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[1]. 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[2]. 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-

tained receptor binding, enhanced tissue penetration and low propensity for drug to drug interactions. In 2013 SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve CliNical Outcome) was published in NEJM[3]. SERAPHIN is the largest and longest-ever trial in PAH. In this Phase III trial 742 patients were randomized to receive placebo or 3 mg or 10 mg of macitentan. The study employed a clearly defined composite morbidity/mortality primary endpoint in order to assess the effect of treatment with macitentan on long-term clinical outcomes. Treatment was continued until patients experienced a primary endpoint event or until a predefined number of confirmed events had occurred. The overall median follow-up duration was 28 months (up to a maximum of 3.5 years on macitentan for some patients). In this way, this event-driven study provides adequate drug-related information about the potential toxicity and the durability of the effect of the drug as well.

Macitentan significantly reduced the risk of morbidity-mortality events, as measured by the composite endpoint, by 45% versus placebo in the 10 mg group up to end of treatment. The positive effect of macitentan on the primary endpoint was observed irrespective of whether or not patients were already treated with other therapies for PAH. Notably, about two thirds of the patients were taking phosphodiesterase-5 inhibitors when they entered the study. Overall, these findings provide further evidence for sequential combination therapy which is a widely used strategy in clinical practice. Macitentan was well tolerated in the SERAPHIN study. Adverse events more frequently associated with the drug were nasopharyngitis, headache, and anemia. The incidence of peripheral edema and liver enzyme elevation was similar in the placebo and macitentan group.

A significant treatment effect was also observed on the combined secondary outcome measure of the impact of macitentan on PAH-related hospitalization and death which was driven by lower rates of hospitalization in the 10mg macitentan treatment group. Hospitalization has a negative impact on patients' quality of life and represents a substantial health care burden. In the REVEAL Registry PAH-related hospitalization was associated with relatively more rehospitalizations and worse survival at 3 years[4]. Despite this considerable impact, information describing the effect of PAH-specific therapies on hospitalization is 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[5]. 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.

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