Prostanoids in Pediatric Pulmonary Arterial Hypertension

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Prostacyclin in PAH:
Discovery by Sir John Vane (1976)
Prostacyclin (PGI2)

- Naturally occurring prostaglandin metabolite of arachidonic acid (PGI2)
- Continuously produced by the vascular endothelium by prostacyclin synthase
- A relative deficiency of prostacyclin may contribute to the pathogenesis of PAH

Mechanisms of Action of Therapies for PH

Endothelin Pathway
- Endothelin-1
- Endothelin receptor A
- Endothelin receptor B
- Endothelial cells
- Arachidonic acid
- Prostaglandin I2
- L-arginine
- L-citrulline

Nitric Oxide Pathway
- Nitric oxide
- Endothelial cells
- L-arginine
- L-citrulline
- Phosphodiesterase type 5 inhibitor
- Endothelial cells
- Prostacyclin (prostaglandin I2)

Prostacyclin Pathway
- Prostacyclin (PGI2)
- Endothelial cells
- Arachidonic acid
- Prostaglandin I2
- Nitric oxide
- Endothelial cells
- L-arginine
- L-citrulline

Exogenous nitric oxide
- Vasoconstriction and antiproliferation
- Phosphodiesterase type 5 inhibitor
- Vasodilation and antiproliferation

PGI2: Mechanism of Action

Prostacyclin (PGI2) has potent vasodilatory, antiproliferative, and antithrombotic effects on vascular smooth muscle cells.

- **Potent properties**
  - Stimulates vascular smooth muscle cell relaxation/vasodilation
  - Inhibits vascular smooth muscle cell proliferation and migration
  - Inhibitor of platelet aggregation
  - Mediator of acute inflammation

- PGI2 was first used as an acute vasodilator in 1980 in a child with IPAH
“Prostanoids”

• Developed to mimic the favorable characteristics of prostacyclin (PGI2) as well as offer alternate modes of delivery, longer half-life or other features to improve risk-benefit ratio and/or quality of life issues associated with epoprostenol delivery.

Prostanoid: Classification

• Parenteral
  – Intravenous (epoprostenol, treprostinil, iloprost)
  – Subcutaneous (treprostinil)
  – Inhaled (iloprost, treprostinil)

• Oral
  – Beraprost
  – Treprostinil (investigational only)
Intravenous Epoprostenol (PGI2)

- Rapidly hydrolyzed in circulation to 6-keto-PGF$_{1\alpha}$ ($t^{1/2} = 3$ min)
- Unstable at room temperature – requires ice packs (thermo-stable formulation recently FDA approved; not yet tested in children)
- Many potential side effects
- Requires continuous intravenous infusion for sustained effect

FDA approved 1995; FC III/IV PAH

Epoprostenol vs. Conventional Therapy
Change from Baseline in 6-Minute Walk Test

Survival Among Patients With IPAH: Epoprostenol vs Conventional Therapy

*Two-sided, by log-rank test.

Long-term Outcome in IPAH With Epoprostenol

**Epoprostenol and Survival in Children**

K-M survival curves comparing survival of nonresponders (n=24) treated with long-term PGI2 with survival of nonresponders (n=22) for whom PGI2 was indicated but unavailable.

*Circulation* 1999

**Pediatric PAH Survival and Treatment success in “Epo Era”**

Kaplan-Meier curves for survival and treatment success in patients in more recent medical era (n=44).

*Circulation* 2004;110:660-665
Epoprostenol delivery system (CADD pump)

Epoprostenol (Flolan®)

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
Epoprostenol Delivery System
Complications

• Localized site infection
• Catheter related bloodstream infections
• CADD pump malfunction
  – bolus effect
  – cessation phenomenon – due to short half life of epoprostenol

Epoprostenol

• Prostacyclin is effective in treating PAH
  – improve pulmonary hemodynamics
  – prolong survival
  – improve symptoms
  – extend exercise tolerance
• Caution
  – numerous side effects
  – inconvenience and risks with continuous infusion
ACC/AHA Consensus PAH Treatment Algorithm


What Is the Optimal Treatment Strategy?

Pediatric PAH Indications for IV epoprostenol: general guidelines

- WHO FC III or IV patient (presence of right heart failure)
- Non-responsive to AVT
- Very young patients (<7yrs); maximize benefit during rapid lung development
- Syncope (particularly if already on oral tx)
- Failed oral trial (how long do you wait?)
- Consider a lower threshold knowing the natural history in children is worse than adults, untreated

Treprostinil (remodulin)

- Longer acting prostacyclin analogue
  - (t½= 4 hours)
- Stable at room temperature
- SQ or IV form
IV/SC Treprostinil Delivery Systems

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

Mean change from baseline (m)

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st - &lt;5</td>
<td>3.3±10</td>
</tr>
<tr>
<td>2nd - 5 to &lt;8.2</td>
<td>1.4±9</td>
</tr>
<tr>
<td>3rd - 8.2 to &lt;13.8</td>
<td>20±8</td>
</tr>
<tr>
<td>4th - &gt;13.8</td>
<td>36.1±10</td>
</tr>
</tbody>
</table>

Lang Survival: SC Treprostinil vs Flolan

Four-year comparative Kaplan-Meier survival analyses of iPAH patients in the study (n= 32) in relation to previously reported data obtained with IV epoprostenol.

The most common adverse event was infusion site pain (82%) which led to discontinuation in 4.9% of patients. Mean dosages were 26.2 ng/kg/min at year 1, 31.9 ng/kg/min at year 2, and 39.8 mg/kg/min at year 3.


SQ Treprostinil - Infusion Site Reaction

- Pain, induration, erythema
- Varies from patient to patient and infusion site to infusion site
- Often improves after several months
- Pain at infusion site may limit use in children
**IV/SC Bioequivalence Study**


**Transition From IV Epoprostenol to IV Treprostinil: Mean 6MW Distance (n=27)**

*27 of 31 patients completed the 12-wk open-label uncontrolled study; 4 patients returned to epo therapy (3 due to leg pain, 1 with worsening PAH symptoms in setting of pneumonia). Most frequent AEs: extremity pain (71%), headache (45%), diarrhea (26%), jaw pain (23%). One patient had syncope; 4 reported worsening dyspnea during titration. Gomberg-Maitland W et al. Am J Respir Crit Care Med. 2005;172:1586-1589.*
IV Epoprostenol to IV Treprostinil transition

- Ivy DD, et al. reported successful transition of 13 pediatric PAH pts from IV epo 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


IV Prostanoids: Minimizing risk for Catheter Related- Blood Stream Infections (CR-BSI)

- Ivy DD et al. described a 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.

Rates of CR-BSI pre and post implementation of Closed-Hub system with protected connections


Treprostinil (IV/SC) in Pediatric PAH: Summary

- If need rapid up-titration, would consider initiation with epoprostenol (shorter half life) and transition later
- May be used after transition from IV epo in a patient already stabilized
- Precautions against CR-BSI should be taken
- May offer improvement in overall quality of life particularly for adolescent patients (no ice, smaller pump)
- SC may be the preferred route for some, particularly with a congenital systemic-pulmonary shunt but site pain may limit use in younger children
Inhaled Prostanoids

• Ventavis (inhaled iloprost)
• Tyvaso (inhaled treprostinil)

Iloprost

• Longer-acting prostacyclin analogue (20- to 30-min half-life)
• Aerosolized delivery system
• Approved for Class III and IV
• Requires frequent inhalations (6 to 9x/d)
• Recommended dose is 2.5-5.0 ucg/inh
• Use in young children challenging
**AIR-Study**  
12 week study (n=203)

- IPAH, PAH/CTD and CTEPH, appetite suppressant use
- Adult patients
- WHO class III or IV
- Randomized to 1 of 4 dosing arms to receive either 2.5ucg or 5.0 ucg 6-9 times/day to maximum tolerated dose (avg dose 38ucg/day)

*Olschewski, et al. NEJM, 2002*

**Inhaled Iloprost: Change From Baseline in 6MWD (AIR Trial)**

**Inhaled Iloprost: Change From Baseline in 6MWD (AIR Trial)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=102)</th>
<th>Iloprost (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>Mean change from baseline (m)</td>
<td>0</td>
</tr>
<tr>
<td>Week 8</td>
<td>Mean change from baseline (m)</td>
<td>-10</td>
</tr>
<tr>
<td>Week 12</td>
<td>Mean change from baseline (m)</td>
<td>-20</td>
</tr>
</tbody>
</table>

**p=0.004**

AIR=Aerosolized Iloprost Randomized.  
6MWD was not the primary end point in the AIR trial.  
AIR-Study (Iloprost)
Result Summary

- Improvement in WHO class ($p<0.05$)
- Improvement in walking distance (36 m, $p=0.004$)
- Improvement in quality of life ($p<0.05$)
- Improvement in hemodynamics
- Well tolerated (side effects: HA, flushing, jaw pain, syncope)
- FDA approved in 2005

*Olschewski, et al. NEJM, 2002*

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Clinical Pharmacology of Prostacyclin Therapy

![Graph showing mean plasma concentration pg/mL over time (h) for IV Treprostinil, SC Treprostinil, and Inhaled iloprost.]

- *IV and SC treprostinil dose was 10ng/kg/min.*

Iloprost in Pediatric PAH

- Evaluated acute and long-term response to iloprost in 22 children (ages 4.5yrs-17.7yrs)
- Acute iloprost lowered PAPm equivalent to iNO/O2 response and reduced FEV$_1$ and FEF$_{25-75}$
- 6 months:
  - FC improved in 35% and decreased in 15%
  - 64% remained on iloprost
  - 9 pts transitioned off IV prostanoid therapy

*Ivy DD, et al., JACC 2008*
Iloprost in Pediatric PAH
6 minute walk (n=13)

Iloprost: Critical Care Setting

- Limited data on use in the pediatric ICU or NICU
- Used on a case by case compassionate use basis when all other treatments fail, particularly in pts with chronic lung disease

Ivy DD, et al., JACC 2008
Iloprost in Critically ill Pediatric PAH: Rationale for Alternate Delivery and Use

– Handheld device not appropriate/reliable for < 7yrs old or critically ill pediatric patient
– Many pediatric PAH pts have chronic lung disease
  • Systemic vasodilators may lead to worsening V/Q mismatch
– Pediatric peri-operative CHD-PAH pts often have systemic hypotension and hemodynamic lability which may prohibit epoprostenol use
– Despite advances, substantial number of pediatric PAH patients fail iNO therapy

Total # treated with iNO: Response to iNO
Columbia NICU 2002-2007

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients (N=370)</th>
<th>Percent of Total</th>
<th>Median Treatment Time (Days) (Range)</th>
<th>Average Treatment Time (Days) (SD)</th>
<th>Percent Treatment Failures</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPHN</td>
<td>145</td>
<td>39%</td>
<td>4 (0.02-84)</td>
<td>6.1 (+/- 9.5)</td>
<td>32%</td>
</tr>
<tr>
<td>CDH</td>
<td>57</td>
<td>15%</td>
<td>7 (0.04-120)</td>
<td>12.2 (+/- 19.2)</td>
<td>60%</td>
</tr>
<tr>
<td>Cardiac</td>
<td>119</td>
<td>32%</td>
<td>5 (0.02-29)</td>
<td>5.5 (+/- 4.4)</td>
<td>N/A</td>
</tr>
<tr>
<td>Prematurity</td>
<td>49</td>
<td>14%</td>
<td>4 (1-102)</td>
<td>17.7 (+/- 26.4)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Challenges in Pediatric Iloprost Delivery

• No consensus on:
  – pediatric dosing
  – delivery system
  – target population

• Special considerations:
  – In general: no Swan – Ganz to assess treatment effect
  – Highly heterogeneous patient population

Pediatric Iloprost Delivery: Challenges

• Lung deposition of aerosolized medication in ventilated infants is often <1% of the normal dose compared with 8-22% for ventilated adults*
  – Low tidal volume, low vital capacity and functional residual capacity lead to shorter time and lower rates of pulmonary deposition

• In vitro model of infant ventilation documented lung deposition of 14% with aeroneb vs. 0.7% with jet nebulization

*Fink JB, et al., ACCP, 2001
Iloprost Delivery: Aeroneb

Delivery systems: Pediatric Iloprost

• Aeroneb
  – Permits small particle size (1-3 micron)
  – Delivery of >14% vs. < 1-10% with other nebulizers (i.e. Acorn)
  – Can hook directly into mechanical ventilator circuit (avoid disruption)
  – Have some experience with oscillator
Early Pediatric Iloprost Experience
NICU/PICU
Columbia University

• 10 pediatric patients
• Treated during 2006-2007
• Disease states treated: (heterogeneous)
  – PPHN, CDH, BPD/CLD, CHD with acute PH crisis, decompensated IPAH/ARDS requiring ECMO
• Delivery system
  – Initial: Ultrasonic nebulizer-acorn >> bronchospasm
  – Current: Aeroneb

Columbia Patient Demographics (n=10)

• Age (range 1 day-4 yrs)
• Neonates (n=6); pediatric (n=4)
• Male:Female = 60%:40%
• Diagnosis
  – Neonatal: CDH (5); PPHN (1)
  – Pediatric: IPAH/ARDS (1); CHD (1); BPD(2)
• Dose range: (1.0 ucg-20 ucg/inhalation)
• Dose frequency: (q 30" [continuous] – q 3 hours)
• Via mechanical ventilator (n=9) and CPAP (n=1)
Table with pt # and dose and frequency

<table>
<thead>
<tr>
<th>Pt #</th>
<th>Max dose</th>
<th>Frequency</th>
<th>Device</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5 ucg</td>
<td>q 3 hrs</td>
<td>Acorn</td>
<td>Vent</td>
</tr>
<tr>
<td>2</td>
<td>2.5 ucg</td>
<td>q 2 hrs</td>
<td>Aeroneb</td>
<td>Vent</td>
</tr>
<tr>
<td>3</td>
<td>2.5 ucg</td>
<td>q 3 hrs</td>
<td>Aeroneb</td>
<td>Vent</td>
</tr>
<tr>
<td>4</td>
<td>2.5 ucg</td>
<td>q 3 hrs</td>
<td>Aeroneb</td>
<td>CPAP</td>
</tr>
<tr>
<td>5</td>
<td>10 ucg</td>
<td>q 1 hr&gt;&gt;q 2hr</td>
<td>Aeroneb</td>
<td>Vent (osc)</td>
</tr>
<tr>
<td>6</td>
<td>5 ucg</td>
<td>q 2 hrs</td>
<td>Aeroneb</td>
<td>Vent</td>
</tr>
<tr>
<td>7</td>
<td>20 ucg</td>
<td>q 30 min</td>
<td>Aeroneb</td>
<td>Vent (osc)</td>
</tr>
<tr>
<td>8</td>
<td>5 ucg</td>
<td>q 1 hr</td>
<td>Aeroneb</td>
<td>Vent (osc)</td>
</tr>
<tr>
<td>9</td>
<td>10 ucg</td>
<td>q 30 min</td>
<td>Aeroneb</td>
<td>Vent</td>
</tr>
<tr>
<td>10</td>
<td>2.5 ucg</td>
<td>q 2 hrs</td>
<td>Aeroneb</td>
<td>Vent</td>
</tr>
</tbody>
</table>

Protocol for Iloprost up-titration:
Maximize Treatment effect

1 ug q 2-3 hours q 1 hour q 30 min

2.5 ug

5 ug

7.5 ug

10 ug

15 ug

Rebound

Rebound
Outcome

Descriptive

• 9/10 patients had transient increase in O2 saturation
• 5/10 still went on to require ECMO
• 7 received additional PH meds
  – Sildenafil; n=3 (1 with worse hypoxia)
  – Bosentan; n=1 (worse hypoxia)
  – Epoprostenol; n=3 (1 dev SVT, 2 with iloprost to wean ECMO - 1 weaned off, 1 remains on)
• 1 patient discontinued due to bronchospasm (acorn)
• 2 patients with chronic lung disease were pre-tx with bronchodilators
• 5/10 survived

Future Direction of Iloprost in Inpatient Pediatric PAH: Goals

• Evaluation of delivery systems
• Assessment of treatment response criteria
• Identify appropriate target populations
• Weaning strategies to treat off the ventilator
• Protocol design to determine proper delivery and dosing, and to assess safety and efficacy
Pediatric Iloprost Treatment Response:
What to measure?

- Oxygenation Index MAP x FiO2 x100/PaO2
- Ventilator settings
- Change in PaO2/ O2 saturation (post-ductal)
- Echocardiographic estimates of PAP:SAP
- Time to extubation
- Need for ECMO
- Survival

Pediatric Iloprost: Summary

- Data for the use of aerosolized Iloprost is limited in pediatric patients
- Early experience suggests a role for iloprost in the neonatal and pediatric critical care setting
- Advantages over other vasodilators include targeted delivery to the lungs with minimal effect on the systemic circulation
- While iNO has been the gold standard for PAH treatment, there are many pediatric patients that do not respond to iNO
Inhaled Treprostinil: A Prostacyclin Analog for Pulmonary Arterial Hypertension

OptiNeb® Ultrasonic Nebulizer

- Battery-operated (rechargeable)
- Single-breath technology
- Each treatment completed in <1 minute
TRIUMPH I: Study Design

Therapy period

Randomize
N=235

Placebo (n=120)

ITRE, 3 breaths q.i.d. (n=115)

ITRE dose was up-titrated up to 9 breaths q.i.d. (54 µg)

Key inclusion criteria
• NYHA class III or IV
• 6MWD of 200 to 450 m
• Bosentan or sildenafil for ≥3 months

ITRE, inhaled treprostinil; 6MWD, 6-minute walk distance; NYHA, New York Heart Association; q.i.d., 4 times daily.

TRIUMPH – 6MWD Median Change: Peak (10 to 60 Minutes Post-Treprostinil Inhaled Dose)

Hodges-Lehmann Estimate of Treatment Effect.
McLaughlin VV et al. Presented at ATS, 2008
TRIUMPH – 6MWD Median Change
Peak and Trough

<table>
<thead>
<tr>
<th>Time</th>
<th>Median Change from Baseline (m)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 Peak</td>
<td>6</td>
<td>p=NS</td>
</tr>
<tr>
<td>Week 6 Peak</td>
<td>18</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>Week 12 Peak</td>
<td>20</td>
<td>&lt;0.0006</td>
</tr>
<tr>
<td>Week 12 Trough</td>
<td>14</td>
<td>&lt;0.007</td>
</tr>
</tbody>
</table>

Peak = between 10—60 min after dose.
Trough = ≥4 hr after dose.
Hodges-Lehmann Estimate of median change from baseline.

TRIUMPH Study Clinical Summary

- Inhaled treprostinil for 12 weeks in combination with oral therapy for PAH significantly improved
  - 6MWD measured at peak and trough
  - NT pro-BNP levels
  - HRQOL
- No significant differences observed between treatment and placebo groups in time to clinical worsening
  - Very few events occurred in either study group during the 12 weeks
- Inhaled treprostinil was well tolerated
  - Systemic AE profile was typical of other prostanoid therapies
  - Cough and throat irritation were considered related to inhalation route of delivery

HRQOL, health-related quality of life.
Inhaled Treprostinil Decreased Pulmonary Vascular Resistance

Data represent experimental doses of ITRE not used in the pivotal study.


Effect of Inhaled Treprostinil on Pulmonary Vascular Resistance Following Treatment* with Sildenafil

- Nitric oxide inhalation
  - 20 ppm for 5 min
- Oral sildenafil
  - 50 mg after PVR returned to baseline
- Inhaled treprostinil
  - 15 µg or 30 µg 1 hour after sildenafil dose
- PVR assessed for 120 min post-inhaled treprostinil

NO, nitric oxide; ppm, parts per million; SIL, sildenafil; ITRE, inhaled treprostinil. * Data are mean ± 95% CI.

*Based on pooled data of all 50 patients. Data represent experimental doses of ITRE not used in the pivotal study.

How Will Inhaled Treprostinil Be Used in Clinical Practice?

• Add-on versus first line?
• What FC?
• To transition from IV prostanoids?

Prostanoid Treatment Options: Summary

<table>
<thead>
<tr>
<th>Product</th>
<th>Delivery</th>
<th>Frequency</th>
<th>Indicated population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flolan® (epoprostenol sodium) Injection</td>
<td>IV</td>
<td>Continuous</td>
<td>NYHA FC III-IV</td>
</tr>
<tr>
<td>Remodulin® IV (treprostinil sodium) Injection</td>
<td>IV</td>
<td>Continuous</td>
<td>NYHA FC II-IV</td>
</tr>
<tr>
<td>Remodulin® SC (treprostinil sodium) Injection</td>
<td>SC</td>
<td>Continuous</td>
<td>NYHA FC II-IV</td>
</tr>
<tr>
<td>Ventavis® (iloprost) Inhalation Solution</td>
<td>Inhaled</td>
<td>6-9 x daily</td>
<td>NYHA III-IV</td>
</tr>
<tr>
<td>Tyvaso (treprostinil sodium) Inhalation solution</td>
<td>Inhaled</td>
<td>4 x daily</td>
<td>NYHA III</td>
</tr>
</tbody>
</table>
REVEAL Registry: Prostacyclin Use by Functional Class

FC III
- IV: 16%
- SC: 0%
- Inhaled: 12%
- Oral: 79%

FC IV
- IV: 29%
- SC: 1%
- Inhaled: 12%
- Oral: 62%

FC, functional class; IV, intravenous; SC, subcutaneous.

Badesch et al. Poster presented at: ATS 2008; May 16-21, 2008; Toronto, Canada.

REVEAL Registry: Treatment of FC IV Patient Enrolled in Last Year

- Oral monotherapy: 19%
- Oral combination: 41%
- Prostacyclin only: 11%
- Prostacyclin + oral: 22%
- No PAH therapy: 7%

63% on oral therapy only

FC, functional class; PAH, pulmonary arterial hypertension.

Badesch et al. Poster presented at: ATS 2008; May 16-21, 2008; Toronto, Canada.
How to decide which therapy?

IV prostanoids  Novel oral agents

Inhaled prostanoids

Time to Initiation of Prostanoid Therapy

- 660 patients; 77% female; mean age, 54 y; mean disease duration, 1.9 y
- Prior to 2000, up to 50% of patients received prostanoids within the first year of diagnosis, which declined to 25% after 2000
- Higher FC, mRAP, and mPAP were associated with initiation of prostanoids

mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure.

Maradit-Kremers, et al. Poster presented at: PHA 2008; June 20-22, 2008; Houston, TX
Therapeutic Strategies

• Least invasive to most invasive
  – Need to follow closely for deterioration or lack of sufficient improvement

• Most invasive up front therapy
  – Similar paradigm to oncologic therapy (up-front invasive therapy)
  – Possibility of transition off to less invasive therapies

Transition of Pediatric PAH Patients from IV Epoprostenol to oral/inhaled agents

• Retrospective review of all pediatric IPAH/FPAH treated at Columbia (1987-2008) who transitioned off IV epo to oral/inhaled drugs

• General criteria for transition off included:
  – FC I/II
  – Age > 6yrs
  – PAPm <35mmHg
  – Normal cardiac index

• Hemodynamics and clinical data were assessed on peak epoprostenol dose vs. off epoprostenol

Melnick L, et al., ATS, 2009
Transition of Pediatric PAH Patients from IV Epoprostenol to oral/inhaled agents: Results

- A total of 14/104 pediatric patients who met general criteria were transitioned off IV epoprostenol (over several months to years; 4/03-7/08)
- 13/14 remained off IV epoprostenol on oral/inhaled medications
- Hemodynamics, exercise capacity (if able) and WHO functional class remained stable off epoprostenol compared to peak epoprostenol dose. (f/u 7±6 mos); Further improvement in WHO FC was seen post epoprostenol (p<0.005)
- All 13 patients are alive at present; (77% ERA, 69% PDE-5 inhibitor, 38% CCB, 8% iloprost)

Melnick L, et al., ATS, 2009

ACC/AHA Consensus PAH Treatment Algorithm

- **Anticoagulate ± Diuretics ± Oxygen ± Digoxin**
  - **Acute Vasoreactivity Testing***
    - Positive
      - **Higher Risk§**
        - Epoprostenol or Treprostinil (IV)
        - Iloprost (inhaled)
        - ERAs or PDE-5 Is (oral)
        - ERAs or PDE-5 Is (oral)
        - Treprostinil (SC)
      - **Lower Risk‡**
        - ERAs or PDE-5 Is (oral)
        - Epoprostenol or Treprostinil (IV)
        - Iloprost (inhaled)
        - Treprostinil (SC)
    - **Negative**
      - **Sustained Response**
        - **Yes**
          - **Continue CCB**
        - **No**
          - **Reassess – consider combo-therapy**
          - **Investigational Protocols**

Summary: Prostanoids in Pediatric PAH

- IV epoprostenol still remains the “gold standard” for the treatment of advanced pediatric PAH
- Newer agents have enabled transition to other prostanoids and even to oral/inhaled agents in carefully selected patients
- Caution should be applied to delay in the institution of prostanoid therapy when using novel oral agents (think about natural history)
- As novel agents are developed so are new challenges in decision making

Pediatric PAH: Where do the prostanoids fit in?

“I’ll be happy to give you innovative thinking. What are the guidelines?”
Safe skiing!!