SERAPHIN trial: raising the standards in the treatment of pulmonary arterial hypertension patients

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Pulmonary arterial hypertension (PAH) is a rare and severe clinical condition characterized by a progressive increase of pulmonary vascular resistance leading to right ventricular failure and premature death. In the past 15 years there was a unique progress in the medical treatment of PAH. Nine drugs belonging to three pharmacological classes (endothelin pathway, nitric oxide and prostacyclin pathway) have been approved by the regulatory authorities. However, the mortality rate continues to be high and the functional and hemodynamic impairments are still extensive in many patients.

Until now, trials of therapies for PAH have been similar in design, with exercise capacity assessed by 6 min walk distance (6MWD) used as a primary end point, and with a randomized study duration ranging from 12 to 16 weeks. 6 min walk test is a simple, well tolerated, noninvasive test that provides valuable information about a patient’s functional status and reflects activities of daily living. Although it has been a useful measurement in previous trials of PAH and is accepted by regulatory authorities, there are various limitations associated with this endpoint; it is insensitive in mildly symptomatic patients and results are confounded by inclusion of patients on background therapies. Importantly, although 6MWD in short-term clinical trials shows improvements, link to longer term outcomes is questionable. The results of a meta-analysis of 22 short-term randomized trials in PAH, involving 3112 patients, showed that improvement in 6MWD does not reflect benefit in clinical outcomes such as death, hospitalization for PAH and initiation of PAH rescue therapy. In fact, 6MWD may not be a true surrogate endpoint for the outcomes we value most in PAH patients: morbidity and mortality.

Given the growing recognition of the need to employ clinically meaningful primary endpoints that directly reflect disease progression experts at the 4th World Symposium on Pulmonary Hypertension in Dana Point recommended the use of a composite clinical outcome endpoint (morbidity and mortality) as the primary endpoint for pivotal phase III PAH trials. Additionally, they proposed that change in 6MWD should be used as a secondary endpoint to provide information on the effect of the tested drug on exercise capacity.

Macitentan is a novel dual endothelin receptor antagonist with sus-
limited. Most randomized controlled trials in PAH have included PAH-related hospitalization as a component of secondary “time to clinical worsening” endpoints and have captured only a relatively low number of hospitalizations due to low numbers of patients and short durations. A recently published post-hoc analysis of all patients in the SERAPHIN study showed that 10 mg of macitentan significantly reduced the risk and annual rate of hospitalization for any cause, in addition to the duration of hospital stay. These treatment effects were driven by reductions in the risk and rate of PAH-related hospitalization. Notably, with regard to PAH-related hospitalizations, the number of hospital days was approximately halved with macitentan compared with placebo. The reduction in PAH-related hospitalization was not offset by an increase in hospitalization for other causes implying that there were no tolerability issues with macitentan treatment.

SERAPHIN is a landmark study that sets a new standard in how the evidence for PAH therapies is measured. Although the 6MWD has been the traditional primary endpoint in clinical trials, there is now a move towards more patient-centered endpoints. Composite endpoints of morbidity-mortality represent a suitable and clinically meaningful primary endpoint, particularly as new PAH trials will be studying patients on background therapies and for longer periods of observation.

REFERENCES