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COMMENTARY

Treatment for pulmonary hypertension due to left heart diseases

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Left heart diseases (LHD), including heart failure with preserved or reduced ejection fraction (HFpEF or HFrEF), are thought to be the most common causes of pulmonary hypertension (PH) and are associated with a poor prognosis. The establishment of an effective therapy is needed.

TREATMENT OF PH-LHD WITH PULMONARY ARTERIAL HYPERTENSION (PAH)-APPROVED DRUGS

LHD causes an increase in left atrial pressure, followed by passive backward transmission of the pressure, leading to increased pulmonary arterial pressure (PAP). Importantly, the elevation of PAP and pulmonary vascular resistance is observed in some patients with LHD due to increased pulmonary artery vasomotor tone and/or pulmonary vascular remodeling. Further, endothelial dysfunction, such as increased endothelin 1 activity and impaired nitric oxide (NO)-dependent vasodilatation, is observed in patients with heart failure. Therefore, the use of pulmonary arterial hypertension (PAH)-approved drugs (endothelin receptor antagonists (ERA), prostaglandin I_2 (PGI_2), phosphodiesterase type-5 inhibitor (PDE5I) and soluble guanylate cyclase stimulator) has been proposed.

CLINICAL TRIALS WITH ERA AND PGI_2

The effects of ERA and PGI_2 on outcome in patients with systolic heart failure (patients with HFrEF) have been assessed in several randomized clinical trials (RCTs). However, patients have not been stratified by the presence or absence of PH in these previous studies.

In two RCTs, the Research on Endothelin Antagonism in Chronic Heart Failure (REACH-1) study[1] and the Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure (ENABLE) study,[2] the safety and efficacy of bosentan for patients with HFrEF were assessed. The REACH-1 trial was interrupted due to drug-induced adverse events (liver function test abnormalities). The ENABLE trial failed to demonstrate any benefits for mortality and hospitalization.

Prostacyclin (PGI_2) therapy by epoprostenol infusion is one of the best treatments available for PAH.[3] Epoprostenol treatment improved symptoms, exercise capacity, and hemodynamics and reduced mortality in patients with idiopathic PAH in RCTs. In the Flolan International Randomized Survival Trial (FIRST), the effects of epoprostenol in patients with severe HFrEF (New York Heart Association Class IIIB or IV) were evaluated.[4] Despite favorable hemodynamic effects, including an increase in cardiac index and decreases in pulmonary capillary wedge pressure and systemic vascular resistance, the trial was terminated early because of a strong trend toward decreased survival in patients treated with epoprostenol.

Thus, the results of those trials using ERA and PGI_2 for patients with heart failure (HF) were negative and disappointing.

CLINICAL TRIALS WITH PDE5I

In contrast to ERA and PGI_2, increasing evidence suggests that PDE5I is effective in patients with PH-LHD. Wu *et al.*[5] have reported a meta-analysis of six RCTs to evaluate the effectiveness of sildenafil for PH-LHD with HFrEF. In the previous issue of *Hypertension Research*, Jiang *et al.*[6] also report a meta-analysis of nine RCTs and one observational study with a control group to evaluate the effectiveness of sildenafil for PH-LHD with HFrEF. Sildenafil therapy is a possible therapeutic method for improving pulmonary hemodynamics and exercise capacity in PH-LHD patients with HFrEF.

PDE5 is abundantly expressed in the vascular smooth muscle in normal hearts, and expression is increased in cardiac myocytes and the vascular smooth muscle of failing hearts. Sildenafil has been shown to activate myocardial cyclic GMP-dependent protein kinase and ameliorate cardiac hypertrophy and remodeling in a mouse model of pressure overload.[7] These effects may contribute to the favorable results of PDE5I in PH-LHD patients with HFrEF. Further studies are needed to clarify the effects of PDE5I on cardiac hypertrophy and remodeling in PH-LHD patients with HFrEF.

For HFpEF patients, one placebo-controlled study has demonstrated a potential therapeutic effect of sildenafil on PH in HFpEF.[8] However, the Phosphodiesterase-Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction (RELAX) trial failed to show a beneficial effect of sildenafil,[9] probably because the HFpEF patients without a catheterization-documented PH complication were also enrolled in the RELAX trial. These results suggest that the beneficial effects of sildenafil cannot be expanded to all patients with heart failure.

Combination therapy with PDE5I and ERA in patients with PAH are used in daily clinical practice.[10] The efficacy and safety of PDE5I combined with an agent used in conventional therapy for HFrEF, such as an angiotensin-converting enzyme inhi-

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bitor, angiotensin receptor blocker, beta blocker or aldosterone receptor antagonist, in PH-LHD patients with HFrEF remains unknown.

CLINICAL TRIALS WITH SOLUBLE GUANYLATE CYCLASE STIMULATOR

In the Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension Riociguat Trial (LEPHT), the effects of riociguat in patients with PH due to HFrEF were evaluated. However, no significant effects were observed on changes in mean PAP as the primary end point.

CONCLUSIONS

Among PAH-approved drugs, sildenafil may be a potential therapeutic drug to ameliorate pulmonary hemodynamics and exercise capacity in PH-LHD patients with HFrEF. However, all previous RCTs had a small sample size and were performed in a single center, and the longest follow-up duration was 1 year. Additional clinical trails are needed to establish the safety and efficacy of sildenafil for PH-LHD with HFrEF. A multicenter clinical trial with sildenafil for PH-LHD patients with HFrEF is ongoing (SilHF trial, NCT01616381). Patients will be followed up for 6 months, and primary end points include global assessment of the patient and a 6-min walk test. The results of this study are expected to contribute more definitive information on the application of sildenafil in PH-LHD.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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