24th Annual
Advances in Heart Disease

Advances in
Pharmacotherapy of PAH

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Faculty Disclosure Statement

for Gabriel Gregoratos, MD

Nothing to disclose relevant to this presentation
‘Venice’ clinical classification of pulmonary hypertension (PH) – 2003

**Group 1**

PAH
- Idiopathic PAH (IPAH)
- Familial PAH
- Associated PAH (APAH):
  - Collagen vascular disease
  - Congenital systemic-to-pulmonary shunts
  - Portal hypertension
  - HIV infection
  - Drugs and toxins
  - Other
  - Associated with significant venous or capillary involvement
  - Persistent pulmonary hypertension of the newborn

2. PH associated with left heart disease

3. PH associated with respiratory disease
   - i.e., COPD, interstitial lung disease

4. PH due to chronic thrombotic and/or embolic disease
   - CTEPH

5. Miscellaneous
   - i.e., sarcoidosis

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1Simonneau et al. J Am Coll Cardiol 2004
As PAH Progresses Cardiac Output Declines

Time

Presymptomatic/Compensated
Symptomatic/Decompensating
Declining/Decompensated

CO=cardiac output, PAP=pulmonary arterial pressure, PVR=pulmonary vascular resistance, RAP=right atrial pressure.
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>Supplemental for hypoxia to maintain oxygen saturations at &gt;90%</td>
</tr>
<tr>
<td>Diuretics</td>
<td>For patients with evidence of right ventricular failure—peripheral edema and/or ascites—important to maintain near-normal intravascular volume</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>For in situ microscopic thrombosis and increased risk of pulmonary thromboembolism due to right ventricular failure and venous stasis</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Not extensively studied, but useful in patients refractory right ventricular failure and/or atrial dysrhythmias</td>
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</tbody>
</table>
Multi-hit Hypothesis for PAH

- Sheer Stress (e.g., congenital heart disease)
- Viruses (e.g., HIV)
- Drugs/toxins (e.g., fenfluramine)
- Inflammation
- Autoimmunity (MCTD)
- Genetic Mutations (e.g., BMPR-2, Kv Channels, PGIS deficiency)

Endothelial cell dysfunction → over- or under-expression of certain Vasoactive and Growth Factors; abnormal Receptor function, and overexpression of Serotonin transporter system

Adapted from Cool CD et al. Chest. 2005;128:565S-571S.
PAH: Rapid Progression and Poor Survival

PAH: Targeted Pharmacotherapy - 2007

• Vasodilators/antiproliferative drugs
  ♥ Calcium channel blockers (nonspecific vasodilators) in vasoreactive patients
  ♥ Prostacyclins (epoprostenol and analogs)
  ♥ Endothelin receptor antagonists (ERAs)
  ♥ Phosphodiesterase 5 (PDE 5) inhibitors
  ♥ Investigational agents
Calcium Channel Blockers and Vaso-Reactivity Testing in PAH

• Vasodilator testing helps determine which patients with PAH might benefit from oral calcium channel blocker treatment
  – Preferred agents for vasodilator testing are intravenous epoprostenol, inhaled NO, or IV adenosine
  – Fewer than 15% of tested patients are acute responders
  – Unstable patients or those with severe right heart failure should not be treated with CCBs or undergo vasodilator testing
• Positive acute vasodilator response which is defined as:
  – A fall of mPAP of $\geq 10$ mm Hg to $\leq 40$ mm Hg with increased or unchanged cardiac output
  – A fall in PVR?

Badesch DB et al. CHEST. 2004;126(suppl):35S-62S.
Calcium Channel Blockers in PAH

- Long term responders only 5-8% (1/2 of acute responders)
- Nifedipine, amlodipine and diltiazem are commonly used (high dose)
- CCBs with major negative inotropic activity (e.g. verapamil) are not recommended
- CCB should not be used in patients with severe right heart failure
Long-Term Response to CCBs in PAH

537 patient cohort

Sitbon et al. Circulation 2005; 111:3105
Prostacyclins (The Gold Standard ?)

- Intravenous: Epoprostenol (Flolan®)*, Trepostinyl (Remodulin®)*
- Subcutaneous: Trepostinyl*
- Inhaled: Iloprost (Ventavis®)* Trepostinyl+
- Oral: Beraprost**

* FDA approved  
+ Investigational/in development  
** Non-FDA approved
Epoprostenol (Flolan®) Indications

- Reduces dyspnea, improves exercise capacity, hemodynamics, WHO class and improves survival
- Original indication: Class III or IV in iPAH or PAH related to CTD
- Also effective in Eisenmenger’s syndrome, portopulmonary HTN, and PAH related to HIV infection (off-label use)
- Contraindicated in severe LV dysfunction
- Administered via continuous central venous infusion
- Very short ½ life
- Requires temperature control (cold pack)
- Still first choice in advanced class III or IV cases
Long-term PAH Survival with IV Epoprostenol

Figure 3. Three-year survival observed in the present study and predicted by the NIH equation using baseline hemodynamics. \( P<0.001 \) at 1, 2, and 3 years.
TREPROSTINIL (Remodulin®)
(analog of Epoprostenol)

- FDA approved for PAH (SC 2002, IV 2005, inhaled is investigational) for NYHA Class II-IV
- Improves exercise capacity
- Reduces symptoms associated with exercise
- Overall benefits similar to those of epoprostenol
- Has safety (longer half-life life) and convenience advantages (no mixing or cold packs, smaller pump) over IV epoprostenol
- No long-term survival data
- Dose (~100 ng/kg/min) is >2x that of epoprostenol
Inhaled Iloprost Rationale

- Provides activity directly to lung
- Minimizes systemic side effects
- Avoids indwelling catheter complications

![Diagram of lung structures]
Inhaled Iloprost: Pharmacokinetics

Half-life: 7 to 10 min
Absolute bioavailability (estimate): ~80%
ILOPROST (Ventavis ®)

- Stable analog of Prostacyclin
- Administered aerosolized by inhalation
- Dose: 2.5-5 mcg/inhalation
- Short half life, but duration of PA pressure reduction is 45-60 min after each inhalation
- May cause less V/Q mismatch than Flolan
- Frequency of administration: at least 6x/ day (up to 9x) for 10-15 min each
- Cost: $60-70,000/year
- No long-term survival data
AIR: Improvement in Clinical Response of 203 patients with NYHA Class III or IV PH

Composite response definition: no death or worsening, 6MWT 10% increase plus NYHA class improvement without death or clinical worsening
AIR: Hemodynamic Parameters*

†P<0.001 for the difference from baseline values

Change from baseline (%)

-30 -25 -20 -15 -10 -5 0 5 10 15 20

PVR CO mPAP

Ventavis® (iloprost) Placebo

†P<0.001 for the difference from baseline values
Endothelin Receptor Antagonists (ERAs)

- Oral (major advantage)
  -- Non selective (block $\text{ET}_A$ and $\text{ET}_B$)
    - Bosentan (Tracleer®) – approved 2001
  -- Selective (block $\text{ET}_A$)
    - Sitaxsentan  – Still Investigational
    - Ambrisentan (Letairis®)  – approved June 2007

Issue of selective vs non selective ERAs is still debated
Bosentan (Tracleer®)

- FDA-approved for the treatment of PAH in class III or IV patients
  —Improves exercise capacity
  —Decreases the rate of clinical worsening
- 62.5 mg bid for first 4 weeks
- Up-titration to a maintenance dose of 125 mg bid if liver function OK
- Contraindicated with glyburide, cyclosporine
- Costs ~ $36,000 annually
Predicted Survival and Observed Survival After Bosentan Treatment

85% and 70% were on bosentan monotherapy at 12 and 24 mos, respectively

Event rate/year (exponential): 5.5%

McLaughlin VV et al. Eur Respir J. 2005;25:244-249.
Monitoring of Bosentan Therapy

- LFTs initially and monthly; stop if >5X ULN
- Liver toxicity reversible with cessation
- Watch for leg edema, nasal congestion
- Hemoglobin initially, 1 and 3 months
- May interfere with hormonal birth control (BCP); barrier methods advisable
- High potential for birth defects: pregnancy class X
- Response takes up to 2 or 3 months
- Should be used with caution in class IV patients and not without RH catheterization to document presence and level of PAH
BREATHE-5: Bosentan in Patients With Eisenmenger Syndrome (off label use)

Tracleer significantly increased exercise capacity

- Mean change from baseline:
  - 6MWD: -10 to +43 meters
  - PVRI: +155 dyn·sec/cm² to -317 dyn·sec/cm²

Tracleer significantly reduced pulmonary vascular resistance index

Baseline values:
- 6MWD: Placebo 366.4 ± 67.6, Tracleer 331.9 ± 82.8
- PVRI: Placebo 2670 ± 1203.3, Tracleer 3425.1 ± 1410.5

Treatment effect:
- 6MWD: p = 0.008
- PVRI: p = 0.04

Background therapies: oral vasodilators, cardiac glycosides.

BENEFiT Study

• Randomized trial – 157 patients

• OBJECTIVE: To demonstrate the efficacy of bosentan in patients with inoperable CTEPH or persistent/recurrent PH post pulmonary endarterectomy

• To evaluate the safety and tolerability of bosentan in this patient population

Bosentan in CTEPH
Summary of BENEFiT Results (off label)

• Clinically relevant improvement in cardiac hemodynamics:
  – PVR decreased ($p < 0.0001$)
  – Cardiac index increased
  – NT-pro-BNP decreased
• Improvement in Borg dyspnea index
• No effect on exercise capacity ($p = ns$)
• Positive trends on other endpoints:
  – Fewer bosentan-treated patients worsened WHO functional class
  – Time to clinical worsening trends in favor of bosentan
• Safety and tolerability:
  – Consistent with previous controlled trials with bosentan in PAH
Ambrisentan ARIES-1 Primary Endpoint: Change in 6MWD at Week 12

N=202.
Placebo-adjusted changes: 10 mg = +51.4 m (P=0.0001)
5 mg = +30.6 m (P=0.0084)

Oudiz RJ. et al. Chest. 2006;130: Abstract 121S.
ARIIES-2: Time to Clinical Worsening With Ambrisentan

Time to clinical worsening = Combined endpoint of death, lung transplantation, atrial septostomy, hospitalization for PAH, addition of other drugs for PAH, or early escape from clinical trial.

### Elevations in LFTs >3x ULN with ERAs

<table>
<thead>
<tr>
<th></th>
<th>Serum aminotransferases concentrations</th>
<th>Placebo 12-week (%)</th>
<th>Active Agent 12-weeks (%)</th>
<th>Active Agent 1-year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ambrisentan (All Doses)</strong> (N=483)</td>
<td>&gt;3 x ULN</td>
<td>2.3%</td>
<td>0.8%</td>
<td>2.8%</td>
</tr>
<tr>
<td><strong>Bosentan 125 mg bid</strong> (n=165) PAH patients only</td>
<td></td>
<td>3%</td>
<td>13%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Tracleer Package Insert. 2007.
Letaris Package Insert. 2007.
PDE-5 Inhibitors

• Oral
  -- Sildenafil *
  -- Tadalafil ** (longer acting)

* FDA approved
** Investigational/in development
Sildenafil (Revatio ®)

- FDA approved in June 2005 for PAH “to improve exercise capacity”
- Dose: Start with 20 mg tid
- Must not be used with nitrates, but compatible with most other drugs
- Metabolized by the liver (CYP3A4 isoenzyme)
- Metabolism slowed in cirrhotics; not affected by renal failure
- May potentiate Warfarin effect
- Oral; relatively inexpensive (∼ $ 12,000/year)
SUPER-1 Study: Improvement in 6-Minute Walk Distance As Early as Week 4

- Placebo (n=66)
- Sildenafil 20 mg tid (n=67)
- Sildenafil 40 mg tid (n=64)
- Sildenafil 80 mg tid (n=69)

*P<.0001 vs placebo.

Change From Baseline (m²)

Week 4
- Placebo: 2
- Sildenafil 20 mg tid: 28
- Sildenafil 40 mg tid: 28
- Sildenafil 80 mg tid: 32

Week 12
- Placebo: -4
- Sildenafil 20 mg tid: 41
- Sildenafil 40 mg tid: 44
- Sildenafil 80 mg tid: 47
PAH: Sildenafil Therapy (SUPER-1)

Observed and Predicted Survival (n=141)

OBSERVED: sildenafil treated

Predicted: NIH

99%  96%  95%

78%  71%  65%

Kaplan-Meier Probability of Event

Number of Days Since Start of Sildenafil Treatment

Rationale for Combination Therapy in PAH

• Simultaneous targeting of multiple pathways
• Synergistic effects between different agents
• Overcomes treatment-limiting toxicity by using lower doses than in monotherapy
• Potential cost advantage of lower doses
• Delay worsening symptoms
• Prevent PAH progression (?)
• Combination therapies are standard of care in other diseases

• **Potential Risks:** Drug-drug interactions due to CYP-450 metabolism
Combination Therapy Regimens in PAH

*Endothelin antagonists and prostanoids*
- Bosentan + epoprostenol [49]
- Bosentan + iloprost [50–52]
- Bosentan + beraprost [51,52]

*Endothelin antagonists and PDE5 inhibitors*
- Bosentan + sildenafil [7,53]

*PDE5 inhibitors and prostanoids*
- Sildenafil + epoprostenol [6,55]
- Sildenafil + iloprost [57–59]
- Sildenafil + beraprost [61]
- Sildenafil + treprostinil [60]
### STEP Study RESULTS:
**Post-inhalation change in 6-MWD (Week 12)**

<table>
<thead>
<tr>
<th></th>
<th>Iloprost + bosentan</th>
<th>Placebo + bosentan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Meters Walked</td>
<td>Change from Baseline</td>
</tr>
<tr>
<td><strong>Baseline (m)</strong></td>
<td>Mean 336 ± 61</td>
<td>Mean 340 ± 73</td>
</tr>
<tr>
<td><strong>Week 12 (m)</strong></td>
<td>Mean 367 ± 84</td>
<td>Mean 343 ± 99</td>
</tr>
<tr>
<td></td>
<td><strong>p-value (vs. baseline)</strong> 0.001</td>
<td><strong>p-value</strong> 0.69</td>
</tr>
<tr>
<td><strong>Placebo-adjusted Difference:</strong></td>
<td>+26 m</td>
<td>p = 0.051</td>
</tr>
</tbody>
</table>

V. McLaughlin et al, AJRCCM December 2006
STEP: Time to Clinical Worsening at 12 Weeks
Iloprost + bosentan: 0 (0%) vs. Placebo + bosentan: 5 (15%)
$p = 0.02$ (Log-rank test)
Sildenafil added to Inhaled Iloprost

Wilkens et al. Circulation 2001
Symptomatic Pulmonary Arterial Hypertension

General treatment measures: oral anticoagulants, diuretics, digitalis, oxygen, {E/A}

Acute vasoreactivity testing {A for IPAH, E/C for other PAH}

Oral CCB {B for IPAH, E/B for other PAH}

Sustained Response?

Continue CCB

Yes < 15%

FC II

• Treprostinil SC {C}
• Sildenafil {A}
• Prostanoid

FC III

• Bosentan* {A}
• Sildenafil* {A}
• Prostanoid

FC IV

• Epoprostenol IV {A}
• Bosentan {B}
• Prostanoid

No ~ 90%

~6-8%

Combination Therapy?

Bosentan ↔ Sildenafil

No improvement or deterioration

Atrial septostomy and/or lung transplantation

Chest 2007; 131:1917
Future Directions

• Combination Therapy (e.g. COMPASS-2 trial)
• Early Therapy (WHO Class I and II)
• Novel agents that target the inflammatory and proliferative processes underlying PAH
  ♥ Statins
  ♥ Rho-kinase inhibitors (Fasudil)
  ♥ PDGF receptor antagonists - Imatinib mesylate (Gleevec)
  ♥ Ghrellin
  ♥ Peroxisome Proliferator-Activated Receptors agonists
  ♥ Vasoactive Intestinal Peptide
  ♥ Serotonin (5-HT) transport antagonists
  ♥ Immunosuppressive agents (Rapamycin)
Inhaled Vasoactive Intestinal Peptide

Petkov et al. JCI 2003;111:1339
Case Report: Imatinib (Gleevec) effect on exercise capacity and hemodynamics in PAH
Thank you!