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ORIGINAL ARTICLE

Impact of Pulmonary Capillary Wedge Pressure on Long-term Mortality in Patients with Pulmonary Arterial Hypertension Treated with Parenteral Trepostinil

Jignesh K. Patel, MD [a*], Youlan Rao, PhD [b], Paul Strachan, MD [a]

[a]Division of Pulmonary and Critical Care Medicine, Department of Medicine, State University of New York at Stony Brook, Stony Brook, NY, USA
[b]Biostatistics, United Therapeutics Corporation, Research Triangle Park, NC, USA

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Background The clinical impact of pulmonary capillary wedge pressure (PCWP) on long-term mortality among patients with pulmonary arterial hypertension (PAH) has been incompletely reported, particularly in relation to concomitant treprostinil administration. The goal of this study was to assess the impact of PCWP on long-term mortality in PAH patients treated with parenteral treprostinil.

Methods We studied a cohort of 743 patients with PAH treated with parenteral treprostinil therapy. The long-term all-cause mortality was compared in patients with baseline mean PCWP $\leq$ 8 mmHg, 8 < PCWP $\leq$ 11 mmHg, and PCWP > 11 mmHg over four-year follow-up.

Results Of the 743 patients studied, 280 patients (37.7%) had a baseline mean PCWP $\leq$ 8 mmHg, 233 patients (31.4%) had a mean PCWP of >8 mmHg and $\leq$11 mmHg, and 230 patients (31.0%) had a mean PCWP >11 mmHg. While patients with higher PCWP had higher mean right atrial and PA pressures, no difference was noted in cardiac output and pulmonary vascular resistance (PVR). All-cause mortality was similar between patients with PCWP $\leq$8 mmHg, 8 < PCWP $\leq$ 11 mmHg, and PCWP > 11 mmHg at one year (10.4% vs 9.9% vs 10.0%, p = 0.980) and four years (16.8% vs 21.9% vs 19.2%, p = 0.353) respectively. In multivariate analysis, PCWP was not independently predictive of four-year all-cause mortality [HR 1.00, 95%CI 0.95–1.05, p = 0.98 (per mmHg)]. Predictors of four-year mortality included older age [HR 1.02, 95%CI 1.00–1.03, p = 0.0091 (per year)], non-Caucasian race, and higher PVR [HR 1.06, 95% CI 1.04–1.08, p < 0.0001 (per Woods Unit)].

Conclusions In this study of patients with PAH receiving parenteral treprostinil, PCWP was not associated with long-term all-cause mortality. Further studies examining prognostic indicators in patients with PAH optimised on guideline-based therapies are warranted.

Keywords Pulmonary capillary wedge pressure • Pulmonary arterial hypertension • Trepostinil

*Corresponding author at: Department of Medicine, Stony Brook University Medical Center, Health Science Center T17-040, USA. Tel.: +1 631 388 3878., Email: jignesh.patel@stonybrookmedicine.edu

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Introduction

Pulmonary arterial hypertension (PAH) is a chronic, debilitating disease associated with significant morbidity and mortality [1,2]. It is defined by mean pulmonary artery pressure >25 mmHg, pulmonary vascular resistance >3 Woods units (WU), pulmonary capillary wedge pressure (PCWP) < 15 mmHg, and the absence of other causes of pulmonary hypertension [2]. The prevalence of PAH in the US is approximately 50,000 to 100,000 individuals [3]. Patient survival has dramatically improved as treatment options for PAH have become more advanced. While a PAH registry from the National Institute of Health from 1981 to 1985 had previously demonstrated a median survival of 2.8 years [4], more recent reports have demonstrated median survival times of more than 7 years given substantial therapeutic advances [5].

The predictors of mortality in PAH include male gender, age >65 years, PAH due to connective tissue disease, higher New York Heart Association (NYHA) functional class, lower 6-minute walk distance (6MWD), higher B-type natriuretic peptide (BNP), higher serum creatinine, pericardial effusion on echo, lower diffusion capacity (DLCO), higher right atrial (RA) pressure, lower cardiac output (CO), and higher pulmonary vascular resistance (PVR) [2,4]. While pulmonary capillary wedge pressure (PCWP) has been touted for its utility in management and prognosis of patients with left heart failure, the clinical impact of PCWP on long-term mortality among patients with PAH has been incompletely reported, particularly in relation to concomitant treprostinil administration. From the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL registry), demographics and outcomes of patients diagnosed with PAH with PCWP 16 to 18mmHg was compared to those with PCWP < 16 mmHg and no difference in mortality rates was noted [6]. The Flolan International Randomized Survival Trial (FIRST) in 1997 which involved epoprosenol infusion in patients with NYHA Class II heart failure and elevated PCWP demonstrated improved cardiac output, decreased PCWP and decreased PVR in patients treated with epoprostenol compared to standard of care [7]. However, no difference in 6MWD or quality of life was noted between the both arms and the trial was terminated early due to a strong trend toward all-cause mortality in the epoprostenol arm.

Pulmonary arterial hypertenstion patients with PCWP in the higher range of ''normal'' may not be true ''PAH'' but rather early heart failure with preserved ejection fraction (HFpEF). These patients may have a suboptimal long-term response to pulmonary vasodilator therapy, especially prostacyclin therapy. Accordingly, we postulated that in patients with PAH treated with parenteral treprostinil, the long-term mortality of patients with higher PCWP would be worse compared to their counterparts with lower PCWP.

Methods

Study Population

The present study included three previously published treatment trials for PAH involving parenteral trepostinil conducted by United Therapeutics. Two trials (TRUST, SC-TRE) were multicentre, randomised, double-blind, placebo-controlled treatment trials [8,9] and one was an open-label extension study of the SC-TRE trial which followed patients being treated with subcutaneous treprostinil for four additional years [10]. For our analyses, data from the SC-TRE (both randomised and open-label studies) and TRUST trials were combined to create one large cohort. Inclusion and exclusion criteria for each trial have been published previously [8,9]. Patients from all trials were included regardless of the treatment allocation.

The study population included 978 patients with PAH treated with parenteral treprostinil therapy. Of these, 235 patients were excluded due to absence of data regarding baseline PCWP. Of the remaining 743 patients, long-term all-cause mortality was compared in patients with baseline mean PCWP ≤ 8 mmHg (lowest tertile), 8 < PCWP ≤ 11 mmHg (intermediate tertile), and PCWP >11 mmHg (highest tertile) over four-year follow-up. Demographic data and clinical history were recorded in these patients. The demographic and baseline medical history data extracted included age, gender, race, height, weight, aetiology of PAH, baseline 6MWD, baseline BORG dyspnoea score, and NYHA functional class. Baseline haemodynamic data recorded included cardiac output (litres/minute) (obtained via thermodilution or Fick), pulmonary vascular resistance [Woods units (WU)], mean right atrial (RA) pressure (mmHg), mean PA pressure (mmHg), and mean PCWP (mmHg). Outcomes of interest were all-cause mortality at one year, two years, three years, and four years.

Statistical Analysis

The present study was confined to 743 patients with PAH treated with parenteral trepostinil for whom right heart catheterisation was performed at baseline. The results of baseline mean PCWP were categorised into PCWP ≤ 8 mmHg (lowest tertile), 8 < PCWP ≤ 11 mmHg (intermediate tertile), and PCWP > 11 mmHg (highest tertile). Categorical variables are presented as percentages and compared with the chi-squared test or Fisher's exact test, if applicable. Continuous variables are presented as means ± standard deviation and compared using one-way ANOVA. Multivariable logistic regression was utilised to determine the independent predictors of all-cause mortality for each consecutive year up to and including four years. Predictors for the logistic regression were selected based on statistical significance in the univariate analysis ($p < 0.05$) and included age, race, PVR, and PCWP. Kaplan-Meier survival curve was constructed to compare mortality over four years between patients with PCWP ≤ 8 mmHg, 8 < PCWP ≤ 11 mmHg, and PCWP > 11 mmHg. SPSS version

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