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GUEST EDITOR'S PAGE

The Long March to a Cure for Pulmonary Hypertension

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Precapillary pulmonary hypertension (PH) caused by a pulmonary vascular disease is defined by right heart catheterization showing a mean pulmonary artery pressure >20 mm Hg, a pulmonary artery wedge pressure ≤15 mm Hg, and an increase in pulmonary vascular resistance ≥3 WUs.[1] Pulmonary vascular diseases causing precapillary PH include pulmonary arterial hypertension (PAH), chronic thromboembolic PH (CTEPH), and PH caused by chronic lung disease (PH-CLD).[1,2] Irrespective of its cause, precapillary PH is associated with impaired quality of life, reduced exercise capacity, and worse survival.[2] Thus, the development of efficacious treatment strategies for precapillary PH represents a major priority for all stakeholders involved in patient care.[2] In recent years, major advances in the understanding and treatment of PAH, CTEPH, and PH-CLD have been achieved, triggering new hopes in the long march to a cure for PH. Asian expert centers have been at the forefront of the fight against PH, and they should be warmly acknowledged for that.

PAH (group 1 of the updated classification of PH) may be idiopathic, heritable (mainly caused by germline mutations in the *BMPR2* gene encoding bone morphogenetic protein receptor type II), induced by drugs or toxins such as appetite suppressants, or associated with other conditions such as systemic sclerosis, portal hypertension, congenital heart disease, schistosomiasis, or HIV infection.[1,2] PAH is a rare disease with an estimated prevalence ranging from 15 to 52 cases per million.[3] It is caused by a progressive pulmonary vascular remodeling, caused by excessive proliferation and apoptosis resistance of microvascular endothelial and smooth muscle cells.[4] Despite recent progress in therapy, long-term prognosis is poor for patients with PAH, with an overall survival of 59% at 5 years.[5] Early intervention translates into better outcomes in PAH, underscoring the importance of developing screening/early diagnosis strategies, especially in high-risk populations such as presymptomatic *BMPR2* mutation carriers or patients with associated diseases, including systemic sclerosis.[6-9]

In the past years, better understanding of the pathophysiology of endothelial cell dysfunction and development of medications targeting 3 major pathways (endothelin-1, nitric oxide, and prostacyclin pathways) have allowed significant improvements in PAH outcomes.[10,11] Combination PAH therapy and timely use of parenteral prostacyclins have translated into better outcomes.[12-15] Refined risk stratification instruments have allowed for better support treatment decisions and for better management of patients with PAH, including appropriate listing for lung transplantation in eligible patients who remain refractory to optimized medical therapy.[16,17] An improved understanding of the key role of the transforming growth factor beta superfamily in PAH has led to novel approaches attempting to rebalance the impaired Smad signaling in PAH, thanks to the use of sotatercept, a novel fusion protein comprising the extracellular domain of human activin receptor type IIA linked to the Fc domain of human immunoglobulin G1.[18-20] Sotatercept is proposed to act by rebalancing signaling between pro-proliferative and antiproliferative pathways in PAH.[20] The phase 2 PULSAR (A Study of Sotatercept for the Treatment of Pulmonary Arterial Hypertension) study showed that subcutaneous sotatercept reduces pulmonary vascular resistance and improves 6-minute walk distance as well as other secondary endpoints, supporting the launch of phase 3 randomized controlled trials. In addition, novel interventional approaches such as pulmonary arterial denervation have been proposed by Chinese clinicians and are currently being investigated worldwide.[21]

CTEPH (group 4 PH) is characterized by chronic occlusion of pulmonary arteries by organized fibrotic thrombi that can be associated with a different degree of small pulmonary vessel disease.[22-24] CTEPH complicates 1% to 3% of acute pulmonary embolism, and it must be emphasized that at least 25% of CTEPH

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cases develop in the absence of a known history of acute pulmonary embolism.[23,24] Better awareness and identification of expert centers (with multidisciplinary teams including thoracic surgeons, interventional cardiologists, radiologists, and PH specialists) are needed for the management of CTEPH, which remains a rare but treatable cause of PH. Indeed, if left untreated, CTEPH can lead to right heart failure and death. Thus, early diagnosis is of major importance, as current surgical, interventional, and medical therapies can markedly improve clinical outcomes with near normalization of pulmonary hemodynamics at rest in the majority of patients treated in expert centers.[23-28] Japanese and Asian teams have been at the forefront of the developments of groundbreaking discoveries for better CTEPH management,[28,29] as well as for Takayasu arteritis sometimes masquerading as CTEPH.[30]

PH-CLD (group 3 PH) is a common cause of PH, associated with poor outcomes and impaired survival in chronic obstructive pulmonary disease and interstitial lung disease such as idiopathic pulmonary fibrosis.[2,31] PH-CLD is usually mild to moderate.[2,31-35] However, it can be severe and difficult to manage with drugs approved for PAH, which may be either ineffective or even deleterious.[31] In the most recent European PH guidelines, severe PH-CLD was defined by mean pulmonary artery pressure >35 mm Hg or mean pulmonary artery pressure ≥25 mm Hg with cardiac index <2.5 L/min/m^2.[2] However, recent studies highlight that pulmonary vascular resistance ≥5 WUs is a better cutoff value predicting poor survival in patients with PH-CLD.[32,33] Such patients with severe PH-CLD should be referred to expert PH centers for comprehensive assessment and consideration of optimized therapies of the pulmonary disease and its hemodynamic consequences.[2,31-35] Until 2021, there was no approved drug for the management of PH-CLD.[2,31] Recently, inhaled treprostinil was approved by the U.S. Food and Drug Administration for the treatment of PH caused by interstitial lung disease, on the basis of results of the INCREASE (Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE) trial showing that inhaled treprostinil improved exercise capacity from baseline, assessed with the use of a 6-minute walk test, compared with placebo.[36] Nevertheless, we are still very far from a cure for PH-CLD, and it remains essential that eligible patients should be referred to expert centers for consideration of the optimal timing of lung transplantation.[2,31]

The world of PH has witnessed important advances in recent years, thanks to an outstanding worldwide collaboration between international pulmonary vascular centers and regularly updated international guidelines and proceedings from the World Symposium on Pulmonary Hypertension.[2,37] Asian centers have played a prominent role in basic, translational, and clinical research in the field. This collaborative research has resulted in marked improvement in clinical outcomes in the fields of CTEPH and PAH and new hopes for the management of PH-CLD.

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