Nintedanib and Pirfenidone: New Medications in the Management of Idiopathic Pulmonary Fibrosis

Brad Zimmermann, PharmD, MBA

Pharmacy Grand Rounds
May 02, 2017
Objectives

• Describe the etiology and causes of Idiopathic Pulmonary Fibrosis (IPF)
• Explain recent updates and changes to the guidelines for treatment of IPF
• Discuss pharmacologic agents, nintedanib and pirfenidone, which are directed at slowing progression of IPF
Abbreviations

• FVC- Forced vital capacity
• 6MWTD- 6 minute walk time distance
• DL_{CO}- Diffusing capacity of lungs for carbon monoxide
• SGRQ- St. George’s Respiratory Questionnaire
• HRCT- High-resolution computed tomography
• GERD- Gastroesophageal reflux disease
Disease Course

- Median life expectancy after diagnosis ~ 3 years
- Chronic progressive breathlessness and/or dry cough
- Bibasilar inspiratory crackles, finger clubbing, worsening pulmonary function tests
- Progression is unpredictable and ultimately fatal

IPF Diagnosis

• Early diagnosis is important due to poor prognosis
• High-resolution computed tomography (HRCT)
• Surgical lung biopsy (not necessary but helpful)

Etiology and Risk Factors

• Mechanism of development is believed to be due to:
  • Repetitive lung injury
  • Abnormal cellular and tissue changes in lung
  • Presence of growth factors in lungs

• Risk Factors:
  • Smoking
  • Exposure to industrial chemicals
  • GERD
  • Genetic predisposition
  • Aging process

Disease Burden

• Prevalence is increasing- about 40,000 new diagnoses each year in U.S.

• U.S. Medicare 2011: 494.5/100,000

Aiello et al. Pulm Pharm & Ther. 2017;44:7-15
Pathophysiology of IPF

Patient Case

• SM, 68 M, presents to clinic with complaints of 2 months of worsening shortness of breath, cough, fatigue and weight loss. His past medical history is significant for 15 pack years of smoking (quit 35 years ago), HTN, HLD and significant GERD. He was diagnosed with COPD 1 year ago but reports little relief when using his albuterol inhaler.
SM, 68M

- Current Meds:
  - Lisinopril 10 mg daily
  - Atorvastatin 20 mg daily
  - Omeprazole 20 mg daily
  - Albuterol inhaler 1-2 puffs q4h prn

- Pulmonary Function Test- FVC = 70%

- Physical exam reveals bibasilar inspiratory crackles and early signs of finger clubbing. Provider recommends further workup.
Question

• Provider is concerned for possible IPF in SM-what should she order, as it is the “gold standard” test for identifying IPF?

• A) Bronchoalveolar lavage
• B) High-resolution CT chest
• C) Surgical lung biopsy
• D) Transbronchial lung biopsy
Question

• Provider is concerned for possible IPF in SM-what should she order, as it is the “gold standard” test for identifying IPF?
  • A) Bronchoalveolar lavage
  • B) High-resolution CT chest
  • C) Surgical lung biopsy
  • D) Transbronchial lung biopsy
Patient Case

Upon pulmonology consult, SM is diagnosed with IPF. The pulmonologist knows that the guidelines have undergone recent updates. Which of the following is not recommended?

A) Nintedanib or pirfenidone  
B) Inhaled corticosteroids  
C) Continuing omeprazole  
D) All of the above are appropriate
Patient Case

Upon pulmonology consult, SM is diagnosed with IPF. The pulmonologist knows that the guidelines have undergone recent updates. Which of the following is not recommended?

A) Nintedanib or pirfenidone
B) Inhaled corticosteroids
C) Continuing omeprazole
D) All of the above are appropriate
# 2015 Guideline Updates - Medications Not Recommended for IPF

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<tr>
<td>Anticoagulation (warfarin)</td>
<td>Strongly against</td>
<td>Conditionally against</td>
</tr>
<tr>
<td>Combo: prednisone + azathioprine + N-acetylcysteine</td>
<td>Strongly against</td>
<td>Conditionally against</td>
</tr>
<tr>
<td>Ambrisentan</td>
<td>Strongly against</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Strongly against</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Macitentan, bosentan</td>
<td>Conditionally against</td>
<td>Strongly against</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Conditionally against</td>
<td>Not addressed</td>
</tr>
<tr>
<td>N-acetylcysteine monotherapy</td>
<td>Conditionally against</td>
<td>Conditionally against</td>
</tr>
<tr>
<td>Anti-pulmonary hypertensive medications for IPF-associated pulmonary hypertension</td>
<td>Reassessment deferred</td>
<td>Conditionally against</td>
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### 2015 Guideline Update Recommendations

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<td>Conditional yes</td>
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Nintedanib

- Dosing: 150 mg capsule PO twice daily with food
- MOA: Tyrosine kinase inhibitor (TKI) that inhibits:
  - Vascular endothelial growth factor receptors
    - VEGF 1,2,3
  - Fibroblast growth factor receptors
    - FGFR 1,2,3
  - Platelet-derived growth factor receptors
    - α, β
Nintedanib Timeline

2010- TOMORROW
Phase II

2013- INPULSIS I/II
Phase III

2014- FDA Approval

2015- EMA Approval

2015- IPF Guidelines
Conditional Recommendation for Use

2015- IPF Guidelines
Conditional Recommendation for Use
Efficacy of a TKI in IPF (TOMORROW)- 2010

- 12 month, phase II trial that randomized 432 patients to varying doses of nintedanib or placebo
- Dose-finding study
- Inclusion Criteria:
  - ≥40 years old diagnosed IPF within 5 years
  - FVC ≥50% predicted
  - DLCO 30-79% predicted
  - HRCT within 1 year of randomization

Richeldi, et al. NEJM. 2011;365:1079-87
### Nintedanib Dose

<table>
<thead>
<tr>
<th>Nintedanib Dose</th>
<th>Annual rate of change in FVC (95% CI to Placebo)</th>
<th>Acute Exacerbation Risk Ratio to Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.19 L</td>
<td>--</td>
</tr>
<tr>
<td>50 mg daily</td>
<td>-0.17 L</td>
<td>0.83</td>
</tr>
<tr>
<td>50 mg 2xday</td>
<td>-0.21 L</td>
<td>0.80</td>
</tr>
<tr>
<td>100 mg 2xday</td>
<td>-0.16 L</td>
<td>0.48</td>
</tr>
<tr>
<td>150 mg 2xday</td>
<td>-0.06 L (-0.14 to 0.02)</td>
<td>0.16 (0.03-0.70)</td>
</tr>
</tbody>
</table>

Efficacy and Safety of Nintedanib in IPF (INPULSIS 1-2) - 2014

- Two, replicate 52-week, randomized, double-blind, phase 3 trials, n=1066

- Inclusion Criteria:
  - ≥40 years old diagnosed IPF within 5 years
  - FVC ≥50% predicted
  - DLco 30-79% predicted
  - HRCT within 1 year of randomization

- Primary Endpoint: Annual rate of decline in FVC

- Secondary Endpoints: Time to first acute exacerbation and change in SGRQ score

## INPULSIS 1-2 Results

<table>
<thead>
<tr>
<th></th>
<th>INPULSIS-1</th>
<th>INPULSIS-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual FVC Rate of Change (mL)</td>
<td>Placebo -239.9</td>
<td>Placebo -207.3</td>
</tr>
<tr>
<td></td>
<td>Nintedanib -114.7</td>
<td>Nintedanib -113.6</td>
</tr>
<tr>
<td></td>
<td>( p &lt; 0.001 )</td>
<td>( p &lt; 0.001 )</td>
</tr>
<tr>
<td>Time to Acute Exacerbation (Hazard Ratio)</td>
<td>Nintedanib 1.15</td>
<td>Nintedanib 0.38</td>
</tr>
<tr>
<td></td>
<td>( p = 0.67 )</td>
<td>( p = 0.005 )</td>
</tr>
<tr>
<td>Change in SGRQ</td>
<td>Placebo +4.39</td>
<td>Placebo +5.48</td>
</tr>
<tr>
<td></td>
<td>Nintedanib +4.34</td>
<td>Nintedanib +2.80</td>
</tr>
<tr>
<td></td>
<td>( p = 0.97 )</td>
<td>( p = 0.02 )</td>
</tr>
</tbody>
</table>

- No significant difference in all-cause mortality HR 0.70 (\( p = 0.14 \))

Richeldi, et al. NEJM. 2014;370:2071-82
Nintedanib- Combined Tomorrow/Inpulsis Evidence

• Goal: estimate the overall treatment effect of nintedanib

• Primary Endpoint: Annual rate of decline in FVC

• Secondary Endpoints: Mortality: All-cause, on-treatment, and respiratory-related vs. placebo
  • On-treatment: HR 0.57 (p= 0.027)
  • All-cause: HR 0.70 (p= 0.095)
  • Respiratory-related: HR 0.62 (p= 0.078)

Nintedanib- Combined Tomorrow/Inpulsis Evidence

• SGRQ: Nintedanib +2.92 vs Placebo +4.97 (p=0.01)

Adapted from: Richeldi et al. Resp Med. 2016;113:74-79
Nintedanib Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Nintedanib (% affected)</th>
<th>Placebo (% affected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>61.5</td>
<td>17.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>24.3</td>
<td>7.1</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12.9</td>
<td>15.6</td>
</tr>
<tr>
<td>Cough</td>
<td>12.9</td>
<td>14.8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11.8</td>
<td>3.0</td>
</tr>
<tr>
<td>Decrease Appetite</td>
<td>11.2</td>
<td>4.7</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>10.5</td>
<td>11.0</td>
</tr>
</tbody>
</table>

- Adverse effects leading to discontinuation
  - 20.6% nintedanib vs. 15.0% placebo

### 2015 Guideline Update Recommendations

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<td>Nintedanib</td>
<td>Conditional yes</td>
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</tr>
<tr>
<td>Pirfenidone</td>
<td>Conditional yes</td>
<td>Conditionally against</td>
</tr>
<tr>
<td>Antacid therapy</td>
<td>Conditional yes</td>
<td>Conditional yes</td>
</tr>
</tbody>
</table>

Pirfenidone

• MOA: Unknown
  • Interferes with TNF-α
  • Inhibits lung fibroblast proliferation

• Dosing:
  • Day 1-7: 267 mg PO 3 times daily
  • Day 8-14: 534 mg PO 3 times daily
  • Day 15+: 801 mg PO 3 times daily

Pirfenidone Timeline

2005- Phase II study in Japan showing favorable efficacy

2010- Phase III Clinical trial in Japan

2011- CAPACITY Phase III

2014- ASCEND Phase III Published

2014- FDA Approval

2014- EMA Approval

2015- IPF Guidelines Conditional recommendation for use
Pirfenidone in Patients with IPF (CAPACITY)

- Two concurrent randomized, double-blind, placebo-controlled trials for 72 weeks

- **Inclusion Criteria**
  - Age 40-80 with IPF
  - Predicted FVC >50%
  - 6MWTD >150 m

- **Exclusion Criteria**
  - Obstructive airway disease
  - Connective tissue disease
  - Other interstitial lung disease
  - Waiting for lung transplant

# Pirfenidone- CAPACITY Results

<table>
<thead>
<tr>
<th></th>
<th>Pirfenidone n=345</th>
<th>Placebo n=347</th>
<th>Absolute Difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease of FVC ≥ 10%</td>
<td>74 (21%)</td>
<td>106 (31%)</td>
<td>9.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Progression-free Survival Time</td>
<td>--</td>
<td>--</td>
<td>0.74</td>
<td>0.025</td>
</tr>
<tr>
<td>Mean change in 6MWTD</td>
<td>-52.8</td>
<td>-76.8</td>
<td>24.0</td>
<td>0.0009</td>
</tr>
<tr>
<td>Mean change in DL\textsubscript{CO}</td>
<td>-8.8</td>
<td>-9.6</td>
<td>0.7</td>
<td>0.301</td>
</tr>
<tr>
<td>Mean change in dyspnea score</td>
<td>12.0</td>
<td>14.5</td>
<td>-2.5</td>
<td>0.405</td>
</tr>
</tbody>
</table>

A Phase 3 Trial of Pirfenidone in Patients with IPF (ASCEND)

• Prospective, randomized, double-blind placebo controlled trial for 52 weeks

• Inclusion Criteria
  • Age 40-80 with IPF
  • Predicted FVC >50%
  • 6MWTD >150 m

• Primary Outcome: Change in % FVC

• Secondary Outcomes: Change in 6MWTD, progression free survival, decrease in FVC ≥10%

ASCEND Results


FVC Difference = 193 mL; p<0.001
ASCEND Results

- Patients with a predicted FVC decline ≥ 10% or who died:
  - Placebo = 88 (31.8%)
  - Pirfenidone = 46 (16.5%)

- Patients without any decline in FVC:
  - Placebo = 27 (9.7%)
  - Pirfenidone = 63 (22.7%)

King Jr, et al. NEJM. 2014;370(22):2083-92
ASCEND Results

- All-cause mortality (pirfenidone vs. placebo)
  - 11 vs 20 (HR 0.55; p=0.10)

- Death from IPF
  - 3 vs 7 (HR 0.44; p=0.23)

- Fewer deaths in pirfenidone group but not significant

King Jr, et al. NEJM. 2014;370(22):2083-92
### Mortality in ASCEND + CAPACITY

<table>
<thead>
<tr>
<th></th>
<th>Pirfenidone</th>
<th>Placebo</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>623</td>
<td>624</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause</td>
<td>22</td>
<td>42</td>
<td>0.52</td>
<td>0.01</td>
</tr>
<tr>
<td>IPF-related</td>
<td>7</td>
<td>22</td>
<td>0.32</td>
<td>0.006</td>
</tr>
</tbody>
</table>

King Jr, et al. NEJM. 2014;370(22):2083-92
# Pirfenidone Adverse Effects

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<tr>
<td>Nausea</td>
<td>36</td>
<td>13.4</td>
</tr>
<tr>
<td>Rash</td>
<td>28.1</td>
<td>8.7</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>17.6</td>
<td>6.1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12.9</td>
<td>8.7</td>
</tr>
<tr>
<td>Upper Respiratory Infection</td>
<td>21.9</td>
<td>20.2</td>
</tr>
<tr>
<td>Anorexia</td>
<td>15.8</td>
<td>6.5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20.9</td>
<td>17.3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11.2</td>
<td>6.5</td>
</tr>
<tr>
<td>Gastroesophageal Reflux</td>
<td>11.9</td>
<td>6.5</td>
</tr>
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Patient Case

• 6 months after beginning therapy with pirfenidone, SM reports continued worsening symptoms of breathlessness. His FVC has declined 12% (now 58%) since his diagnosis 6 months ago. His provider is worried that pirfenidone isn’t helping given his rapidly declining lung function. What should she do?
Patient Case

• A) Continue pirfenidone
• B) Switch to nintedanib
• C) Combination pirfenidone + nintedanib
• D) Treatment failure- discontinue pirfenidone
Patient Case

• A) Continue pirfenidone
• B) Switch to nintedanib
• C) Combination pirfenidone + nintedanib
• D) Treatment failure- discontinue pirfenidone
Nathan, et al.

• Source population: CAPACITY + ASCEND

• Purpose: To examine effect of continued pirfenidone treatment following a clinically meaningful decline in FVC (≥10% decrease in FVC)

Nathan, et al.

- Outcomes after 6 months of continued treatment following an initial decline of predicted FVC ≥10%

<table>
<thead>
<tr>
<th></th>
<th>Pirfenidone (n=34)</th>
<th>Placebo (n=68)</th>
<th>Relative difference (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥10% decline in FVC or death</td>
<td>2 (5.9%)</td>
<td>19 (27.9%)</td>
<td>-78.9</td>
<td>0.009</td>
</tr>
<tr>
<td>No further decline in FVC</td>
<td>20 (58.8%)</td>
<td>26 (38.2%)</td>
<td>53.8</td>
<td>0.059</td>
</tr>
<tr>
<td>Death</td>
<td>1 (2.9%)</td>
<td>14 (20.6%)</td>
<td>-85.7</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Nathan, et al.

• Results: Patients had fewer deaths and had lower risk of a second FVC decline $\geq 10\%$ if they were taking pirfenidone vs. placebo group.

• This is the first evidence to suggest that continuing treatment with pirfenidone, even with IPF progression, may confer a meaningful benefit.

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GERD and IPF?

- Microaspiration of gastric contents can damage pulmonary parenchyma
  - GERD itself does NOT = microaspiration
- Acid suppression is currently recommended; however, the evidence is mixed
- PPIs will not stop microaspiration, simply alter the pH of aspirated contents

Role of Acid Suppression

- Proton-pump-inhibitors may:
  - Induce production of antioxidants
  - Decrease lung epithelial cell apoptosis
  - Scavenge reactive oxygen species
  - Stabilize lung function or decrease exacerbations

- Retrospective analysis has linked acid suppression to smaller decreases in FVC loss from baseline to 30 weeks (0.07L; p=0.05)

- No randomized trials evaluating acid suppression

Should Every IPF Patient be on Acid Suppression?

• Kreuter et al investigated the placebo groups from CAPACITY and ASCEND in a post-hoc analysis

• n=624, 291 (47%) on acid suppression and 333 (53%) were not

• Patients with FVC <70% and on acid suppression had higher rates of pulmonary infections vs. no acid suppression, (14% vs 6%, p= 0.021)

• No significant difference in disease progression

Patient Case Wrap-Up

- After reviewing the available data, it is reasonable for SM’s provider to continue pirfenidone, as well as omeprazole given his history of GERD
Conclusion

• Over 1 year, both nintedanib and pirfenidone are effective at reducing lung function decline

• No evidence to support one agent over another (nintedanib or pirfenidone)

• Pirfenidone may reduce the likelihood of experiencing a decline in percent predicted FVC ≥ 10%

• Pirfenidone is linked to improved survival

• Acid suppression may reduce decline in lung function
Nintedanib and Pirfenidone: New Medications in the Management of Idiopathic Pulmonary Fibrosis

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May 02, 2017

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