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Endothelin antagonism and uric acid levels in pulmonary arterial hypertension: Clinical associations

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BACKGROUND: Elevated serum uric acid is detected in pulmonary arterial hypertension (PAH) and is associated with poor patient outcomes. High serum uric acid is an independent risk factor for cardiovascular disease and renal impairment. We analyzed the effects of endothelin receptor antagonism on serum uric acid in PAH patients participating in the Sitaxentan to Relieve Impaired Exercise (STRIDE)-2/2X trial, and the impact of uric acid on 6-minute walk distance (6MWD), time to clinical worsening (TtCW) and survival.

METHODS: In the 18-week, double-blind, placebo-controlled STRIDE-2 trial, 246 PAH patients were randomized and received matched placebo, sitaxentan 50 or 100 mg orally once daily, or open-label bosentan 125 mg twice daily. STRIDE-2X was a 1-year, open-label extension of STRIDE-2.

RESULTS: Baseline serum uric acid was similar between groups. Increased serum uric acid was a significant risk factor for 1-year mortality and TtCW. Compared with placebo, sitaxentan 50 and 100 mg and bosentan all reduced serum uric acid ($p < 0.05$). Reduced serum uric acid correlated with increased 6MWD ($p = 0.0037$).

CONCLUSIONS: Endothelin receptor antagonism reduces serum uric acid in PAH patients, and this reduction is associated with improved survival and longer TtCW. Further prospective studies are needed to investigate the pathogenic role of serum uric acid in PAH and its prognostic potential.

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Hyperuricemia, or elevated serum uric acid concentration, is detected in patients with pulmonary arterial hypertension (PAH).[1,2] Serum uric acid concentration associates with PAH severity and may predict mortality.[3–6] However, few studies have shown beneficial effects of lowering serum uric acid concentrations in patients with PAH.

Epidemiologic studies have reported a relationship between serum uric acid levels and various cardiovascular conditions. Uric acid may be an independent risk factor for both cardiovascular disease[7,8] and chronic kidney disease (CKD).[9] Clinically, lowering uric acid has both cardiovascular and renal benefits.[10–13]

Endothelin (ET)-1 is a potent endogenous vasoconstrictor with additional roles in cell proliferation, endothelial dysfunction, inflammation and fibrosis.[14] The ET system is dysregulated in PAH, and ET receptor antagonism is standard treatment for PAH.[15] Both mixed $ET_{A/B}$ and selective ET_A receptor antagonists effectively treat PAH.[16]

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The Sitaxentan to Relieve Impaired Exercise (STRIDE)-2 trial compared the selective ET_A receptor antagonist sitaxentan with the mixed $ET_{A/B}$ antagonist bosentan in 246 patients with PAH.[17] Herein the effects of sitaxentan and bosentan on serum uric acid in PAH patients participating in STRIDE-2 and its open-label extension (STRIDE-2X[18]) were analyzed, as well as the impact of serum uric acid on 6-minute walk distance (6MWD), time to clinical worsening (TtCW) and survival. Although sitaxentan was voluntarily withdrawn from the market in December 2010 because of a newly identified pattern of idiosyncratic hepatic injury, this research provides information on the effects of ET receptor antagonism on serum uric acid concentration that may be valuable to the PAH community.

Methods

The rationale and study design for the randomized, double-blind, placebo-controlled STRIDE-2 trial have been reported.[17] Briefly, patients with PAH were randomized 1:1:1:1 to receive sitaxentan 50 or 100 mg or matched placebo orally once daily, or open-label bosentan 125 mg twice daily for 18 weeks. STRIDE-2X was an open-label extension of STRIDE-2.[18] Patients were eligible if they completed the STRIDE-2 trial or had prematurely discontinued placebo or sitaxentan 50 mg in STRIDE-2 because of lack of clinical response. Patients randomized to sitaxentan 100 mg or bosentan in STRIDE-2 continued their treatment; patients randomized to sitaxentan 50 mg in STRIDE-2 received sitaxentan 100 mg in STRIDE-2X. Patients randomized to placebo in STRIDE-2 were re-randomized 1:1 to sitaxentan 100 mg or bosentan in STRIDE-2X.

Study population

Patients in World Health Organization (WHO) Functional Class (FC) II, III or IV, 12 to 78 years of age, with symptomatic PAH were eligible if they had: (1) PAH that was idiopathic or associated with connective tissue disease or with specific cardiac defects; (2) mean pulmonary artery pressure >25 mm Hg at rest, pulmonary capillary wedge pressure or left ventricular end-diastolic pressure ≤ 15 mm Hg and pulmonary vascular resistance ≥ 3 Wood units (obtained by right heart catheterization within 6 months of study enrollment); and (3) baseline 6MWD ≥ 150 meters and ≤ 450 meters. For patients <18 years of age, body weight was ≥ 50 kg. Patients were excluded for significant medical conditions, including hepatic dysfunction (transaminase level >1.5 times the upper limit of normal), renal insufficiency or history of left-sided heart disease; if they were on a prostaglandin, phosphodiesterase inhibitor or an ET receptor antagonist; or if they had received any new type of PAH treatment within 30 days before study entry. The study was conducted according to ethical principles stated in the Declaration of Helsinki (1996) and applicable guidelines on good clinical practice. The protocol was approved by local institutional review committees. Written informed consent was obtained from all patients.

Outcome measures and statistical analyses

Change from baseline to Week 18 in serum uric acid was analyzed for the overall population and by diuretic use (yes vs no) and use of allopurinol (yes vs no). Between-treatment difference, p value and 95% confidence interval (CI) were obtained from a parametric analysis of covariance with treatment as a factor and baseline value as the covariate. Additional clinical parameters were assessed similarly. The cumulative distribution function of the change in serum uric acid from baseline to Week 18 was analyzed using the Kolmogorov–Smirnov test to assess treatment differences.

Correlation between change in uric acid and change in the ratio of blood urea nitrogen (BUN):creatinine was evaluated with Pearson's product-moment correlation and Spearman's rank-order correlations; in both cases, Fisher's z transformation was used.

The relationship of change in serum uric acid and change in 6MWD from baseline to Week 18 was investigated using Spearman's correlation and regression analyses.

Multivariate Cox regression analyses were conducted to investigate the relationship of serum uric acid to 1-year mortality and clinical worsening (defined as hospitalization for PAH, death, transplantation, atrial septostomy, initiation of new chronic PAH treatment, or combined WHO FC deterioration and $\geq 15\%$ decrease in 6MWD from baseline). Patients who discontinued or completed the study without having an event were censored at their last visit. Model 1 included treatment groups (sitaxentan 100 mg vs bosentan); age; gender; baseline serum uric acid level dichotomized (>7 mg/dl vs ≤ 7 mg/dl) or categorized as high (>9 mg/dl), moderate (>7 mg/dl to ≤ 9 mg/dl), mild (>5.5 mg/dl to ≤ 7 mg/dl) or low (≤ 5.5 mg/dl)[19]; change from baseline to Week 18 in serum uric acid; and baseline hemodynamic data (mean pulmonary arterial pressure, mean right atrial pressure and cardiac index). Model 2 included diuretic use (yes vs no) and reduction in creatinine (per 0.1 mg/dl) in addition to the factors included in Model 1. Model 3 included baseline creatinine (per 0.1 mg/dl) in addition to the factors included in Model 2.

Kaplan–Meier analyses with log-rank tests were used to compare the time to death and TtCW in patients receiving bosentan or sitaxentan 100 mg who had an increase from baseline to last visit in serum uric acid with patients having a decrease or no change from baseline to last visit in serum uric acid. $p < 0.05$ was considered statistically significant.

Receiver operating characteristic (ROC) curves, which illustrate sensitivity and specificity of biomarker levels, assessed the relationship of change from baseline to Week 18 in serum uric acid with TtCW and time to death.

Results

In this post hoc analysis, 246 patients from STRIDE-2/2X were assessed. Patients' characteristics, primary and secondary study end-points and safety data have been reported previously.[17] Briefly, STRIDE-2 demonstrated that sitaxentan 100 mg significantly improved exercise capacity and WHO FC compared with placebo; 50 mg was sub-therapeutic. Comparisons between sitaxentan and open-label bosentan were strictly observational because of the inability to blind the bosentan arm.

Baseline serum uric acid concentrations were not different among groups (Table 1) and not normally distributed; they displayed only a mild departure from normality. Compared with placebo, bosentan and sitaxentan 50 and 100 mg reduced serum uric acid by Week 18 (Table 1 and Figure 1). Changes were significant or marginally significant compared with placebo when patients were assessed by diuretic use (Table 1). Only 17 of the 246 (6.9%) patients