PROTOCOL PAPER

Effects of Dual Initial Combination Therapy With Macitentan Plus Riociguat or Macitentan Plus Selexipag on Hemodynamics in Patients With Pulmonary Arterial Hypertension (SETOUCHI-PH Study)
— Protocol of a Multicenter Randomized Control Trial —

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Background: The latest guideline from the European Society of Cardiology and European Respiratory Society recommends initial combination therapy with oral pulmonary arterial hypertension (PAH)-specific drugs in PAH patients with World Health Organization functional class (WHO-FC) II or III. However, whether this initial combination therapy improves hemodynamics and clinical failure events regardless of the combination of PAH-specific drugs remains unknown. This study was designed to evaluate whether the initial combination therapy with macitentan plus riociguat or macitentan plus selexipag showed equal efficacy in reducing pulmonary vascular resistance (PVR) 8 months after administration.

Methods and Results: This study is a multicenter randomized control trial. PAH subjects with WHO-FC II or III will be randomized (1:1) into initial combination therapy with either macitentan plus riociguat or macitentan plus selexipag, and will be observed 8 months after the initiation of treatment. The primary endpoint will be the difference in the change ratio of PVR from baseline to after 8 months of treatment.

Conclusions: The SETOUCHI-PH study will clarify whether initial combination therapy with macitentan plus riociguat or macitentan plus selexipag results in equal reductions in PVR 8 months after administration.

Key Words: Combination therapy; Macitentan; Riociguat; Selexipag

Pulmonary arterial hypertension (PAH) is associated with a poor prognosis and a significant elevation in pulmonary artery pressure and pulmonary vascular resistance (PVR) caused by idiopathic, heritable, and collagen diseases, congenital heart diseases, and drugs. Nitric oxide (NO), prostacyclin, and endothelin pathways are primarily associated with the pathogenesis of PAH.[1]

NO and prostacyclin production decreases and endothelin production increases in patients with PAH. Recently, various drugs acting on these pathways have been developed for the treatment of PAH. Prostaglandin I$_2$ IP receptor agonists, endothelin receptor antagonists, phosphodiesterase 5 inhibitors, and soluble guanylate cyclase stimulators are currently available worldwide. Patients treated with these

Figure. Study flow chart. CT, computed tomography; ECG, electrocardiogram; MRI, magnetic resonance imaging.

PAH-specific drugs show improved hemodynamics, exercise capacity, and survival.[2]

A sufficient reduction in pulmonary artery pressure and PVR is known to contribute to the improved long-term survival of patients with PAH.[3] Initial combination therapy, which involves the concomitant administration of multiple drug combinations early in therapy before confirming the clinical response to a single medication, is thought to lead to good hemodynamic responses. AMBITION (A Study of First-Line Ambrisentan and Tadalafil Combination Therapy in Subjects With Pulmonary Arterial Hypertension [PAH]) showed that initial combination therapy with ambrisentan and tadalafil reduced the risk of clinical failure events compared with monotherapy.[4] The latest guideline from the European Society of Cardiology (ESC) and European Respiratory Society (ERS) recommends dual initial combination therapy with oral PAH-specific drugs in PAH patients with World Health Organization functional class (WHO-FC) II or III.[5] However, whether initial combination therapy can improve hemodynamics and clinical failure events regardless of the combination of PAH-specific drugs is unknown.

Recently developed PAH-specific drugs include macitentan (an endothelin receptor antagonist), riociguat (a soluble guanylate cyclase stimulator), and selexipag (an IP receptor agonist).[6,7] The SETOUCHI-PH (Effects of Dual Initial Combination Therapy With Macitentan Plus Riociguat or Macitentan Plus Selexipag on Hemodynamics in Patients With Pulmonary Arterial Hypertension) study has been designed to evaluate whether initial combination therapy with macitentan plus riociguat or macitentan plus selexipag results in equal reductions in PVR 8 months after administration.

Methods

Study Design
SETOUCHI-PH is an ongoing multicenter prospective open-label randomized control evaluation of equivalence study. The study was approved by the Ethics Committee at Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (Protocol no. 1509–006) and the ethics committees of each participating center. The study has been registered with the UMIN Clinical Trial Registry (ID: UMIN000035389) and will be conducted in compliance with the Declaration of Helsinki. Written informed consent will be obtained by trial investigators from all participants prior to enrolment.

Participants
Inclusion Criteria To be eligible for inclusion in the study, patients need to meet any of the following criteria: (1) mean pulmonary artery pressure ≥25 mmHg, pulmonary artery wedge pressure ≤15 mmHg, and PVR ≥3 wood units by right heart catheterization within 1 month of providing consent; (2) WHO-FC II or III; (3) age ≥20 years; and (4) provision of written informed consent prior to participation.

Exclusion Criteria Patients meeting any of the following criteria will be excluded from the study: (1) pulmonary hypertension without PAH; (2) the use of PAH-specific drugs; (3) the use of drugs contraindicated for use with macitentan, riociguat, and selexipag; (4) bleeding or at risk of bleeding; (5) among women, pregnancy or suspected pregnancy or breast-feeding; (6) the presence of atrial fibrillation; (7) the presence of renal dysfunction (creatinine >1.5 mg/dL); (8) the presence of liver dysfunction (serum aspartate aminotransferase or alanine aminotransferase >2-fold standard values); (9) the presence of hypotension (systolic blood pressure <90 mmHg); (10) the presence of low cardiac output (cardiac index <2.0 L/min/m²); (11) having received an investigational agent within 3 months; and (12) deemed inappropriate for inclusion in the study by the attending physician.

Study Outline and Randomization
Patients fulfilling all the inclusion criteria, including

Table. Evaluation Schedule

Assessment	Enrolment	Observation period						Postobservation period	
		Day 1	Day 2	Day 3	Day 7	12 weeks	32 weeks	1 year	2 year
Informed consent	×								
Clinical symptoms	×	×	×	×	×	×	×	×	×
Adverse events		×	×	×	×	×	×	×	×
Vital signs	×	×	×	×	×	×	×	×	×
Body weight	×						×		
Laboratory test	×			×	×	×	×	×	×
Chest radiography	×			×	×	×	×	×	×
Electrocardiogram	×			×	×	×	×	×	×
Echocardiography	×			×	×	×	×	×	×
Chest CT	×								
V/Q scan	×								
Lung function test	×						×		
RHC	×						×	(×)	(×)
6MWD	×			×	×	×	×	×	×
cMRI (optimal)	(×)						(×)	(×)	(×)

6MWD, 6-min walk distance; cMRI, cardiac magnetic resonance imaging; CT, computed tomography; RHC, right heart catheterization; V/Q scan, ventilation/perfusion scan.

providing written informed consent, will be enrolled and subsequently randomized (1:1) to receive macitentan (10 mg, q.d.) plus riociguat (0.5 mg, t.i.d.) or macitentan (10 mg, q.d.) plus selexipag (0.2 mg, b.i.d.). Randomization will be performed using a computer-generated random sequence web response system. Patients will be stratified by age (<65 and ≥65 years), mean pulmonary artery pressure (<40 and ≥40 mmHg), and cardiac index (2.0–3.0 and ≥3.1 L/min/m²).

The study design is shown in **Figure**. Assessments during the study period are listed in **Table**. Patients will be administered macitentan (10 mg, q.d.) on Day 1. On Day 3, a blood examination will be performed to determine the presence or absence of side effects, such as liver and renal dysfunction. If there are no signs of side effects, then riociguat (1 mg, t.i.d.) or selexipag (0.2 mg, b.i.d.) will be added. On Day 7, chest radiography, laboratory tests, electrocardiography, 6-min walk distance (6MWD) tests, and echocardiography will be performed. If there are no signs of side effects, the patient will be discharged from hospital. Titration of riociguat and selexipag will be possible according to the medical package insert. At 12 weeks, chest radiography, laboratory tests, electrocardiography, 6MWD tests, and echocardiography will be performed. At 32 weeks, chest radiography, laboratory tests, electrocardiography, 6MWD tests, echocardiography, lung function tests, and right heart catheterization will be performed. Safety and tolerability will be assessed during the observation period. The medications permitted for the treatment of right heart failure include diuretics and oxygen therapy.

Outcomes

Primary Outcome The primary outcome of this study is the difference in the change ratio of PVR from baseline to after 8 months of treatment between the macitentan plus riociguat and macitentan plus selexipag groups.

Secondary Outcomes Key secondary outcomes of this study are differences between the macitentan plus riociguat and macitentan plus selexipag groups in B-type natriuretic peptide (BNP), echocardiographic parameters, pulmonary function parameters, hemodynamic parameters and 6MWDs. Differences are defined as differences in values for each of these parameters between follow-up and baseline.

Safety Outcomes Safety will be assessed based on: adverse events reported throughout the study; clinical laboratory tests, including liver and renal function tests; vital signs, including hypotension; and physical examinations. Adverse events, including death and worsening of PAH, will be assessed.

Data Monitoring

The study has recruited 9 hospitals in Japan. Members of the steering committee designed the study and are responsible for its oversight. Significant adverse events will be immediately reported to the steering committee by investigators. On-site or telephone monitoring, including source document verification, will be conducted.

Sample Size and Power Calculation

Since the start of recruitment in April 2019, no interventional studies of the effects of dual initial combination therapy with macitentan plus riociguat or macitentan plus selexipag on hemodynamics in patients with PAH have been reported. Therefore, we estimated the sample size based on the effect of each treatment option (selexipag or riociguat) on hemodynamic changes. Previously, riociguat was reported to reduce PVR by a mean (±SD) of 223±260 dyn/s/cm⁵,[8] whereas selexipag was reported to reduce PVR by a mean (±SD) of 130±310 dyn/s/cm⁵.[9] Based on these studies and a PVR of 80 dyn/s/cm⁵ as the non-inferiority margin (β=0.2, 1-sided α=0.05), 68 patients (n=34 in each group) are required. With 10% of patients estimated to withdraw during the study period, the final enrolment was set at 76 patients (n=38 patients).

Statistical Analysis

Primary and secondary outcomes will be analyzed using the full study population. Patients who withdraw or

discontinue treatment will be excluded from the full study population. The safety analysis will be conducted in the safety analysis population, which will include all patients who were randomized to 1 of the groups and received at least 1 dose of either riociguat or selexipag.

Baseline variables will be presented as frequencies and proportions for categorical data and as the mean±SD for continuous data. Patient characteristics will be compared using Pearson's χ^2 test or Fisher's exact test for categorical data and Student's t-test for continuous data. The primary outcome analysis will be based on an analysis of covariance (ANCOVA; level of significance set at $\alpha=0.05$) for the PVR change rate. Adjusted covariates will include baseline age, baseline sex, baseline blood pressure, baseline WHO-FC, and baseline BNP. Secondary outcomes will be analyzed in the same manner as the primary outcome. Adverse events will be evaluated during the safety analysis. The frequencies of adverse events will be compared using Fisher's exact test. All comparisons are planned, and all P values will be 2-sided; P<0.05 will be considered statistically significant. All statistical analysis will be performed using IBM SPSS Statistics 25 (IBM, Armonk, NY, USA). A statistical analysis plan will be developed by the principal investigator and biostatistician before completion of patient recruitment and data fixation.

Discussion

An algorithm for the treatment of PAH in Europe and Japan recommends initial combination therapy for patients with WHO-FC II or III.[5,10] A prospective event–double-blind randomized control study of initial combination therapy with ambrisentan and tadalafil (AMBITION) affected this algorithm. PAH patients with WHO-FC II or III who had not previously received treatment were assigned in a 2:1:1 ratio to be administered initial combination therapy with 10mg ambrisentan plus 40mg tadalafil, 10mg ambrisentan plus placebo, or 40mg tadalafil plus placebo.[4] The primary endpoint was the first clinical failure, defined as the first occurrence of a composite of death, hospitalization for worsening PAH, and disease progression. The hazard ratio for the primary endpoint in the initial combination therapy group vs. the monotherapy group was 0.5. Initial combination therapy with ambrisentan and tadalafil resulted in a significantly lower risk of clinical failure events than the risk associated with ambrisentan or tadalafil monotherapy.[4] AMBITION is the only prospective study confirming an improvement following initial combination therapy. However, AMBITION showed the efficacy of initial combination therapy compared with monotherapy, and no study has compared each initial combination therapy. Furthermore, whether initial combination therapy regardless of the PAH-specific drugs administered results in similar outcomes is unknown. To address this, we aim to conduct a multicenter prospective open-label randomized control study of initial combination therapy with macitentan plus riociguat or macitentan plus selexipag.

We defined the primary endpoint as the change ratio of PVR from baseline to after 8 months of treatment. The ITALY study evaluated hemodynamic parameters after initial combination therapy with tadalafil and ambrisentan in patients with PAH,[11] showing an improvement in PVR by 41% after treatment. This is considered to be clinically relevant, but the sample size was very small (n=19). A decrease in PVR with PAH therapies has been associated with improvements in clinical outcomes.[12–14] We designed the treatment period in the SETOUCHI-PH study to be 32 weeks because riociguat and selexipag require dose titration. The dose of riociguat can be increased at least every 2 weeks, and the dose of selexipag can be increased at least once a week. Because we want to evaluate the effects of the maximum dose of these drugs, we set the treatment period to 32 weeks. We designed the SETOUCHI-PH study to evaluate equivalence because we speculate that initial combination therapy will contribute to good hemodynamic outcomes regardless of the PAH-specific drugs used.

Disclosures

H.I., K.N. are members of *Circulation Reports*' Editorial Team. The remaining authors have no competing interests to declare.

IRB Information

This study and its protocol were approved by the Ethics Committee at Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (Protocol no. 1509–006) on January 15, 2019. This study is registered with the UMIN Clinical Trial Registry (ID: UMIN000035389).

Data Availability

There is a plan to make individual participant data (IPD) and related data dictionaries available. We will share IPD that underlie the results reported in the article after deidentification. The study protocol will be available. Data sharing will begin from 6 months and end 2 years after article publication. Data will be shared with researchers who provide a methodologically sound proposal to achieve aims in the approved proposal. Data are available at UMIN-ICDR (https://www.umin.ac.jp/icdr/index-j.html).

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