Recent Advances in Idiopathic Pulmonary Fibrosis

Hyun Kim, M.D.
Pulmonary and Critical Care Medicine
University of Minnesota
Outline

- Case
- IPF
  - Clinical
  - Proposed mechanisms of disease
- Treatment
- Summary
65 year old male referred by pulmonologist for evaluation of pulmonary fibrosis

Cough and dyspnea on exertion for 1 year

Review of systems: + heartburn; no arthralgias or rash

Exposures: mold in basement; no birds or hot tubs
Case - PMSFH

- No significant past medical history
- Medications: esomeprazole, guiaifenesin, loratadine
- Social History: never smoker; worked in sales, currently part-time chauffer
- Family History: No pulmonary fibrosis, no rheumatologic disease
Case – Physical Exam

- RR 16, O2 saturation 94% room air
- Bibasilar fine inspiratory crackles
- No clubbing
- No rash
Pulmonary Function Test

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>2.22L</td>
<td>66%</td>
</tr>
<tr>
<td>FVC</td>
<td>2.66L</td>
<td>59%</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>84%</td>
<td></td>
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<tr>
<td>TLC</td>
<td>4.14L</td>
<td>59%</td>
</tr>
<tr>
<td>DLCO</td>
<td>11.17</td>
<td>41%</td>
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</table>
Idiopathic Pulmonary Fibrosis

- Most common of the interstitial lung diseases
- Progressive, fatal fibrotic lung disease
- No known cause or cure
- Distinct diagnostic criteria
IPF Clinical Presentation

- Older age (50s and older)
- Men more commonly affected than women
- Majority have history of cigarette smoking

Clinical findings in IPF

- Age: 66 yr (40 - 70), two-thirds > 60 yr
- Dyspnea on exertion > 6 mo 95%
- Cough 90%
- Fine crackles 90%
- Clubbing 60-70%
- Weight loss, malaise, fatigue 30-50%
- Fever rare
Diagnosis of IPF

Suspected IPF

Identifiable causes for ILD?

No

HRCT

UIP *
Possible UIP *
Inconsistent w/ UIP *

Surgical Lung Biopsy

UIP ⊥
Probable UIP ⊥ / Possible UIP ⊥
Non-classifiable fibrosis ⊥

MDD

IPF

IPF/Not IPF per Table 6

Not IPF

†Refer to Table 5 for definitions.

ATS/ESR/JRS/ALAT statement. AJRCCM 2011;183: 788
Usual Interstitial Pneumonia

*Fibroblastic focus*
Usual Interstitial Pneumonia

Temporal and spatial heterogeneity
Usual Interstitial Pneumonia
Epidemiology of IPF

- Incidence in US 48,000
- Prevalence in US 132,000-200,000
- Mortality of pulmonary fibrosis increasing
  - 40,000 deaths/year
  - Higher than mortality rate of AML or multiple myeloma
- Most common cause of death in IPF is pulmonary fibrosis

Raghu et al, AJRCCM 2006;174;810-816
Olson et al, AJRCMM 2007;176:277-284
Incidence and Prevalence of IPF

Raghu et al, Lancet Respir Med, 2014 May
Who is at risk?

- Smoking
  - More than 20 pk-yrs

- GERD
  - Significant increased prevalence of GERD

- Microbial agents
  - Possible chronic viral infection?

- Environmental exposures
  - Metal dusts, wood dust, farming, raising birds, hair dressing, vegetable dust/animal dust, livestock

ATS/ESR/JRS/ALAT statement. AJRCCM 2011;183: 788
Pathogenesis of IPF
Alveolar Epithelium

- IPF lungs exhibit markedly abnormal alveolar epithelium

- Alveolar epithelial cells release cytokines/growth factors:
  - PDGF, TGF-β, TNF-α, endothelin-1, CTGF
Fibroblast in IPF

- Fibroblastic foci = areas of myofibroblast proliferation and matrix deposition
- Intermediate phenotype between fibroblast and smooth muscle
  - Express contractile proteins
- “Activated”: increased ECM production
  - Growth factors, cytokines, GF receptors, integrins, oxidants
- Reduced rates of apoptosis
IPF Fibroblast

IPF Mesenchymal Progenitor Cell:
Cell-of Origin For IPF Fibroblast

Self-renewal → Differentiation

Aging
Inflammation
Cytokines
ECM

Progression of Disease

Bitterman et al, JCI 2014
Gene Mutations in IPF

- TGF-β1 gene polymorphisms
  - May worsen disease progression
- Surfactant proteins C and A2 gene mutations
- Telomerase mutations
- MUC5B promoter polymorphism
  - Present in 38% of IPF versus 9% of control patients

Is IPF Caused by a Virus?

- γ-herpesviruses cause pulmonary fibrosis in animals
  - Equine herpesvirus, murine herpesvirus-68, asinine herpesvirus

- Herpesvirus saimiri DNA found in IPF lung biopsies but not control (pulmonary fibrosis of known etiology) lung biopsies

- Herpesvirus saimiri subclinical infection in 4.0-7.3% of people

Mod Pathol 2013;1-12
Prognosis of IPF
IPF Survival

Median survival from most studies 2-5 yrs

-Survival is heterogeneous:
-5 yr survival 40%
-10 yr survival 25%

Chest 2011; 140:221

FIGURE 4. Survival of patients with IPF from the time of initial PFT, with transplantation recipients excluded. See Figure 2 legend for expansion of abbreviations.
Survival in UMN IPF patients

% patients affected

Rapid Progressors n=26
Usual Survivors n=40
Slow Progressors n=27

Gillen et al, Submitted for publication 2014
Treatment Options

- No FDA-approved medical treatment in U.S.
- Pirfenidone approved in Europe, Japan and Canada
- Lung Transplantation
- “Anti-fibrotic” therapy/clinical trials
- Stem cells?
  - Small phase 1 trials
<table>
<thead>
<tr>
<th>Title</th>
<th>Drug</th>
<th>Year</th>
<th>No.</th>
<th>Endpoint</th>
<th>Result</th>
<th>Journal</th>
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<tr>
<td>GIPF-001</td>
<td>Interferon gamma</td>
<td>2004</td>
<td>330</td>
<td>Progression</td>
<td>Trend – mild to mod dz</td>
<td>NEJM</td>
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<td></td>
<td>Pirfenidone</td>
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<td>BUILD-1</td>
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<td>Etanercept</td>
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<td>826</td>
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<td>STEP</td>
<td>Sildenafil</td>
<td>2010</td>
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<td>TOMORROW</td>
<td>Nintedanib (BIBF 1120)</td>
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<td>432</td>
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<td>Trend</td>
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<tr>
<td>Capacity 2</td>
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<td>Thalidomide</td>
<td>2012</td>
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<td>Cough</td>
<td>Pos</td>
<td>Ann Int Med</td>
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<td>PANTHER</td>
<td>Pred+AZA+NAC</td>
<td>2012</td>
<td>341</td>
<td>FVC</td>
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<td>NEJM</td>
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<td>ACE-IPF</td>
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<td>Co-trimoxazole</td>
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<td>ASCEND</td>
<td>Pirfenidone</td>
<td>2014</td>
<td>555</td>
<td>FVC</td>
<td>Pos</td>
<td>NEJM</td>
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<td>INPULSIS 1&amp;2</td>
<td>Nintedanib</td>
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<td>1066</td>
<td>FVC</td>
<td>Pos</td>
<td>NEJM</td>
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<td>PANTHER</td>
<td>NAC</td>
<td>2014</td>
<td>264</td>
<td>FVC</td>
<td>Neg</td>
<td>NEJM</td>
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</table>
CAPACITY (PIPF-004 and PIPF-006)

- Multicenter, randomized, placebo-controlled, blinded phase 3 studies of pirfenidone vs placebo
- P004 showed significant reduction in FVC decline vs placebo
- P006 showed no difference in FVC
- Fewer deaths in pirfenidone group (3% vs 7%) but not statistically significant

Lancet 2011;377:1760
FAILED TREATMENTS FOR IPF: the bad guys

- Prednisone + azathioprine + NAC (PANTHER)
  - Increases mortality

- Warfarin (ACE-IPF)
  - Increases mortality
Now for the good news...
ASCEND

- Multicenter phase 3 RCT pirfenidone vs placebo
- 555 patients randomized
- FEV1/FVC ratio >80%
- Pirfenidone slowed progression of disease
  - Reduced rate of decline of FVC
  - Improved progression free survival (p<0.001)
  - Overall well tolerated, some GI and skin side effects
Figure 2. Primary and Key Secondary Efficacy Outcomes during the 52-Week Study Period.
# ASCEND & CAPACITY pooled data

Table 2. Mortality in the ASCEND and CAPACITY Trials.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pirfenidone</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)†</th>
<th>P Value‡</th>
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<tbody>
<tr>
<td>ASCEND trial</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>No. of patients</td>
<td>278</td>
<td>277</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From any cause</td>
<td>11 (4.0)</td>
<td>20 (7.2)</td>
<td>0.55 (0.26–1.15)</td>
<td>0.10</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>
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<tr>
<td>Pooled data from ASCEND and CAPACITY trials</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>623</td>
<td>624</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From any cause</td>
<td>22 (3.5)</td>
<td>42 (6.7)</td>
<td>0.52 (0.31–0.87)</td>
<td>0.01</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>0.003</td>
</tr>
</tbody>
</table>

NEJM 2014; 370:2083
Nintedanib

- Multiple tyrosine kinase inhibitor
  - VEGF, FGF, PDGF
- Decreases fibrosis in mouse model
- Significant diarrhea in almost 2/3 of patients
Figure 1. Annual Rate of Decline and Change from Baseline over Time in Forced Vital Capacity (FVC) in INPULSIONS-1 and INPULSIONS-2, According to Study Group.

Between-group differences (the FVC value in the nintedanib group vs. the value in the placebo group) are shown for the adjusted rate of decline in FVC (Panels A and C) and the mean observed change from baseline at week 52 (Panels B and D). I bars indicate standard errors for the adjusted annual rate of decline in FVC and the observed change from baseline.
N-acetylcysteine (NAC)

- Anti-oxidant
- ?oxidative stress in IPF
PANTHER: NAC vs Placebo

A. Change from Baseline in FVC

B. Table showing outcome measures, t-statistic, and p-value for interaction:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>t-Statistic</th>
<th>P Value for Interaction</th>
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<tbody>
<tr>
<td>FVC</td>
<td></td>
<td>0.16</td>
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<tr>
<td>DLCO corrected</td>
<td></td>
<td>0.02</td>
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<tr>
<td>CPI</td>
<td></td>
<td>0.04</td>
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<tr>
<td>Alveolar-arterial gradient</td>
<td></td>
<td>0.70</td>
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<tr>
<td>Walk distance</td>
<td></td>
<td>0.20</td>
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<tr>
<td>Oxygen saturation AUC</td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>Walk distance to desaturation</td>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td>Minutes walked</td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>SF-36 aggregate physical score</td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>SF-36 aggregate mental score</td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>EuroQoL score</td>
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<td>0.51</td>
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<tr>
<td>EuroQoL thermometer response</td>
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<td>0.56</td>
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<tr>
<td>St. George’s total score</td>
<td></td>
<td>0.19</td>
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<tr>
<td>St. George’s symptoms score</td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>St. George’s activity score</td>
<td></td>
<td>0.20</td>
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<tr>
<td>St. George’s impacts score</td>
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<td>UCSD SOBQ total score</td>
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<tr>
<td>ICECAP summary score</td>
<td></td>
<td>0.10</td>
</tr>
</tbody>
</table>
# PANTHER Trial
## NAC vs Placebo

### Table 3. Clinical Events and Safety.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Acetylcysteine (N=133)</th>
<th>Placebo (N=131)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events — no. (%)</td>
<td>25 (18.8)</td>
<td>20 (15.3)</td>
<td>0.45</td>
</tr>
<tr>
<td>Respiratory</td>
<td>9 (6.8)</td>
<td>9 (6.9)</td>
<td>0.97</td>
</tr>
<tr>
<td>Infectious</td>
<td>6 (4.5)</td>
<td>6 (4.6)</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td><strong>9 (6.8)</strong></td>
<td><strong>2 (1.5)</strong></td>
<td><strong>0.03</strong></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0</td>
<td>6 (4.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Death (95% CI) — %†</td>
<td>4.9 (2.2–10.6)</td>
<td>2.5 (0.8–7.5)</td>
<td>0.30</td>
</tr>
<tr>
<td>Disease progression (95% CI) — %‡</td>
<td>27.1 (20.1–36.0)</td>
<td>26.5 (19.5–35.4)</td>
<td>0.82</td>
</tr>
<tr>
<td>Death or hospitalization (95% CI)</td>
<td>17.5 (11.9–25.4)</td>
<td>15.6 (10.2–23.3)</td>
<td>0.59</td>
</tr>
</tbody>
</table>
Ongoing IPF Clinical Trials

- RAINIER: phase 2 trial of simtuzumab
- BMS: phase 2
- RIFF: phase 2
- FG3019: phase 2 trial of anti-CTGF
- Pirfenidone EAP
- Nintedanib EAP
Symptom management

- Sildenafil (STEP)
- Thalidomide
- Morphine
- Oxygen
- Pulmonary rehabilitation
- Palliative care
- Patient education and support
Sildenafil for IPF

- NEJM 2010; 363:620-8. STEP-IPF
- Sildenafil vs placebo for IPF
  - 12 weeks of treatment
  - Small but significant improvement in dyspnea and quality of life, diffusion capacity and PaO2
  - Not designed to evaluate survival
  - Not FDA-approved for this indication
Thalidomide Treatment in IPF

- Persistent dry cough affects up to 86% of patients with IPF
- Ten of 11 patients treated with thalidomide had marked to complete resolution of cough
- Mechanism is unclear: ? Anti-inflammatory effect or direct inhibition of pulmonary sensory nerve fibers
Thalidomide to Treat Cough in IPF

- 24 IPF patients randomized to thalidomide or placebo
- Decreased cough severity and improved quality of life
- Side effects: constipation, dizziness, malaise

Ann Intern Med 2012;157:398
Lung Transplantation

LIMITATIONS:

- Age limit 65 - 70 yrs
  - 2/3 IPF patients diagnosed are > 60 yo
- Concomitant illness limits eligibility
- Lung transplantation outcomes unpredictable
- IPF lung transplant median survival = 55.5 months*

*Chest 2011; 140:221
IPF Acute Exacerbation

- Worsening dyspnea over 30 days or less
- New bilateral ground glass opacities and/or consolidations on background of UIP on HRCT
- No alternative explanation, such as infection, heart failure, or PE
- Pathology: diffuse alveolar damage superimposed on UIP
- Mean survival of 1.5 months
- Treatment: steroids; CSA or other immunosuppressants

Acute Exacerbation of IPF - Epidemiology

- Incidence (4-19% per year)
- Mortality (55%-100%)
- Acute exacerbation cause of death in 50% of patients with IPF

Kubo et al, Chest 2005; 128: 1475-1482

<table>
<thead>
<tr>
<th>TABLE 2. Outcome in Acute Exacerbation of UIP Diagnosed During Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Report</td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td>Ambrosini et al⁵</td>
</tr>
<tr>
<td>Parambil et al⁴⁰</td>
</tr>
<tr>
<td>Kim et al⁴</td>
</tr>
<tr>
<td>Kondoh et al⁸</td>
</tr>
<tr>
<td>Akira et al¹</td>
</tr>
<tr>
<td>This report*</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

*Includes 2 cases of acute exacerbation of NSIP and 1 case of acute exacerbation of chronic HP.
Histopathology of Acute Exacerbation of IPF

- Pathologic pattern = Diffuse alveolar damage (75% of cases)
- Organizing pneumonia
- Extensive fibroblastic foci

What Should You Do If You Suspect ILD or IPF?

- ILD should be on differential for chronic cough and insidious dyspnea
- IPF is a progressive fatal disease
- Consider referral to ILD center for MDD
  - Treatment options are limited
  - Symptom management
  - Lung transplant and consideration of enrollment in clinical trial
Referral Improves Prognosis

Referral to Interstitial Lung Disease Center improves survival (Am J Respir Crit Care Med 2011; 184: 842-827)

- Independent of FVC, age, gender, insurance, education, severity

<table>
<thead>
<tr>
<th>Time to referral*</th>
<th>5 yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 yr</td>
<td>70%</td>
</tr>
<tr>
<td>1 - 2 yrs</td>
<td>55%</td>
</tr>
<tr>
<td>2 - 4 yrs</td>
<td>35%</td>
</tr>
<tr>
<td>&gt; 4 yrs</td>
<td>15%</td>
</tr>
</tbody>
</table>

*from onset of dyspnea
ILD Clinic Referral

- Median survival of patients enrolled in clinical trial higher than nonstudy patients
  - 52 months vs 34 months*

*Chest 2011;140:221
“I say that scirrhus of the lung is present when the spongy substance of lung has degenerated into a flashy and indolent mass”

Aunbrugger Leopold, Inventum Novum, Vienna 1761
U of MN ILD Program

- Hyun Kim, M.D.
- David Perlman, M.D.
- Peter Bitterman, M.D.
- Craig Henke, M.D.
- Maneesh Bhargava, M.D.
- Wajahat Khalil, M.D.
- Rade Tomic, M.D.
- Katie Ferguson, R.N.
- Beth Mullan, R.N.
- Alan Panelli

Study Coordinators:
- Tommy Goodwin
- Cheryl Edin Stibbe
- Patt Carlson