatment of other causes of shortness of breath
  - Cardiac disease
  - Anemia

## Difficult Discussions: Oxygen

- Visual reminder of patient’s disease and weakness
- Complicates daily activities
- Durable medical company (DME) limitations
  - Cheaper cumbersome rolling tanks
  - Access to high flow regulators is limited
  - Supply of oxygen may be limited due to limited reimbursement
- Difficult to adjust oxygen from another room
- Complicates travel and limits flights
- DMEs have limited knowledge of the difference in IPF / ILD patients O2 needs versus those of emphysema patients

## Difficult Discussions

- Lung transplantation
  - Generally up to age 65
  - No other major organ disease
  - Timing of transplant listing
- Palliative care / hospice
  - Symptom management
  - Home needs and family support
  - Home nursing support

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Clinical Perspectives on the Diagnosis and Treatment of Idiopathic Pulmonary Fibrosis

Difficult Discussions for Patients

- Do I tell my family?
  - “I don’t want them to worry.”
- How do I tell my family?
- How do I explain this disease to my family?
- I don’t want to be treated like an invalid.
- How do I discuss end of life decisions with my wife and children?
- How do I create a will and a living will?

Classification of ILDs

- Etiology
  - Infection
  - Occupational/environmental exposures
  - Drug induced
  - Radiation induced
  - Connective tissue disease/vasculitis
  - Idiopathic
  - Malignancy
- Timing of presentation
  - Acute
  - Subacute
  - Chronic
- Pattern of Infiltrates
- Age at presentation

Diagnostic Considerations

- Younger (20-50 yo)
  - Sarcoidosis
  - Connective tissue disease
  - LAM
  - Pulmonary LCH
  - Familial IPF
  - Hermansky Pudlak
  - Gaucher’s
- Gender
  - Female
    - Premenopausal
    - LAM
    - Tuberculosis
    - Connective tissue disease
    - RALD is more common in men
  - Male
    - Pneumoconiosis

Schwarz MI, et al. Interstitial Lung Disease, 5th edition

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A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis


CONCLUSIONS
Pirfenidone, as compared with placebo, reduced disease progression, as reflected by lung function, exercise tolerance, and progression-free survival, in patients with idiopathic pulmonary fibrosis. Treatment was associated with an acceptable side-effect profile and fewer deaths. (Funded by InterMune, ASCEND ClinicalTrials.gov number, NCT01562881.)
Clinical Perspectives on the Diagnosis and Treatment of Idiopathic Pulmonary Fibrosis

**Pirfenidone: Effects on Mortality**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pirfenidone</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCEND trial</td>
<td>No. of patients</td>
<td>278</td>
<td>277</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>No. (%)</td>
<td>11 (4.0)</td>
<td>20 (7.2)</td>
<td>0.55 (0.26 - 1.15)</td>
</tr>
<tr>
<td>Related to idiopathic pulmonary fibrosis</td>
<td>3 (1.1)</td>
<td>7 (2.5)</td>
<td>0.44 (0.11 - 1.72)</td>
<td>0.23</td>
</tr>
<tr>
<td>Pooled data from ASCEND and CAPACITY trials</td>
<td>No. of patients</td>
<td>623</td>
<td>624</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>No. (%)</td>
<td>22 (3.5)</td>
<td>42 (6.7)</td>
<td>0.52 (0.31 - 0.87)</td>
</tr>
<tr>
<td>Related to idiopathic pulmonary fibrosis</td>
<td>7 (1.1)</td>
<td>22 (3.5)</td>
<td>0.32 (0.14 - 0.76)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*Data from the two CAPACITY studies were censored at 1 year to standardize the follow-up for the three studies.
†Hazard ratios are for the pirfenidone group, as compared with the placebo group. And were calculated with the use of the Cox proportional hazards model.
‡P values were calculated with the use of the log-rank test.
§Death related to idiopathic pulmonary fibrosis was defined as death that occurred during the period from randomization to 28 days after the last dose of the study drug. This category was evaluated in a blinded fashion by an independent mortality assessment committee in the ASCEND trial and by clinical investigators in the CAPACITY trials.

**Adverse Events**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Pirfenidone (N=278)</th>
<th>Placebo (N=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (%),</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>70 (25.2)</td>
<td>82 (29.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>100 (36.0)</td>
<td>37 (13.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>72 (25.9)</td>
<td>64 (23.1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>62 (22.3)</td>
<td>60 (21.7)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>61 (21.9)</td>
<td>56 (20.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>58 (20.9)</td>
<td>48 (17.3)</td>
</tr>
<tr>
<td>Rash</td>
<td>78 (28.1)</td>
<td>24 (8.7)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>41 (14.7)</td>
<td>49 (17.7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>49 (17.6)</td>
<td>36 (13.0)</td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
<td>26 (9.4)</td>
<td>50 (18.1)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>39 (14.0)</td>
<td>36 (13.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>32 (11.5)</td>
<td>38 (13.7)</td>
</tr>
<tr>
<td>Back pain</td>
<td>30 (10.8)</td>
<td>37 (13.4)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>49 (17.6)</td>
<td>17 (6.1)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>33 (11.9)</td>
<td>30 (10.8)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>44 (15.8)</td>
<td>18 (6.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>36 (12.9)</td>
<td>24 (8.7)</td>
</tr>
<tr>
<td>Decrease in weight</td>
<td>35 (12.6)</td>
<td>22 (7.9)</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>33 (11.9)</td>
<td>18 (6.5)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>31 (11.2)</td>
<td>18 (6.5)</td>
</tr>
</tbody>
</table>

**The New England Journal of Medicine**

**Original Article**

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D., Ph.D., Roland M. du Bois, M.D., Galen Hugh-Jones, M.D., Arturo Azuma, M.D., Ph.D., Kevin K. Brown, M.D., Ulrich Costabel, M.D., Vincent Gattin, M.D., Ph.D., Kevin H. Fehlbrandt, M.D., David M. Hanley, M.D., Yvonne Irie, M.D., Ph.D., Dang Son Kim, M.D., Martin Ruhl, M.D., Ph.D., Andrew C. Richardson, O.M., Paul W. Noble, M.D., Moïse Selman, M.D., Didier Schaub, M.D., Michael Scherrer, M.D., India E. Shaw, M.D., Michel Stahl, M.D., Michael Stucki, M.D., Richard F. Swanson, M.D., Massimo Trani, M.D., Martin Tzvetanov, M.D., and the IMPACT Trial Investigators.

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INPULSIS Studies

Adverse Events

CONCLUSIONS
In patients with idiopathic pulmonary fibrosis, nintedanib reduced the decline in FVC, which is consistent with a slowing of disease progression; nintedanib was frequently associated with diarrhea, which led to discontinuation of the study medication in less than 5% of patients. (Funded by Boehringer Ingelheim; INPULSIS-1 and INPULSIS-2 ClinicalTrials.gov numbers, NCT01354644 and NCT01354772.)
### Key Inclusionary Criteria

<table>
<thead>
<tr>
<th>ASCEND (Pirfenidone)</th>
<th>INPULSIS (Nintedanib)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis per ATS/ERS guidelines (adjudicated)</td>
<td>Diagnosis per ATS/ERS guidelines (adjudicated)</td>
</tr>
<tr>
<td>Symptoms &gt;12 months</td>
<td>Diagnosis within 5 years*</td>
</tr>
<tr>
<td>Diagnosis 6-48 months</td>
<td>Age ≥ 40</td>
</tr>
<tr>
<td>Age 40-80*</td>
<td>FVC ≥ 50%</td>
</tr>
<tr>
<td>FVC 50%-90%</td>
<td>DLCO 30%-79%</td>
</tr>
<tr>
<td>6MWT ≥ 150 meters</td>
<td>6MWT ≥ 150 meters</td>
</tr>
</tbody>
</table>

N=13 inclusion criteria  
N=7 inclusion criteria  
* = notable differences

### Key Exclusionary Criteria

<table>
<thead>
<tr>
<th>ASCEND (Pirfenidone)</th>
<th>INPULSIS (Nintedanib)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking within 3 months</td>
<td>FEV1 / FVC&lt;70%*</td>
</tr>
<tr>
<td>Other known cause for ILD</td>
<td>Expected to receive LTx within a year</td>
</tr>
<tr>
<td>Expected to receive LTx within a year</td>
<td>Bleeding risk*</td>
</tr>
<tr>
<td>Significant, cardiac, liver, or kidney* disease</td>
<td>Thrombotic risk*</td>
</tr>
<tr>
<td>his asthma or COPD / BD response</td>
<td>Major surgery planned</td>
</tr>
<tr>
<td>Con Meds: Steroids, cytotoxic agents, and other agents with previous proposed use for IPF</td>
<td>Significant cardiac or liver disease</td>
</tr>
<tr>
<td>Con Meds</td>
<td>Con Meds</td>
</tr>
<tr>
<td>N=26 exclusion criteria</td>
<td>N=19 exclusion criteria</td>
</tr>
</tbody>
</table>
* = notable differences

### 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 prophylaxis</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>Titer of anti-HEp-2 autoantibodies</td>
</tr>
<tr>
<td>Similuromab</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>OAV576</td>
<td>Anti-L-13</td>
<td>40</td>
<td>Safety, tolerability, FVC</td>
</tr>
<tr>
<td>Tralokinumab</td>
<td>Anti-L-13</td>
<td>302</td>
<td>Change in FVC from baseline</td>
</tr>
<tr>
<td>STM-100</td>
<td>sP66</td>
<td>32</td>
<td>Adverse events</td>
</tr>
<tr>
<td>EUS-90020</td>
<td>LFA Receptor</td>
<td>300</td>
<td>Rate of change in FVC</td>
</tr>
</tbody>
</table>
Cause of Death in Patients with PF

- Pulmonary Fibrosis: 61%
- Ischemic Heart Disease: 23%
- Lung Cancer: 3%
- Pneumonia: 9%
- Congestive Heart Failure: 1%
- Cerebrovascular Disease: 1%
- Other: 1%

GERD Treatment and Survival

- Taking GERD medications
- Not taking GERD medications

IPF Management Checklist

- Risk factor reduction
- Patient education
  - Advocacy group involvement
- Focus on comorbidities
  - Mental health needs
  - GERD, OSA, CAD, PH, VTE, etc.
- Supplemental oxygen
- Age-appropriate vaccinations
- Discussion about available medical therapies
- Pulmonary rehabilitation
- Clinical trials
- Lung transplant evaluation
- Address end of life issues: palliative and hospice care

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