Research Proposal

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Title of project: **Treatment of Pediatric Pulmonary Arterial Hypertension Using Oral Selexipag**

A. Study Rationale and Background

Pulmonary arterial hypertension (PAH) in children is a severe disease with significant morbidity and mortality [1]. Survival and functional status can be significantly improved by available treatment, which generally consists of combination therapy targeting the endothelin pathway, nitric oxide pathway, and prostacyclin pathway.

This study will focus on the prostacyclin pathway, which targets receptors on endothelial cells within the pulmonary vasculature and leads to vasodilatation. Endothelial cells contain prostacyclin synthase enzymes in high concentrations and secrete prostaglandin I2 (PGI2), or prostacyclin. PGI2 causes vascular smooth muscle relaxation through an upregulation of the intracellular level of cAMP [2]. Traditionally, this pathway has been targeted through intravenous prostacyclins such as epoprostenol and treprostanil, requiring the use of subcutaneous infusions or a central line.

Selexipag is an orally active non-prostanoid selective agonist of the prostacyclin receptor, with vasodilatory, antiproliferative, and anti-inflammatory properties. Selexipag was FDA-approved in adults after the 2015 GRIPHON trial in 1156 adults showing decreased rates of death and complications from progressive disease [3]. Studies of the safety and efficacy of off-label use of selexipag in children are limited, but have shown some promising effects in case series and small cohorts [4-6].

B. Study Aims

Evaluate the safety and efficacy of oral selexipag in children

a) as add on therapy to dual endothelin receptor antagonist / phosphodiesterase -5inhibitor (ERA/PDE5i) treatment in patients not previously receiving prostacyclin receptor-targeting agents

b) as an alternative to intravenous or inhaled prostacyclin medications in patients also on ERA/PDE5i therapy

C. Methods

This will be a retrospective observational study including children from two pediatric PAH centers (Columbia University Medical Center and Children's Hospital of Colorado). Demographics, symptoms, adverse events, WHO functional class, echocardiography, hemodynamics, 6MWD, CPET, NT-proBNP will be collected at baseline and early and late follow up.

Data parameters (6MWD, NT-proBNP, catheterization and echocardiographic data) will be compared at baseline and follow-up. Two -tailed, paired Student's t tests will be used to compare key variables before and after selexipag initiation or transition from intravenous prostacyclin to oral selexipag, with a p value <0.05 considered statistically significant.

We expect an N of 25-35 patients once data collection at our Colorado site is complete, for which we will be powered to detect approximately one half a standard deviation of difference between groups

(irrespective of measure). As the number of subjects will be fixed in this study, more explicit power analysis will be done after data collection is complete.

D. Study Drugs: None
E. Medical Device: None
F. Study Questionnaires: None
G. Study Subjects: Study population will include patients who received care at the two above centers, diagnosed with PAH by cardiac catheterization at <18 years of age, and treated with oral selexipag. Diagnosis of PAH is defined as mean pulmonary arterial pressure ≥25 mm Hg, mean pulmonary capillary wedge pressure ≤15 mm Hg, and pulmonary vascular resistance index (PVRi) ≥3 Woods units*m2.
H. Recruitment of subjects: Subjects will be recruited from retrospective chart review. This study will apply for waiver of consent.
I. Confidentiality of Study Data: Chart review will be done only on secure, password protected computers. All patient identifiers will be removed from the electronic data set prior to analysis, and each patient will be assigned a unique study ID number. A separate file correlating this study number with patient identifiers will be kept in a secure, password protected database. Only the study personnel will have access to the file, which will be kept on encrypted endpoint devices.
J. Potential Conflict of Interest: None
K. Location of the Study: Columbia/CUMC and Children's Hospital of Colorado
L. Potential Risks: Not applicable
M. Potential Benefits: There will be no direct benefit to the participant.
N. Alternative Therapies: Not Applicable
O. Compensation to Subjects: None
P. Costs to Subjects: None
Q. Minors as Research Subjects: Not Applicable
R. Radiation or Radioactive Substances: Not Applicable

References:

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3. Sitbon, O., et al., *Selexipag for the Treatment of Pulmonary Arterial Hypertension.* New England Journal of Medicine, 2015. **373**(26): p. 2522-2533.
4. Gallotti, R., et al., *Single-Center Experience Using Selexipag in a Pediatric Population.* Pediatric Cardiology, 2017. **38**(7): p. 1405-1409.
5. Geerdink, L.M., H. Bertram, and G. Hansmann, *First-in-child use of the oral selective prostacyclin IP receptor agonist selexipag in pulmonary arterial hypertension.* Pulmonary Circulation, 2017. **7**(2): p. 551-554.
6. Hansmann, G., et al., *Selexipag for the treatment of children with pulmonary arterial hypertension: First multicenter experience in drug safety and efficacy.* J Heart Lung Transplant, 2020.