Inhaled Therapy in Pediatric Pulmonary Hypertension

Dunbar Ivy, MD

Outline

- Rationale of Inhaled therapy
- Adult / Pediatric iloprost trials
- Adult / Pediatric treprostiniil trials
- Adult ambulatory iNO trial

Disclosures

- The University of Colorado receives fees for Dr Ivy to be a consultant for Actelion, Gilead, Lilly, Pfizer, and United Therapeutics

Inhaled Prostacyclin: Rationale

- Provide prostacyclin directly to lung
- Vasodilate ventilated pulmonary regions
- Minimize systemic side effects
- Avoid catheter complications

Max and Rossaint: EJP 1999
PAH Treatment


Iloprost Inhalation System

• Technology
  – Breath-actuated
  – Patient specific adaptation
  – Consistent and accurate dosing
  – Micro-aerosol for deep pulmonary delivery
  – Treatments 7-9 X / Day


Aerosolized Iloprost Randomized Study

AIR: Study Design

Objective
Randomized, double-blind, placebo-controlled study (37 European centers in 11 countries) to assess efficacy of iloprost

Duration
12 weeks iloprost vs placebo

Patients
203 patients with NYHA Class III or IV
• IPAH (50%)
• Associated with connective tissue disease (17%)
• Anorexigen use (4.5%)
• Chronic thromboembolic PH (28%)

AIR: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 102)</th>
<th>Iloprost (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA FC (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>58%</td>
<td>59%</td>
</tr>
<tr>
<td>IV</td>
<td>42%</td>
<td>41%</td>
</tr>
<tr>
<td>6 MWD (m)</td>
<td>315</td>
<td>332</td>
</tr>
<tr>
<td>mPAP (mm Hg)</td>
<td>53.8</td>
<td>52.8</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>3.8</td>
<td>3.8</td>
</tr>
<tr>
<td>PVR (dyn sec·cm⁻⁵)</td>
<td>1041</td>
<td>1029</td>
</tr>
<tr>
<td>HR (BPM)</td>
<td>81.8</td>
<td>83.9</td>
</tr>
</tbody>
</table>


AIR Study: Primary Endpoint

**Clinical Improvement Endpoint**

- ≥10% Increase in 6 Minute Walk Distance
- Improvement in NYHA Functional Class (≥ 1 Class)
- No Clinical Deterioration or Death

AIR: Patient Improvement

Approximately 5:1 Improvement vs. Placebo (Composite Endpoint)

<table>
<thead>
<tr>
<th></th>
<th>Iloprost (n=68)</th>
<th>Placebo (n=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent responders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No death or deterioration</td>
<td>96</td>
<td>87</td>
</tr>
<tr>
<td>6MWD ≥10% increase 30 min after inhalation</td>
<td>43</td>
<td>26</td>
</tr>
<tr>
<td>NYHA Class improvement</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>Composite clinical endpoint</td>
<td>19</td>
<td>4</td>
</tr>
</tbody>
</table>

p = 0.0033


AIR: Improvement in 6MWD 30 Minutes Post Inhalation

- Ventavis® (n=64)
  - + 31 m
  - P < 0.01
- Placebo (n=65)
  - - 9 m
  - P < 0.01

Randomized Study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension.

**McLaughlin et al. Am J Respir Crit Care Med. 2006;174:1257-1263.**

**STEP: Study Design**

**Objective**
- Primary: Evaluate safety of adding iloprost to an endothelin receptor antagonist (ERA)
- Secondary: Efficacy endpoints (Clinical worsening, Functional class, Hemodynamics, 6MWT)

**Duration**
- Iloprost or placebo added for 12 weeks to stable monotherapy with an ERA

**Patients**
- 67 patients with PAH
  - 55% iPAH; 45% associated PAH
  - 94% NYHA class III

**STEP: Study Design**

Prospective, randomized, double-blind, placebo-controlled, parallel-group

- ERA 125mg BID
- Iloprost 2.5 mcg
- Iloprost 5mcg (n=34)
- Placebo
- Placebo (n=33)

- At least 16 weeks
- 1 Dose 12 weeks
- Baseline randomization 3 months

**STEP: Primary Endpoint (Safety)**

- Patients treated an ERA tolerated the addition of inhaled iloprost
  - Up to 5 mcg 6 to 9 times per day during waking hours

- Dosing
  - Mean daily inhaled dose was 27 mcg
  - Mean number of inhalations per day was 5.6

- Safety trends were consistent with those observed in the larger AIR trial

**McLaughlin VV et al. Am J Respir Crit Care Med. 2006;174:1257-1263.**
STEP: Summary

- Randomized, double-blind, placebo controlled trial in PAH evaluating add-on therapy with an ERA
- Safe in Combination
  - Safety trends were consistent with those observed in the larger AIR trial
  - Compliance: 93.8% vs. 93.9% (Iloprost vs. placebo) were compliant with study drug
  - No patient discontinued or reduced the dose of ERA during the study


Effects of Inhaled Iloprost in Children with Pulmonary Arterial Hypertension

Ivy DD, Doran AK, Smith KJ, Mallory GB, Beghetti M, Barst RJ, Brady D, Law Y, Parker D, and Abman SH

Pediatric Iloprost: Study Population

Patients on iloprost n=22

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPAH</td>
<td>11 (50%)</td>
</tr>
<tr>
<td>FPAH</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>PAH-CHD</td>
<td>10 (45%)</td>
</tr>
<tr>
<td>Repaired (9)</td>
<td></td>
</tr>
<tr>
<td>Unrepaired (2)</td>
<td></td>
</tr>
<tr>
<td>Residual defect (0)</td>
<td></td>
</tr>
</tbody>
</table>

Ivy et al. JACC 2008;51:161-169

Iloprost: WHO Functional Class

N = 20/22  Improved 7 / Worsened 3

Ivy et al. JACC 2008;51:161-169
Acute Iloprost: FEF 25-75

5 of 14 showed a decrease in the FEF 25-75 of more than 15% (range 17-53%)

Mean Δ: -10% 

Standard error of the mean: 3.6% 

P-value: 0.038 (2-tailed paired t-test)

Patient Status at Data Cut-off Subgroups

- Continued Iloprost: 14/22 (64%) 
  8/9 IV prostanoid transition
- Reasons for Discontinuation: 8/22 (36%) 
  Reactive Airways (2) 
  IV prostanoid for deterioration (4) 
  Death (2)

20mcg/mL Iloprost

<table>
<thead>
<tr>
<th></th>
<th>10 mcg/mL (0.5 mL chamber)</th>
<th>20 mcg/mL (0.25 mL chamber)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of solution emitted</td>
<td>0.46 mL</td>
<td>0.25 mL</td>
</tr>
<tr>
<td>Dose emitted</td>
<td>4.54 mcg</td>
<td>4.97 mcg</td>
</tr>
<tr>
<td>Fine particle fraction (% &lt; 4.7 µm)</td>
<td>95.4%</td>
<td>90.1%</td>
</tr>
<tr>
<td>Simulated dose delivery time</td>
<td>10 min</td>
<td>3.8 min</td>
</tr>
</tbody>
</table>

*Validation data based on particle sizing into an Andersen Cascade Impactor with a manually generated 28.3 L/min 15-second inhalation cycle breathing pattern (data on file, Actelion Pharmaceuticals)

Treprostinil Inhalation System

- 4 Treatments per day 
- 6 mcg / breath 
- 3-9 breaths per treatment 
- Equivalent to less than 15 ng/kg/min IV treprostinil
TRIUMPH-1

TReprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension


Objectives

- **Primary**
  - Determine effect of inhaled treprostinil on exercise capacity (6MWD) in patients with PAH currently treated with oral monotherapy

- **Secondary**
  - Time to clinical worsening
  - Change in
    - Borg dyspnea score @ wk 12
    - NYHA functional class @ wk 12
    - Trough 6MWD @ wk 12
    - Peak 6MWD @ wk 12
    - Opt/SILWHF (questionnaire) @ wk 12
    - PAH signs and symptoms at week 12
  - Safety and tolerability of inhaled treprostinil

- **Ancillary**
  - NT pro-BNP levels

Study Design

- Randomized (1:1), placebo-controlled, multicenter, multinational, phase 3 trial
- Inhaled treprostinil or placebo QID for 12 weeks
  - Therapy initiated at 18 µg (3 breaths) QID
  - Dose escalation permitted up to a maximum of 54 µg (9 breaths) QID
  - Administered via OptiNeb™ ultrasonic nebulizer

Key Inclusion Criteria

- Aged 18 to 75 years
- Diagnosis of idiopathic; familial; or CVD-, HIV-, or anorexigen-associated PAH
- Receiving stable dose of bosentan 125 mg b.i.d. or any dose of sildenafil for ≥3 months
- 6MWD of 200 to 450 m
- Stable NYHA functional class III or IV
- Resting mean PAP ≥25 mmHg, PCWP ≤15 mmHg, and PVR >3 mmHg/L/min

b.i.d., twice daily; CVD, collagen vascular disease; HIV, human immunodeficiency virus; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.

Sildenafil doses ranged from 20-80 mg/d.

### Maximum Inhaled Treprostinil Dose

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Inhaled treprostinil</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum dose achieved, mean ± SD, µg</td>
<td>50 ± 10</td>
<td>52 ± 7</td>
</tr>
<tr>
<td>Time to maximal dose, mean ± SD, d</td>
<td>23 ± 18</td>
<td>22 ± 17</td>
</tr>
</tbody>
</table>


### Median Improvement From Baseline in Peak 6MWD

![Graph showing median improvement from baseline in peak 6MWD](image)


### Median Change From Baseline in NT Pro-BNP Levels

![Graph showing median change from baseline in NT Pro-BNP levels](image)

Median baseline value (pg/mL): Placebo (n=87): 690, Inhaled treprostinil (n=86): 602


### Inhaled Treprostinil in Pediatrics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Initiation (n = 29)</th>
<th>6 Months (n = 23)</th>
<th>12 Months (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose in breaths per treatment (1 breath = 6 µg)</td>
<td>1–3</td>
<td>8 ± 1.73</td>
<td>7.8 ± 1.9</td>
</tr>
<tr>
<td>Time to maximum dose (weeks)</td>
<td>5.7 ± 4.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breaths, median (range)</td>
<td>8 (3–9)</td>
<td>9 (3–9)</td>
<td>9 (3–9)</td>
</tr>
<tr>
<td>Frequency (treatments/day)</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total daily dose (µg), mean ± SD</td>
<td>24–72</td>
<td>192 ± 41.6</td>
<td>187.2 ± 45.6</td>
</tr>
</tbody>
</table>

The American Journal of Cardiology Volume 110, Issue 11 2012, 1704 - 1709
### Inhaled Treprostinil in Pediatrics

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Baseline</th>
<th>Follow up on iTre</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWD (meters)</td>
<td>13</td>
<td>456±72</td>
<td>498±70</td>
<td>0.017</td>
</tr>
<tr>
<td>Workload (Watts)</td>
<td>9</td>
<td>54±29</td>
<td>67.7±29.1</td>
<td>0.0002</td>
</tr>
<tr>
<td>Peak VO2</td>
<td>11</td>
<td>25.5±10.0</td>
<td>27.4±10.2</td>
<td>0.04</td>
</tr>
<tr>
<td>BNP</td>
<td>13</td>
<td>93±77</td>
<td>58±62</td>
<td>0.003</td>
</tr>
</tbody>
</table>

- **Discontinued in 4 patients**
  - Cough and bronchospasm (n=3)
  - Clinical deterioration (n=1)

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**Figures**

- **Figure 1**: Graph showing improvements in 6-minute walking distance (6MWD) and workload from baseline to follow-up.
- **Figure 2**: Bar chart illustrating improvements in clinical parameters.

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**References**

- The American Journal of Cardiology Volume 110, Issue 11 2012 1704 - 1709
Inhaled Treprostinil: Acute Dosing

- 13 children with known and treated PAH underwent cardiac catheterization as part of routine follow-up.
- Hemodynamics were obtained at baseline and with inhaled nitric oxide [40 ppm] plus oxygen.
- Following return of hemodynamics to baseline, iTRE was administered and hemodynamics repeated.
- iTRE was administered using the OPTINEB® ultrasonic nebulizer.
- Total dose of iTRE delivered was based upon patient size and tolerability.
  - 3-6 breaths [18-36 mcg] administered initially, followed by 3-6 breaths [18-36 mcg] for a maximum of 9 breaths [54 mcg]

Refined Inline Placement

Hemodynamic change with inhaled nitric oxide and inhaled treprostinil

- A Phase 2, Placebo Controlled, Double-Blind, Randomized, Clinical Study to Determine Safety, Tolerability and Efficacy of Pulsed, Inhaled Nitric Oxide (INO) Versus Placebo as Add-On Therapy in Symptomatic Subjects With Pulmonary Arterial Hypertension (PAH)
  - Primary endpoint
    - Change in PVR from baseline to Week 16
  - Secondary Endpoints
    - Change in 6MW
    - TTCW
    - Change in WHO FC
    - Change Borg Dyspnea Score
    - Change in PRO – Camphor

Inhaled Nitric Oxide