Bayer HealthCare

Disease Backgrounder

Pulmonary Hypertension

Pulmonary hypertension (PH) is a disorder in which the pressure in the pulmonary arteries is above normal.[1] It is a devastating and rapidly progressive condition that can have a dramatic impact on quality of life and the ability to carry out normal activities of everyday living.[2,3] There are five main types of PH which affect patients in different ways, all of which can lead to heart failure and death.[1] Currently available pharmacological treatments are only approved to treat one of the five types of PH, pulmonary arterial hypertension (PAH), and all treatments have significant limitations.[4,5] Even for PAH, which is the most studied form of PH, the mortality rate can be higher than that of certain forms of cancer including breast and colorectal cancers.[6,7] As a result there is an urgent need for more research to improve understanding of how all types of PH can be diagnosed and treated effectively.[4,8]

Prevalence of PH

PH affects people worldwide and encompasses multiple disease subtypes.[9] People of all ages including children can develop PH although it is most likely to be diagnosed between 40-50 years of age.[10] There are no definitive figures for the prevalence of PH, but it is thought that there are more than 25 million patients globally.[11]

Symptoms and diagnosis

Each individual patient may have a different etiology and manifestation of PH. Early PH is often asymptomatic and by the time symptoms appear, disease progression is usually well advanced[12] and irreversible. The most common symptoms of PH include shortness of breath particularly upon physical exercise (exertional dyspnea), fatigue, dizziness and fainting, all of which are worsened by exertion.

As the symptoms of PH are non-specific diagnosis can be delayed by as much as two years.[8] Early diagnosis and accurate identification of the PH types are essential as, with earlier diagnosis and appropriate treatment, almost two-thirds of PH patients survive for longer than five years.[10] While echocardiogram, electrocardiogram, exercise testing (e.g. six-minute walk test), certain blood markers (e.g. cardiac troponin T and/or B-type natriuretic peptide) and other tests can be helpful in diagnosing the disease, a definitive diagnosis requires inserting a special pressure-sensing catheter into the right side of the heart (right heart catheterization).[13]

Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension

According to the clinical classification of PH (Dana Point), there are five different types of PH, based on different underlying causes. The five types are: pulmonary arterial hypertension (PAH), pulmonary

hypertension owing to left heart disease (e.g. PH-LVD), pulmonary hypertension owing to lung diseases and/or hypoxemia (e.g. PH-COPD or PH-ILD), chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary hypertension with unclear multifactorial mechanisms (miscellaneous PH).[9,13]

PAH

PAH is a life-threatening disorder in which the pressure in the pulmonary arteries is above normal. PAH is characterized by morphological changes to the endothelium of the arteries of the lungs causing remodeling of the tissue, vasoconstriction and thrombosis. As a result of these changes, the blood vessels in the lungs constrict, making it more difficult for the heart to pump blood through to the lungs. PAH affects an estimated 50 people per million adults and accounts for only a small portion of the overall PH population.[14,15] It is more prevalent in younger women than men and PAH is often associated with other diseases such as congenital heart disease, chronic liver disease or connective tissue diseases. In most cases PAH has no known cause and in some cases it can be inherited.[1] Although PAH is the only type of PH for which several pharmacological treatments are approved, new treatments are urgently needed in order to improve the prognosis for PAH patients.

CTEPH

CTEPH is a life-threatening disorder in which the pressure in the pulmonary arteries is above normal. This is caused by blood clotting and thromboembolic occlusion of pulmonary vessels. The pathogenesis however is not yet completely understood, although CTEPH may evolve after prior episodes of acute pulmonary embolism.[16] The current standard treatment for proximal CTEPH is pulmonary endarterectomy (PEA). However, while European Society of Cardiology (ESC) guidelines recommend that patients are assessed for PEA by an experienced surgeon[17] it is estimated that, globally, only one in four patients receives a surgical assessment.[18] Furthermore, an estimated 20 – 40% of patients are inoperable and in some cases PH persists or reoccurs after surgery.[19] These patients would need an effective pharmacological treatment. So far, however, none of the specific PAH therapies have shown conclusive effects and functional benefits in patients with CTEPH and no approved treatment exists for this indication.

Unmet medical needs in the treatment of PH

Currently available drug treatments are only approved to treat PAH and have significant limitations.[4,5] This means that for patients living with four out of the five types of PH, such as CTEPH or those with PH owing to left ventricular dysfunction (PH-LVD) which is associated with a worse prognosis than the underlying disease alone,[20] there are currently no approved pharmacological treatment options. As a result there is a need for more research to improve understanding of how all five types of PH can be treated effectively.[8,4]

Riociguat (BAY 63-2521) is the first of a novel class of therapeutics called soluble guanylate cyclase (sGC) stimulators, designed to stimulate the sGC enzyme, which generates cyclic guanosine monophosphate (cGMP), independently of nitric oxide.[21] It has been developed as an oral therapy in response to the significant, high unmet needs that exist in the treatment of PH and tailored to the specific needs of patients suffering from this personal and deadly condition. Riociguat is currently undergoing clinical trials as a potential new approach to the treatment of PAH and CTEPH as well as PH-LVD. The trials are ongoing but results to date suggest that riociguat has a clinical profile which will make it a strong candidate for standard therapy in patients living with PAH and inoperable CTEPH and potentially in other forms of the condition.[21,22,23]

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