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EDITORIAL COMMENT

# Pulmonary Arterial Hypertension Therapy in Pulmonary Hypertension Associated With Lung Diseases*

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Pulmonary hypertension (PH) is a condition that affects pulmonary circulation, with a prevalence rate up to about 1% worldwide. The leading cause is left heart disease, whereas the second common cause is lung disease.[1] The most frequently encountered lung diseases are chronic obstructive pulmonary disease (COPD), combined pulmonary fibrosis and emphysema (CPFE), and interstitial lung disease (ILD). In the absence of lung disease, chronic hypoxia predisposes individuals to the development of PH, particularly at high altitude (defined as an elevation >2,500 m above sea level).[2] Whether by impaired ventilation/perfusion matching from alveolar destruction in COPD, loss of pulmonary capillary beds from fibrosis in ILD, or hypoxic vasoconstriction caused by low inspired oxygen tension at high altitude, a common pathway leading to right ventricular dysfunction in lung disease is the elevation of pulmonary arterial pressure.[3] Patients with PH associated with lung diseases are divided into severe and nonsevere. The 2022 European Society of Cardiology/European Respiratory Syndrome guidelines for the diagnosis and treatment of PH used pulmonary vascular resistance (PVR) as the parameter to distinguish severe (PVR >5 WU) and nonsevere (PVR ≤5 WU).[4] Overall, the management for PH with lung disease is focused on the underlying lung disease itself. Except for lung transplantation, other treatment is supportive, such as oxygen supplement and rehabilitation. As for medications approved for pulmonary arterial hypertension (PAH), there are limited data in PH with lung diseases. For PH associated with COPD or emphysema, randomized trials showed inconsistent results.[5-7] Among these studies, the SPHERIC-1 (Sildenafil and Pulmonary HypERtension In COPD) trial showed sildenafil reduced PVR in severe PH associated with COPD.[7] As for another subset of PH with lung disease, PH associated with ILD, the INCREASE trial[8] demonstrated improved 6-minute walk distance in patients treated with inhaled treprostinil.[7] However, most previous trials showed negative results.[9-12] Some medications were even associated with adverse outcomes.[11,12] Vasodilators may even cause V/Q mismatch in this group of patients, leading to worsened oxygenation and pulmonary pressure. Inhalation therapy might overcome this negative effect. Therefore, the 2022 European Society of Cardiology/European Respiratory Syndrome guidelines only suggested individualized therapy for patients with severe PH associated with lung disease. Treatment for PH with lung disease remains a great challenge.

In this issue of *JACC: Asia*, Tanabe et al[13] conducted an analysis based on data from the Japan Respiratory Pulmonary Hypertension Study. They identified 270 patients with PH associated with either interstitial pneumonia or CPFE. The authors further divided patients into mild (PVR ≤5 WU) or severe (PVR >5 WU) PH and mild (percent predicted forced vital capacity ≥70% and percent predicted forced expiratory volume in 1 second ≥60%) or severe (percent predicted forced vital capacity <70% or percent predicted forced expiratory volume in 1 second <60%)

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ventilatory impairment (VI). In 239 treatment-naive patients, 97 patients received initial treatment (medication within 2 months after diagnosis). The rest were classified as the noninitial treatment group. Responders were those with improved World Health Organization functional class, a PVR decrease >15%, or a 6-minute walk distance increase >15% at the first follow-up. Tanabe et al[13] found that although there was no significant difference in survival between the initial and noninitial treatment, the response rate to the initial treatment for PH patients with interstitial pneumonia or CPFE was significantly higher in the severe PH and mild VI groups compared to all other groups (48.2% vs 21.8%).

The authors identified a specific subgroup of patients in PH associated with lung diseases likely to benefit from initial PAH therapy. However, there are some important considerations before this finding is clinically applied. First, disease diagnosis may be challenging in certain cases. Some cases with mild lung disease may in fact be PAH with lung disease instead of lung disease leading to PH. This fundamental question of diagnosis is crucial. The authors' group is working on a study to quantify the involvement of lung disease. Second, there was no record of how clinicians decided to start medication. For PAH, the treatment strategy is based on a comprehensive risk assessment. We know that not all PH patients with lung disease benefit from PAH medication. Based on this study, the simple PVR >5 WU criteria and the degree of ventilatory impairment may serve as indicators for the initiation of PAH medication. A prospective study designed to identify which subset of PH patients with lung disease benefit from PAH-targeted medication would better answer this question. Third, there was no difference in the survival rate between the initial and noninitial treatment. The authors explained that there were more cases with severe PH in the initial treatment group. They suggested that a similar survival rate in a more severe group indicated the effectiveness of treatment, but we need further study to support this concept. Fourth, there was no detail of how medications were used in this study, such as sequence, duration, and dosage. The authors did mention that combination therapy was sequentially applied to those with inadequate response. Considering that previous randomized trials demonstrated inconsistent results of PAH-targeted medication for PH with lung disease,[4-7] further studies, preferably randomized trials, are needed to provide robust evidence for the medication strategy. Besides these major issues, there are still some other limitations to consider when interpreting this study. These include inevitable selection bias of a registry study and the relatively small case number.

In conclusion, Tanabe et al[13] provided insight into a challenging field. In PH patients associated with lung disease, those with severe PH and mild VI are most likely to benefit from initial therapy. Despite some limitations of this study, clinicians may consider starting PAH therapy soon after diagnosis in this specific subset of patients after careful assessment. We need more prospective studies addressing the details of this approach, especially the criteria for treatment initiation and medication strategy. Before stronger evidence is available, these patients need individualized therapy provided by experienced clinicians.

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