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Hospitalization and Survival in Patients Using Epoprostenol for Injection in the PROSPECT Observational Study

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BACKGROUND: Few studies have prospectively reported outcomes in patients with pulmonary arterial hypertension (PAH) treated with epoprostenol in the modern-day era of oral therapy and combination treatments. The Registry to Prospectively Describe Use of Epoprostenol for Injection (Veletri, prolonged room temperature stable-epoprostenol [RTS-Epo]) in Patients with Pulmonary Arterial Hypertension (PROSPECT) was established to prospectively describe the course of PAH in patients prescribed RTS-Epo.

METHODS: PROSPECT is a multicenter, US-based drug registry of primarily group 1 patients with PAH treated with RTS-Epo who were parenteral-naive or parenteral-transitioned at enrollment. Patients were followed until discontinuation of RTS-Epo, withdrawal, loss to follow-up, death, or end of study (maximum 1 year). One-year freedom from hospitalization (FH) and survival estimates were summarized by prostacyclin history (parenteral-naive or parenteral-transitioned), sex, and chronic renal insufficiency (CRI).

RESULTS: A total of 336 patients were included. The overall 1-year FH estimate was 51.0% ± 2.8% and was lower in parenteral-naive patients than parenteral-transitioned patients (42.8% ± 4.3% vs 57.1% ± 3.7%, respectively; $P = .002$). FH estimates were lower in male patients than female patients (38.3% ± 5.9% vs 54.6% ± 3.2%, respectively; $P < .015$) and in patients with CRI than patients without CRI (17.0% ± 8.4% vs 53.7% ± 2.9%, respectively; $P < .001$). The overall 1-year survival estimate was 84.0% ± 2.1%. Survival was poorer in parenteral-naive patients, male patients, and patients with CRI.

CONCLUSIONS: Risk of hospitalization and mortality remain high in patients with PAH. In particular, patients who are parenteral-naive at initiation of RTS-Epo therapy, male patients, and patients with CRI require close monitoring and aggressive clinical management.

CHEST 2015; 147(2):484-494

Manuscript received April 24, 2014; revision accepted September 3, 2014. originally published Online First October 9, 2014.

ABBREVIATIONS: 6MWD = 6-min walk distance; BSI = blood stream infection; CRI = chronic renal insufficiency; CTD = connective tissue disease; IPAH = idiopathic pulmonary arterial hypertension; NYHA FC = New York Heart Association functional class; PAH = pulmonary arterial hypertension; PPH = primary pulmonary hypertension; PROSPECT = Registry to Prospectively Describe Use of Epoprostenol for Injection (Veletri, prolonged room temperature stable-epoprostenol [RTS-Epo]) in Patients with Pulmonary Arterial Hypertension; REVEAL Registry = Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management Registry; RTS-Epo = room temperature stable-epoprostenol; WHO = World Health Organization

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Pulmonary arterial hypertension (PAH) is a rare, progressive disease characterized by increasing pulmonary vascular resistance and pressures, resulting in right-side heart failure, dyspnea, and decreasing functional status.[1] Untreated, the median survival time in idiopathic pulmonary arterial hypertension (IPAH) is 2.8 years, with estimated survival rates of 68% at 1 year, 48% at 3 years, and 34% at 5 years.[2] While outcomes have improved with the advent of new therapies, further progress is needed. In The Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL Registry), the 1-year, 3-year, 5-year, and 7-year survival rates from time of diagnostic right-sided heart catheterization in a more diverse group of patients with PAH were 85%, 68%, 57%, and 49%, respectively.[3]

Hospitalization has been suggested as an indicator of poor survival; death, lung transplantation, and hospitalization have been identified as clinical efficacy measures in PAH clinical research.[4] Additionally, in a study evaluating definitions of clinical worsening as a predictor of proximate (within 1 year) risk for subsequent major events (ie, death, transplantation, or atrial septostomy), hospitalization was independently associated with poor survival: the 1-year survival rate in patients hospitalized was only 71.4% ± 1.5%.[5]

Epoprostenol is an IV synthetic prostacyclin shown to improve exercise capacity and World Health Organization (WHO) functional class, while prolonging survival.[1,6-9] Epoprostenol remains the recommended treatment of the most advanced cases of PAH.[10] There are limited data documenting the long-term rates of hospitalization and survival beyond 12 weeks with epoprostenol. Prior studies of survival in patients on epoprostenol have been limited to patients with primary pulmonary hypertension (PPH, now known as IPAH) in an era where prostacyclins were the only available therapy, and are limited to single-center cohort studies.[1,8,9,11]

Epoprostenol for injection (Veletri, prolonged room temperature stable-epoprostenol [RTS-Epo]) is a US Food and Drug Administration (FDA)-approved formulation of epoprostenol that has improved stability over the standard formulation of epoprostenol at room temperature.[12] The Registry to Prospectively Describe the Use of RTS-Epo in Patients with Pulmonary Arterial Hypertension (PROSPECT) is a multicenter, prospective, observational registry of patients who were prescribed RTS-Epo. The registry longitudinally describes the modern-day course of patients with PAH treated with epoprostenol (RTS-Epo), by evaluating a broad range of clinical and patient-reported outcomes for 1 year after enrollment. The objective of this analysis is to assess the baseline characteristics and the risk of hospitalization and mortality in this cohort.

Materials and Methods

Registry Design and Participants

Participants were enrolled between September 2010 and January 2012 at 50 PAH centers across the United States, all of which received institutional review board approval. Patients were eligible if they had been diagnosed with PAH (group 1 pulmonary hypertension) and were parenteral-naive or parenteral-transitioned from another formulation of epoprostenol or treprostinil therapy to RTS-Epo. Patients were followed for a maximum of 1 year or until discontinuation of RTS-Epo, withdrawal of consent, loss to follow-up, death, or end of study.

Data Collection

Patient data were collected at enrollment and quarterly intervals (months 3, 6, 9, and 12) (e-Table 1). No treatments or assessments were mandated by the protocol. Clinical characteristics, medical history, and comorbid conditions, including pulmonary function tests, echocardiogram, New York Heart Association functional class (NYHA FC) evaluation, and 6-min walk distance (6MWD) were collected using the most recent clinical visits, hospitalization, and/or telephone contacts. The treating physician determined renal insufficiency by selecting a checkbox in the electronic case report form. Among those patients who had a creatinine recorded, estimated glomerular filtration rate was computed. Dosing regimen and titration schedule for RTS-Epo and concomitant PAH medications were also collected quarterly.

Outcomes

Clinical outcomes from PROSPECT included demographics and disease characteristics of patients receiving RTS-Epo. Safety outcomes included all-cause deaths and hospitalizations and blood stream infections (BSIs). All outcomes were stratified by patient demographics and disease characteristics. Hospitalizations were assigned by the treating physician as related to the use of RTS-Epo, due to PAH, both, or neither. Reports of BSIs leading to hospitalization or death were also collected. Hospitalizations for initiation of RTS-Epo were not collected. Hospitalizations were coded using the MedDRA coding dictionary (version 14.0).

Deaths were collected during the course of the study. Patients who discontinued the study for any reason were censored on the date of discontinuation.

Statistical Analysis

Baseline demographic and clinical characteristics were summarized using percentages for categorical variables and means ± SD for

Drs Frantz and Schilz contributed equally to this manuscript.

FUNDING/SUPPORT: Actelion Pharmaceuticals US, Inc, the sponsor of PROSPECT, provided funding and support for the analysis presented.

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DOI: 10.1378/chest.14-1004