The Role of Trimetazidine on Right Ventricle Function in Pulmonary Arterial Hypertension in National Cardiovascular Center Harapan Kita Hospital (TRIMETA-PH)

STUDY PROTOCOL AND STATISTICAL ANALYSIS

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This study is a single centre, randomized, double-blind, placebo-controlled, proof of concept study of trimetazidine effect in RV function of PAH patients. The study protocol was approved by the institutional review board in National Cardiovascular Center Harapan Kita Hospital Universitas Indonesia (NCCHK-UI). The member of committee were involved in the study design, protocol review, and guidance throughout the study conduct. All patients gave written informed consent.

Study Population

Patients which eligible for the study were recruited from (NCCHK-UI) PAH outpatient clinic. Patients were selected based on following inclusion and exclusion criteria. Inclusion criteria including age 18-65 years old, presence of precapillary pulmonary hypertension mPAP $\geq$ 25 mmHg with left ventricle end diastolic pressure (LVEDP) or mean left atrial pressure (mLAP) $\leq$ 15 mmHg, WHO functional class II or III, evidence of RV dysfunction with RVEF < 45% according to cardiovascular magnetic resonance imaging (CMR), and stable dose of pulmonary vasodilator therapy in the 4 weeks before randomization.

Exclusion criteria including LVEDP or mLAP > 15 mmHg, WHO functional class IV, pregnancy or lactation, severe renal dysfunction with estimated glomerular filtration < 30 ml/min/1.73 m2 or routine hemodialysis, presenting malignant arrhythmia, left ventricular ejection fraction (LVEF) < 50%, claustrophobia, and Parkinson disease.

Study Protocol

Patients who met the following inclusion and exclusion criteria will be randomized in 1:1 ratio to receive twice-daily 35 mg trimetazidine or twice-daily placebo on top of their standard PAH regime for 3 months. Study procedure included cardiac catheterization at baseline, physical examination, SF-36 functional capacity questionnaire, and CMR examination at baseline and after 3 month treatment. Follow-up visits will be recorded during annual PAH outpatient visit at months 1,2, and 3. Adherence to study medication was encourage throughout study period including phone call reminder and pill counts during annual outpatient visit. All adverse event were recorded, including major adverse cardiovascular event (MACE) which defined as severe deterioration of health resulting in death, risk of death, hospitalization, or disability.

Participants required right heart catheterization to evaluate the eligibility. Right heart and pulmonary artery catheterization was performed from the right femoral vein approach. Multipurpose (MP) catheter was used to record mPAP (MP 90cm, Mach1^{TM}, Boston Scientific. Left heart catheterization was performed from right femoral artery using pigtail 6F catheter to record LVEDP (pigtail6F, Boston Scientific). In the case of PAH due to congenital heart disease with left to right shunt, we measured mLAP using MP catheter directly from the appropriate shunt. Pressure recordings were analyzed using Siemens Axiom Sensis XP.

Participants underwent CMR (Phillips Achieva 1.5 Tesla) examination at baseline and after 3 months treatment to assess RVEF, LVEF, LV and RV end diastolic volume (RVEDV and LVEDV0, RV and LV end systolic volume (RVESV and LVESV), and fibrosis using native T1 mapping. General RV and LV structure and function protocol

were conducted according to SMCR guideline 2013. Cardiac fibrosis analysis was performed using Look Locker imaging protocol. All CMR analysis was done using circle CVI42 version 5.9 software (Circle Cardiovascular imaging inc. Canada).

Functional class was assessed during monthly visit according to WHO. Their functional status was calculated using short form health survey (SF-36) questionnaire which was recorded at baseline and after 3 months treatment.

Study Outcomes

The primary outcome was the differences of RVEF after 3 months therapy of trimetazidine or placebo group. Secondary outcomes included the differences of clinical outcomes, WHO functional class, functional capacity based on SF-36 questionnaire, lactate dehydrogenase and others CMR parameters after 3 months therapy of trimetazidine or placebo group.

Statistical Analysis

The type I error was set two-sided 0.005 with power of 80%. Approximately a minimum 18 patients with PAH and RV dysfunction will be randomized in 1:1 ratio to trimetazidine and placebo group after adjusting to 10% of dropout. A two-sided p value <0.05 was considered statistically significant. Baseline demographic, clinical, laboratory, heart catheterization, and CMR parameters were compared between trimetazidine and placebo group at baseline. Normal distribution of continuous and categorical data were displayed as mean $\pm$ standard error mean and percentage respectively. Categorical data were analyzed using either fisher exact test if one of the data column less than 5 or

Chi square test for larger data. Numerical data were analyzed using independent t tests between trimetazidine and placebo group. Multivariate analysis of covariance (ANCOVA) was performed to determine treatment effect. All analyses were performed using SPSS version 23 (SPSS inc, IBM, Armonk, New York).

TRIMETA-PH Study Protocol