Acute vasoreactivity testing using inhaled treprostinil: Comparison of echocardiography and measured hemodynamics

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Study Description

(1) Study purpose and rationale

Pulmonary arterial hypertension is a clinical syndrome characterized by abnormal elevation of blood pressure within the pulmonary circulation due to pulmonary arterial vasoconstriction, platelet activation, in situ thrombosis, and vascular remodeling which lead to pre-capillary obstruction and increased pulmonary vascular resistance. Ultimately, this can lead to right ventricular failure and death. Treatment is directed at improving clinical symptoms, increasing exercise tolerance and extending survival. Prostanoids, including prostacyclin I2 and prostaglandin E1, have potent vasodilator and platelet anti-aggregator properties. Pulmonary vasodilatation reduces workload of the right ventricle, increases pulmonary blood flow, and lowers the pulmonary arterial pressure resulting in improvement of pulmonary arterial hypertension symptoms and exercise capacity. Therefore, prostanoids were first used to treat PAH beginning in the 1980s. Epoprostenol, first FDA approved in 1995 to treat PAH WHO functional class III-IV, was shown to be efficacious in two prospective, open-label, randomized trials to improve exercise capacity. However, it must be administered via continuous intravenous infusion through a central venous catheter, has a short half-life of 2 to 3 minutes, and is unstable at room temperature. Treprostinil, FDA approved in 2002 to treat APH WHO functional class II-IV, was also shown in two randomized, placebo-controlled trials to improve exercise capacity and long-term survival benefit. Previously, this medication also required administration via continuous intravenous infusion through a central venous catheter or continuous subcutaneous infusion, however it has a half-life of 4.6 hours and is thermostable. In addition to the risks associated with intravenous or subcutaneous administration including infection and subcutaneous infusion site pain, the systemic administration of prostanoids may cause nonselective pulmonary vasodilatation and worsen ventilation/perfusion matching. Iloprost, FDA approved in 2004, is an inhaled form of prostanoid that has been shown to improve hemodynamics; including lowering mean PAP, improving systemic oxygen saturation, lowering the ratio of PVR to systemic vascular resistance; and improving exercise capacity. However, this medication must be administered via nebulizer 6 to 9 times per day with each treatment administration lasting 10 to 15 minutes each. Inhaled treprostinil was approved for adult use in 2010 and requires only 4 administrations per day. A placebo controlled study in adult patients using inhaled treprostinil (TRIUMPH) demonstrated safety and improved exercise capacity in adults with inhaled treprostinil added to background therapy. Evaluation of inhaled treprostinil use in children is limited to one retrospective and one prospective study. A retrospective analysis of 29 children treated with inhaled treprostinil for ≥ 6 weeks demonstrated improved exercise capacity, peak oxygen consumption, and PAH WHO functional class when added to background targeted PAH therapy. Echocardiography analysis demonstrated a decrease in mean tricuspid gradient and follow-up catheterization showed improved right heart parameters, however they were not statistically significant.[i] A prospective analysis in 13 children demonstrated inhaled nitric oxide and inhaled treprostinil significantly decreased mean pulmonary artery pressure and pulmonary vascular resistance index.[ii]

This proposed prospective interventional study will compare echocardiogram and cardiac catheterization measurements obtained in pediatric and adult patients with pulmonary arterial hypertension during inhalation of 21% oxygen, inhaled nitric oxide, and inhaled treprostinil. Echocardiogram data will include cardiac volume, cardiac function, tricuspid regurgitation, pulmonary regurgitation, TAPSE (RV systolic function), RV longitudinal strain, TdS (RV diastolic function), RV SAX diameter change (systolic axillary), FAC (fractional exchange area of RV), IVC diameter/collapsibility and RA size & area. Cardiac catheterization data will include mean right atrial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, mean systemic blood pressure, aortic pressure, pulmonary-to-systemic blood flow, pulmonary-to-systemic resistance and cardiac index (RA, PA, AoP, Qp, Qs, Qp/Qs, Rp, Rs, Rp/Rs, and CI) during inhalation of 21% oxygen, inhaled nitric oxide, and treprostinil. Further, we will evaluate WHO functional class, 6-minute walk distance at annual visit and 1 year follow up as well as survival at 1 year follow up.

(2) Study design and statistical procedures

The primary aim of this study is to compare echocardiogram and cardiac catheterization parameters in PAH

pediatric and adult patients while inhaling 21% oxygen, inhaled nitric oxide or inhaled treprostinil. The proposed study is a prospective interventional study. This study will enroll approximately 20 pediatric and adult patients over a 12 to 18 month period undergoing routine scheduled echocardiograms and cardiac catheterization in the outpatient pediatric cardiology office or the cardiac catheterization lab as part of their routine pulmonary arterial hypertension management. We will evaluate WHO functional class, 6-minute walk distance, and survival. Data to be collected include echocardiogram measurements (cardiac volume, cardiac function, tricuspid regurgitation, pulmonary regurgitation, TAPSE (RV systolic function), RV longitudinal strain, TdS (RV diastolic function), RV SAX diameter change (systolic axillary), FAC (fractional exchange area of RV), IVC diameter/collapsibility, and RA size & area). Cardiac catheterization data will include mean right atrial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, mean systemic blood pressure, aortic pressure, pulmonary-to-systemic blood flow, pulmonary-to-systemic resistance and cardiac index during inhalation of 21% oxygen, inhaled nitric oxide, and treprostinil. Prior retrospective analysis of 29 children treated with inhaled treprostinil for ≥ 6 weeks demonstrated improved exercise capacity, peak oxygen consumption, and PAH WHO functional class when added to background targeted PAH therapy. Echocardiogram analysis demonstrated a decrease in mean tricuspid gradient and follow-up catheterization showed improved right heart parameters, however they were not statistically significant.[iii] A prospective analysis in 13 children demonstrated inhaled nitric oxide and inhaled treprostinil significantly decreased mean pulmonary artery pressure and pulmonary vascular resistance index.[iv]
Statistical analysis will include a paired student's t-test of the above measure parameters between inhaled room air and nitric oxide, as well as inhaled room air and treprostinil.

(3) Study procedures
Pediatric and adult patients in the outpatient cardiology clinic for scheduled routine follow up visits will undergo echocardiography while breathing 21% oxygen (room air) and after the administration of 4 to 6 puffs of nebulized treprostinil via the OPTINEB system. Echocardiogram images will be obtained and further analyzed to obtain measurements including; cardiac volume, cardiac function, tricuspid regurgitation, pulmonary regurgitation, TAPSE (RV systolic function), RV longitudinal strain, TdS (RV diastolic function), RV SAX diameter change (systolic axillary), FAC (fractional exchange area of RV), IVC diameter/collapsibility, and RA size & area).
Pediatric and adult patients admitted to the cardiac catheterization lab for scheduled routine follow up visits will undergo cardiac catheterization. Measurements will be obtained under three conditions including 21% oxygen, 80ppm inhaled nitric oxide, and inhaled treprostinil. Cardiac catheterization data will be obtained including; mean right atrial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, mean systemic blood pressure, aortic pressure, pulmonary-to-systemic blood flow, pulmonary-to-systemic resistance and cardiac index. Basic hemodynamic parameters will also be monitored for the duration of the cardiac catheterization including heart rate, mean arterial blood pressure, arterial oxygen saturation and central venous pressure/right atrial pressure.
We will determine WHO functional class and 6-minute walk distance at initial presentation and follow-up at 1 year. We will also determine 1 year survival in all tested patients.
Finally, baseline patient characteristics such as age, sex, weight, diagnosis, and medications will be obtained from the electronic medical records.

(4) Study drugs or devices
Treprostinil nebulized via the OPTINEB-ir Model ON-100/7 ultrasonic nebulizer (hand-held, ultrasonic, single-breath nebulizer, Metropolitan Medical Inc., Winchester, VA, USA) via anesthesia mask with a flow-inflating bag (for sedated patients breathing through a natural airway) or the manual mode of the anesthesia system in synchrony with the OPTINEB's inhalation indicator (for anesthetized patients breathing through an endotracheal tube or laryngeal mask airway). FDA approved device for adult, children and neonates (??).

(5) Study Instruments
No study questionnaires will be used in this study.

(6) Study subjects
Our target population will include all pediatric and adult patients undergoing scheduled echocardiography and cardiac catheterization as part of annual pulmonary arterial hypertension management in the outpatient pediatric cardiology clinic and MSCHONY cardiac catheterization lab. Patients will be excluded if they have a history of an

adverse reaction to treprostinil.

(7) Recruitment
The patient's physician of record or a member of the medical team caring for the patient will ask subjects and/or parents of subjects who meet the inclusion criteria if they are willing to discuss participation in a research study. If they are agreeable, we will approach the patient and family to obtain consent/assent. We will obtain consent/assent in the hospital either on admission to the outpatient cardiology clinic or cardiac catheterization lab or at the visit prior to the annual follow up in the office of the cardiologist.

(8) Informed Consent Process
Informed consent will be obtained from patients or parents of patients and informed assent from patients who qualify to give assent. Informed consent/assent will be obtained by the investigators (i.e. Drs. Krishnan, Zuckerman, Haxel, or ….) at the time of recruitment in the form of a written consent requiring either the parent or patient's signature. In-person or phone interpreters will be provided for non-English speaking parents and patients to translate the written consent. No visual aids will be utilized.

(9) Confidentiality of study data
Every reasonable effort will be made to protect the confidentiality of patients' records. All personal information will be handled in strictest confidence and in accordance with data protection laws. The investigators only will collect the data. The patient identification number will be used in the echocardiogram images and cardiac catheterization lab. There will be some personal information collected by the investigators to allow accurate records in case of needed review. After collection, the study subjects will be given a unique identifier for further reference. The analysis of the data will be performed on de-identified data by the investigators with the help of a statistician. No personal information will be attached to the data analysis.

(10) Privacy Protections
Study subjects' personal and identifying information will be held in the strictest of confidence and in accordance with data protection laws. The investigators only will collect the data. After collection, the study subjects will be given a unique identifier for further reference. The analysis of the data will be performed on de-identified data by the investigators with the help of a statistician.

(11) Potential risks
There are risks of headache, flushing, hypotension, jaw pain with initial mastication, diarrhea, nausea, blotchy erythematous rash, musculoskeletal aches in legs/feet, cough, sore throat, desaturation, dyspnea and chest tightness with inhaled treprostinil. Subjects recruited for the study will have previously or currently used inhaled treprostinil to treat pulmonary arterial hypertension. Likely, this population would have discontinued treprostinil use if the adverse effects were intolerable. Therefore, the subjects will likely have minimal adverse effects.
There is a risk of infection during cardiac catheterization. The procedure will be performed under sterile techniques to prevent infection.

(12) Data and Safety Monitoring
Data and Safety monitoring will occur on an ongoing basis by the clinicians and staff caring for the subjects as they are all admitted to the MSCHONY outpatient cardiology clinic and cardiac catheterization lab. Any unanticipated problems will be alerted to the investigators in a timely manner.

(13) Potential benefits
There are no benefits to the study subject.

(14) Alternatives
There will be no alternative treatment. Patients will either consent to the study and be enrolled or not participate.

(15) Research at External Sites
Pediatric Cardiac Catheterization Unit (MSCHONY 3 Tower) and Pediatric Cardiology Outpatient Clinic

(MSCHONY 2 North). This will not involve patients from non-Columbia University sites.

(16) Columbia as Lead Institution
This is not a multi-center study.

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[i] Krishnan U, Takaatsuki S, Ivy DD, Kerstein J, Calderbank M, Coleman E, Rosenzweig EB. "Effectiveness and safety of inhaled treprostinil for the treatment of pulmonary arterial hypertension in children." Am J Cardiology. Dec 2012. 1;110 (11): 1704-9.

[ii] Takatsuki S, Parker DK, Doran AK, Friesen RH, Ivy DD. "Acute pulmonary vasodilator testing with inhaled treprostinil in children with pulmonary arterial hypertension." Pediatric Cardiology. April 2013; 34 (4):1006-12.

[iii] Krishnan U, Takaatsuki S, Ivy DD, Kerstein J, Calderbank M, Coleman E, Rosenzweig EB. "Effectiveness and safety of inhaled treprostinil for the treatment of pulmonary arterial hypertension in children." Am J Cardiology. Dec 2012. 1;110 (11): 1704-9.

[iv] Takatsuki S, Parker DK, Doran AK, Friesen RH, Ivy DD. "Acute pulmonary vasodilator testing with inhaled treprostinil in children with pulmonary arterial hypertension." Pediatric Cardiology. April 2013; 34 (4):1006-12.