Treatment of Pulmonary Hypertension

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Disclosure

• The speaker cannot identify any potential conflict of interest and has no relationships that should be disclosed

Objectives

• Pharmacist Objectives:
  – Identify the pathophysiology, clinical presentation, and diagnostic criteria for pulmonary hypertension
  – Review treatment goals and strategies for each pulmonary hypertension functional class
  – Discuss new and emerging therapies for the treatment of pulmonary hypertension

• Technician Objectives:
  – Discuss the clinical presentation of pulmonary hypertension
  – Recognize medications used for the treatment of this disease state
  – Identify dosage forms and administration for pulmonary hypertension therapies

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Epidemiology

- The age-standardized death rate in the USA ranges between 4.5 and 12.3 per 100,000 population
- Women accounted for 61% of all pulmonary hypertension hospitalizations in 2001-02 and 63% in 2009-2010
- Over the past decade, death rates for black patients were approximately 40% higher than white patients

Definition

- Pulmonary hypertension (PH) ≠ pulmonary arterial hypertension (PAH)
- Abnormal elevated pressures in the pulmonary vasculature which often results in right ventricular failure
- Characterized by different pathological lesions in the pulmonary vasculature depending on the underlying cause

Prevalence

Age-Standardized Death Rates of Pulmonary Hypertension as Any Cause of Death Among All Ages by State, 2010

Pathophysiology

- Ohm’s Law
  - Change in pressure = flow x resistance
  - $P_{pa} - P_{pv} = CO \times PVR$
  - $P_{pa} = (CO \times PVR) + P_{pv}$
  - The $P_{pv}$ is estimated by the pulmonary capillary wedge pressure ($PCWP$)
  - $P_{pa} = (CO \times PVR) + PCWP$
- Pulmonary hypertension = mean pulmonary artery pressure ($mPAP$) $\geq 25$ mmHg at rest

Key

- $P_{pa}$ = mean pulmonary arterial pressure
- $P_{pv}$ = mean pulmonary venous pressure
- $CO$ = right-sided cardiac output
- $PVR$ = pulmonary vascular resistance
Pathophysiology

\[ Ppa = (CO \times PVR) + PCWP \]

- Increased flow:
  - Atrial/ventricular septal defects
  - Patent ductus arteriosus
  - Liver cirrhosis

- Increased pulmonary venous resistance:
  - Mitral valve disease
  - Left ventricular systolic or diastolic dysfunction
  - Constrictive pericarditis
  - Restrictive cardiomyopathy
  - Pulmonary versus obstruction (eg, pulmonary veno-occlusive disease)

- Increased pulmonary vascular resistance:
  - Idiopathic PAH
  - Connective tissue disease
  - HIV infection
  - Congenital heart disease
  - Pulmonary emboli
  - Intermittent lung disease
  - Hyperventilation syndromes
  - Parenchymal lung disease

Right Ventricular Failure

Signs and Symptoms

- Dyspnea
- Fatigue
- Chest pain
- Syncope
- Peripheral edema
- Palpitations

Pathogenesis

Clinical Classification

1. Pulmonary Arterial HTN (PAH)
   - Idiopathic PAH
   - Heritable PAH
   - Drug- and toxin-induced PAH
   - Persistent PH of newborn
   - Associated with:
     - CTD
     - HIV infection
     - Portal hypertension
     - CHD
     - Scleroderma
     - Chronic hemolytic anemia
     - Chronic hypoxic anemia
   - PVOD and/or PCH

2. PH Due to Left Sided Heart Disease
   - Systolic dysfunction
   - Diastolic dysfunction
   - Valvular disease

3. PH Owing to Lung Diseases and/or Hypoxia
   - COPD
   - ILD
   - Other pulmonary disease with mixed restrictive and obstructive pattern
   - Sleep disordered breathing
   - Alveolar hypoventilation disorders
   - Chronic exposure to high altitude
   - Developmental abnormalities

4. CTEPH

5. PH with Unclear Multifactorial Mechanisms
   - Hematologic disorders
   - Systemic disorders
   - Metabolic disorders
   - Others
**Drug and Toxin Induced PAH**

**Definite**
- Aminorex
- Fenfluramine
- Dexfenfluramine
- Toxic rapeseed oil
- Benfluorex

**Possible**
- Cocaine
- Phenylpropanolamine
- St. John's Wort
- Chemotherapeutic agents
- SSRIs
- Pergolide

**Likely**
- Amphetamine
- L-tryptophan
- Methamphetamines

**Unlikely**
- Oral contraceptives
- Oestrogen
- Cigarette smoking

**Diagnosis**
- PH is commonly diagnosed at a late stage of the disease and is associated with poor survival
- 6-minute walk test
- Chest X-Ray
- ECG
- CT scan
- Pulmonary function test
- ECHO
- Right heart catheterization

**Functional Assessment: PAH**

**Class I**
- Patients with PH with exertional limitation of physical activity
- Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope

**Class II**
- Patients with PH with exertional limitation of physical activity
- They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope

**Class III**
- Patients with PH with inability to carry out any physical activity
- These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity

**Class IV**
- Patients with PH with inability to carry out any physical activity without symptoms.
- These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity

**Unexplained dyspnea and/or suspected pulmonary hypertension**
- History: Symptoms, Signs, ECG, lab tests, pulmonary function test
- 6 minute walk test, HRCT, MRI, ECHO

**Group 2 (Left Heart Disease) or Group 3 (Pulmonary disease) likely?**
- Segmental perfusion defects
- Ventilation perfusion scan
- Consider Group 4 (CTEPH) or group 1 (PVOD)

**MPAP ≥ 25 mmHg, PCWP ≤ 15 mmHg**

**Right heart catheterization**

**Search for other causes**

**Start treatment**

**Regular follow-up (ECG – 6MWT – exercise testing – lab tests: ECHO – RHC)**
Treatment Goals

- Alleviate symptoms
- Decrease progression of disease
- Improve functional class, exercise capacity, and quality of life
- Improve pulmonary hemodynamics
- Prolong survival


Treatment: PAH Specific Measures

<table>
<thead>
<tr>
<th>Vasoreactivity test positive</th>
<th>Vasoreactivity test negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blocker</td>
<td>ERA (FC II, III, and IV)</td>
</tr>
<tr>
<td>In case of inadequate response</td>
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<tr>
<td></td>
<td>Prostacyclin analogues (FC III and IV)</td>
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<tr>
<td></td>
<td>In case of inadequate response</td>
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<tr>
<td></td>
<td>Sequential combination therapy</td>
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<tr>
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</tbody>
</table>

Vasoreactivity Test for PAH

- Vasoreactivity testing with:
  - Epoprostenol IV 2-10 ng/kg/min
  - Adenosine IV 50-250 mcg/kg/min
  - NO inhaled 10-80 parts per million for 5 minutes
- Positive response defined as decrease in the pulmonary artery pressure >10 mmHg, a pulmonary artery pressure of ≤40 mmHg, and an unchanged or increased cardiac output

Calcium Channel Blocker

<table>
<thead>
<tr>
<th>Calcium Channel Blocker</th>
<th>Dose</th>
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</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>120-240 mg</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>540-900 mg</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>2.5-40 mg</td>
</tr>
</tbody>
</table>

Agents are titrated every 2-4 weeks to clinical effect. Verapamil should be avoided due to negative inotropic effects.

Vasoreactivity Test for PAH

- Long term response to CCB in idiopathic PAH (at least 1 year)
  - n=557
  - Positive response <10% of IPAH patients
    - Less severe disease at baseline

- In the overall population, 16 PAH patients [2.4% (95% CI 1.2–3.6)] were considered long-term CCB responders:
  - 12 [9.4% (95% CI 4.4–14.5)] with anorexigen use
  - 2 [1.6% (95% CI 0–3.8)] with HIV infection
  - 1 [0.7% (95% CI 0–1.9)] with PoPH
  - 1 [0.6% (95% CI 0–1.8)] with CTD

Vasoreactivity Test for PAH

- Response in non-idiopathic PAH
  - 6.5% of patients had an acute response to vasoreactivity testing (n=43)

Vasoreactivity Test for PAH

- Limitations of Clinical Trials
  - Small number of patients
    - Sufficiently powered clinical trials uncommon
  - Short duration
    - High costs associated with extended length studies to achieve sufficient power
  - Endpoints
    - 6MWD: the most common primary endpoint
    - Established predictor of survival
    - Consistent relationship has not been observed between change from baseline in 6-MWD and survival, PAH-associated hospitalisation, or PAH therapy escalation
Treatment

• Prostacyclin analogues
  – Epoprostenol (Flolan®, Veletri®)
  – Treprostinil (Remodulin®, Tyvaso®, Orenitram®)
  – Iloprost (Ventavis®)
  – Selexipag (Uptravi®)

• Endothelin-1 receptor antagonists (ERAs)
  – Ambrisentan (Letairis®)
  – Bosentan (Tracleer®)
  – Macitentan (Opsumit®)

• PDE-5 inhibitors
  – Sildenafil (Revatio®)
  – Tadalafil (Adcirca®)

• cGMP inducer
  – Riociguat (Adempas®)

Prostacyclin Analogues

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
<th>Usual Starting Dose and Titration Schedule</th>
<th>Half-life</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol</td>
<td>Continuous infusion</td>
<td>2 ng/kg/min increased by 1-2 ng/kg/min every 15 minutes until dose limiting side effects occurs</td>
<td>2.7 min</td>
<td>Central line infections, flushing, N/V, hypotension, headache, flulike symptoms, jaw pain</td>
</tr>
<tr>
<td>Treprostinil</td>
<td>Continuous infusion</td>
<td>1.25 ng/kg/min increased by 1.25 ng/kg/min weekly for first 4 weeks then 2.5 ng/kg/min thereafter</td>
<td>4 hours</td>
<td>Headache, N/V, infusion site reactions and pain, flulike symptoms, jaw pain</td>
</tr>
</tbody>
</table>

**Prostacyclin Analogues**

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<tbody>
<tr>
<td>Iloprost</td>
<td>Oral Inhalation</td>
<td>2.5 mcg 6-9 times per day (no more frequently than every 2 hours); increase to 5 mcg 6-9 times per day (max 45 mcg)</td>
<td>20-30 min</td>
<td>flushing, hypotension, headache, flu-like symptoms, trismus, cough</td>
</tr>
<tr>
<td>Selexipag</td>
<td>Oral tablet</td>
<td>200 mcg BID; increase the dose by 200 mcg BID at weekly intervals to the highest tolerated dose up to 1600 mcg BID</td>
<td>6.2-13.5 hours</td>
<td>headache, diarrhea, jaw pain, nausea, myalgia, vomiting, flushing, rash, arthralgia</td>
</tr>
</tbody>
</table>

- **GRIPHON Trial**
  - **GRIPHON (PGi2 Receptor agonist In Pulmonary arterial HypertensiON)**
    - Event driven, Phase III, randomized double-blind trial comparing selexipag to placebo

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Number of Patients</th>
<th>Primary Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAH, age 18-75 yrs; 20% treatment naïve; 47% monotherapy; 33% combination therapy</td>
<td>1,156</td>
<td>Time to first morbidity/mortality</td>
<td>Selexipag decreased time to M/M by 40% (HR 0.60; 99% CI: 0.46, 0.78) vs. placebo (log-rank p &lt; 0.0005)</td>
</tr>
</tbody>
</table>

- **Prostacyclin Analogues: Cost Comparison**
  - **Epoprostenol**
    - 0.5 mg vial: $19.44
    - 1.5 mg vial: $46.94
  - **Flolan**
    - 0.5 mg vial: $22.43
    - 1.5 mg vial: $54.17
  - **Veletri**
    - 0.5 mg vial: $27.07
    - 1.5 mg vial: $45.50
  - **Remodulin**
    - 1 mg/mL: $1474.00
    - 2.5 mg/mL: $3685.00
    - 5 mg/mL: $7370.00
    - 10 mg/mL: $14740.00
  - **Tyvaso**
    - 0.6 mg/mL: $585.00
  - **Orenitram**
    - 0.125 mg (10): $58.50
    - 0.25 mg (10): $117.00
    - 1 mg (10): $468.00
    - 2.5 mg (10): $1170.00
  - **Iloprost**
    - 10 mcg/mL (1 mL): $128.40
    - 20 mcg/mL (1 mL): $128.40
  - **Selexipag**
    - 200 mcg (60): $11208.00
    - 1600 mcg (60): $17424.00

- **Due to epoprostenol short half life, interrupting drug delivery may lead to rebound PH or death**
- **Selexipag metabolized via CYP2C8**
- **Dose adjustments**
  - Epoprostenol: No renal or hepatic dose adjustments necessary
  - Oral treprostinil: Mild hepatic impairment, initiate at 0.125 mg BID, Moderate hepatic impairment, avoid use
  - Selexipag: Moderate hepatic impairment, start dose at 200 mcg once daily and increase dose by 200 mcg once daily at weekly intervals
**Endothelin-1 receptor antagonists (ERAs)**

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<tbody>
<tr>
<td>Bosentan (Tracleer®)</td>
<td>Oral tablet</td>
<td>62.5 mg twice daily for 4 weeks then increase to 125 mg twice daily; if &lt;40 kg, dose remains 62.5 mg twice daily</td>
<td>5 hours</td>
<td>Respiratory tract infections, peripheral edema, headache, anemia, chest pain, syncope; BBW for hepatotoxicity and teratogenicity</td>
</tr>
<tr>
<td>Ambrisentan (Letairis®)</td>
<td>Oral tablet</td>
<td>5 mg daily then increase to 10 mg daily</td>
<td>9-15 hours</td>
<td>Peripheral edema, headache, nasal congestion, flushing; BBW for hepatotoxicity and teratogenicity</td>
</tr>
<tr>
<td>Macitentan (Opsumit®)</td>
<td>Oral tablet</td>
<td>10 mg daily (max)</td>
<td>48 hours</td>
<td>Nasopharyngitis, bronchitis, anemia, Headache</td>
</tr>
</tbody>
</table>

**SERAPHIN Trial**

- Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN)

**Endothelin-1 receptor antagonists (ERAs): Cost Comparison**

- **Bosentan**
  - 62.5 mg (30): $4932.00
  - 125 mg (30): $4932.00

- **Ambrisentan**
  - 5 mg (30): $8842.73
  - 10 mg (30): $8842.73

- **Macitentan**
  - 10 mg (15): $4311.00
PDE-5 inhibitors

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil (Revatio*)</td>
<td>Oral tablet</td>
<td>IV bolus 5 mg or 20 mg TID (4-6 hours apart) IV: 2.5 or 10 mg TID</td>
<td>4 hours</td>
<td>Epistaxis, headache, dyspea, flushing, NAION, hearing loss</td>
</tr>
<tr>
<td>Tadalafil (Adcirca*)</td>
<td>Oral tablet</td>
<td>40 mg once daily</td>
<td>35 hours</td>
<td>Headache, myalgias, nasopharyngitis, flushing, respiratory tract infections, hypotension, hearing or vision loss</td>
</tr>
</tbody>
</table>

- Sildenafil and tadalafil metabolized via CYP3A4
- Dose adjustments
  - Sildenafil: No dose adjustments necessary
  - Tadalafil: Mild or moderate renal impairment, start with 20 mg once daily. Severe renal impairment, avoid use. Mild or moderate hepatic impairment, consider starting dose of 20 mg once daily
- Contraindicated with nitrates and riociguat

PDE-5 inhibitors: Cost Comparison

- Revatio
  - IV
    - 10 mg/12.5 mL (12.5 mL): $251.24
  - Oral Suspension
    - 10 mg/mL (112 mL): $6561.89
  - Tablets (Revatio Oral)
    - 20 mg (90): $3281.09
- Adcirca
  - 20 mg (60): $3002.40

cGMP Inducer

<table>
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<tr>
<th>Drug</th>
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<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riociguat (Adempas*)</td>
<td>Oral tablet</td>
<td>IV bolus 1 mg TID; Increase dosage by 0.5 mg at 2 week intervals as tolerated; MAX 2.5 mg TID</td>
<td>12 hours</td>
<td>Headache, dyspea, gastritis, dizziness, nausea, diarrhea, hypotension, vomiting, anemia, gastrointestinal reflux, and constipation</td>
<td>0.5-2.5 mg tablets (42): $4185.56</td>
</tr>
</tbody>
</table>
cGMP Inducer

- Dose adjustments: Not recommended in patients with severe renal and hepatic impairment
- Contraindicated with nitrates and PDE-5 inhibitors
- REMS Program — Adempas

Combination Therapy

- Recommended in patients who do not show an adequate response to single agent treatment
  - The majority of PAH patients will eventually receive combination therapy
- In case of inadequate clinical response with double combination therapy, triple combination therapy should be attempted
- In WHO-FC IV patients initial combination therapy may also be considered
- Combination therapy can either include an:
  - ERA + PDE-5 inhibitor
  - Prostacyclin + ERA
  - Prostacyclin + PDE-5 inhibitor/sGC stimulator
AMBITION Trial

- Randomized, multicenter study of first line ambrisentan and tadalafil combination therapy in subjects with pulmonary arterial hypertension
- Compared 2 treatment strategies
  - Upfront combo (ambrisentan + tadalafil) vs. monotherapy (ambrisentan or tadalafil)
- Event-driven trial
  - 500 newly diagnosed patient with group 1 PAH who had class II or III symptoms compared the combination of 10 mg of ambrisentan and 40 mg of tadalafil with either agent alone
- Primary objective: time to clinical failure
- Secondary objectives: safety and tolerability, 6MWD at peak and trough levels

Supportive Therapy

- Reduce salt and fluid intake
- Physical activity within symptom limit
- Vaccinations
  - Influenza
  - Pneumococcal
- Smoking cessation
- Administration of oxygen

AMBITION TRIAL

- The combined regimen administered on average for eighteen months resulted in:
  - Reduction in the rate of clinical failure (18% vs. 31%)
  - Improved exercise capacity (49 vs. 24 meters)
  - Decreased hospitalizations

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Combination (n=253)</th>
<th>Monotherapy (n=247)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause deaths (%)</td>
<td>3.6</td>
<td>3.2</td>
</tr>
<tr>
<td>Hospitalization (%)</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Improvement in 6-minute walking (m)</td>
<td>49.0</td>
<td>23.8</td>
</tr>
</tbody>
</table>

Supportive Therapy

- Anticoagulation
  - In PAH there is evidence of coagulopathies with increased risk of thrombosis
  - Use of oral anticoagulation, in the absence of contraindications should be considered in PAH
  - CTEPH patients should receive lifelong anticoagulation
  - The role of NOACs is unknown
- Diuretics
  - Recommended in the case of right sided decompensation
- Digoxin
  - May be helpful for inotropic support and maintenance of sinus rhythm
- Long term oxygen therapy
Case

- RH is a 56 yo male who presents to the ED with cellulitis. The physician decides to admit the patient and start IV antibiotics. You proceed to complete a medication reconciliation and the patient reveals he is on an epoprostenol pump. What are some questions you should ask the patient?

Pharmacist Role

- Avoidance of dosing errors
  - Dose/weight/concentration/rate
- Maintain appropriate par levels
- Nursing in-service

Case

- Is the medication currently infusing?
- Which specialty pharmacy do you use to fill the epoprostenol?
- When does the pump need to be refilled?

Pharmacist Role

- Medication Reconciliation
- Work with specialty pharmacy
  - Ensure medication is available
- Regulatory compliance (REMS)
- Medication Access

Pharmacist Role

- Patient assistance programs
  - Opsumit Voucher Program
  - 30-day free trial
  - Adcirca
    - $20 Co-pay Assistance Program
  - Letairis
    - The Letairis Education and Access Program (LEAP)
  - Tyvaso
    - Access Solutions and Support Team (ASSIST)

- Side Effect Management
  - Prostanoids are limited by patient reported adverse effects
  - Vasodilatory effects
    - Headaches
    - Flushing
    - Nasal congestion
    - Cool cloths
    - Lower room temperature
  - Diarrhea/N&V
    - Imodium/Lomotil
    - Antiemetics
  - Central Line infections
    - Use of appropriate antimicrobial agent
    - Prostanoids may be temporarily infused through a dedicated peripheral line
    - Trepotestin may be given subQ

References

- Rubin LJ. Diagnosis and management of pulmonary arterial hypertension: ACCP Evidence-Based Clinical Practice Guidelines. Introduction. Chest. 2004;126:7S-10S.