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EDITORIAL COMMENT

Pulmonary Arterial Hypertension Management in Asia

State of the Art From Japan, and Next Steps*

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Pulmonary arterial hypertension (PAH) is a relatively rare disease and comprises a group of progressive vascular disorders that may result in functional debilitation, cardiopulmonary complications, and a potentially fatal outcome. Evidence-based disease management through the increased use of guidelines to direct appropriate testing, diagnosis, and medical therapy for PAH has been associated with improved prognosis.[1-3] Therapeutic advances and success in the West have not only raised public awareness of PAH, but also given impetus to proactive detection and management of the disorder.

In Asia, efforts are underway to map the epidemiology of PAH in a number of countries, while disease management increasingly emphasizes adherence to guidelines. Accurate mapping of the epidemiology of PAH requires meticulous input of diagnostic data from clinical centers with expertise in performing biomarker testing, cardiothoracic imaging (eg, echocardiography, ventilation-perfusion scan, cardiac magnetic resonance), invasive hemodynamics (eg, right heart catheterization [RHC]), cardiopulmonary exercise testing, and other investigations. In particular, RHC must be performed appropriately according to guidelines to rule out pulmonary hypertension secondary to left heart disease, document pulmonary vascular resistance, and determine pulmonary vasoreactivity. However, high-quality, multicenter nationwide registry data are scarce in Asia, as highlighted in a systematic review by Leber et al.[4] Among 14 of 29 registry studies that included RHC data and reported incidence and/or prevalence of PAH, only 3 were Asian (2 in adults and 1 in children), whereas 23 were from the West (17 in adults and 6 in children).[4] Registry data are crucial for improving our understanding of temporal trends and changes in disease epidemiology, patient survival, practice patterns, and treatment appropriateness.

In this issue of *JACC: Asia*, Tamura et al[5] present a nationwide analysis of characteristics of PAH patients and their therapeutic regimens during treatment initiation (defined as a period of up to 6 months following the initial visit). Data were compiled from the Japan Pulmonary Hypertension Registry (JAPHR) during 2 periods, 2008-2015 and 2016-2020. 2016 was chosen as the start of the second period because macitentan, selexipag, and iloprost were approved in Japan that year. The study found that overall, tadalafil and macitentan were 10-fold more frequently prescribed than their counterparts, sildenafil and ambrisentan, respectively (Figure 3 from Tamura et al[5]). Interestingly, although beraprost has been readily available in Japan, South Korea, and Mainland China, selexipag was instead found to be the most frequently prescribed prostacyclin analog for all PAH etiologies.[5]

One of the strengths of the study[5] is the inclusion of invasive hemodynamics in all PAH patients. The prerequisite of RHC data ensures accurate diagnosis and accounting of cases with increased certainty. A recent (2022) systematic review including 15 international studies (largely from Western Europe and

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the United States) that had performed RHC suggested a prevalence of 3.7 per 100,000, an incidence of 0.43 cases per 100,000 person-years, and a 1-year survival of 87%.[3] In a systematic review of PAH registry studies that included RHC for diagnosis, the estimated annual incidence and prevalence were 0.15-1.4 per 100,000 and 1.24-93 per 100,000, respectively.[4] In Japan, the prevalence of PAH was estimated at 3.2 per 100,000 and the incidence at 70-100 cases/y.[6] Collectively, these data confirm the rarity of PAH and encourage large-scale multicenter collaborations.

The study by Tamura et al[5] highlights the successes in multilateral collaboration involving the Japanese Government's Agency for Medical Research and Development, pharmaceutical industry partner(s), hospitals, universities, and academic medical centers,[5] which enabled the growth of the JAPHR from 8 pulmonary hypertension centers to 49 contributing institutions, and the collection of detailed information on over 600 PAH patients. The high-quality PAH care and management in Japan is evident in the guideline-directed use of diagnostic work-up investigations, high rates of combination therapy,[7] and a decline in the proportion of patients with severe PAH (New York Heart Association functional class III-IV) from 55.7% (2008-2015) to 43.5% (2016-2020). As combination therapy is indicative of a high standard of care, its increase from 47.8%-57.5% is an indication of improvement in PAH management over time.[5]

Accumulating evidence suggests that standard of care and access to guideline-directed PAH management are improving in East Asia and approaching parity with that of the West. During the last decade, PAH registries in Korea (Korean Registry of Pulmonary Arterial Hypertension)[8] and China[9,10] have also yielded epidemiological data to inform clinical practice. More recently, a large-scale Chinese nationwide PAH registry including over 2,000 patients and detailed data on prescription pattern and treatment response was published.[11] It is noteworthy that idiopathic/hereditary PAH (~50%-51%) was most common in Japan, whereas connective tissue disease-related PAH (49.8%) and congenital heart disease-related PAH (45.2%) were reportedly most common in Korea[8] and China,[11] respectively. Although recruitment bias and differences in clinical practice and health care systems could be factors that influenced the differences, it is possible that genetic factors are at play. One may ponder the next steps in the evolution of large-scale registries. As the field transitions from a clinical phenotype-based classification of PAH to one that is molecular,[12] it is foreseeable that genome sequencing data and pharmacogenetic and epigenetic variables may be applied to risk assessment, stratification, and guided treatment of PAH patients. The implementation of these variables into registries will usher in a new era of epidemiological monitoring.

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