Advances in the Treatment of Pulmonary Arterial Hypertension

Faculty

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Disclosures

Dr. Coons: Has nothing to disclose in relation to this presentation
Learning Objectives

- Highlight the clinical and economic consequences of delayed diagnosis, suboptimal treatment, and hospitalizations in PAH
- Discuss the importance of PAH pathobiology and the role of various pathways as treatment targets in the development of PAH-specific treatment
- Describe the pharmacologic properties of current and newer PAH-specific regimens and their place within current guidelines and treatment algorithms
- Implement practices to reduce medication and management errors, address side effects and barriers to adherence, and improve transitions of care in patients with PAH

Patient Case

- HL is a 43-year-old mother of three who presented with a 2-month history of dyspnea on exertion and fatigue with minimal activities
- She reports a 1-year use of phentermine for weight loss prior to symptom onset
- She also reports that her mother had PAH and died at the age of 47 years
- She was diagnosed with PAH (heritable vs drug-induced) based on RHC

Definition of PH vs PAH

<table>
<thead>
<tr>
<th>Right Heart Catheterization Confirmed</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased mPAP ≥25 mm Hg</td>
<td>PH</td>
</tr>
<tr>
<td>Increased mPAP AND Normal PCWP ≥15 mm Hg</td>
<td>PAH</td>
</tr>
</tbody>
</table>

Epidemiology

- WHO Group 1
- Incidence: 15 per million people
- Demographics
  - Mean age, 50 ± 14 years
  - 80% female
- 56% have symptoms with minimal activity or at rest
- Delay from symptom onset to diagnosis: 27 months


REVEAL Registry: Survival

- Predicted Survival by NIH Equation
- REVEAL Weighted to Match NIH Cohort


Hospitalizations and Costs

- Hospitalization for worsening PAH
  - Associated with poor prognosis
  - Costly
- Total healthcare costs: ~$8000 per-patient-per-month

Pathogenesis


Therapeutic Targets


cGMP
cAMP
Vasoconstriction and proliferation
Endothelin receptor A
Exogenous nitric oxide
Endothelin-receptor antagonists
Endothelin receptor B
Phosphodiesterase type 5 inhibitor
Vasodilation and antiproliferation
Phosphodiesterase type 5
Vasodilation and antiproliferation
Prostacyclin derivatives
Nitric Oxide Pathway
Endothelin Pathway
Prostacyclin Pathway

Pharmacotherapy Timeline

1960-1980: Empiric/various vasodilators
1980: Oral anticoagulants, calcium channel blockers, lung/heart transplantation
1996: Epoprostenol
2001: Bosentan
2002: Treprostinil SQ
2004: Treprostinil IV, iloprost
2005: Sildenafil
2007: Ambrisentan
2009: Tadalafil, treprostinil inhaled
2010: Thermostable epoprostenol
2013: Riociguat, macitentan, treprostinil oral
2015: Selexipag

SQ = subcutaneous; IV = intravenous.
**Oral Therapies**

**PDE-5 Inhibitors (PDE5i)**

**Endothelin Receptor Antagonists (ERA)**

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**PDE-5 Inhibitors**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication</th>
<th>Dosing</th>
<th>Pharmacologic Properties and Other Special Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>Improves exercise ability in early stage PAH</td>
<td>20 mg PO tid</td>
<td>- Dual antagonist of ET-1A &amp; 1B receptors - Tracleer® Access Program (REMS, LFTs, Hb, pregnancy at baseline; monthly LFTs, Hb, pregnancy at baseline; monthly pregnancy)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg IV tid (short-term use in patients unable to take PO)</td>
<td></td>
</tr>
<tr>
<td>Tadalafil</td>
<td>Improves exercise ability</td>
<td>40 mg PO daily</td>
<td>- Avoid if CrCl &lt;30 mL/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg PO daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg IV tid (short-term use in patients unable to take PO)</td>
<td></td>
</tr>
</tbody>
</table>

**Endothelin Receptor Antagonists**

<table>
<thead>
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<th>Pharmacologic Properties and Other Special Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosentan</td>
<td>Improves exercise ability and decrease rate of clinical worsening in WHO FC III-IV</td>
<td>62.5 mg PO bid, then 125 mg PO bid after 4 weeks</td>
<td>- Dual antagonist of ET-1A &amp; 1B receptors - Tracleer® Access Program (REMS, LFTs, Hb, pregnancy at baseline; monthly LFTs, Hb, pregnancy at baseline; monthly pregnancy)</td>
</tr>
<tr>
<td>Ambesnten</td>
<td>WHO FC II-III</td>
<td>10 mg PO daily</td>
<td>- Selective ET-1 antagonist - Letairis® Education and Access Program (REMS, LFTs, Hb, pregnancy at baseline; monthly pregnancy)</td>
</tr>
<tr>
<td>Macitentan</td>
<td>Delays progression of PAH</td>
<td>10 mg PO daily</td>
<td>- Tissue selective - Lipophilic - Dual antagonist of ET-1A &amp; 1B receptors - Opsumit® REMS (LFTs, Hb, pregnancy at baseline; monthly pregnancy)</td>
</tr>
</tbody>
</table>

**Legend:** tid = three times daily; PO = by mouth; CrCl = creatinine clearance; REMS = risk evaluation and mitigation strategy; LFTs = liver function tests; Hb = hemoglobin; PAH = pulmonary arterial hypertension; WHO = World Health Organization; IV = intravenous; REMS = risk evaluation and mitigation strategy; IV = intravenous.
Prostacyclins
- Epoprostenol
- Treprostinil
- Iloprost

Epoprostenol

CADD = continuous ambulatory delivery device.


Treprostinil

### Parenteral Prostacyclins

<table>
<thead>
<tr>
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<th>Indication</th>
<th>Dosing</th>
<th>Pharmacologic Properties and Other Special Considerations</th>
</tr>
</thead>
</table>
| **Epoprostenol** | WHO FC III-IV    | 2 ng/kg/min titrated to dose-limiting adverse effects (usual range, 20-40 ng/kg/min) | Half-life 4-6 minutes  
- Back-up cassette/pump  
- Protect from light  
- Ice pack (Flolan® only)  
- Requires reconstitution and further dilution (25% saline or sterile water: Veletri® special diluent: Flolan®)  
- Every 24-hour cassette change |
| **Treprostinil SC** | WHO FC III-IV | 1.25 ng/kg/min titrated to dose-limiting adverse effects (usual range, 40-80 ng/kg/min) | Half-life 4 hours  
- Back-up pump  
- Stable at room temperature  
- SQ: Undiluted, every 72-hour syringe change  
- IV: Requires further dilution, every 48-hour cassette change |
| **Treprostinil IV** | WHO FC III-IV | 1.25 ng/kg/min titrated to dose-limiting adverse effects (usual range, 40-80 ng/kg/min) | Half-life 4 hours  
- Back-up pump  
- Stable at room temperature  
- SQ: Undiluted, every 72-hour syringe change  
- IV: Requires further dilution, every 48-hour cassette change |

### Inhaled Prostacyclins

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication</th>
<th>Dosing</th>
<th>Other Special Considerations</th>
</tr>
</thead>
</table>
| **Iloprost**     | WHO FC III-IV    | 2.5-5 mcg given 4 to 6 times per day (maximum, 20 mcg/day) | Only administered via I-neb® AAD® System  
- Use higher concentration ampule (20 mcg/mL) for patients with extended treatment time or at 5-mcg dose |
| **Treprostinil** | Increases walk distance in WHO FC III | 3 breaths QID  
- 3 breaths every 3 breaths up to 9 breaths QID | Only administered via Tyvaso® Inhalation System |

QID = four times daily.

AAD = adaptive aerosol delivery.

Newer Oral Therapies

- Riociguat
- Oral Treprostinil
- Selexipag

Riociguat

- Indicated to improve exercise capacity, WHO FC, and delay clinical worsening in patients with:
  - PAH
  - Persistent/recurrent chronic thromboembolic pulmonary hypertension (after surgery or for inoperable disease)
- Initiate 1 mg PO tid, titrate in 0.5-mg increments every 2 weeks up to 2.5 mg PO tid
  - Start 0.5 mg PO tid if risk for hypotension or with concomitant strong CYP and P-gp inhibitors
  - Avoid if CrCL <15 mL/min or if on hemodialysis
- Adempas® REMS program (teratogenicity)

CYP = cytochrome P450; P-gp = p-glycoprotein.
Treprostinil Diolamine
Extended Release

- Indicated to improve exercise capacity in patients with WHO FC II-III symptoms
- Initiate 0.25 mg PO bid or 0.125 mg PO tid
- Titrate by 0.125 to 0.5 mg PO increments bid to tid every 3 to 4 days or longer
- Maximum dosing per patient tolerability
- Administer with food to improve bioavailability
  - High calorie, high-fat meal


Selexipag

- Selective IP receptor agonist
- Type of prostanoid receptor found in lungs (regulates vascular tone, platelet activity, immunologic responses)
- Similar mode of action to prostacyclin, but a non-prostanoid
- Approved to delay disease progression and reduce risk of hospitalization for PAH
- Initiate 200 mcg PO bid and uptitrate weekly as tolerated to maximum of 1600 mcg PO bid


Adverse Reactions

<table>
<thead>
<tr>
<th>Medication/Class</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE5i</td>
<td>Headache, dyspepsia, flushing, epistaxis, insomnia, hypotension, visual changes</td>
</tr>
<tr>
<td>Riociguat</td>
<td>Headache, dizziness, dyspepsia, gastroesophageal reflux, nausea, diarrhea, vomiting, hypotension, anemia, constipation, teratogenicity</td>
</tr>
<tr>
<td>ERAs</td>
<td>Headache, flushing, peripheral edema, nasal congestion, sinusitis, transaminitis, liver injury, anemia, teratogenicity</td>
</tr>
<tr>
<td>Prostacyclins</td>
<td>Nausea, vomiting, diarrhea, flushing, jaw pain, headache, rash, erythema, hypotension, leg pain</td>
</tr>
<tr>
<td>Selexipag</td>
<td>Headache, diarrhea, jaw pain, nausea, myalgia, vomiting, extremity pain, flushing</td>
</tr>
</tbody>
</table>

PDE5i = phosphodiesterase-5 inhibitor; ERA = endothelin receptor antagonist.
**Parenteral Prostacyclins: Line-Related Complications**

- **SQ**: Injection-site pain, swelling
  - Preemptive site management (eg, topical analgesics)
- **IV**: Catheter-related infection, bacteremia, thrombosis
  - ↑ risk of Gram-negative infection (treprostinil > epoprostenol)
- Need for extensive education/training, support


**Drug Interactions**

<table>
<thead>
<tr>
<th>Medication/Class</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE5i</td>
<td>Strong CYP3A4 inhibitors/inducers, nitrates, alpha-blockers, alcohol</td>
</tr>
<tr>
<td>Riociguat</td>
<td>Strong CYP and P-gp inhibitors/inducers, PDE5is, non-specific PDE inhibitors (eg, theophylline, dipyridamole), nitrates, antacids, smoking</td>
</tr>
<tr>
<td>ERAs</td>
<td>Strong CYP3A4 and CYP2C19 inhibitors/inducers, warfarin, oral contraceptives – Bosentan: Cyclosporine, glyburide</td>
</tr>
<tr>
<td>Prostacyclins</td>
<td>Vasodilators, antiplatelets, anticoagulants – Treprostinil: Gemfibrozil, rifampin</td>
</tr>
<tr>
<td>Selexipag</td>
<td>Strong CYP2C8 inhibitors</td>
</tr>
</tbody>
</table>

CYP = cytochrome P450; P-gp = p-glycoprotein.

**Adjunctive Treatments**

- Diuretics
- Digoxin
- Oxygen
- Warfarin
Treatment Guidelines

Initial Therapy with PAH-Approved Drugs

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>WHO-FC II</th>
<th>WHO-FC III</th>
<th>WHO-FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA or IB</td>
<td>Ambrisentan</td>
<td>Bosentan</td>
<td>Macitentan†‡</td>
</tr>
<tr>
<td>IB</td>
<td>Ambrisentan</td>
<td>Bosentan</td>
<td>Epoprostenol IV</td>
</tr>
<tr>
<td>IB</td>
<td>Ambrisentan</td>
<td>Bosentan</td>
<td>Iloprost inhaled</td>
</tr>
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<td>IB</td>
<td>Ambrisentan</td>
<td>Bosentan</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>IB</td>
<td>Ambrisentan</td>
<td>Bosentan</td>
<td>Tadalafil</td>
</tr>
<tr>
<td>IB</td>
<td>Ambrisentan</td>
<td>Bosentan</td>
<td>Treprostinil SC inhaled†</td>
</tr>
<tr>
<td>IIa C</td>
<td>Iloprost IV†</td>
<td>Treprostinil IV</td>
<td>Ambrisentan</td>
</tr>
<tr>
<td>IIa C</td>
<td>Iloprost IV†</td>
<td>Treprostinil IV</td>
<td>Bosentan</td>
</tr>
<tr>
<td>IIb</td>
<td>Beraprost†</td>
<td>Ambrisentan</td>
<td>Iloprost inhaled</td>
</tr>
<tr>
<td>IIb</td>
<td>Beraprost†</td>
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<td>Macitentan†‡</td>
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<td>Tadalafil</td>
</tr>
<tr>
<td>IIb</td>
<td>Beraprost†</td>
<td>Ambrisantian</td>
<td>Treprostinil SC, IV, inhaled†</td>
</tr>
</tbody>
</table>

Orange: Mortality and morbidity as primary endpoint in randomized controlled study or reduction in all-cause mortality (prospectively defined).
*Level of evidence is based on the WHO-FC of the majority of the patients of the studies. †Approved only: by the FDA (macitentan, riociguat, treprostinil inhaled); in New Zealand (iloprost IV); in Japan and S. Korea (beraprost). ‡Positive opinion for approval of the CHMP of EMA.


Approaches to the Treatment of PAH

• Sequential therapy

• Up-front combination therapy
  – AMBITION trial (tadalafil + ambrisentan vs monotherapy with either)
  – Hazard ratio, 0.50 (95% confidence interval, 0.35-0.72; P<0.001) for composite of clinical failure events in favor of combination group vs pooled monotherapy

sGC = soluble guanylate cyclase stimulator.


Specialty Pharmacy

• Complex and costly medications/delivery systems

• Types of services
  – Clinical counseling and support
  – Local nursing support and training
  – Prior authorization
  – Medication delivery
Medication Safety

• Ensure communication across transitions of care
• Policy/protocol/guideline development and oversight
• Prostacyclin vigilance
  – Determine essential order details for prostacyclins: type of agent, route, pump, timing of next dose, dosing weight, current dose, titration schedule, vial concentration (treprostinil) or vial size (epoprostenol), amount of medication and diluent for mixing, type of diluent, infusion rate, back-up cassette availability (epoprostenol)


Patient Counseling

• Expectations from treatment/goals of care
• Dosing/administration/product preparation
• Catheter and line care
• Adherence
• Specialty pharmacy and nursing contact
• Maintain an accurate medication list
• Updated dosing sheet from specialty pharmacy
• Monitoring and follow-up
• Symptom recognition
• Emotional support
• Adverse events
• Health maintenance
  – Diet/exercise
  – Immunizations
  – Pregnancy/contraception

PAH “Clinical Pearls”

• Improved clinical outcomes have been realized in PAH through advancements in pharmacotherapy
• There are now 14 FDA-approved medication formulations with more in the pipeline
• Pharmacists are well-positioned, and essential, to safe and effective PAH care in a team-based setting

FDA = US Food and Drug Administration.
Questions?

Thank you for your attention!