What's New in Interstitial Lung Disease?

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Objectives

• Review diagnosis of ILD
• Summarize current literature involving diagnosis and treatment for ILD
What are Interstitial Lung Diseases?

Alphabet Soup:
• IPF: Idiopathic Pulmonary Fibrosis
• NSIP: Non-specific Interstitial Pneumonia
• IIP: Idiopathic Interstitial Pneumonia
• COP: Cryptogenic Organizing Pneumonia
• AIP: Acute Interstitial Pneumonia
• RBILD: Resp Bronchiolitis Interstitial Pneumonia
• DIP: Desquamative Interstitial Pneumonia
• Rheumatological related
What are Interstitial Lung Diseases?

- Diffuse parenchymal lung disease
  - DPLD of known cause eg, drugs or association eg, rheumatic disease
  - Idiopathic interstitial pneumonia (IIPs)
  - Granulomatous DPLD eg, sarcoidosis
  - Other forms of DPLD eg, LAM, PLCH, etc

- Non-familial (>80 percent)
- Familial (2 to 20 percent)

- Chronic fibrosing
  - Idiopathic pulmonary fibrosis
  - Idiopathic nonspecific interstitial pneumonia

- Acute/subacute fibrosing
  - Cryptogenic organizing pneumonia
  - Acute interstitial pneumonia

- Smoking-related
  - Respiratory bronchiolitis interstitial lung disease
  - Desquamative interstitial pneumonia
Diagnostic Work Up?

Interstitial lung disease (immunocompetent host)

- History, physical exam, routine labs, recent and old chest x-rays, pulmonary function tests (assess chronicity/progression/stability)

Remove/avoid identified potential cause (environmental/iatrogenic)

- Clinical recovery?
  - Yes: No further diagnostic steps
  - No: Appropriate clinical setting
    - Serology for specific connective tissue diseases
    - Biopsy: skin, muscle, sinus/nasal septum, kidney

Specific systemic disease?

- Yes: Further evaluation and management appropriate to underlying disease
- No: HRCT: characterize lung/pleural/mediastinal disease to assess pattern ILD and choose location for possible BAL/biopsy

IPF: no further diagnostic steps

- Yes: Classic findings for UIP?
  - Yes: Suggestive of sarcoidosis, berylliosis, hypersensitivity, pneumonitis, lymphangitic carcinomatosis, PLCH, eosinophilic pneumonia
  - No: Surgical lung biopsy by thorascopy or thoracotomy

Indeterminant pattern or pattern suggestive of NSIP, OP

- Bronchoscopy with BAL and TBB
  - Not diagnostic
  - Diagnostic

Raghu G. Am J Respir Crit Care Med 1995; 151:909
Case 1

- 67 year-old man:
- Chronic cough
- Dyspnea with minimal exertion

- Lungs: bibasilar inspiratory crackles, no wheezing
- Cardiovascular: regular, loud second heart sound
- Extremities: warm, trace edema, no joint swelling, + clubbing

- PFT with restriction (Ratio of 89%), TLC 48% DLCO 25%
## Use of HRCT in Diagnosing ILD

<table>
<thead>
<tr>
<th>UIP Pattern (All 4 Features)</th>
<th>Possible UIP (All 3 Features)</th>
<th>Inconsistent With UIP (Any)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Subpleural basal predominance</td>
<td>- Subpleural, basal predominance</td>
<td>- Upper or mid-lung predominance</td>
</tr>
<tr>
<td>- Reticular abnormality</td>
<td>- Reticular abnormality</td>
<td>- Peribronchovascular predominance</td>
</tr>
<tr>
<td>- Honeycombing with/without traction bronchiectasis</td>
<td>- Absence of features listed as inconsistent with UIP (column 3)</td>
<td>- Extensive ground glass abnormality (extent &gt; reticular abnormality)</td>
</tr>
<tr>
<td>- Absence of features listed as inconsistent with UIP (column 3)</td>
<td></td>
<td>- Profuse micronodules (bilateral, predominantly upper lobe)</td>
</tr>
</tbody>
</table>

HRCT: Definite UIP

Extensive honeycombing

Traction bronchiectasis

Basal and subpleural predominance
Diagnosis of IPF

- The appropriate clinical picture + “definite” UIP on HRCT makes the diagnosis of IPF
  - Lung biopsy is NOT required for diagnosis
- Multidisciplinary discussion improves the accuracy of the diagnosis
- The level of agreement between observers and diagnostic confidence improves as more data (clinical, radiographic, pathologic) are provided

Raghu G et al. AJRCCM 2011;183:788
Flaherty KR et al. AJRCCM 2004; 170:904
Updated IPF Treatment Guidelines

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis
An Update of the 2011 Clinical Practice Guideline


This guideline is dedicated to the memory of Mr. William Cunningham (June 7, 1935–October 23, 2014)

This official Clinical Practice Guideline of the American Thoracic Society (ATS) was approved by the ATS, May 2015, the European Respiratory Society (ERS), April 2015, the Japanese Respiratory Society (JRS), April 2015, and the Latin American Thoracic Association (ALAT), April 2015

Raghu G et al. AJRCCM 2015; 192: 2
## Guideline Recommendations

### Table 2. Comparison of Recommendations in the 2015 and 2011 Idiopathic Pulmonary Fibrosis Guidelines

<table>
<thead>
<tr>
<th>Agent</th>
<th>2015 Guideline</th>
<th>2011 Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New and revised recommendations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulation (warfarin)</td>
<td>Strong recommendation against use*</td>
<td>Conditional recommendation against use†</td>
</tr>
<tr>
<td>Combination prednisone + azathioprine + N-acetylcysteine</td>
<td>Strong recommendation against use†</td>
<td>Conditional recommendation against use†</td>
</tr>
<tr>
<td>Selective endothelin receptor antagonist (ambrisentan)</td>
<td>Strong recommendation against use†</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Imatinib, a tyrosine kinase inhibitor with one target</td>
<td>Strong recommendation against use*</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Nintedanib, a tyrosine kinase inhibitor with multiple targets</td>
<td>Conditional recommendation for use*</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Pirfenidone</td>
<td>Conditional recommendation for use*</td>
<td>Conditional recommendation against use†</td>
</tr>
<tr>
<td>Dual endothelin receptor antagonists (macitentan, bosentan)</td>
<td>Conditional recommendation against use†</td>
<td>Strong recommendation against use*</td>
</tr>
<tr>
<td>Phosphodiesterase-5 inhibitor (Sildenafil)</td>
<td>Conditional recommendation against use†</td>
<td>Not addressed</td>
</tr>
<tr>
<td><strong>Unchanged recommendations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antacid therapy</td>
<td>Conditional recommendation for use†</td>
<td>Conditional recommendation against use†</td>
</tr>
<tr>
<td>N-acetylcysteine monotherapy</td>
<td>Conditional recommendation against use†</td>
<td>Conditional recommendation against use†</td>
</tr>
<tr>
<td>Antipulmonary hypertension therapy for idiopathic pulmonary fibrosis-associated pulmonary hypertension</td>
<td>Reassessment of the previous recommendation was deferred</td>
<td>Conditional recommendation against use†</td>
</tr>
<tr>
<td>Lung transplantation: single vs. bilateral lung transplantation</td>
<td>Formulation of a recommendation for single vs. bilateral lung transplantation was deferred</td>
<td>Not addressed</td>
</tr>
</tbody>
</table>

*⩢⩢⩢⩢⩢, moderate confidence in effect estimates.
†⩢⩢⩢⩢⩢, low confidence in effect estimates.
‡⩢⩢⩢⩢⩢, very low confidence in effect estimates.

Raghu G et al. AJRCCM 2015; 192: 2
PANTHER Trial (Prednisone, Azathioprine, and N-Acetylcysteine) for Pulmonary Fibrosis

Resulted in Increased Early Death

2014 Trials

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis
Luca Richeldi, M.D., Ph.D., Roland M. du Bois, M.D., Ganesh Raghu, M.D., Arata Azuma, M.D., Ph.D.,
Kevin K. Brown, M.D., Ulrich Costabel, M.D., Vincent Cottin, M.D., Ph.D., Kevin R. Flaherty, M.D.,
David M. Hansell, M.D., Yoshikazu Inoue, M.D., Ph.D., Dong Soon Kim, M.D., Martin Kolb, M.D., Ph.D.,
Andrew G. Nicholson, D.M., Paul W. Noble, M.D., Moisés Selman, M.D., Hiroyuki Taniguchi, M.D., Ph.D.,
Michèle Brun, M.Sc., Florence Le Mauf, M.Sc., Mannaï Girard, M.Sc., Susanne Stowasser, M.D.,
Rozsa Schlenker-Herceg, M.D., Bernd Disse, M.D., Ph.D., and Harold R. Collard, M.D.,
for the INPULSIS Trial Investigators*

A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis
Talmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D.,
Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D.,
Ian Glaspoole, M.B., B.S., Ph.D., Marilyn K. Glassberg, M.D., Eduard Gorina, M.D.,
Peter M. Hopkins, M.D., David Kardatzke, Ph.D., Lisa Lancaster, M.D.,
David J. Lederer, M.D., Steven D. Nathan, M.D., Carlos A. Pereira, M.D.,
Steven A. Sahn, M.D., Robert Sussman, M.D., Jeffrey J. Swigris, D.O.,
and Paul W. Noble, M.D., for the ASCEND Study Group*

Randomized Trial of Acetylcysteine in Idiopathic Pulmonary Fibrosis
The Idiopathic Pulmonary Fibrosis Clinical Research Network*
Randomized Trial of Acetylcysteine in Idiopathic Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

• **Study Population:**

• 264 patients with IPF:
  – 35 - 85 years
  – FVC ≥50% Predicted and DLCO ≥30% predicted

• **Treatment:** N-Acetylcysteine (600 mg) or Placebo 3 times daily

• **Primary end point:** change in FVC

NAC offered NO significant benefit in preventing FVC decline in patients with IPF

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>NAC</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔFVC (liters)</td>
<td>−0.18</td>
<td>−0.19</td>
<td>0.77</td>
</tr>
<tr>
<td>Acute Exacerbation</td>
<td>2.3%</td>
<td>2.3%</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

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

Talmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D., Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D., Ian Glaspole, M.B., B.S., Ph.D., Marilyn K. Glassberg, M.D., Eduard Gorina, M.D., Peter M. Hopkins, M.D., David Kardatzke, Ph.D., Lisa Lancaster, M.D., David J. Lederer, M.D., Steven D. Nathan, M.D., Carlos A. Pereira, M.D., Steven A. Sahn, M.D., Robert Sussman, M.D., Jeffrey J. Swigris, D.O., and Paul W. Noble, M.D., for the ASCEND Study Group*
Pirfenidone

- Pirfenidone is an orally-available small molecule that exerts systemic anti-fibrotic effects
- The target of pirfenidone is unknown
  - Has anti-fibrotic and anti-inflammatory activities *in vivo* and *in vitro*

Trial endpoints

• Primary
  • Change from baseline to week 52 in percentage of the predicted FVC% (≥10% fall in FVC)

• Secondary
  • Change in 6MW distance, progression free survival (≥50 m fall in 6MW, death)

Change in FVC

Decreased FVC

Decreased Walk Distance

Progression Free Survival

Hazard ratio, 0.57 (95% CI, 0.43–0.77)
P<0.001

# ADVERSE EVENTS

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Pirfenidone (N=278)</th>
<th>Placebo (N=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea (%)</td>
<td>100(36.0)</td>
<td>37(13.4)</td>
</tr>
<tr>
<td>Rash (photosensitivity)</td>
<td>78(28.1)</td>
<td>24(8.7)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>49(17.6)</td>
<td>17(6.1)</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>GERD</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>
<tr>
<td>Transaminitis</td>
<td>8(2.9)</td>
<td>2(0.7)</td>
</tr>
</tbody>
</table>

King TE et al. NEJM 370;22:2083
Conclusions

- Pirfenidone decreases the decline in breathing tests over 52 weeks
- Pirfenidone has a benefit in terms of risk of death
Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

for the IMPULSIS Trial Investigators*

Nintedanib – IMPULSIS Trial
Nintedanib

- Nintedanib is an orally-available intracellular inhibitor that targets multiple tyrosine kinases:
  - VEGF receptors
  - FGF receptors
  - PDGF receptors

Change in FVC

Time to First AE IPF

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>INPULSIS 1</th>
<th>INPULSIS 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nintedanib N=309</td>
<td>Placebo N=204</td>
<td>Nintedanib N=329</td>
</tr>
<tr>
<td>Any AE</td>
<td>298 (96.4%)</td>
<td>181 (88.7%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>190 (61.5%)</td>
<td>38 (18.6%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>70 (22.7%)</td>
<td>12 (5.9%)</td>
</tr>
<tr>
<td>Transaminitis</td>
<td>15 (4.9%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>MI</td>
<td>5 (1.6%)</td>
<td>1 (0.5%)</td>
</tr>
</tbody>
</table>

Conclusions

- Nintedanib decreases the decline in breathing tests over 52 weeks
Injourny Trial

• Combination of Nintedanib with add on Pirfenidone
• Full dose nintedanib (150mg bid) with add on pirfenidone (801mg tid) vs nintedanib alone x 12 weeks
• Primary endpoint of GI Adverse events
  – 69.8% in combination group vs 53% in nintedanib group
• Secondary endpoint: Mean change in FVC
  – 13.3ml in combination group vs 40.9ml in nintedanib group

Vancheri C. Am J Respir Crit Care Med. 2017 Sep 10
Pirfenidone with Nintedanib

- Pirfenidone with add on Nintedanib x 24
- Tolerated by 78% of subjects
  - More complaints of diarrhea in combination
- No change in liver toxicity rate

Flaherty K. ERS 2017 Sept 14
Future Treatments in IPF?

• Galapagos
  – Drug GLPG1690
  – Autotaxin Inhibitor
  – Phase II study

Future Treatments in IPF?

• FibroGen
  – Drug FG-3019
  – Inhibits connective tissue growth factor
  – Phase II study

Future of diagnosis of UIP

• Current: HRCT and lung biopsy
  – Role of Cryobiopsy?

• The future: Genomic testing?
  – Veracyte Envisia Genomic Classification
    • Used to differentiate UIP vs non UIP on TBBx
Scleroderma ILD

• Scleroderma II trial
  – Mycophenolate mofetil (MMF) vs Cyclophosphamide in patients with Scleroderma ILD

• Both with improvement in FVC

• MMF better tolerated
  – Less leukopenia and pancytopenia

• No change in survival between the two groups

Pulmonary Rehabilitation for ILD

- Education, exercise, support
- Optimizes functional capacity
- Increases social interactions
- Reduces Symptoms
Oxygen Therapy

• Maintain SpO2> 89%
• Can do more with oxygen
• Assess **regularly** with 6 minute walk tests
Case 2

- 57 year old male with fibrotic NSIP on imaging and biopsy
- Required 10L at rest and 15L with exertion
- Inspiratory Crackles in all lung fields
- FVC 1.69 (39%) FEV1 1.49 (44%) FEV1/FVC 0.89 DLCO 5.0 (20%)
Lung Transplant 3 weeks later
IPF and NSIP

Referral to transplant
• Histologic or radiographic evidence of UIP or fibrotic NSIP
• FVC < 80% pred or DLCO < 40% pred

Listing for Transplant
• 10% or greater decrease in FVC during 6 months of follow-up
• 15% or greater decrease in DLCO

Weill D. J Heart Lung Transplant. 2015;24:1
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>SLT (N=16,226)</th>
<th>BLT (N=29,457)</th>
<th>TOTAL (N=45,683)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD/Emphysema</td>
<td>6,826 (42.1%)</td>
<td>7,856 (26.7%)</td>
<td>14,682 (32.1%)</td>
</tr>
<tr>
<td><strong>Idiopathic Pulmonary Fibrosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5,561 (34.3%)</td>
<td></td>
<td>5,442 (18.5%)</td>
<td>11,003 (24.1%)</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>792 (4.9%)</td>
<td>1,667 (5.7%)</td>
<td>2,459 (5.4%)</td>
</tr>
<tr>
<td>Alpha-1</td>
<td>228 (1.4%)</td>
<td>7,191 (24.4%)</td>
<td>7,419 (16.2%)</td>
</tr>
<tr>
<td>Idiopathic Pulmonary Arterial Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>91 (0.6%)</td>
<td></td>
<td>1,250 (4.2%)</td>
<td>1,341 (2.9%)</td>
</tr>
<tr>
<td><strong>Pulmonary Fibrosis, Other</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>758 (4.7%)</td>
<td></td>
<td>1,125 (3.8%)</td>
<td>1,883 (4.1%)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>65 (0.4%)</td>
<td>1,167 (4.0%)</td>
<td>1,232 (2.7%)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>301 (1.9%)</td>
<td>857 (2.9%)</td>
<td>1,158 (2.5%)</td>
</tr>
<tr>
<td>Retransplant: Obliterative Bronchiolitis</td>
<td>338 (2.1%)</td>
<td>440 (1.5%)</td>
<td>778 (1.7%)</td>
</tr>
<tr>
<td>Connective Tissue Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 (1.2%)</td>
<td></td>
<td>481 (1.6%)</td>
<td>681 (1.5%)</td>
</tr>
<tr>
<td>Obliterative Bronchiolitis (Not Retransplant)</td>
<td>110 (0.7%)</td>
<td>381 (1.3%)</td>
<td>491 (1.1%)</td>
</tr>
<tr>
<td>LAM</td>
<td>142 (0.9%)</td>
<td>330 (1.1%)</td>
<td>472 (1.0%)</td>
</tr>
<tr>
<td>Retransplant: Not Obliterative Bronchiolitis</td>
<td>210 (1.3%)</td>
<td>246 (0.8%)</td>
<td>456 (1.0%)</td>
</tr>
<tr>
<td>Congenital Heart Disease</td>
<td>93 (0.6%)</td>
<td>333 (1.1%)</td>
<td>426 (0.9%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>7 (0.0%)</td>
<td>30 (0.1%)</td>
<td>37 (0.1%)</td>
</tr>
<tr>
<td>Other</td>
<td>504 (3.1%)</td>
<td>661 (2.2%)</td>
<td>1,165 (2.6%)</td>
</tr>
</tbody>
</table>

For some retransplants, a diagnosis other than retransplant was reported, so the total number and percentage of retransplants may be greater.
Adult Lung Transplants

Survival by Age Group

Median survival (years): 18-34=6.5; 35-49=6.7; 50-59=5.3; 60-65=4.5; >65=3.6

Yusen RD. JHLT 2015;32:965
Adult Lung Transplants
Survival by Diagnosis
(Transplants: January 1990 – June 2013)

Median survival (years):
Alpha-1=6.5; CF=8.5; COPD=5.5; IPF=4.7; IPAH=5.7; Sarcoidosis=6.1
Questions?