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Long-term sildenafil added to intravenous epoprostenol in patients with pulmonary arterial hypertension

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KEYWORDS:
sildenafil;
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pulmonary arterial hypertension;
survival;
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BACKGROUND: In pulmonary arterial hypertension (PAH), adding oral sildenafil to intravenous epoprostenol improved 6-minute walk distance (6MWD) and hemodynamics and delayed time to clinical worsening in a 16-week randomized, placebo-controlled trial (Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil [PACES-1]).

METHODS: Patients completing PACES-1 could receive sildenafil (titrated to 80 mg, three times daily, as tolerated) in an open-label extension study (PACES-2) for $\geq$ 3 years; additional therapy was added according to investigator judgment. Survival and changes from PACES-1 baseline in World Health Organization Functional Class and 6MWD were captured.

RESULTS: In an open-label setting, 6MWD, an effort-dependent outcome measure, was known to have improved or to have been maintained in 59%, 44%, and 33% of patients at 1, 2, and 3 years, respectively; functional class was known to have improved or to have been maintained in 73%, 59%, and 46%. At 3 years, 66% of patients were known to be alive, 24% were known to have died, and 10% were lost to follow-up. Patients with PACES-1 baseline 6MWD $<$ 325 meters without 6MWD improvement during the first 20 weeks of sildenafil treatment subsequently had poorer survival.

CONCLUSIONS: Although reliable assessments of safety and efficacy require a long-term randomized trial, the addition of sildenafil to background intravenous epoprostenol therapy appeared generally to be well tolerated in PAH patients.

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Pulmonary arterial hypertension (PAH) is characterized by a progressive increase of pulmonary vascular resistance (PVR) leading to right heart failure and death.[1,2] Pulmonary vasculature remodelling, vasoconstriction, and thrombosis in situ contribute to increased PVR; endothelial dysfunction appears to play a key role.[2]

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Approved PAH-specific medical therapies target prostacyclin, nitric oxide (NO), and endothelin pathways. Prostacyclin promotes vascular smooth muscle relaxation through increased cyclic adenosine monophosphate production and also inhibits smooth muscle cell growth and platelet aggregation.[2] NO diffusing through the endothelium signals an increase in the production of cyclic guanosine monophosphate (cGMP), which produces smooth muscle relaxation.[3] Because phosphodiesterase type 5 (PDE5) metabolizes cGMP in endothelial cells, PDE5-inhibitor treatment increases the pool of cGMP, thereby increasing vasodilation. Endothelin-1 is a potent vasoconstrictor and mitogen, and endothelin-receptor antagonists (ETRAs) oppose these endothelin-1 actions.[2]

Oral sildenafil, a PDE5 inhibitor, and intravenous (IV) epoprostenol, a synthetic prostacyclin, each improve outcomes in patients with PAH as monotherapy.[4,5] These 2 agents target separate pathways that appear to contribute to the pathobiology of PAH. The Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil (PACES-1) trial provided a 16-week, randomized, placebo-controlled evaluation of the addition of oral sildenafil (80 mg, three times daily, as tolerated) to background IV epoprostenol. This combination increased the 6-minute walk distance (6MWD), delayed the time to clinical worsening, and improved hemodynamic parameters compared with IV epoprostenol treatment alone.[6] Patients who completed PACES-1 were eligible to enroll in PACES-2, (ClinicalTrials.gov Identifier: NCT00147641), an open-label extension (OLE) of PACES-1, in which all patients received sildenafil in addition to epoprostenol until the last enrolled patient received 3 years of sildenafil treatment. We report here the results for these patients.

Methods

Local Institutional Review Boards or independent Ethics Committees approved the protocol.

Study design

This study was conducted between November 2003 and April 2009 at 45 sites in 10 countries, ending when the last patient enrolled in the OLE completed 3 years of sildenafil treatment, including 16 weeks of PACES-1 sildenafil treatment (if receiving the active drug in PACES-1).

Regardless of therapy received in PACES-1,[6] all patients entering PACES-2 received sildenafil at 20 mg, three times daily, then titrated to 40, and then to 80 mg, three times daily, as tolerated, with doses separated by $\geq$ 6 hours. Patients could reduce the dose of sildenafil to a minimum of 20 mg, three times daily. Patients unable to tolerate sildenafil at 20 mg three times daily were withdrawn and monitored for survival. The epoprostenol dosage could be changed at the discretion of the investigator at any time during the study.

The PACES-1 baseline constituted the baseline for the OLE. Follow-up assessments were conducted at 20 and 24 weeks and every 3 months thereafter. Laboratory safety assessments were performed at baseline, Week 16 of PACES-1, then at the first 3-month visit in PACES-2 (ie, Week 36 relative to the PACES-1 baseline), and every 6 months thereafter.

Patients

Patients with idiopathic PAH (IPAH), heritable PAH (HPAH), or PAH associated with anorexigen use, connective tissue disease (CTD), or corrected congenital heart defect, who completed PACES-1 (or received an increased epoprostenol dose due to clinical deterioration in PACES-1 and completed all end-of-study assessments and $\geq$ 4 weeks of PACES-1) and gave informed consent were eligible to enter the OLE.

Exclusion criteria have been published for PACES-1.[6] Briefly, patients were not permitted to use nitrates or NO donors, protease inhibitors, or α-blockers. Oral anti-coagulants, digitalis, diuretics, calcium channel blockers in acute responders, and supplemental oxygen were permitted. After a protocol amendment in September 2007, patients could receive ETRAs and other prostacyclin analogs in PACES-2 if the investigator judged that additional therapy was warranted.

Patients who permanently discontinued sildenafil study treatment were monitored for survival whenever possible.

Outcome measures

At all visits, 6MWD and World Health Organization Functional Class (WHO FC) were assessed. The 6MWD test was performed as close to trough levels of sildenafil as possible. Descriptive summaries without significance testing are presented. Missing data for 6MWD and FC were imputed using the worst value for non-missing adjacent values. "Missing" scores indicated that a score was missing at a target visit, and no subsequent score was recorded.

The survival status of all patients, including those who discontinued study treatment (when possible), was documented yearly. Kaplan-Meier estimates of 1-, 2-, and 3-year survival were calculated overall and by PACES-1 baseline 6MWD (dichotomized as $<$ 325 or $\geq$ 325 meters) and PAH etiology (both prespecified). Because missing follow-up data for some patients who discontinued treatment likely would lead to biased overestimates, the proportions of patients known to be alive at 1, 2, and 3 years were also calculated.

A Cox regression was used to explore the relationship between change in the 6MWD during 20 weeks of sildenafil treatment and subsequent survival. In this latter analysis, change from baseline in 6MWD was defined as the change between Week 0 and Week 20 for patients randomized to sildenafil in PACES-1, and the change between Week 16 and Week 36 (i.e., Month 9 visit) for patients randomized to placebo in PACES-1. "Time 0" for survival, the dependent variable, was Week 20 for PACES-1 sildenafil patients and Week 36 for PACES-1 placebo patients.

A post hoc Cox regression analysis was used to assess the association of 17 baseline covariates with survival: 6MWD, WHO FC, PAH etiology, mean pulmonary arterial pressure (PAP), mean PAP/mean arterial pressure, systolic and diastolic PAP, right atrial pressure, mixed venous oxygen saturation, heart rate, pulse pressure, mean systemic arterial pressure, PVR, PVR index, systemic vascular resistance (SVR), SVR index, PVR/SVR, cardiac index, cardiac output, and pulmonary capillary wedge pressure. "Time 0" for all patients was baseline of the PACES-1 study. Univariate and multivariate analyses were conducted.

The number of patients with changes in intravenous epoprostenol dose was collected. The mean number of signs and symptoms of complications of epoprostenol (or alternative prostacyclin analog) use (e.g., headache, jaw pain, flushing) was recorded. Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities and were assessed for severity and relation to