New Therapies and Trials in IPF

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I have the following real or perceived conflicts of interest that relate to this presentation:

- InterMune (Drug Study Steering committees)
- F. Hoffmann-La Roche/Genentech (Drug Study Steering committees)
- Actelion (Drug Study Steering Committees)
- ImmuneWorks (Scientific Advisory Committee)
- GlaxoSmithKline (Consultant)
- Boehringer Ingelheim (Consultant)
- Daiichi Sankyo (Consultant)
- Tracon (Consultant)
- NIH IPFnet (Principal investigator)
- UpToDate (Editor, Author)

Diffuse Parenchymal Lung Diseases or Interstitial Lung Diseases (ILD)

- Heterogeneous group of noninfectious, nonmalignant processes of the lower respiratory tract (interstitial pneumonias) that commonly result
  - Symptoms: dyspnea and cough
  - Signs: crackles on chest exam; (clubbing)
  - PFTs: restrictive ventilatory impairment
  - Chest imaging: diffuse interstitial opacities
  - Lung biopsy: granulomatous or interstitial inflammation and fibrosis
  - Outcome: often progressive and often fatal

Diffuse Parenchymal Lung Diseases

Non-familial (≥80%)

Familial (20%)

Chronic Fibrosing

Acute/Subacute Fibrosing

Smoking-related

Idiopathic pulmonary fibrosis
Idiopathic nonspecific interstitial pneumonia

Cryptogenic organizing pneumonia
Acute interstitial pneumonia

Respiratory bronchiolitis ILD
Desquamative interstitial pneumonia
Approach to the Diagnosis of ILD: It Often Takes A Village!

Primary Care, Pulmonologists, Rheumatologists, Radiologists, Pathologists

Clinical
- History
- Physical
- Laboratory
- PFTs

Radiology
- Chest X-ray
- HRCT

Pathology
- Surgical lung biopsy

Multidimensional and multidisciplinary


Idiopathic Pulmonary Fibrosis

- Specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring in adults (55–75 years),
- Associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP).

Incidence and prevalence of IPF increases markedly with age

Clinical course of IPF/UIP is variable and may be difficult to predict.
IPF is not an inflammatory disorder...

It is a fibroproliferative disorder preceded by epithelial activation.

Primary Sites of Ongoing Injury and Repair Are the Fibroblast Foci

Multiple microfoci of epithelial injury

Type 2 pneumocyte proliferation and activation

Focal fibroblast proliferation

IPF may represent a primary failure of the alveolar epithelium, due in part to age-related changes in cellular function.
The FDA granted Esbriet (pirfenidone) and Ofev (nintedanib) fast track, priority review, orphan product, and breakthrough designations.

Why has it taken so long to get here?

Current animal models are NOT useful in the development of novel therapies for IPF because animal models do NOT produce a fibrotic injury that looks or acts in any way like IPF/UIP!

Need to rely more on translational rather than basic science.

IPFnet is a network of ~26 medical centers across the U.S.A. dedicated to the study of IPF
We “confused” ourselves about the value of prednisone (with or without cytotoxic agents)!

Why Did We Use Corticosteroids to Treat IPF?

- Rationale: treat inflammation, slow fibroblastic proliferation and prevent irreversible fibrosis
- Some patients experience a precipitous decline when steroids were stopped, so, they appeared to be working
- No other therapy available

“If you remember I did mention possible side effects.”

ILD: Responsiveness to Treatment

- OP
- NSIP
- Eos Pn
- RB-ILD
- DIP
- “LIP”
- Vasc
- Bronchiolitis
- DAD
- DAH
- LAM
- PAP
- UIP
- Familial IPF
- AIP
- Amyloid

We “over” valued underpowered, poorly designed studies of therapies.
Cyclophosphamide Appears to Improve Survival in IPF

We “ignored” the widely recognized adverse events associated with common therapies.
We could not agree on disease definition.

Treatment Trials

NO GLOBAL INVOLVEMENT UNTIL ~2000:
- More precise diagnosis
- Pharmaceutical company interest
- Patient encouragement and advocacy

What have we tried...

<table>
<thead>
<tr>
<th>Year</th>
<th>Trial Name</th>
<th>Drug/Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>Johnson Cyclophosphamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Winterbauer Azathioprine</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Douglas Colchicine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Raghu IFN-γ</td>
<td></td>
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<tr>
<td></td>
<td>Ziesche IFN-γ</td>
<td></td>
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<tr>
<td></td>
<td>Kubo Warfarin</td>
<td></td>
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<tr>
<td></td>
<td>Azuma Pirfenidone</td>
<td></td>
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<tr>
<td></td>
<td>Demedts NAC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>King IFN-γ</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BUILD Bosentan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti-CCL2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti-CTGF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti-TGFβ</td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>ASCEND Pirfenidone</td>
<td></td>
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</tbody>
</table>

Slide courtesy of Luca Richeldi
There is no cure for IPF/UIP.

Can we slow the progression or improve survival of IPF/UIP?

- IFIGENIA Trial
- PANTHER trial
- NAC Trial
- INPLUSIS-1 and INPLUSIS-2
- ASCEND Trial

IFIGENIA
NAC + azathioprine + steroids
**IMPLICATIONS FOR PATIENT CARE**

**“NAC Treatment for IPF”**

- Addition of NAC to low-dose prednisone and azathioprine may help to preserve pulmonary function in patients with IPF.
- However, a drop-out rate of ~30% (including deaths) raised concerns regarding the clinical relevance and robustness of the treatment effect.

**IFIGENIA Trial**

- Therapy with acetylcysteine at a dose of 600 mg three times daily, added to prednisone and azathioprine, preserves vital capacity and \( D_{LCO} \) in patients with idiopathic pulmonary fibrosis better than does standard therapy alone.

**CONCLUSIONS**


**PANTHER**

- NAC + azathioprine + steroids
Time Until Disease Progression or Death
(Decrease in Forced Vital Capacity of ≥10%)

Kaplan–Meier Curve

HR 1.46 (95% CI: 0.70–3.05)

P = 0.30

Time Until Hospitalization or Death

Kaplan–Meier Curve

HR: 3.74 (95% CI: 1.68–8.34)

p<0.001

Time until Death

Kaplan–Meier Curve

HR 9.26 (95% CI: 1.16–74.1)

P = 0.01

Increased risks of death and hospitalization were observed in patients with idiopathic pulmonary fibrosis who were treated with a combination of prednisone, azathioprine, and NAC, as compared with placebo. These findings provide evidence against the use of this combination in such patients. (Funded by the National Heart, Lung, and Blood Institute and the Cowlin Family Fund; ClinicalTrials.gov number, NCT00650091.)
Trials had higher incidence of adverse events than placebo.

**IMPLICATIONS FOR PATIENT CARE**

**“Treatment of IPF”**
- Compelling evidence against the use of the combination of azathioprine, prednisone, and NAC for patients with IPF who have mild-to-moderate impairment in pulmonary function.
- Death rates in clinical trials are below historical expectation.

**Demonstrates Mild to Moderate IPF Patients Have a Low Mortality Rate**

**Death Rate in IPF Has Declined?**
- IPF patients in placebo groups from INSPIRE and CAPACITY Trials (n=622)
N-acetylcysteine (NAC) offered no significant benefit with respect to the preservation of FVC in patients with idiopathic pulmonary fibrosis with mild-to-moderate impairment in lung function.
**NAC Trial: Conclusions**

- As compared with placebo, acetylcysteine offered no significant benefit with respect to the preservation of FVC in patients with idiopathic pulmonary fibrosis with mild-to-moderate impairment in lung function.

**INPULSIS**

**Nintedanib**

**Possible Mechanisms of Nintedanib Action**

- Triple kinase inhibitor
- Phosphatase activator
- Antiangiogenic, antitumor activity

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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 Mauff, M.Sc., Mannaig 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*

**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.
Annual rate of change in FVC was significantly lower in the nintedanib

INPULSIS – 1

INPULSIS – 2

Nintedanib Reduces Loss of FVC

INPULSIS – 1

INPULSIS – 2

A significantly greater proportion of patients in nintedanib group had no absolute decline in the % predicted FVC ≥5% points

<table>
<thead>
<tr>
<th>Table 1: Nintedanib Increases Yearly FVC in Patients with IPF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 52</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>FVC (L)</strong></td>
</tr>
<tr>
<td><strong>FVC % Predicted</strong></td>
</tr>
</tbody>
</table>

Time to 1st acute exacerbation

INPULSIS – 1

INPULSIS – 2
Common Nintedanib Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>INPULSIS-1 (n = 309)</th>
<th>Placebo (n = 204)</th>
<th>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>

INPULSIS trials: CONCLUSION

- “Nintedanib reduced the decline in FVC, which is consistent with a slowing of disease progression…”
- “There was significant differences in favor of nintedanib for the time to first acute exacerbation and the change from baseline in the total SGRQ score in INPULSIS-2 but not INPULSIS-1.”
- “Nintedanib was frequently associated with diarrhea, which lead to discontinuation of the study medication in less than 5% of patients.”

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

Tilmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D., Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D., Ian Glasspole, M.B., B.S., Ph.D., Marilyn K. Glassberg, M.D., Eduard Gorina, M.D., Peter M. Hopkins, M.D., David Kardaszke, 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

Possible Mechanisms of Pirfenidone Action

- Antifibrotic
- Molecular target unclear
- Active in several animal models of fibrosis (lung, liver, kidney)

Primary Efficacy Analysis: Treatment with pirfenidone resulted in a significant between-group difference in the rank ANCOVA analysis (P<0.000001)

<table>
<thead>
<tr>
<th>Week</th>
<th>Pirfenidone (N=278)</th>
<th>Placebo (N=277)</th>
<th>Absolute Difference</th>
<th>Relative Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>0</td>
<td>2.5%</td>
<td>2.5%</td>
<td>54.0%</td>
</tr>
<tr>
<td>26</td>
<td>5</td>
<td>7.9%</td>
<td>2.4%</td>
<td>58.0%</td>
</tr>
<tr>
<td>39</td>
<td>12</td>
<td>12.3%</td>
<td>12.8%</td>
<td>57.8%</td>
</tr>
<tr>
<td>52</td>
<td>15</td>
<td>15.3%</td>
<td>12.8%</td>
<td>47.9%</td>
</tr>
</tbody>
</table>

Supportive Analysis of the Primary Endpoint: Treatment group difference of 193 mL at Week 52, a 45% relative reduction in the mean change in FVC

<table>
<thead>
<tr>
<th>Week</th>
<th>Pirfenidone (N=278)</th>
<th>Placebo (N=277)</th>
<th>Absolute Difference</th>
<th>Relative Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>235 ml</td>
<td>428 ml</td>
<td>193 ml</td>
<td>45.1%</td>
</tr>
<tr>
<td>26</td>
<td>235 ml</td>
<td>428 ml</td>
<td>193 ml</td>
<td>45.1%</td>
</tr>
<tr>
<td>39</td>
<td>235 ml</td>
<td>428 ml</td>
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<td>52</td>
<td>235 ml</td>
<td>428 ml</td>
<td>193 ml</td>
<td>45.1%</td>
</tr>
</tbody>
</table>
ASCEND Study Supportive Analysis:
Annual rate of FVC decline at week 52 favored Pirfenidone (Linear Slope Analysis)

- Absolute Difference, 116 mL/yr
- Relative reduction: 41.5%
- P<0.0001*

Linear slope analysis: Mixed model with linear time effect adjusted for age, height, and sex

More Pirfenidone Patients Maintain Walk Distance or Survive

- Proportion of patients with ≥50 m decline or death (%)
- Absolute Difference: 3.7% vs. 10.9% vs. 10.9% vs. 9.8%
- Relative Difference: 24.1% vs. 39.7% vs. 31.8% vs. 27.5%
- Rank ANCOVA p-value: 0.401, 0.119, 0.041, 0.036

* Tested for multiple comparisons using the Hochberg procedure

Progression-free Survival*: Pirfenidone reduced the risk of disease progression or death by 43%

- HR 0.57 (95% CI, 0.43–0.77)
- P<0.001†

ASCEND Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Pirfenidone (%) (N = 278)</th>
<th>Placebo (%) (N = 277)</th>
<th>Δ (%)</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>Dyspepsia</td>
<td>17.6</td>
<td>6.1</td>
<td>11.5</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>Dizziness</td>
<td>17.5</td>
<td>13</td>
<td>4.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12.9</td>
<td>8.7</td>
<td>4.2</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>14.7</td>
<td>17.7</td>
<td>-3</td>
</tr>
<tr>
<td>Cough</td>
<td>25.2</td>
<td>29.6</td>
<td>-4.4</td>
</tr>
<tr>
<td>IPF</td>
<td>9.4</td>
<td>18.1</td>
<td>-8.7</td>
</tr>
</tbody>
</table>

* Time to death or disease progression (confirmed ≥10% decline in FVC or confirmed ≥50 m decline in 6MWD)† Log-rank test

Treatment with pirfenidone for 52 weeks significantly reduced disease progression, as measured by
- Changes in % predicted FVC (p<0.000001)
- Changes in 6-minute walk distance (p=0.036)
- Progression-free survival (p<0.0001)

Treatment with pirfenidone reduced all-cause mortality and treatment emergent IPF-related mortality in pooled analyses at week 52.

Pirfenidone was generally safe and well tolerated.

Pirfenidone, as compared with placebo, reduced disease progression in patients with IPF.

Treatment was generally safe, had an acceptable side effect profile and was associated with fewer deaths.

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**IPF Comorbidities**

- GERD
- Combined Pulmonary Fibrosis and Emphysema (CPFE)
- Pulmonary arterial hypertension (PAH)
- Lung cancer
Goals of effective IPF management

- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent and treat complications
- Prevent and treat exacerbations
- Prevent disease progression
- Reduce mortality

Cough, Depression, Sleep, Pulmonary rehab., GERD, Supplemental Oxygen

New approaches needed??

- Pirfenidone
- N-acetylcysteine (Flumucil®)
- Nintedanib
- Sildenafil (advanced disease)

Lung transplantation

These goals should be reached with a minimum of side effects from treatment

IPF Drugs in the Works

- Gilead: Simtuzumab (anti-LOXL2)
- Fibrogen: FGCL (anti-CTGF)
- Centocor: CTX 0888 (anti-CCL2)
- Novartis: QAX 576 (anti-IL13)
- Promedior: PRM151 (Petaxin-2)
- Biogen: ST 100 (anti integrin αVβ6)
- MedImmune: Tralokinumab (anti-IL13)
- Sanofi: SAR156597 (anti IL-4 and IL-13)

THANK YOU FOR ATTENTION.