Recent Trials in Pulmonary Artery Hypertension

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Pulmonary artery hypertension (PAH) is a serious disorder where chronically elevated pulmonary vascular resistance may lead to right heart failure and death. Disease progression is inevitable and occurs inspite of disease-specific drugs such as prostacyclins and its analogues, phosphodiesterase type 5 inhibitors and endothelin receptor antagonist. Some newer drugs in recent trials have been found to positively alter the disease progression and quality of life. Subsequent approval by FDA in October 2013 of two such drugs – macitentan and riociguat – in management of PAH has further underlined their importance. Various trials with percutaneous interventional therapies like modifications of atrial septostomy with fenestrated stents in PAH and role of segmental balloon angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension are encouraging. Recently a first in human study of pulmonary artery (PA) denervation in idiopathic PAH has also been reported.

SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome)

Pulido T, Adzerikho I, Channick RN, *et al*. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013;369:809–18.

Present therapies for PAH have been adopted on the basis of short-term trials with exercise capacity as the primary end-point. This long-term trial assessed the efficacy of macitentan, a new dual endothelin-receptor antagonist using primary end-point of morbidity and mortality. Inclusion criteria included patients 12 years of age or older who had idiopathic or heritable PAH or PAH related to connective-tissue disease, repaired congenital systemic-to-pulmonary shunts, human immunodeficiency virus (HIV) infection, or drug use or toxin exposure. A total of 742 patients were randomly assigned to placebo, macitentan 3 mg or macitentan 10 mg in once a day dosages. Stable oral or inhaled therapy other than endothelin receptor antagonists was allowed at entry. The primary end-point was the time from the start of treatment to the first occurrence of a composite end-point of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids, or worsening of PAH. A total of 287 patients had a primary end-point event over a median treatment period of 115 weeks. The primary end-point occurred in 46.4% in placebo, 38.0% in macitentan 3 mg group (hazard ratio 0.70, p=0.01) and 31.4% of the patients in macitentan 10 mg group (hazard ratio 0.55, p <0.001). The effect of macitentan was observed regardless of whether the patient was receiving therapy for PAH at baseline.

Perspective

In this long-term event-driven study, macitentan was found to significantly reduce morbidity and mortality in patients with PAH.

PATENT 1 (Pulmonary Arterial Hypertension Soluble Guanylate Cyclase-Stimulator Trial 1)

Ghofrani HA, Galie N, Grimminger F, *et al*. Riociguat for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2013;369:330–40.

Riociguat, a soluble guanylate cyclase stimulator, has been previously shown to improve hemodynamic variables and exercise capacity in patients with PAH in phase 1 and 2 clinical studies. Riociguat has a dual mode of action, acting with endogenous nitric oxide and also directly stimulating soluble guanylate cyclase

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independently of nitric oxide availability. In this phase 3, double-blind study, 443 patients with symptomatic PAH were randomly assigned to receive placebo, riociguat in individually adjusted doses of up to 2.5 mg three times daily (2.5 mg-maximum group), or riociguat in doses that were capped at 1.5 mg three times daily (1.5 mg-maximum group). Patients with symptomatic PAH (idiopathic, familial, or associated with connective-tissue disease, congenital heart disease, portal hypertension with liver cirrhosis, or anorexigen or amphetamine use) were included if they had a pulmonary vascular resistance greater than 300 dyn.sec.cm^{-5}, a mean pulmonary-artery pressure of at least 25 mmHg and a 6-minute walk distance of 150–450 m. Both treatment naive and patients who were receiving endothelin-receptor antagonists or non-intravenous prostanoids were eligible. The primary end-point was the change from baseline to the end of week 12 in the 6-minute walking distance. Secondary end-points included the change in pulmonary vascular resistance, NT-proBNP levels, WHO functional class, time to clinical worsening, score on the Borg dyspnea scale, quality-of-life variables and safety. At 12 weeks, the 6-minute walk distance increased by a mean of 30 m in the 2.5 mg-maximum group and decreased by a mean of 6 m in the placebo group (p<0.001). There were also significant improvements in pulmonary vascular resistance (p<0.001), NT-proBNP levels (p<0.001), WHO functional class (p=0.003), time to clinical worsening (p=0.005) and Borg dyspnea score (p=0.002).

Perspective

Riociguat, a soluble guanylate cyclise stimulator, significantly improved exercise capacity and secondary efficacy end-points in patients with PAH.

CHEST 1 (Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator Trial)

Ghofrani HA, D'Armini AM, Grimminger F, *et al*. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med*. 2013;369:319–29.

Chronic thromboembolic pulmonary hypertension is characterized by obstruction of the pulmonary vasculature by residual organized thrombi, leading to increased pulmonary vascular resistance and progressive pulmonary hypertension. Pulmonary endarterectomy is the treatment of choice but all patients are not the candidates. In this phase 3, multicenter, randomized, double-blind, placebo-controlled study 261 patients with inoperable chronic thromboembolic pulmonary hypertension or persistent or recurrent pulmonary hypertension after pulmonary endarterectomy were randomly assigned to receive placebo or riociguat. The primary end-point was the change from baseline to the end of week 16 in the 6-minute walking distance. At week 16, the 6-minute walk distance had increased by a mean of 39 m in the riociguat group, as compared with a mean decrease of 6 m in the placebo group (p<0.001). Pulmonary vascular resistance decreased by 226 dyn.sec.cm^{-5} in the riociguat group and increased by 23 dyn.sec.cm^{-5} in the placebo group (p<0.001). Riociguat was also associated with significant improvements in the NT-proBNP level (p<0.001) and WHO functional class (p=0.003).

Perspective

Riociguat significantly improved exercise capacity and pulmonary vascular resistance in patients with chronic thromboembolic pulmonary hypertension who were ineligible for surgery or who had persistent or recurrent pulmonary hypertension after pulmonary endarterectomy.

PADN-1 Study (First-in-Man Pulmonary Artery Denervation for Treatment of Pulmonary Artery Hypertension)

Chen SL, Zhang FF, Xu J, *et al*. Pulmonary artery denervation to treat pulmonary arterial hypertension: the single-center, prospective, first-in-man PADN-1 study (first-in-man pulmonary artery denervation for treatment of pulmonary artery hypertension). *J Am Coll Cardiol*. 2013;62:1092–100.

Baroreceptors and sympathetic nerve fibers are localized in or near the bifurcation area of the main pulmonary artery (PA). It was previously demonstrated in an animal study that pulmonary artery denervation (PADN) completely abolished the experimentally elevated PA pressure responses to occlusion of the left interlobar PA. In this single-center study, 21 patients were assigned to pulmonary denervation group or control group. PADN was performed at the bifurcation of the main PA, and at the ostial right and left PA. Serial echocardiography, right heart catheterization and a 6-minute walk test (6MWT) were performed. The primary end-points were the change of PA pressure (PAP), tricuspid excursion (Tei) index and 6MWT at 3 months follow-up. Compared with the control group, at 3 months follow-up, the patients who underwent the PADN procedure showed significant reduction in mean PAP (from 55±5

to 36±5 mmHg, $p<0.01$), and significant improvement of the 6MWT (from 324±21 to 491±38 m, $p<0.006$) and of the Tei index (from 0.7±0.04 to 0.50±0.04, $p < 0.001$).

Perspective

This study reported the favorable effect of pulmonary denervation on functional capacity and hemodynamics in patients with idiopathic PAH not responding optimally to medical therapy. As it has been a single-center non-randomized study in a small number of patients, further randomized study is required to confirm the efficacy of PADN.