CHEST

Sex Differences in Response to Tadalafil in Pulmonary Arterial Hypertension

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BACKGROUND: Pulmonary arterial hypertension (PAH) is a progressive disease with high rates of morbidity and mortality. Current therapies improve symptoms, functional capacity, and, in select cases, survival. Little is known about patient factors that may predict the likelihood of patient-important, clinically relevant responses to therapy such as the 6-min walk distance (6MWD) and health-related quality of life (HRQoL).

METHODS: Data from the randomized clinical trial of tadalafil in PAH were used. Adjusted logistic regression models were created to examine the relationship between baseline characteristics and odds of achieving the minimal important difference (MID) in three parameters, defined as either a > 33-m increase in 6MWD, a > 5-unit increase in physical component summary score of the Medical Outcomes Study Short Form-36 (SF-36), or a > 5-unit increase in mental component summary score of the SF-36.

RESULTS: The study included 405 subjects. Younger age, male sex, lower baseline 6MWD, and disease etiology were associated with greater odds of achieving the MID for the 6-min walk test. Active treatment, younger age, and male sex were associated with greater odds of achieving the MID for the physical component summary score. Male sex was associated with greater odds of achieving the MID for the mental component summary score.

CONCLUSIONS: Age, sex, baseline functional capacity, and disease etiology are variably associated with the likelihood of achieving clinically relevant responses in patient-important outcomes to PAH-specific therapy such as 6MWD and HRQoL. The increased likelihood of response in men compared with women is a novel finding and may reflect pathophysiologic differences between sexes. CHEST 2015; 147(1):188-197

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ABBREVIATIONS: 6WMD = 6-min walk distance; 6MWT = 6-min walk test; cGMP = cyclic guanosine monophosphate; CTD = connective tissue disease; ERA = endothelin receptor antagonist; ET-1 = endothelin-1; HRQoL = health-related quality of life; MCS = mental component summary; MID = minimal important difference; NO = nitric oxide; PAH = pulmonary arterial hypertension; PCS = physical component summary; PHIRST = Pulmonary Arterial Hypertension and Response to Tadalafil; SF-36 = Medical Outcomes Study Short Form-36; sGC = soluble guanylate cyclase; WHO FC = World Health Organization functional class

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Pulmonary arterial hypertension (PAH) is a chronic, progressive disease of the pulmonary vasculature that leads to right-sided heart failure and death.[1] Despite advances in our understanding of the pathogenesis and pathobiology of PAH, morbidity and mortality rates remain high. Newer therapies, directed at reducing pulmonary vascular load, have been shown to improve symptoms, quality of life, functional capacity, and, in the case of IV epoprostenol, survival.[2-11] However, PAH remains a disease without a cure in the absence of lung transplantation.

In chronic disease without cure, assessing therapeutic efficacy should be determined by improvements in clinical outcomes that are relevant to delaying or reversing the pathogenesis of the disease, to improving the patient's experience with the disease, or, ideally, both. Most clinical trials of novel therapies in PAH have used the 6-min walk test (6MWT) as the primary outcome, based upon associations with functional classification, hemodynamics, and survival demonstrated in various cohorts of patients with PAH.[2,4-8,12-14] Accordingly, regulatory agencies have approved pharmacologic agents for PAH therapy based upon small but statistically significant changes in 6MWT in randomized clinical trials. Further, while prior studies have suggested that achievement of absolute thresholds of 6-min walk distance (6MWD) (eg, $>$400 m) is associated with improved survival in PAH, incremental improvements in 6MWD and health-related quality of life (HRQoL) may also be essential components of assessing patient-important, clinically relevant treatment response.[15] These parameters may represent intermediate end points (ie, true clinical end points that are not the ultimate end point of the disease) and, therefore, achievement of the minimal important difference (MID) for these parameters may be of value to the patient even in the absence of a mortality benefit.[16]

There are surprisingly few studies examining predictors of response to therapy in PAH. Several investigators have examined the relationship between baseline characteristics and survival, demonstrating associations between demographic, clinical, functional, and hemodynamic characteristics and survival in various cohorts of PAH.[15] However, few studies have looked at the relationship between baseline characteristics and outcomes other than survival. Using pooled data from six randomized, placebo-controlled trials of endothelin receptor antagonists (ERAs), Gabler and colleagues[17] found significant differences in change in 6MWT in response to therapy by sex and race, with women and white people experiencing greater increases in 6MWT than men and black people, respectively. The absence of other literature examining predictors of response to PAH therapy likely reflects the lack of validation of clinically relevant changes in surrogate end points in PAH studies (ie, clinically relevant changes in 6MWT or other patient-important measures).

Previously, our group described an estimate of the MID in the 6MWT for patients with PAH.[18] The MID, defined as the smallest change or difference in an outcome measure, perceived as beneficial, that would justify a change in the patient's medical management, was determined to be around 33 m.[19] Clinically relevant changes in HRQoL are also important in PAH and may predict clinical deterioration and survival.[20,21] Identifying clinical characteristics that are associated with clinically relevant improvements in intermediate measures in response to specific PAH therapy offers the opportunity to tailor treatment strategies and to define distinct disease phenotypes. Therefore, we sought to define patient characteristics associated with patient-important, clinically relevant changes in 6MWT and HRQoL, using data from the large clinical trial of tadalafil in PAH.

Materials and Methods

The Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) trial was a double-masked, placebo-controlled, 16-week study of 405 patients with PAH, including both treatment-naive patients and patients on background therapy with the ERA bosentan.[5] The primary outcome was change from baseline to week 16 in 6MWD. Secondary outcome measures included HRQoL as assessed by the Medical Outcomes Study 36-item Short Form (SF-36) version 2 collected at baseline and at week 16. The 6MWT was performed according to consensus guidelines.[22]

Clinically relevant changes in 6MWT and SF-36 were defined based upon the literature defining the MID for these parameters (33 m for the 6MWT and 5 units for the physical component summary [PCS] score and mental component summary [MCS] score of the SF-36).[18,23] Analyses were conducted to assess the relationship between baseline characteristics of study subjects and achievement of MID in the 6MWT and summary components of the SF-36. First, simple, unadjusted univariable analyses using two-sample Student *t* (or Wilcoxon) tests for continuous variables and the χ^2 (or Fisher exact) test for categorical variables were performed. Then multivariable logistic regression models were created to assess the odds of achieving the MID for either parameter based upon clinical characteristics. These models included potential confounders of the relationship between demographic and clinical parameters and achieving the MID, such as age, height, BMI, sex, baseline World Health Organization functional class (WHO FC), baseline walk distance, and disease type. Since only a subset of subjects underwent baseline and end-of-study catheterization (complete data were available on 69 subjects), change in hemodynamic variables were not included in these multivariable models.

Variables selected for the multivariate models were based on both statistical and clinical significance. In addition, backward variable selection