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Long-term treatment, tolerability, and survival with sub-cutaneous treprostinil for severe pulmonary hypertension

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KEYWORDS:
pre-capillary pulmonary hypertension;
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BACKGROUND: Randomized controlled trials have resulted in improved outcomes in pulmonary arterial hypertension; however, they are biased by stringent inclusion criteria, pre-specified patient sub-sets, and study durations. In addition, common practice is to start oral therapies ahead of the more potent and titratable prostanoid therapies, despite advanced disease states at diagnosis. The objectives of our prospective registry were to evaluate long-term effects on functional class, 6-minute walking distance, hemodynamics, and survival, and also long-term tolerability of first-line sub-cutaneous treprostinil, a prostacyclin analog, in patients with severe pulmonary hypertension.

METHODS: Data were collected from patients with functional class III/IV pre-capillary pulmonary hypertension (Dana Point groups 1 and 4; mean right arterial pressure $\geq$ 10 mmHg, and/or cardiac index $\leq$ 2.2 liters/min/m^2). Treprostinil dose adjustments were driven by clinical symptoms and side effects.

RESULTS: The study included 111 patients (1999 to 2010). Of these, 13 (12%) stopped treatment prematurely because of drug side effects, 11 (9.9%) underwent double lung transplantation, and 49 (44.1%) died of any cause (41 on treatment, 8 after early drug discontinuation). Overall survival rates at 1, 5, and 9 years were 84%, 53%, and 33%. In patients who were able to tolerate treatment $>$ 6 months, survival rates were 57% at 9 years.

CONCLUSION: First-line treatment of severe pre-capillary pulmonary hypertension with sub-cutaneous treprostinil is safe and efficacious over many years. If up-titration beyond 6 months is tolerated, effective doses are reached and outcomes are good.

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Pre-capillary pulmonary hypertension (PH) is a severe condition. According to the National Institutes of Health (NIH) registry,[1] idiopathic and heritable pulmonary arterial hypertension (PAH) have a median untreated time to death of 2.8 years. Although these conditions are rare,[2] the associated forms of PAH[3] and chronic thromboembolic PH (CTEPH)[4] may be more common. The pathogenesis of PH is poorly understood, but imbalances between vasoconstrictive/proliferative (eg, endothelin) and vasodilator/antiproliferative mediators (eg, prostacyclin and nitric oxide) have been identified,[5] indicating occlusive pulmonary vascular remodeling.

Currently approved PH-targeted drugs are primarily vasodilators and fall into 3 classes: prostanoids, endothelin-receptor antagonists, and phosphodiesterase type-5 inhibitors. These treatments improve symptoms, quality

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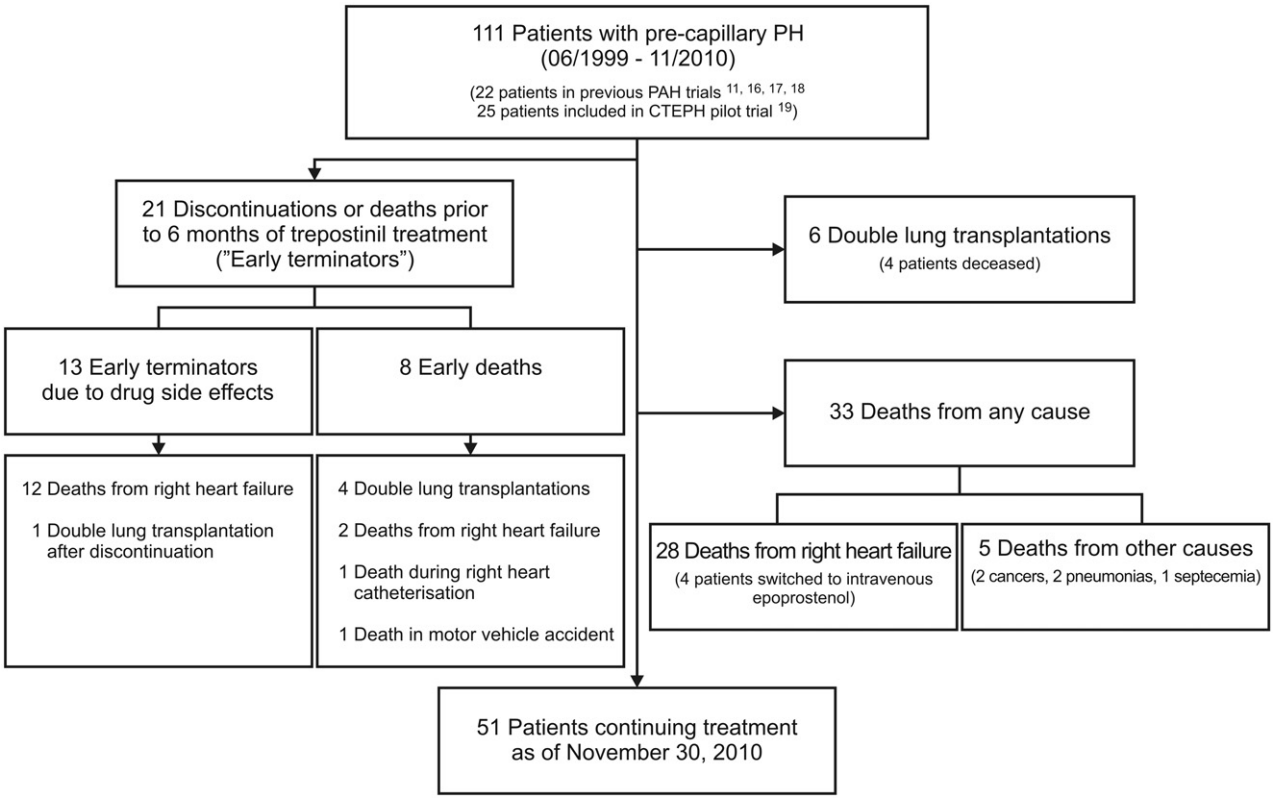

Figure 1 Patient disposition. CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

of life,[6] exercise capacity, hemodynamics, and outcomes,[7] but the disease still carries annual mortality rates of 10% to 15%.[8,9]

More than 66% of newly diagnosed PH patients present in World Health Organization functional classes (WHO FC) III and IV.[8,10] According to our current understanding of the disease pathology, most of the pulmonary vessels are dysfunctional or occluded at these stages. Although current evidence-based guidelines do not specify first-line treatments, we have pursued an aggressive treatment strategy.

Treprostinil is a stable prostacyclin analog (Remodulin®, United Therapeutics, Research Triangle Park, NC) with an elimination half-life of 4.6 hours. Treprostinil has similar acute hemodynamic effects as epoprostenol, exerting vasodilatation of pulmonary and systemic arteries and inhibition of platelet aggregation. Treprostinil can be given sub-cutaneously (SC), thus avoiding risks inherent with chronic intravenous drug administration.

A double-blind, randomized, placebo-controlled trial documented that treprostinil improved exercise capacity, indices of dyspnea, signs and symptoms of PH, cardiopulmonary hemodynamics, and quality of life. However, because local side effects limited dose up-titration, the benefit of SC treprostinil over 12 weeks was modest.[11]

Practical and psychologic support is an essential component of individualized care for patients receiving SC infusion therapy because it takes time for them to learn how best to manage their pain and cope with the infusion pump system.

The objectives of our registry were to evaluate in patients with severe pre-capillary PH the long-term effects on WHO FC, 6-minute walking distance (6MWD), hemodynamics, and survival, as well as long-term tolerability of first-line SC treprostinil.

Patients and methods

The database used in this study has been under the auspices of the Ethics Committee of the Medical University of Vienna (#972/2009). Patients provided written informed consent. Patient disposition is shown in Figure 1.

Study design

This prospective registry included patients (aged ≥ 18 years) with advanced pre-capillary PH who received first-line treatment with SC treprostinil. Inclusion criteria were (1) pre-capillary PH[10] Dana Point groups I or IV, (2) WHO FC III or IV, and (3) a mean right atrial pressure (mRAP) ≥ 10 mmHg and/or a cardiac index (CI) ≤ 2.2 liters/min/m^2. Diagnoses were established according to guidelines.[12] Date of diagnosis and baseline corresponded to the date of the first diagnostic right heart catheterization, which was 3 days to 3 months before treatment initiation. Patients were stable on therapies that included anti-coagulants, cardiac glycosides, diuretics, and supplemental oxygen.

Assessments

Patients were seen every 3 to 6 months as outpatients, parallel to monthly consultations at their primary care physicians. We counted