Changing Tracks: Transitioning From One Therapy to Another

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Disclosures

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Objectives

• Identify appropriate patients and rationale for therapy transitions.
• Describe methods used to transition patients from one therapy to another using case examples.
• Discuss the outcomes of therapy transitions.
Prostacyclin Therapy

- Flolan (epoprostenol)- Considered Gold Standard Treatment. Continuous IV therapy via central line and CADD pump.

- Remodulin (treprostinil)- Now delivered SQ or IV via central line and 407c Mini-med or CADD-MS pump.

- Ventavis (iloprost) – Inhaled via specialized nebulizer 6-9 times/day.
Why Change?

- What is the rationale for transitioning patients?
- Which patients are appropriate to transition?
- Is it safe?
• Why change?
Epoprostenol - Flolan

- “Gold standard” treatment
  - Most experience, FDA approved ‘95
  - Increases survival
  - Class IV patients
- Half-life < 6 minutes
- Continuous intravenous infusion
- Pulmonary and systemic vasodilator
- Inhibits platelet aggregation
**Administration of Flolan**

- Stable at room temperature for 8 hours only
  - Good chilled x 48 hours
- Requires ice packs to keep chilled during infusion (special carrying cases)
- Must be reconstituted from powder with special buffered diluent
  - Patients mix drug daily
- Sudden withdrawal can cause rebound PH
  - Low infusion rates – 46-98 ml/DAY
  - No extension sets, prime catheter before beginning infusion
Remodulin - treprostinil

- Longer half-life – 4 hours
- Can be given subcut. or IV
- Stable at room temperature
- Multidose vials, can be mixed with NS
- Comparable dose to Flolan is 1.5-2 x
- Subcutaneous form associated with significant site pain
- Higher incidence of Gram Neg infections suggested by recent CDC review.
• **Why change?**
  
  • Indwelling central lines – QOL limitation, care, local and systemic infection
  
  • Need for supplies and requirement for mixing, and storing drug
  
  • Need for ice pack for flolan
  
  • Risks of drug interruption
Case #1 – Freedom from Ice Packs
Case #1

- 35 y/o male with IPAH
  - Initially diagnosed in 2001, untreated
  - Inpatient transfer 3-04, PAM 48, CO 2.7
  - Discharged on Flolan and sildenafil after 1 mo in hosp
- On Flolan 14 months, dose 23 ng/kg/min., also on sildenafil 100 mg TID, 6 MWT 467 m, Class II
- Rapid switch to Remodulin 28 ng/kg/min.
  - Monitored overnight and discharged with fewer side effects, 6 MW unchanged
How we do it

• Specialty pharmacy RN comes to assist with transition
  – Have Flolan and Remodulin dose charts handy
• Calculate Remodulin dose needed (1.25 x Flolan dose)
  – 20 ng/kg/min x 1.25 = 25 ng/kg/min (Ex.)
• Prepare Remodulin and pumps
• Baseline VS and pulse ox
• Stop Flolan, withdraw, noting dead space volume
  – Keep line sterile in case patient needs to go back on Flolan
• Flush with saline and prime catheter with Remodulin
• Connect and start Remodulin
Case #1

- At 21 mo post switch:
  - Remodulin dose 35 ng/kg/min
  - 6 MWT 519 meters
- Patient reports fewer side effects, especially less jaw pain
- Greater mobility and freedom – CRONO5 pump
- Very happy, serves as our “poster child”
Case #2 – No more pain
Remodulin Site Pain

• Difficult to predict which patient will have pain or how much
• Numerous remedies have been proposed and tried, not one seems to work for every patient
• Long term patients may start running out of sites, debilitating nature of chronic pain
Ventavis - iloprost

- Inhaled form of prostacyclin
- Used in Europe for several years, FDA approved 2005
- Two doses – 2.5 mcg and 5.0 mcg
- Need 6-9 inhalations/day, while awake
- Treatment plus cleaning takes about 20 min.
Case #2

• 20 yr. old female presented with ASD, Eisenmenger’s in 1999.
  – PAP 176/64, mean 104, PCWP 12, Fick CO 4.3
  – WHO Class III symptoms
• Enrolled in UT-15 subcutaneous experimental protocol in October 1999
• Did well, managed site pain and gradually titrated dose up to peak of 90 ng/kg/min in 2003
• In August 2004 sildenafil was added because of PAH symptoms and inability to increase Remodulin due to side effects (primarily site pain)
Case #2

- In 2005 began to suspect she was not using Remodulin continuously due to medication dispensing history.
- Starting Dec 2005, Remodulin was decreased to 54 ng/kg/min by December 2006.
- Patient refused IV catheter, opted for Ventavis.
- Patient was able to wean down to 41 ng/kg/min without PAH symptoms.
- 6 MWT 330 meters 11-27-06 (down from 364)
How we did it
How we did it

• CAVEAT: how we did it doesn’t make it right

• Other methods have equivalent rationale
How we did it

• Devised outpatient transition schedule to Ventavis over 4 weeks:
  – Week 1-Ventavis 2.5 mcg, 4 treatments per day; Decrease Remodulin to 31 ng/kg/min
  – Week 2-Ventavis 2.5 mcg, 6 treatments per day; Decrease Remodulin to 21 ng/kg/min
  – Week 3-Ventavis 5 mcg, 6 treatments per day; Decrease Remodulin to 10 ng/kg/min
  – Week 4-Continue Ventavis 6 treatments per day, stop Remodulin
Case #2

- Patient disappeared to Mexico!
- Returned to clinic March 2007
- Remains on sildenafil 100 mg TID, compliant with Ventavis 5 mcg, 6x/day
- No signs of RHF
- 6 MWT down to 288 m
- Patient still refusing subcut or IV prostacyclin
- Considering addition of ERA
Transitioning from Parenteral Prostanoid to Oral agents
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• Rationale: Pills are cheaper, easier to take, no risks of systemic infection, no significant risk of drug interruption, no unusual requirements for storage and transportation
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• Whom do we consider for transition

• How do we do it

• Are they “as good”

• How do we define “as good”

- “This study demonstrates that it is possible to safely and effectively transition carefully selected clinically stable patients with persistent PAH in WHO class II and III receiving continuous prostacyclin infusions to oral bosentan.
- A significant proportion of patients (15 of 23 patients; 65%) were able to transition to oral bosentan at the end of the 12-week transition period.
- Late failures and delayed elevation in liver function tests lowered the number of successful transitions to 9 of 23 patients (40%).”
- No deaths either short or long term.

Suleman & Frost, 2004

- Similar study of 22 patients from multiple centers transitioned patients off prostanoid to oral bosentan over a 2 month period.
- 10/22 were transitioned off.
- 3 deteriorated (two died)
- 12 failed transition and of these two died of these patient in spite of resumption of full therapy.
- Of the 7 who remained off – good walk and BDI and echo stable for median 17 months.

Steiner MK, Hill NS et al.
Message

- The greatest likelihood of success is in those on lower doses of prostanoid, less sick (ie II rather than III, better walk), shorter duration of illness
- Monitor very closely. At the slightest signs of clinical worsening (subjective or objective) increase prostanoid and stabilize patient.
- Choose objective parameters to monitor the patients for sign of deterioration.
Message

• The greatest likelihood of success is in those on lower doses, less sick (ie II rather than III), shorter duration of illness

• Monitor very closely. At the slightest signs of clinical worsening (subjective or objective) increase prostanoid and stabilize patient.

• THIS IS ABOUT FEELING BETTER ON SIMPLER MEDICATION - NOT ABOUT ACCEPTING GREATER RISK AND WORSE FUNCTION.
IV Epoprostenol to subcut. 
Treprostinil,

8 wk placebo controlled study
Transition patients from epoprostenol to either subcutaneous remodulin or placebo
Objective was to prove the utility of treprostinil compared to epoprostenol.

Rubenfire, et al., CHEST 2007
IV Epoprostenol to subcut.
Treprostinil,

22 patient
In hospital transition and 24 hr post transition monitoring
2:1 randomization Tre:Pbo
Stable patients
Followed at 4 and 8 weeks

Rubenfire, et al., CHEST 2007
IV Epoprostenol to subcut. 
Treprostinil,

Patients:
Stable, II or III, 6MWD of at least 250 m.,
Age 18-75
No dose changes in 15 days, epo ≥ 3 months
Dose ≤ 75ng/kg/min

Rubenfire, et al., CHEST 2007
# Method of Transition

<table>
<thead>
<tr>
<th>Dose Transition Day</th>
<th>Epoprostenol Dose</th>
<th>Study Drug Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unchanged</td>
<td>10% starting epoprostenol dose</td>
</tr>
<tr>
<td>2</td>
<td>80% starting epoprostenol dose</td>
<td>30% starting epoprostenol dose</td>
</tr>
<tr>
<td>3</td>
<td>60% starting epoprostenol dose</td>
<td>50% starting epoprostenol dose</td>
</tr>
<tr>
<td>4</td>
<td>40% starting epoprostenol dose</td>
<td>70% starting epoprostenol dose</td>
</tr>
<tr>
<td>5</td>
<td>20% starting epoprostenol dose</td>
<td>90% starting epoprostenol dose</td>
</tr>
<tr>
<td>6</td>
<td>5% starting epoprostenol dose</td>
<td>110% starting epoprostenol dose</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>110% starting epoprostenol dose plus additional 5 to 10% as needed</td>
</tr>
<tr>
<td>8*</td>
<td>0</td>
<td>Additional 5 to 10% as needed</td>
</tr>
<tr>
<td>9*</td>
<td>0</td>
<td>Additional 5 to 10% as needed</td>
</tr>
<tr>
<td>10*</td>
<td>0</td>
<td>Additional 5 to 10% as needed</td>
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<td>11*</td>
<td>0</td>
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<td>12*</td>
<td>0</td>
<td>Additional 5 to 10% as needed</td>
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<tr>
<td>13*</td>
<td>0</td>
<td>Additional 5 to 10% as needed</td>
</tr>
<tr>
<td>14*</td>
<td>0</td>
<td>Additional 5 to 10% as needed</td>
</tr>
</tbody>
</table>

Rubenfire, et al., CHEST 2007
IV Epoprostenol to subcut. Treprostinil,

- 14 on Tre; 8 on PBO
- All Pbo patients deteriorated.
- One TRe patient had syncopal spell during transition.
- The remainder transitioned relatively uneventfully.
- Tre patient experienced a mean decrease in walk of -35 m. (due to 1 outlier)
IV epo to Sc. Tre

- This study was proof of efficacy
- Unlikely to be something you would want to do - BUT
- Some patients are at risk of infection and sc offers significantly less risk of infection, drug interruption, catheter interruption
- Sub cut IS limited by pain – the ability to achieve acceptably high therapeutic levels of drug.
Transition from IV Epo to IV Tre

• Question: can stable PAH pts. on Epo be transitioned to Tre using a rapid switch protocol
• Stable patients NYHA I (2); II (10)

Transition from IV Epo to IV Tre

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Demographics</th>
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</thead>
<tbody>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Gender (female:male)</td>
</tr>
<tr>
<td>Etiology</td>
</tr>
<tr>
<td>Idiopathic PAH (n)</td>
</tr>
<tr>
<td>Familial PAH (n)</td>
</tr>
<tr>
<td>PAH associated with repaired ASD (n)</td>
</tr>
<tr>
<td>Baseline 6 min walk distance, m</td>
</tr>
<tr>
<td>Baseline Borg scale</td>
</tr>
<tr>
<td>Epoprostenol dose (ng/kg/min)</td>
</tr>
<tr>
<td>Time on epoprostenol, (yr)</td>
</tr>
</tbody>
</table>

Results are given as mean ± SD [range].
PAH, Pulmonary Arterial Hypertension; ASD, Atrial septal defect.

Transition from IV Epo to IV Tre
How?

• Evacuate epo line
• 1:1 ng/kg/min dose of epo to tre
• Prime line with remodulin
• Switch the pumps over
• Subsequent outpatient up titration – patients ended up with a 1.5-3.0 fold increase over 12 weeks.

Transition from IV Epo to IV Tre 6MWD

Transition from IV Epo to IV Tre

- Hemodynamics also done. No change
- Fewer and less severe side effects
- One patient had a pump failure (3hrs) without symptoms.
- 2 patients had SAE (one hemoptysis and one line infection*)

Transition from IV Epo to IV Tre

- It is feasible to do rapid transit
- Increase the dosage pre-emptively (we do a 30% increase over baseline Epo)
- Make sure why you are changing is reasonable:
  - Line infection per CDC appears higher
Conclusions:

• When going from “more aggressive therapy” to less
  – Make sure you have carefully chosen your patients
  – Use an objective parameter/s to follow
  – Don’t hesitate to change back

• When going from one parenteral to another
  – Recognize the different safety and risk profiles & discuss them with your patients
  – Increase doses appropriately
  – Emphasize careful sterile techniques – people get sloppy
Take Home Message

• If it ain’t broke don’t fix it.
• Selected patients can be successfully transitioned from one therapy to another.
• Patients require careful follow-up monitoring after the transition.
• Teamwork always helps!
Questions
Contact Information

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