CHEST

Original Research

PULMONARY VASCULAR DISEASE

Baseline and Follow-up 6-Min Walk Distance and Brain Natriuretic Peptide Predict 2-Year Mortality in Pulmonary Arterial Hypertension

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Background: **Six-minute walk distance (6MWD) and brain natriuretic peptide (BNP) levels at baseline and after initiation of treatment have been associated with survival in patients with pulmonary arterial hypertension. Our objective was to determine the individual and additive ability of pretreatment and posttreatment 6MWD and BNP to discriminate 2-year survival in patients with pulmonary arterial hypertension.**

Methods: **We included patients enrolled in two randomized clinical trials of ambrisentan who had 2-year follow-up (N = 370). 6MWD and BNP were assessed before and after 12 weeks of treatment. Receiver operating characteristic curve analyses were performed to identify optimal cutoffs that defined subgroups with a high 2-year mortality. Classification and regression tree analysis was used to determine the incremental prognostic value of combined assessments.**

Results: **6MWD at baseline and after 12 weeks of therapy were similarly discriminatory of 2-year survival (c-statistics = 0.77 [95% CI 0.70-0.84] and 0.82 [95% CI 0.75-0.88], respectively), whereas change in 6MWD from baseline to week 12 was not discriminating. The same observation was true of BNP at baseline and after 12 weeks of therapy (c-statistics = 0.68 [95% CI 0.60-0.76] and 0.74 [95% CI 0.66-0.82], respectively). After consideration of baseline 6MWD, there was no prognostic information added by the week 12 6MWD or BNP at either time point.**

Conclusions: **6MWD and BNP values at baseline or week 12 identified a population with an elevated risk of death at 2 years. A repeat assessment of 6MWD or BNP after 12 weeks of ambrisentan therapy did not provide additional prognostic information beyond that obtained from baseline values.**

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Abbreviations: 6MWD = 6-min walk distance; 6MWD-B = 6-min walk distance at baseline; ARIES = Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study; BNP = brain natriuretic peptide; CART = classification and regression tree; CTD = connective tissue disease; IPAH = idiopathic pulmonary arterial hypertension; NPV = negative predictive value; PAH = pulmonary arterial hypertension; PAH-CTD = pulmonary arterial hypertension associated with connective tissue disease; PPV = positive predictive value; RCT = randomized clinical trial; REVEAL Registry = Registry to Evaluate Early and Long-Term Pulmonoary Arterial Hypertension Disease Management; ROC = receiver operating characteristic

Pulmonary arterial hypertension (PAH) is a progressive pulmonary vasculopathy associated with reduced survival. Studies of new treatments have demonstrated variable impact on symptoms, functional capacity, quality of life, and mortality. Accurate risk stratification of the patient with PAH is important, as it could inform selection of appropriate treatment. Indeed, current guidelines advocate for the serial assessment of certain biomarkers as a means to determine the effectiveness of a given treatment strategy, and some have recommended that failure to meet certain goals should warrant escalation of treatment.[1]

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Six-minute walk distance (6MWD) is an easily obtained, reproducible metric which has been used as the primary outcome for nearly every randomized

clinical trial (RCT) in PAH.[2] Higher baseline or post-treatment 6MWD is associated with better survival.[3-5] Brain natriuretic peptide (BNP) is a neurohormone released by the myocardium in response to pressure and/or volume overload, and BNP has been a secondary outcome measure in many RCTs in PAH. Higher baseline and follow-up circulating BNP levels have been associated with an increased risk of mortality in PAH.[6] The discriminative utility and the optimal cut-offs of these biomarkers necessary to distinguish high-risk from low-risk patients in the clinic are less clear.

We determined whether baseline and follow-up 6MWD and plasma BNP levels discriminated between patients who died or were alive at 2 years in RCTs of patients treated with ambrisentan. We also determined whether the changes with treatment in 6MWD and plasma BNP levels from baseline to 12 weeks discriminated outcomes. Some of the results of these analyses have been previously reported in the form of an abstract.[7]

Materials and Methods

This study was approved by the Institutional Review Board of the University of Pennsylvania (approval No. 814307). Additional details of the methods and statistical analysis are provided in e-Appendix 1.

ARIES (Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study)-1 and ARIES-2 were concurrent, phase 3, double-blind, placebo-controlled RCTs of ambrisentan for the treatment of PAH.[8] Patients were randomized to placebo or ambrisentan at doses of 5 mg or 10 mg (ARIES-1) and 2.5 mg or 5 mg (ARIES-2) for 12 weeks. ARIES-E was the long-term extension study for subjects who completed ARIES-1 or ARIES-2, the details of which have been previously published.[9] In ARIES-E, subjects receiving placebo in ARIES-1 or ARIES-2 were randomized in a blinded fashion to ambrisentan doses as described; those receiving ambrisentan during the first 12 weeks were continued on their current dose. Subjects continued their ambrisentan at fixed doses for 24 weeks, after which their dose could be further adjusted as clinically indicated.

Detailed inclusion and exclusion criteria for ARIES-1 and ARIES-2 (and ARIES-E) have been published previously.[8] Three hundred and eighty-three subjects received at least one dose of ambrisentan in ARIES-1, ARIES-2, or ARIES-E and comprised the study cohort. This included three subjects who completed ARIES-1 or ARIES-2 but did not enter ARIES-E. Subjects with missing 2-year vital status were excluded from the primary analyses, but were included in sensitivity analyses.

6MWD and BNP level were assessed at baseline (6MWD-B and BNP-B, respectively) and after 12 weeks of ambrisentan (6MWD-12w and BNP-12w, respectively). Survival data were collected prospectively for all subjects. After completion of ARIES-E, site investigators provided the vital status of each subject at the last known date or date of death. These data were used to determine vital status at 2 years after the first dose of ambrisentan.

Results

There were 383 subjects in the study cohort (Fig 1). We excluded 13 who did not have 2-year survival status data from the primary analyses, leaving 370 subjects in the study sample for the 6MWD analysis. Thirty-seven additional subjects were excluded from the BNP analyses due to missing baseline BNP values, leaving 333 in the study sample. Baseline demographics of the study samples and those excluded are presented in Tables 1 and 2, for descriptive purposes only. Most patients had idiopathic PAH (IPAH), while approximately one-third had connective tissue disease (CTD). The mean ± SD 6MWD-B (n = 370) and 6MWD-12w (n = 350) were 348 ± 85 m and 388 ± 90 m, respectively. The study sample for the 6MWD analysis was similar to those excluded except that those excluded were more likely to have PAH associated with CTD (PAH-CTD) (Table 1). The median (interquartile range [IQR]) BNP-B (n = 333) and BNP-12w (n = 317) were 138 (47-350) pg/mL and 77 (28-188) pg/mL, respectively. The study sample for the BNP analysis was similar to those excluded except that excluded subjects tended to be somewhat younger (Table 2). Imputation for missing data was performed and is described in e-Appendix 1.

Of the 370 subjects, 348 (94%) were still receiving ambrisentan monotherapy at 12 weeks, one (0.3%) was receiving ambrisentan therapy plus other PAH therapy, and 22 (5.9%) had an unknown treatment regimen as these patients had discontinued the therapeutic part of the study. At 2 years, 214 (58%) remained on ambrisentan monotherapy, 45 (12%) added therapy to ambrisentan, and 111 (30%) were unknown as they had discontinued the therapeutic part of the study.

The cumulative incidence of death at 2 years was 15% (n = 55). Data on cause of death were available for 42 subjects (76%); right ventricular failure

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