Implantable system for treprostinil and lung transplantation: case series from delivery for pulmonary arterial hypertension study

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Abstract
The implanted system for treprostinil has been described in previous publications. There is no information published about how to handle this system around lung or heart–lung transplantation. We present the experience from the DelIVery for Pulmonary Arterial Hypertension study. Seven subjects from five pulmonary arterial hypertension centers were included in this retrospective chart review. All subjects were participating in the previously described DelIVery for pulmonary arterial hypertension study. Seven subjects with implanted pumps have been listed for lung or heart–lung transplant. Six subjects underwent lung or heart–lung transplantation and one remains on the transplant list. Three different methods of patient management for transplant were used. In three subjects, the implanted system was filled with saline prior to transplantation and treprostinil was infused via an external system. Three subjects had their drug-filled implanted pump and catheter system explanted at the time of transplant. One patient had the drug-filled implanted system removed prior to being listed for transplantation. Four subjects were hospitalized while waiting for transplantation. In conclusion, the implanted system for treprostinil is an important advance in the care of pulmonary arterial hypertension subjects. The experience described here provides three effective strategies for managing the implanted system around lung or heart–lung transplantation. The optimal strategy will depend on patient characteristics and lung transplant program preferences and wait list times.

Keywords
treprostinil, prostacyclin, internal device

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Purpose
The purpose is to provide options for preparing pulmonary arterial hypertension (PAH) subjects with the implanted system for treprostinil (IST) for transplant and potential issues with each option.

Background
PAH is a progressive disease. Despite best management, subjects may still require lung or heart–lung transplantation. The IST delivery has been described previously. Advantages of IST versus traditional treprostinil therapy delivery methods include improved quality of life, fewer infections, and greatly reduced time spent managing medication. The novel central venous catheter for the IST was designed to prevent occlusion due to blood ingestion into the catheter. The catheter has a one-way valve on the vascular end that prevents blood ingestion, but also prevents aspiration of the drug from the catheter. Because the drug cannot be aspirated from the catheter, clinicians should consider using one of the procedures described in the Methods.
section during a system explant in an effort to reduce the risk of overdose to the patient when lung or heart–lung transplantation is planned.

PAH subjects that are deteriorating despite infused prostanoid therapy are often considered for lung or heart–lung transplantation. Subjects may present in acute decompensated right heart failure or experience a more gradual decline that motivates transplant evaluation. Treprostinil therapy is no longer needed after lung transplantation. No data have been published on how the IST is handled around lung or heart–lung transplantation. This manuscript describes the techniques and considerations to reduce the risk of complications during transplantation in patients implanted with IST.

**Methods**

There are three methods that clinicians in the DelIVery for PAH study used to enable lung transplantation for subjects with the implanted treprostinil delivery system.

*Method 1: saline transition prior to transplant*

The saline transition prior to transplant method involved removing treprostinil from the implanted pump’s reservoir and filling it with saline. Accuracy ratios are known to decrease over time with the implanted system and has been disclosed in prior publications. The target dose for the external system was determined by multiplying the programmed dose by the accuracy ratio from the last few refills of the implanted pump. Treprostinil was removed from the reservoir and the reservoir was rinsed with two aliquots of 5 mL of saline. The reservoir was then filled with 40 mL of saline (the maximum capacity of the pump). The implanted pump continued to deliver drug based on the prior infusion settings while treprostinil was delivered from the implanted catheter. Due to gradual dilution of the drug by the saline, the dose of treprostinil being delivered through the implanted system decreased over time. The dilution occurs in a predictable manner due to mixing of treprostinil and saline in the pump tubing and catheter. A modeling tool was developed that factors in the infusion flow rate, the system accuracy, and the catheter length. This modeling tool determines the time at which diluted drug will exit the catheter, and the time until the system delivers only saline. See Fig. 1 for illustration of the drug and saline locations in the implantable system. An external line was placed to deliver treprostinil. Treprostinil from the external line was then increased gradually to keep the total delivered dose of treprostinil stable. Once the transition was complete and the system was delivering only saline, the implanted pump was reprogrammed to minimal flow settings (0.006 mL/day). The pump and catheter system could then be explanted prior to transplant, at the time of transplant, or post-transplant.

*Method 2: explant drug-filled system prior to transplant*

In this method, the implanted pump remained filled with drug at the time of explant but was programed to minimal flow settings and an external line was placed to deliver treprostinil. The target dose for the external system was determined by multiplying the programed dose by the accuracy ratio from the last few refills of the implanted pump.

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**Fig. 1.** Illustration of saline transition.
A surgeon or other physician trained in implanting the system removed the treprostinil-filled pump and catheter system. Great care was taken to ensure that there was no leakage of undiluted treprostinil into the patient during the process.

**Method 3: explant drug-filled system by transplant surgeon on day of transplant**

With removal of the drug-filled system on the day of transplantation, no transition to an external system to deliver treprostinil was required. Prior to lung transplantation, the transplant surgeon was trained in removal of the implantable system. On the day of transplantation, the pump was set to minimum settings during the procedure, just prior to explant. Then, the transplant surgeon removed the drug-filled pump and catheter system taking care to avoid any spillage of undiluted treprostinil into the patient.

**Explanting the pump and catheter system**

Removal of the implanted system should only be performed by trained physicians familiar with the system. See Fig. 2 for key details of the implanted system. The patient was brought to the operating room and the catheter and pump system were evaluated with fluoroscopy to identify the site of the sutureless connector and pump. The sutureless connector is what allows the catheter to be separated from the pump. Identifying the sutureless connector provides the explanting physician with an orientation of the pump and helps to prevent inadvertently cutting into the catheter. After generous local anesthesia, an incision was made in the pectoral region overlying the anchoring device of the catheter. This was then dissected, and the sutures were removed from the anchoring device. Using gentle traction, the catheter was pulled from the vasculature. A suture was then tied firmly around the catheter just before the sleeve valve at the end of the catheter. This served to fully occlude the catheter and prevent any inadvertent leakage of undiluted treprostinil. The anchoring sleeve was then removed from the catheter. A barrier was used to prevent any drug leakage while the pump was liberated.

A second incision was made in the abdominal region to open the pump pocket and gain access to the pump with connected catheter. The catheter was dissected free. The four sutures attaching the pump to the abdominal wall were cut. Using gentle traction, the catheter was then pulled toward the pocket. Once the catheter was fully liberated, the pump and catheter were removed together without disconnecting the catheter from the pump. The pocket was then closed and skin sutured.

**Results**

Five subjects from the Delivery for PAH clinical study underwent bilateral lung transplants, a single patient underwent heart and lung transplant, and one is waiting for transplant. Three different methods were used to facilitate transplants for subjects with the IST. Three of the subjects followed Method 1—saline transition prior to transplant, one followed Method 2—explant drug-filled system by the ISR implanting physician prior to transplant, and three followed Method 3—explant drug-filled system by transplant surgeon on day of transplant. The summary of the transition methods for the seven subjects are shown in Table 1.
| Subject ID  | M100100007 | M100100010 | M100500007 | M100500008 | M100700004 | M100600001 | M100600008 |
|------------|------------|------------|------------|------------|------------|------------|------------|
| PAH managing center | Los Angeles VA | Los Angeles VA | University of Chicago | University of Texas Southwestern Medical Center | Arizona Pulmonary | Brigham and Women’s Hospital | Brigham and Women’s Hospital |
| Transplant date | 21 Jul 15 | 29 Sep 18 | 11 Dec 16 | Listed | 22 Aug 16 | 8 Sep 18 | 8 Feb 19 |
| Transplant performed/planned | Bilateral lung | Heart–lung | Bilateral lung | Bilateral lung | Bilateral lung | Bilateral lung | Bilateral lung |
| Transplant center | UCLA | UCSF | Loyola | N/A | St. Joseph’s | Brigham and Women’s Hospital | Mass Gen Hospital |
| Implanted system filled with saline prior to transplant? | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Date? | 9 Jul 15 | No | 12 May 16 | No | 31 Jul 16 | No | No |
| Hospitalized while waiting for transplant? | Yes | Yes | Yes | Yes | Yes | No | No |
| External delivery of Treprostinil started? | Yes | No | Yes | Yes | Yes | No | No |
| Date? | 9 Jul 15 | 13 May 16 | 28 Jul 17 | 31 Jul 16 | 86 | 85 | 44 |
| Treprostinil dose (ng/kg/min) Prior to transplant? | 103 | 77 | 62 | 149 | 86 | 85 | 44 |
| Pump and catheter explanted? | No | Yes | Yes | Yes | Yes | Yes | Yes |
| Date? | 29 Sep 18 | 11 Dec 16 | 28 Jul 17 | 22 Aug 16 | 8 Sep 18 | 8 Feb 19 | 8 Feb 19 |
| Who? | Transplant surgeon | Transplant surgeon | Delivery implanting surgeon | Transplant surgeon | Transplant surgeon | Transplant surgeon | Transplant surgeon |
| Outcome | Died 6 Jul 16 due to embolic strokes following complicated course post-transplant | Successful transplant; discharged to transitional care on 22 Oct 18 | Died 12 Dec 16 due to hemorrhagic shock from transplant procedure | No transplant as of 2 Oct 19 | Successful transplant; discharged to home on 3 Sep 16 | Successful transplant; discharged to home on 21 Sep 18 | Successful transplant; discharged to rehab on 13 Mar 19 |
Two case studies of Method 1—saline transition prior to transplant, are presented. The planning tool shows the expected dosing profiles of the implanted system and the external system in Figs 3 and 4. The Dose Profile was developed with data from the managing physician specifically for these subjects prior to the saline transition procedure (see Figs 3 and 4). The managing physician planned the external delivery system up titration and entered the dose and transition times on the worksheet (see Figs 3 and 4).

For the one case using Method 3—explant drug-filled system by transplant surgeon on day of transplant, the explant of IST was performed by the trained transplant

Fig. 3. Saline transition dosing profile for case study 1.
surgeon. The IST was explanted after the patient was placed on cardio-pulmonary bypass and prior to removal of the native heart and lung organs.

Four of six subjects survived to discharge, and all are still alive at the writing of this manuscript. One patient died approximately one year after transplant from embolic strokes following a complicated clinical course post-transplant. One patient died the day following transplant due to hemorrhagic shock from the transplant procedure. There were no reported complications associated with
saline transition or removal of the implanted system. The seventh patient remains on the transplant list.

Ten percent of the 60 subjects enrolled in the DelIVery for PAH clinical study had lung or heart–lung transplants within eight years of their initial implant of the IST. The timing of their transplants relative to implant of the IST delivery system is shown in a Kaplan–Meier analysis (see Fig. 5). The transplant probability at 7.2 years was 13.4% with a 95% confidence interval of 6.2–27.6%.

Discussion

In general, PAH expert programs are distinct from lung transplant programs, having different physicians, coordinators, and support staff. Across the country, each lung transplant program has their own protocols and procedures. Best practices reflect a fusion of data and local cultures and tradition. Timing of lung transplantation may be urgent, such as a patient on veno-arterial extra corporeal membrane oxygenation, or more measured in pace such as a patient with slowly declining right ventricular function who remains ambulatory at home but has a high lung allocation score. Furthermore, waitlist times may vary from a few days to many months. Understanding this variability in local culture and clinical circumstances, handling of the implanted system was left to the discretion of each PAH team working with their local transplant team.

As is evident from the diversity of methods used in handling IST around lung or heart–lung transplantation, there is no single best strategy. Filling the implanted pump with saline and transitioning the patient to an external pump system has the advantages of removing all treprostinil from the implanted system prior to transplantation. This prevents any inadvertent overdosing of treprostinil during catheter and pump manipulation during transplantation. Furthermore, the complex process of transitioning to an external pump system is accomplished in a controlled fashion when expertise is available. The main disadvantage of filling the implanted pump with saline is that subjects then require an external pump and its attendant side effects and risks. If subcutaneous delivery is chosen, then subjects will experience site pain. If intravenous delivery is chosen via a central line or a peripherally inserted central line, then there is a small but real risk of infection that could derail the lung transplant process. Transition to a saline-filled system may be preferred in subjects that are acutely ill and will remain in the hospital until transplanted. Hospital staff are then able to manage the external pump.

Explanting a drug-filled system prior to transplantation has the advantages of removing all implanted material prior to lung transplantation. The timing of explantation may be chosen to ensure all needed personnel are present including pump experts and surgical team members. Disadvantages include that the explantation procedure does require some degree of sedation and this could destabilize an already very ill patient. Furthermore, the patient will then require an external system for treprostinil delivery with attendant risks of site pain or bacteremia.

The third strategy of explanting a drug-filled system at the time of lung transplantation has the advantages of continuing uninterrupted delivery of treprostinil until transplant. The patient will not be burdened with relearning an
external pump system and site pain is avoided. The main disadvantages are that the timing of lung transplants is hard to predict and assembling a team of personnel with expertise in the pump and catheter may not be possible. This could be overcome by training the transplant team in advance of the transplant surgery. Additionally, manipulating a treprostinil-filled system could result in inadvertent delivery of undiluted treprostinil that could lead to precipitous hypotension.

The advantages and the scientific reasoning for selecting the three strategies to enable lung or heart–lung transplantation are summarized in Table 2.

Conclusions
The eight-year experience from the DelIVery for PAH study confirms that the IST is not a barrier to safe lung or heart–lung transplantation. The decision of whether to transition to an external infusion system and or remove treprostinil from the implanted system is best made collaboratively by considering patient-specific factors, pulmonary hypertension specialist preferences, and lung transplant team preferences. An understanding of the advantages and disadvantages presented above will facilitate optimal real-world outcomes.

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Conflict of interest
J.A.M., A.A.L., and M.M. are employees of Medtronic, the sponsor of this study. M.G.-M. and B.B. consult for United Therapeutics.

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Author contributions
J.P.F., M.G.-M., S.M.S., R.C.B., and A.B.W. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, including the methods and especially any adverse effects. J.A.M., M.G.-M., S.M.S., R.C.B., and A.B.W. contributed substantially to the data acquisition and interpretation, and the writing of the manuscript. A.A.L., M.M., and J.A.M. contributed substantially to the writing of the manuscript. Additionally, Dr Jeremy P. Feldman, as the primary author, and Dr Robert C. Bourge, Principal Study Investigator and Publication Chair, serve as Guarantors of the Delivery for PAH Study data acquisition, analysis, and writing of the manuscript.

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Table 2. Summary of advantages and disadvantages of the three strategies.

|                      | Saline transition | Explant drug-filled system pre-transplant | Explant drug-filled system at transplant |
|----------------------|-------------------|------------------------------------------|------------------------------------------|
| Advantages           | No risk of treprostinil overdose at transplant | Allows “scheduled” removal by an IST trained team to reduce inadvertent risk of treprostinil overdose. | No transition to external system required prior to transplantation. |
| Disadvantages        | External treprostinil system needed until transplant (IV or SQ) and associated risks (catheter infection) | May destabilize an already ill patient. Risk of inadvertent treprostinil overdose from handling a drug-filled system at time of Removal. External treprostinil system needed until transplant with associated risks (catheter infection) | Assumes transplant surgeon who performs the procedure will be knowledgeable about IST removal. Risk of inadvertent treprostinil overdose from handling a drug-filled system at time of transplantation. |