NEW THERAPIES IN ADVANCED HEART & LUNG DISEASE

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Disclosures

I have nothing to disclose

Overview of Pulmonary Hypertension

- mPAP ≥ 25 mmHg at rest assessed by RHC
- Pulmonary Arterial Hypertension (PAH)
  - mPAP ≥ 25 mmHg
  - PAWP ≤ 15 mmHg
  - PVR > 3 Wood units
  - ↑ PAP associated with adverse changes:
    - In pulmonary vasculature and at the level of the right ventricle
    - Absence of lung disease and left-sided heart disease

Selexipag (Uptravi®)
- Oral, selective prostacyclin IP receptor agonist
- 2015 – FDA approval for treatment of PAH, WHO Group 1
  - Delay disease progression and reduce risk of hospitalization for PAH

Approval of Selexipag

Primary Composite Endpoint

Selexipag for Treatment of PAH
- Phase 3, randomized, double-blind, placebo controlled trial
  - 1156 patients enrolled
- Primary end point
  - Death or complication related to PAH
    - Disease progression
    - Worsening PAH

Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selexipag</td>
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</table>

End Points Related to PAH and Death

<table>
<thead>
<tr>
<th>End Points Related to PAH and Death</th>
<th>Baseline Characteristics</th>
<th>Placebo</th>
<th>Selexipag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or complication related to PAH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease progression event</td>
<td></td>
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</tr>
</tbody>
</table>

Study Conclusion

- Treatment with selexipag resulted in 40% reduction of death or complication related to PAH.
- Benefits primarily attributable to reduction in hospitalization and reduction in other disease progression event.
- Observed benefit was similar regardless of dose when titrated to highest tolerated dose.
Selexipag Prescribing Information

- Dose: 200 mcg BID PO
  - Increase by 200 mcg BID at weekly intervals as tolerated dose up to 1600 mcg BID
  - Maintenance dose determined by tolerability
  - Moderate hepatic impairment: start 200 mcg QD
    - Increase dose by 200 mcg daily at weekly intervals as tolerated up to 1600 mcg
- Interactions: avoid strong CYP2C8 inhibitors

Future Directions

- Consider as alternative to prostacyclins
  - Limited experience with transitioning from prostacyclins to selexipag
- TRANSIT-1: Evaluation of Transition from Inhaled Treprostinil to Oral Selexipag
  - Prospective, multicenter, open-label, single group, Phase 3B study
  - Eligibility: stable PAH patients with inhaled treprostinil, WHO FC II/III, 6MWF >/= 300 m on background therapy with ERA, PDE-5 inhibitor or riociguat
  - Objective: evaluate tolerability and safety of transition

Idiopathic Pulmonary Fibrosis

- Chronic, progressive, fatal lung disease characterized by irreversible loss of lung function
- The most common interstitial lung disease referred for lung transplantation

Updates in Therapy for Idiopathic Pulmonary Fibrosis
Pathophysiology of IPF


Updated IPF Guidelines

Pirfenidone (Esbriet)

- Oral anti-fibrotic therapy with pleiotropic effects
  - inhibits synthesis of TGF-β and TNF-α
    - active role in fibrosis and inflammation
  - Initial phase 3 study CAPACITY 006
    - Did not show reduction in decline in FVC

ASCEND

ASCEND study

- 555 patients enrolled & randomized
  - Pirfenidone 2403 mg/day vs. placebo
- Primary end point:
  - change in FVC or death at week 52
- Secondary end point:
  - Change in 6MWD and progression-free survival at week 52

Primary & Secondary Efficacy Outcomes

- Change in FVC or death at week 52
- Change in 6MWD and progression-free survival at week 52

Adverse Events

- GI upset
- Photosensitivity
- Rash
- Transaminitis

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n=275)</th>
<th>Pirfenidone (n=280)</th>
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</thead>
<tbody>
<tr>
<td>Cough</td>
<td>35 (12.8)</td>
<td>49 (17.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>46 (16.9)</td>
<td>66 (23.6)</td>
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<tr>
<td>Dizziness</td>
<td>56 (20.3)</td>
<td>68 (24.3)</td>
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<tr>
<td>Rash</td>
<td>2 (0.7)</td>
<td>8 (2.9)</td>
</tr>
<tr>
<td>Rash</td>
<td>34 (12.4)</td>
<td>36 (12.9)</td>
</tr>
<tr>
<td>Transaminitis</td>
<td>59 (21.4)</td>
<td>59 (20.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (4.7)</td>
<td>18 (6.4)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>13 (4.7)</td>
<td>19 (6.8)</td>
</tr>
<tr>
<td>GI upset</td>
<td>13 (4.7)</td>
<td>18 (6.4)</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>6 (2.2)</td>
<td>9 (3.2)</td>
</tr>
<tr>
<td>Transaminitis</td>
<td>6 (2.2)</td>
<td>7 (2.5)</td>
</tr>
</tbody>
</table>

Nintedanib (Ofev)

- Oral intracellular inhibitor targets multiple tyrosine kinases implicated in fibrogenesis
- FDA approved for treatment of IPF
INPULSIS TRIAL

- 1066 patients randomized to nintedanib 150mg BID or placebo
- Primary end point
  - Annual rate of decline in FVC over 52 weeks
- Secondary end points
  - Time to first acute exacerbation
  - Change in score on St. George’s Respiratory Questionnaire
Adverse Events

- GI upset
- Transaminitis

Future Directions

- Utility after lung transplant to treat fibrosis/chronic allograft dysfunction?
- Case reports in lung transplant recipients
  - Pirfenidone – conflicting results
  - Nintedanib – reported with beneficial clinical effects
- Limitations – costs and side effects vs. benefits

Summary

- New therapies recently approved for advanced heart and lung diseases
  - PAH – selexipag
  - IPF – nintedanib, pirfenidone
- If patients can be stabilized, the need for lung transplantation may slowly decline
- More experience is needed to further evaluate their long-term impact
References