Intravenous / Subcutaneous Prostacyclin
International PH Conference
San Francisco, CA
Dunbar Ivy, MD

Disclosures
- Steering Committee: Gilead/GSK, Actelion
- Consultant: Actelion, Gilead, Pfizer, United Therapeutics
- Investigator Initiated Grants: Actelion, Gilead

Outline
- Intravenous Epoprostenol
- Treprostinil Subcutaneous / Intravenous
- Combination Therapy

Pulmonary Arterial Hypertension: Goals of Therapy
- Improve hemodynamics
- Improve exercise capacity
- Improve functional class
- Prevent clinical worsening
- Improve survival
- Ultimately improve quality of life

PAH Treatments

Sir John R Vane 1927-2004

Prostacyclin:
- Natively occurring prostaglandin metabolite of arachidonic acid
- Promotes vasodilation
- Prevents and reverses platelet aggregation
- Antiproliferative
- Inhibits vascular cell migration
- Improves endothelial dysfunction
- Improves ET-1 clearance
- Cardiac instability
Prostacyclin stimulation of cyclic AMP in platelets

Prostacyclin inhibits formation of platelet thrombus on blood vessel wall

Ratio
Thromboxane:Prostacyclin

PAH: Prostacyclin Synthase Expression is Decreased in in the Lung

First Human Use of Prostacyclin: Persistent Fetal Circulation
- 3.77 kg term infant with hypoxemia
- In cath lab, boluses of PGI2 resulted in reversal of shunt
- Continuous infusion for 2 days at low dose (0.066 mcg/kg/min)
- Discontinuation after 2 days

Continuous IV Prostacylin (n=3; 24-48 hrs) Causes Sustained decrease in pulmonary resistance

Whittle, Moncada, Vane, 2011


Am J Respir Crit Care Med 1999;159:1925-1932

Lock JE, Olley PM, Cossart F, Sayer PR, Rowe RD. Lancet 313:1943, 1979

Long-Term Treatment of PAH with Continuous IV Epoprostenol: Maintenance Effect? Palliative Bridge to Transplantation

Epoprostenol in Heart Failure: FIRST

Flolan™ (epoprostenol sodium) Therapy for PAH

IV Epoprostenol in IPAH: Change in 6MWD at 8 and 12 Weeks

Survival Among Patients With PPH Epoprostenol vs Placebo

IV Epoprostenol Approved 1995

- PPH and PAH associated with Scleroderma - NYHA Class III/IV with inadequate response to conventional therapy
- pH 10.2 - 10.8; increasingly unstable at lower pH
- Unstable at RT; requires cold packs
- Rapidly hydrolyzed at neutral pH in blood
- Serum half-life of 6 minutes or less
- Continuous IV infusion via CVL and battery-operated pump
Epoprostenol
Functional improvement

Total: 39 children (25 IPAH, 14 APAH)

Improved 6-MWD

Follow-up Improved WHO functional class

p<0.003

Baseline Follow-up 11.4 ± 7.1 months

Distance

n=28

600

500

400

300

200

100

0

Baseline Follow-up

WHO IV WHO III WHO II WHO I

<1 year 1-2 yrs 2-3 yrs m15

Percentage

0

20

40

60

80

100

-60

-40

-20

0

20

40

60

80

100

Distance (m)

Follow-up Improved WHO functional class

n=39

Improved 6-MWD

n=28

p<0.003

Prostacyclin for Congenital Heart Disease


Prostanoids

Generic Name

Epoprostenol

Treprostinil

Iloprost

EPO For Injection

Manufacturer

GlaxoSmithKline

United Therapeutics

Actelion

Ciba/Therex

Approval

Jan 1995

May 2002

May 2004 (IV)

July 2009 (inh)

Dec 2004

April 2010

Class

III, IV

III, IV

III, IV

Indications

PPH, PH due to scleroderma

PAH WHO Group 1

PAH WHO Group 1

Route

Continuous IV

Cont. SQ or IV

Inhaled

Continuous IV


Transition off IV Epoprostenol

N=14/104

mPAP<35 / Nl CI / FC I/II


Transition off IV Epoprostenol

P<0.003 for OFF EPO vs. Peak EPO

N=14/104

mPAP<35 / NI CI / FC III


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Prostanoid Side Effects

- Flushing
- Headache
- Diarrhea
- Nausea/emesis
- Jaw pain
- Leg pain
- Hypotension
- Dizziness
- Syncope
- Cough (inhaled)
- Delivery complications (IV/SQ)

Vary according to drug and route of delivery

Treprostinil (treprostinil sodium) Injection

- Prostacyclin analogue
- Stable at room temperature
- Longer half-life: 4.5 hours
- Administered subcutaneous or intravenous

Treprostinil Subcutaneous Delivery

- Advantages
  - No central line
  - Smaller infusion pump
  - Longer half life
- Disadvantages
  - Significant site pain ??

Over 750 prostacyclins synthesized

Chemically stable prostacyclin analogue BW 15-AU (5-15, treprostinil)


Subcutaneous Treprostinil: Change From Baseline in 6MWD by Dose Quartile

- Mean change from baseline (m)
- 1st Quartile 3.3±1.0 (n=45)
- 2nd Quartile 1.4±0.9 (n=50)
- 3rd Quartile 20±8 (n=49)
- 4th Quartile 36±10 (n=53)

Long-term Survival Study Results

Overall Survival Rates:
- 6-Year Kaplan-Meier Survival Analysis

Monotherapy Survival Rates:
- 6-Year Kaplan-Meier Survival Analysis

Survival was not significantly different compared with the entire cohort.


IV/SC Bioequivalence Study

Levy M, Celermajer DS, Bourges-Petit E, del Cerro MJ, Bajolle F, Bonnet D, Necker-M3C, Université Paris-Descartes, Paris, France

Subcutaneous Treprostinil in Pediatric Pulmonary Hypertension


SC Treprostinil in Children: Population (n=8)
- 2 idiopathic & 1 heritable PAH
- 5 PAH associated with a congenital heart defect
  - 3 after correction of a cardiac defect:
    - 1 TGA
    - 1 tetralogy of Fallot (portal hypertension)
  - 1 ducus arterious closed at 6 months of age
- 2 PAH associated with small defects.
  - 1 small VSD with PAH from birth
  - 1 small ASD with PAH diagnosed at 6 years of age
- Median age 5 y (1.7 -17 y)


SC Treprostinil in Children
- Clinical deterioration in 7 children
  - Worse 6MWT, aggravation of PAH on echo, increase in RV diastolic pressure, ...
  - 5 in FC III, 2 in FC IV
- Switch from IV epoprostenol in 1 child


SC Treprostinil in Children: Right Heart catheterization

**RHC control (n=5)**

- Effect of treprostinil on CO
  - Before: 3.2 L/min
  - After: 3.6 L/min

- Effect of treprostinil on PVR
  - Before: 21 Woods units
  - After: 17 Woods units


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**IV Treprostinil Administration**

- Requires higher dose (up to 2.5 times) as compared to Flolan
- Longer half life: 3-4 hours
- Stable at room temp for 48 hrs for IV and 72 hrs for SQ
- No Ice Packs
- Every other day mixing
- Antiplatelet effects and drug stability allow for slow infusions with smaller pumps

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**IV Epoprostenol to IV Treprostinil transition**

- Transition of 13 pediatric PAH pts from IV epro to IV treprostinil
  - 2 deaths, 2 transitions to other therapies
  - Transitioned in hospital over 24 hours (rapid or slow)
  - Patients maintained their exercise capacity
  - Higher dose, fewer side effects
  - Several central line infections however, reported before current recommendations for treprostinil line care were implemented


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**Fewer Side Effects Following Transition from IV Epoprostenol to IV Treprostinil**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>6 mo</th>
<th>12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Rash</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.5</td>
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<tr>
<td>Jaw Pain</td>
<td>0.0</td>
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</tr>
<tr>
<td>Leg Pain</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>GI</td>
<td>0.0</td>
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**Miniaturization with Treprostinil**

- CRONO Five
- CADD MS-3
A higher incidence of gram negative BSI with IV Treprostinil

<table>
<thead>
<tr>
<th>Drug</th>
<th>Overall BSI Range (per 1000 medicine days)</th>
<th>Overall gram negative BSI Range (per 1000 medicine days)</th>
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<tbody>
<tr>
<td>Remodulin</td>
<td>2.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Flolan</td>
<td>1.10</td>
<td>0.25</td>
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IV Prostanoids: Minimizing risk for Catheter Related- Blood Stream Infections (CR-BSI)

- Single center experience using closed-hub system and waterproofing precautions during showering with IV prostanoids in children to minimize CR-BSI
- 50 patients receiving prostanoids
- Closed-hub system and maintenance of dry catheter hub connections significantly reduced the incidence of CR-BSI (particularly infections caused by gram-negative pathogens) in patients receiving intravenous treprostinil.


CVC Hub Contamination Following Disconnection with Wet Threads

Connection Cover with Glad Press and Seal®

Closed-Hub System for Reducing Risk of BSI1,2

- Decreased exposure of CVC hub; changed weekly
- Split-septum devices: Q-Syte™, Interlink®

1 Akagi et al. Circ J. 2007 Jul;71:920-926
2 Do et al. J Infect Dis. 1999;179:442-448
RW1

Will require comment on pooled mean and significance or lack of.. in numbers

Ron Walls, 10/8/2008
Effect of Increasing Treprostinil Diluent pH on BSI


Combination Therapy with Prostacyclin

BREATHE-2: Effect of Bosentan and Epoprostenol on Hemodynamics at Week 16

Parameter

<table>
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<tr>
<th>Parameter</th>
<th>Pbo/Epo (n=11)</th>
<th>Bos/Epo (n=22)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPR (% change)</td>
<td>-23 ± 6</td>
<td>-36 ± 4</td>
<td>0.08</td>
</tr>
<tr>
<td>CI (% change)</td>
<td>38 ± 13</td>
<td>49 ± 11</td>
<td>0.6</td>
</tr>
<tr>
<td>PVR (% change)</td>
<td>-26 ± 7</td>
<td>-35 ± 5</td>
<td>0.3</td>
</tr>
<tr>
<td>mPAP (% change)</td>
<td>-2 ± 4</td>
<td>-9 ± 6</td>
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<td>mRAP (% change)</td>
<td>0 ± 1</td>
<td>-2 ± 1</td>
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Bos, bosentan; CI, cardiac index; Epo, epoprostenol; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; Pbo, placebo; PVR, pulmonary vascular resistance; TPR, total pulmonary resistance.

All data are presented as mean % change from baseline ± standard error of the mean.


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6MWD: Change From Baseline to Week 16 (PACES)


Change in 6MWD from baseline (m)

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<tr>
<td>6MWD</td>
<td>-20-020-40-60-80-100</td>
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<td>&lt;0.001</td>
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6MWD, 6-minute walk distance.

Addition of Sildenafil Delayed Clinical Worsening and Reduced Deaths (PACES)


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6MWD, 6-minute walk distance.

Summary

- IV epoprostenol still remains the “gold standard” for the treatment of advanced pediatric PAH
- Does the delay in aggressive PH therapy worsen long term outcome in children?
- Combination therapy is appealing
THANKS

- Robyn Barst
- Damien Bonnet
- Erika Rosenzweig
- Ian Adatia
- Maria Jesus del Cerro

- Steve Abman
- John Kinsella