Perioperative Treprostinil in Pediatric Patients Undergoing the Fontan Operation

Study Protocol and Statistical Analysis Plan

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in Pediatric Patients Undergoing the Fontan Operation

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Background Information

The Fontan operation is performed in patients with single ventricle physiology as the final step to create a circulation in series. First performed in 1971 (Fontan et al, Thorax 1971) for patients with tricuspid atresia, it has since has been modified to serve as the completion phase for all patients with single ventricle physiology. Currently, approximately 1000 Fontan operations are performed per year in the United States (Jacobs et al, World J Pediatr Congenit Heart Surg 2013).

The Fontan operation results in passive systemic venous return to the pulmonary arteries, and as such, a low pulmonary vascular resistance is critical to post-operative recovery and favorable long-term outcomes. It has been well described that a transient increase in pulmonary vascular resistance occurs in the immediate post-operative period as a result of the inflammatory response to surgery with or without cardiopulmonary bypass, manifest clinically as a higher Fontan pressure and higher transpulmonary gradient (the difference between the Fontan pressure and atrial pressure). It is likely due to endothelial dysfunction in the pulmonary arteries with a decrease in vasodilator and increase in vasoconstrictor mediators.

Inhaled nitric oxide as a pulmonary vasodilator has been shown to improve flow through the Fontan circuit (Goldman et al, Circulation 1996) and, in a small case series (Miyaji et al, JTCVS 2003), epoprostenol has been shown to assist in transitioning single ventricle patients off nitric oxide. A recent prospective, non-randomized trial of sildenafil immediately post Fontan did not show a difference in outcomes (Mendoza et al, Cardiol Young 2014).

At many centers, a fenestration is created at the time of the Fontan operation to allow a 'pop-off' of systemic venous blood to the pulmonary venous atrium to maintain low Fontan pressures and cardiac output. While this comes at the expense of hypoxemia, in the immediate post-operative period where a transient increase in pulmonary vascular resistance is seen, it yields a shorter duration of chest tube drainage, length of stay, and smoother post-operative course. At Lucile Packard Children's Hospital (LPCH), our surgeons perform the Fontan operation without cardiopulmonary bypass and without a fenestration, citing the hypoxemia, risk of thromboembolism and need for an additional, subsequent, procedure to close the fenestration as their rationale for this approach.

Patients undergoing a Fontan procedure at LPCH have a median length of hospital stay of ~16 days (McCammond et al, Pediatr Cardiol 2012). Nationally, the median length of stay in the largest series is closer to 8 days (Rogers et al, JACC 2012). We believe that the transient elevation in pulmonary vascular resistance resulting from the surgical insult, greater amount of dissection required (our procedures are done without cardiopulmonary bypass), and lack of a fenestration lead to longer duration of chest tube drainage and length of stay seen in our patients. The use of a fenestration in other institutions allows maintenance of cardiac output during this period of limited pulmonary blood flow and reduces Fontan pressures to limit pleural drainage, but does not reduce pulmonary vascular resistance.

Objectives/Purpose

We hypothesize that perioperative use of subcutaneous treprostinil will minimize the surgically-induced elevation in pulmonary vascular resistance, improve postoperative hemodynamics, decrease the need for post-operative fluid resuscitation, and ultimately result in decreased duration of chest tube drainage and shorter hospital length of stay.

In addition, we believe those shown to be particularly responsive to the postoperative treprostinil may be identifiable pre-operatively using vasodilator testing during their routine pre-operative cardiac catheterization.

Study Design

Randomized, blinded, placebo controlled study in which patients undergoing the Fontan operation at LPCH who are enrolled in the study will receive treprostinil (or saline) in the perioperative period. Subcutaneous treprostinil is normally diluted in normal saline. The placebo group will receive saline alone. Patients will be randomized 1:1 (treprostinil : placebo).

Selection and Exclusion of Subjects

All pediatric patients will be considered eligible if they are undergoing a primary Fontan operation and/or pre-Fontan cardiac catheterization at LPCH.

Exclusion criteria:

1. Platelet count < 50K
2. Dermatologic condition that renders the patient unable to tolerate a subcutaneous infusion (can still take part in inhaled vasodilator testing during cardiac catheterization)
3. Currently receiving any vasodilator therapy specifically for the purpose of pulmonary vasodilation (e.g. Phosphodiesterase Type 5 inhibitor, Endothelin receptor antagonist, Prostacyclin)

Treatment of Subjects

The study will be comprised of 2 parts:

1. *Acute, vasodilator testing with inhaled treprostinil (in the catheterization lab) at the time of pre-operative Fontan catheterization*

   The protocol for administration of inhaled treprostinil has been previously published (Takatsuki et al, Pediatrc Cardiol 2013) and involves 3-6 breaths (18-36 μg) initially, repeated 5 minutes later if no effect with 9 breaths (54 μg) total. Repeat hemodynamics will be performed after drug administration to measure Fontan/pulmonary artery pressure, pulmonary vascular resistance and cardiac index.

2. *Perioperative infusion of subcutaneous treprostinil surgical Day 0 to Day 7.*

   Based on our experience with treprostinil in patients with pulmonary

arterial hypertension (Siehr et al, JHLT 2013) and single ventricle physiology, we propose the following protocol for subcutaneous treprostinil administration in the perioperative period:

The subcutaneous catheter will be placed in the operating room (to minimize discomfort) and the initial infusion (either 2 ng/kg/min or saline-only placebo) will be started after anesthetic induction. Treprostinil will be increased by 2 ng/kg/min every 3 hours to a target dose of 10 ng/kg/min within 24 hours. We anticipate the patient will be on 4ng/kg/min at the completion of the Fontan procedure when transferred to the cardiac intensive care unit. The dose will remain at 10 ng/kg/min through day five, though may be decreased if significant hypotension occurs. Beginning on postoperative day six, the dose will be decreased by 2 ng/kg/min every 8 hours with plans for treprostinil to be discontinued by postoperative day seven.

Assessment of Efficacy

The primary outcome is chest tube duration (days). Chest tube removal (the usual determinant of length of stay) is performed, per protocol, when the total output is less than 2 ml/kg/24 hours. Secondary outcomes include hospital length of stay (days), total volume of chest tube output, time to extubation, amount of fluid intake per 24 hours, blood product administration per 24 hours, urine output per 24 hours, markers of cardiac output (lactate, mixed venous saturation, chemistry panel

looking at end organ function such as BUN, creatinine, liver function tests), in hospital mortality and 12 month mortality. Hemodynamics will include Fontan and atrial pressures while indwelling catheters are present, systolic blood pressure and heart rate over the first 96 hours post-operative. All data collected are part of standard care for this population in our institution.

Cardiac catheterization derived pre-operative hemodynamics, and response to inhaled treprostinil will be recorded and compared to post-operative hemodynamics and post-operative course to determine whether post-operative response to subcutaneous treprostinil correlates with pre-operative testing and to determine whether pre-operative hemodynamics and response to treprostinil "testing" in the catheterization lab can predict which patients received the most benefit from treprostinil.

Assessment of Safety/Adverse Events and report

A research coordinator will track adverse events, which will be immediately reported to Drs. Siehr and Feinstein. The research staff, led by Dr. Siehr, will be responsible for reporting these events to the IRB. A DSMB will meet after the initial six patients are enrolled and quarterly thereafter.

An adverse event is any untoward medical experience occurring to a subject during a clinical trial whether or not it is related to the study drug. An adverse event may include an intercurrent illness, injury, or any other concomitant impairment of the subject's health, as well as abnormal laboratory findings if deemed to have clinical significance. Adverse events may also include worsening of

an existing symptom or condition or post-treatment events that occur as a result of protocol-mandated procedures.

A serious adverse event (SAE) is an adverse event occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

In addition, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and require medical/surgical intervention to prevent one of the outcomes listed above. Life-threatening means that the subject was, in the view of the investigator, at immediate risk of death from the event as it occurred. It does not mean that the event, had it occurred in a more severe form, might have caused death.

An adverse event or SAE occurring during the study must be documented in the subject's source documents and on the appropriate CRF page. Information relating to the adverse event such as onset and cessation date and times, intensity, seriousness, relationship to study drug, and outcome is also to be documented in the CRF. Where possible, adverse events should be recorded using standard medical terminology. If several signs or symptoms are clearly related to a medically defined

diagnosis or syndrome, the diagnosis or syndrome should be recorded on the CRF page, not the individual signs and symptoms.

All adverse events should be followed until either resolution (or return to normal or baseline values), until they are judged by the investigator to no longer be clinically significant, or for at least 4 weeks if the adverse event extends beyond the final visit. All SAEs that occur during the study will be followed until resolution, death, or the subject is lost to follow-up even if they are ongoing more than 4 weeks after completion of the final visit. Supplemental measurements and/or evaluations may be necessary to investigate fully the nature and/or causality of an adverse event or SAE. This may include additional laboratory tests, diagnostic procedures, or consultation with other healthcare professionals. CRF pages should be updated with any new or additional information as appropriate.

The investigators shall report all serious adverse events in English to UT GDS by fax (+ 1 919-313-1297/ +44 (0) 1932 573888) (US/ex-US) or e-mail (drugsafety@unither.com) using a MedWatch 3500A Form/CIOMS I Form (US/ex-US). Cases requiring expedited reporting to the regulatory authority should be sent to UT GDS on or before the date Investigator send the report to the authority and should be the exact document Investigator is submitting to the regulatory authority. All other serious cases should be submitted within 10 days of Investigator initial awareness. For purposes of reportability, UT GDS Day 0 will be the date when we receive the case report from Investigator.

The investigators further agrees to make available promptly to UT GDS such records (e.g., source documents) as may be necessary and pertinent for UT GDS to further investigate a case report.

Should the Investigator receive follow-up information for any serious adverse event reports, Investigator shall be responsible for reporting all follow up to UT GDS by fax (+ 1 919-313-1297/ +44 (0) 1932 573888) (US/ex-US) or e-mail (drugsafety@unither.com) using a MedWatch 3500A Form/CIOMS I Form/MedWatch 3500A Form (US/ex-US), based upon the timelines above, and should be the exact document the Investigator is submitting to the regulatory authority;

In accordance with FDA, European, and national regulations, the sponsor will notify the FDA, other competent authorities, and all participating investigators of any adverse event that is considered to be possibly attributable to study drug and is both serious and unexpected. The investigator must report these adverse events to their IRB or EC in accordance with applicable national regulations and guidelines set forth by the IRB or EC.

Study Discontinuation

The study will end when 42 patients (21 each in the treprostinil and placebo group) have been enrolled. All patients will be under the direct care of physicians in the Division of Pediatric Cardiology throughout the treatment portion of the protocol (in the cardiac catheterization lab, the cardiac intensive care unit, and

acute care floor). Phone follow up with their primary cardiologist and family will be collected 12 months post-operatively.

Statistics, including power calculations and details of data analysis plan

Chest tube duration (days) was analyzed on the natural logarithm scale. The geometric mean of chest tube days in the historical cohort of 138 patients (unselected, date of operation 2004-2012) was 11.8 days and the standard deviation (log scale) was 0.52. With 42 subjects randomized 1:1 we have 80% power to detect a 33% reduction in CT days. These calculations are based on the use of a two-sample t-test with sample sizes 42 and 138 and a one-sided significance level of 5%.

Data handling and record keeping

All data will be kept in RedCap in a dedicated, HIPAA compliant, database. The patient will be coded by as 001 - 042 based on date of enrollment. Only the research staff will have access to the database and all exported data for analysis will be free of identifying information. Data will be entered on a Stanford secured, encrypted, password protected computer.

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