Implanted System for Treprostinil

Jeremy Feldman MD
Director Pulmonary Hypertension Program
Medical director of Research
Arizona Pulmonary Specialists
Why Bother?

- Same medicine as IV/SQ
- Requires surgery
- Risk of pump malfunction
- Eventual need for pump replacement
SQ Treprostinil
Problems with Existing Systems

- Intravenous
  - Central venous catheter
  - Bathing/swimming
  - Infections

- Subcutaneous
  - Site pain
  - Bathing/swimming

- Inhaled
  - Ceiling on efficacy

- Oral
  - Ceiling on efficacy
  - Side effects
Implanted System

- Already in use pump
  - Reservoir 40 ml
  - 10mg/ml (? 20mg/ml)
  - Up to 3 month refill interval
  - 7 year batter life

- Novel tunneled catheter system
  - No backflow
  - Long term high patency rates
Patient Selection - Goldielocks

- Not too fat
  - Pump sutured to abdominal wall

- Not too sick
  - Procedure requires either GETA or deep MAC

- Not too well
  - Maybe existing system working adequately

- Reliable

- Already tolerating SQ or IV treprostinil
Preparation

- Insure pt understands procedure
- Insure pt understands aesthetics
- Coordinate with surgeon, OR, company, ICU
- Coordinate who/where refills
- RHC/optimization of patient
- PAH-experienced anesthesiologist
- Removal of tunneled catheter and PICC / mid line placement
- Understand venous anatomy
Day of the Procedure

- NPO after midnight except for PAH medications
- Anticoagulants previously stopped
- Arterial line placed in preop
- Vasopressin infusion on pump with guardrails
- ICU bed confirmed
- Implanting team pre-OR huddle
Operating Room

- Induction of anesthesia
- Pump preparation on back table
- Fluoroscopy in room
- Abdominal pocket developed in parallel with vascular access
- Peripheral treprostinil infusing
Ready- Set- Go
Back Table
Explant
Exchange
Reprogramming
Recovery/ICU

- Extubation/stabilization
- Bridge bolus (transition to implanted system)
- Verification of alarms
- Abdominal binder
- discharge
Post Discharge

- Keep dry for 3 days, no submerging for 2 weeks

- Within 1 week
  - Surgical wound check
  - Emphasize use of abdominal binder

- 1 month
  - PAH check

- 3 months
  - First refill

- Routine follow up
  - Separate from refills
Refills
Treprostinil Administered to Treat Pulmonary Arterial Hypertension Using a Fully Implantable Programmable Intravascular Delivery System
Results of the DellIVERY for PAH Trial

Robert C. Bourge, MD; Aaron B. Waxman, MD, PhD; Mardi Gomberg-Maitland, MD; Shelley M. Shapiro, MD, PhD; James H. Tarver III, MD; Dianne L. Zwicke, MD; Jeremy P. Feldman, MD; Murali M. Chakinala, MD; Robert P. Frantz, MD; Fernando Torres, MD; Jeffrey Cerkvenik, MS; Marty Morris, MS; Melissa Thalin, RN, BSN, MBA; Leigh Peterson, PhD; and Lewis J. Rubin, MD

BACKGROUND: The use of systemic prostanoids in severe pulmonary arterial hypertension (PAH) is often limited by patient/physician dissatisfaction with the delivery methods. Complications associated with external pump-delivered continuous therapy include IV catheter-related bloodstream infections and subcutaneous infusion site pain. We therefore investigated a fully implantable intravascular delivery system for treprostinil infusion.

METHODS: A multicenter, prospective, single-arm, clinical trial (DellIVERY for Pulmonary Arterial Hypertension) was conducted by using an implantable intravascular delivery system. The implanted pumps were refilled percutaneously at least every 12 weeks. The primary end point was the rate of catheter-related complications using the new model 10642 catheter compared with a predefined objective performance criterion of 2.5 per 1,000 patient-days based on the literature.

RESULTS: Patients (n = 60) with severe PAH (World Health Organization group 1) receiving a stable dose of IV treprostinil for at least 4 weeks received an implantable device and were followed up for 12.1 ± 4.4 months. Six catheter-related complications occurred, corresponding to a complication rate of 0.27 per 1,000 patient-days. The 97.5% upper one-sided confidence bound of 0.59 was less than the predefined criterion of 2.5 per 1,000 patient-days (P < .0001). Plasma treprostinil levels at 1 week postimplantation were highly correlated with baseline levels (r = 0.91; P < .0001). The delivery system management time as reported by the patients was 2.5 ± 1.7 hours per week preimplantation, and this time decreased to 0.6 ± 0.8 hour per week at 6 months’ postimplantation (P < .0001). All patients rated overall satisfaction with the implantable system as good, very good, or excellent at 6 weeks and 6 months. There were no catheter-related bloodstream infections or catheter occlusions.

CONCLUSIONS: The implantable intravascular delivery system delivered treprostinil to patients with PAH with a low rate of catheter-related complications and a high rate of patient satisfaction.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT01321073; URL: www.clinicaltrials.gov

CHEST 2016; 150(1):27-34

KEYWORDS: central venous catheters; drugs; health-related quality of life; pulmonary arterial hypertension; pulmonary hypertension; treprostinil
Results

- No change in 6MW
- 75% reduction in time spent per week on treprostinil (0.6 hrs vs 2.5 hours)
- Dose ratio 0.82
- Dramatic reduction in catheter and pump related adverse events compared to usual practice 0.27/1,000 pt days
- No bacteremia
# Complications

## TABLE 2 Complications Related to the Procedure or System During 22,013 Patient-Days of Follow-up

<table>
<thead>
<tr>
<th>Complication and Relatedness</th>
<th>No. of Occurrences</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant procedure related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
<td>Prior to catheter insertion; Resolved by cardioversion</td>
</tr>
<tr>
<td>Fever, unknown origin</td>
<td>1</td>
<td>Admitted for observation; negative culture results</td>
</tr>
<tr>
<td>Pump pocket infection</td>
<td>1</td>
<td>Resolved after surgical modification and antibiotics</td>
</tr>
<tr>
<td>Legionella pneumonia with septic shock, renal failure, and DVT at the PICC line site</td>
<td>1</td>
<td>Subject recovered after 34-day hospitalization</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>1</td>
<td>Urinary catheterization required</td>
</tr>
<tr>
<td>Catheter related (primary end point)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter dislocations</td>
<td>3</td>
<td>Dislocated catheters removed and replaced via surgical procedures</td>
</tr>
<tr>
<td>Venous stenosis</td>
<td>1</td>
<td>187 days’ postimplantation</td>
</tr>
<tr>
<td>Damaged catheter</td>
<td>1</td>
<td>Catheter migrated over the refill port and was pierced with the needle during refill</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1</td>
<td>Associated with subclavian venous access; required chest tube; discharged 2 days; postimplantation</td>
</tr>
<tr>
<td>Pump-related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pump pocket seroma</td>
<td>2</td>
<td>Fluid from pump pocket in 2 subjects aspirated at 13 and 70 days after implantation</td>
</tr>
<tr>
<td>Pump refill process related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refill reactions</td>
<td>3</td>
<td>3 subjects treated due to local and/or systemic reaction shortly after refill</td>
</tr>
<tr>
<td>Programmer related</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total system-related complications</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>
Totally Implantable IV Treprostinil Therapy in Pulmonary Hypertension Assessment of the Implantation Procedure

Aaron B. Waxman, MD, PhD; Hugh T. McElderry, MD; Mardi Gomberg-Maitland, MD; Martin C. Burke, DO; Edgar L. Ross, MD; Malcolm M. Bersohn, MD, PhD; Sanjog S. Pangarkar, MD; James H. Tarver, MD; Diane L. Zwickie, MD; Jeremy P. Feldman, MD; Murali M. Chakinala, MD; Robert P. Frantz, MD; Geoffrey B. Thompson, MD; Fernando Torres, MD; Richard L. Rauck, MD; Kathy Clegg, RN; Louise Durst, RN; Pei Li, PhD; Marty Morris, MS; Kara L. Southall, BS; Leigh Peterson, PhD; and Robert C. Bourge, MD

BACKGROUND: Prostacyclins improve symptoms and survival in pulmonary arterial hypertension (PAH). In response to risks associated with external delivery systems, an implantable IV infusion system was developed. A multicenter, prospective, single-arm, clinical trial (DeliIVery for PAH) was conducted to evaluate this system for treprostinil in PAH. This analysis describes the findings related to the implant procedure.

METHODS: Patients (N = 64) with PAH (World Health Organization group 1) receiving stable IV treprostinil were enrolled. Patients were transitioned to a temporary peripheral IV infusion catheter prior to the procedure. System implantation was performed at 10 centers under general anesthesia or deep IV sedation by clinicians from various specialties. Central venous access was via the cephalic, subclavian, jugular, or axillary vein. Using an introducer and fluoroscopic guidance, the distal tip of the infusion catheter was placed at the superior caval-atrial junction. The catheter was tunneled from the venous access site to an abdominal subcutaneous pocket, where the pump was placed.

RESULTS: Of the 64 patients enrolled, four exited prior to implantation. All 60 implant procedures were successful. At baseline, all patients were receiving treprostinil via an external pump at a mean dose of 71.4 ± 27.8 ng/kg/min (range: 22-142 ng/kg/min). The implant averaged 102 ± 32 min (range: 47-184 min). Clinically significant implant procedure-related complications included one pneumothorax, two infections, and one episode of atrial fibrillation. There were three postimplantation catheter dislocations in two patients. Common implant-related events that were not complications included implant site pain (83%) and bruising (17%).

CONCLUSIONS: The procedure for inserting a fully implantable system for treprostinil was successfully performed, with few complications.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT01321073; URL: www.clinicaltrials.gov.

CHEST 2017; 152(6):1128-1134
Patient Education
Update on the Implanted Remodulin Pump
April 10, 2017 By Dr. Jeremy Feldman
This week we learned that the much-awaited arrival of the Implanted Pump System for Remodulin would be further delayed. The FDA did not grant Medtronic and United Therapeutics approval. Details are scant but the announcement indicated that the device might be approved in the beginning of 2018. PAH Patients and doctors alike were let down by the delay. The delay does not... [Read more...]

FAQ's: Implanted Remodulin Pump, Right Heart Catheterization, PAH & Pregnancy
April 2, 2016 By Dr. Jeremy Feldman
Your Questions Answered. Our readers have submitted some great questions. We value your questions and encourage you to continue to tell us about your interests and questions. What is happening with the Implanted Remodulin Pump? The FDA recently announced they are not ready to approve the implanted pump system for delivery of continuously infused Remodulin. They are... [Read more...]

Entire Implantable System for Remodulin Approved by the FDA
July 31, 2018 By Dr. Jeremy Feldman
It is finally here! The Food and Drug Administration approved Remodulin in its implantable delivery system for treatment of Pulmonary Arterial Hypertension. We have been providing updates on the 8-year study that investigated the use of an implanted pump to deliver Remodulin, removing the need for external pumps and are excited to announce it is finally approved. The pump... [Read more...]

Liquidia: Exciting New Clinical Trial in Pulmonary Arterial Hypertension
April 19, 2018 By Dr. Jeremy Feldman
Clinical trials are essential to improving the care of PAH patients. These clinical trials allow us to determine if new medicines are safe and effective. Clinical trials also allow us to make improvements to existing treatments. For example, we are eagerly awaiting the approval of the implanted pump for intravenous Remodulin. Another example of a company that is trying to... [Read more...]

Update on the Implantable System for Remodulin
February 13, 2018 By Dr. Jeremy Feldman
The first visit at a PH center can be very overwhelming. Many patients receive the news that they have a serious life...
Key Points

- Not every patient is appropriate for implanted treprostinil

- Comprehensive assessment by PAH team expert in implantation

- Implantation is a team sport
  - PAH specialists, implanter, anesthesia, preop/postop assessment/care

- Systems must be in place for refills and monitoring