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Transition from parenteral to oral treprostinil in pulmonary arterial hypertension

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BACKGROUND: Parenteral prostanoids are effective treatment for pulmonary arterial hypertension, but long-term pump infusion systems have significant delivery-related safety and convenience limitations.
METHODS: Subjects with a favorable risk profile transitioned from parenteral to oral treprostinil using a protocol-driven titration during 5 days of inpatient observation. Baseline and Week 24 assessments included 6-minute walk distance, echocardiogram, right heart catheterization, pharmacokinetics, treatment satisfaction and quality of life. Thirty-three subjects (76% female, mean age 50 years) enrolled; 85% were using subcutaneous treprostinil with a median dose of 57 (range 25 to 111) ng/kg/min. Participants were using background, approved non-prostanoid therapy, including 9 on 2 oral therapies; baseline right atrial pressure and cardiac output were in the normal range. All 33 subjects transitioned to oral treprostinil therapy within 4 weeks, but 2 transitioned back to parenteral drug before Week 24. At Week 24, subjects were taking a median total daily dose of 44 (15 to 75) mg, with 25 of 31 using a 3-times-daily regimen at 7- to 9-hour intervals.
RESULTS: The 6-minute walk distance was preserved (median +17 m [-98 to 95 m]) at its baseline of 446 m. Hemodynamic variables, including pulmonary vascular resistance, were similar at Week 24 except for mixed venous saturation, which dropped from a median of 71% to 68% ($p < 0.001$). Overall quality of life and treatment satisfaction measures did not change; however, mood-related symptom and treatment convenience subscores improved. Common adverse effects included headache, nausea, flushing and diarrhea.
CONCLUSIONS: Lower risk patients managed on parenteral treprostinil may be candidates for transition to a more convenient, oral form of the drug.
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Pulmonary arterial hypertension (PAH) is a rare but progressive and often fatal disease. Treatment options have expanded greatly in the past 20 years,[1] providing many patients with safer, more convenient therapies. However, parenteral prostanoids are still favored for the highest risk patients,[2] and >4,500 patients in the USA are presently using pump-based, parenteral prostacyclin therapy. Intravenous prostacyclin therapy increases the risk of bloodstream infection and thrombosis.[3,4]

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Subcutaneous treprostinil therapy frequently causes site pain, which can be severe and require analgesics.[5,6] Patients prefer oral therapy options, but, to date, prospective trials transitioning parenteral therapy patients to more convenient non-prostanoid therapies have been disappointing.[7,8]

An oral, extended-release treprostinil tablet (Orenitram; United Therapeutics, Silver Spring, MD) was approved in 2013. We anticipated that some patients using parenteral treprostinil would request transition to oral treprostinil as an option, especially if they were having difficulties with the parenteral delivery system. Pharmacokinetic studies of oral treprostinil in PAH subjects demonstrated sustained concentrations for a group of participants on a dosing regimen of 6 mg twice daily[9] and provided a basis to estimate initial and target doses of oral treprostinil for patients currently using parenteral drug. We did not allocate any participants to a placebo control because the only previous placebo-controlled transition trial (from intravenous epoprostenol to subcutaneous treprostinil) clearly put stably treated participants at unacceptable risk.[10] In lieu of a placebo control, participants consented to extensive objective evaluation, including baseline and 6-month testing for exercise tolerance, right ventricular (RV) function (by echocardiography), pharmacokinetics and invasive hemodynamics.

Methods

Six centers enrolled participants in this open-label, 24-week study. Detailed enrollment criteria, measurements and transition procedures are presented in the Supplementary Material (available online at www.jhltonline.org/). Briefly, eligible patients weighed at least 40 kg and were using parenteral treprostinil (doses of 25 to 150 ng/kg/min) for a diagnosis of World Health Organization (WHO) Group 1 PAH. All approved PAH therapies (including parenteral treprostinil) had to be active for at least 90 days, with stable doses for 30 days. Our goal was to enroll "low-risk" participants, as defined recently in Table 13 of the 2015 ERS/ESC guidelines for the treatment of PAH.[2] Specifically, patients must have demonstrated WHO Functional Class I or II symptoms with baseline cardiac index >2.2 liters/min/m^2, right atrial pressure <11 mm Hg and 6-minute walk distance (6MWD) ≥ 250 meters. Endothelin receptor antagonist (ERA) or phosphodiesterase-5 inhibitor (PDE-I) treatments were required in addition to parenteral treprostinil. Beyond the specific enrollment criteria, the investigators intended to recruit patients who had previously required parenteral therapy but had subsequently demonstrated a durable, favorable therapeutic response to parenteral drug. All patients provided written informed consent to participate after an independent institutional review board approved the study protocol for each site.

The primary end-point was successful transition to oral therapy, that is, the percentage of patients who completely transitioned

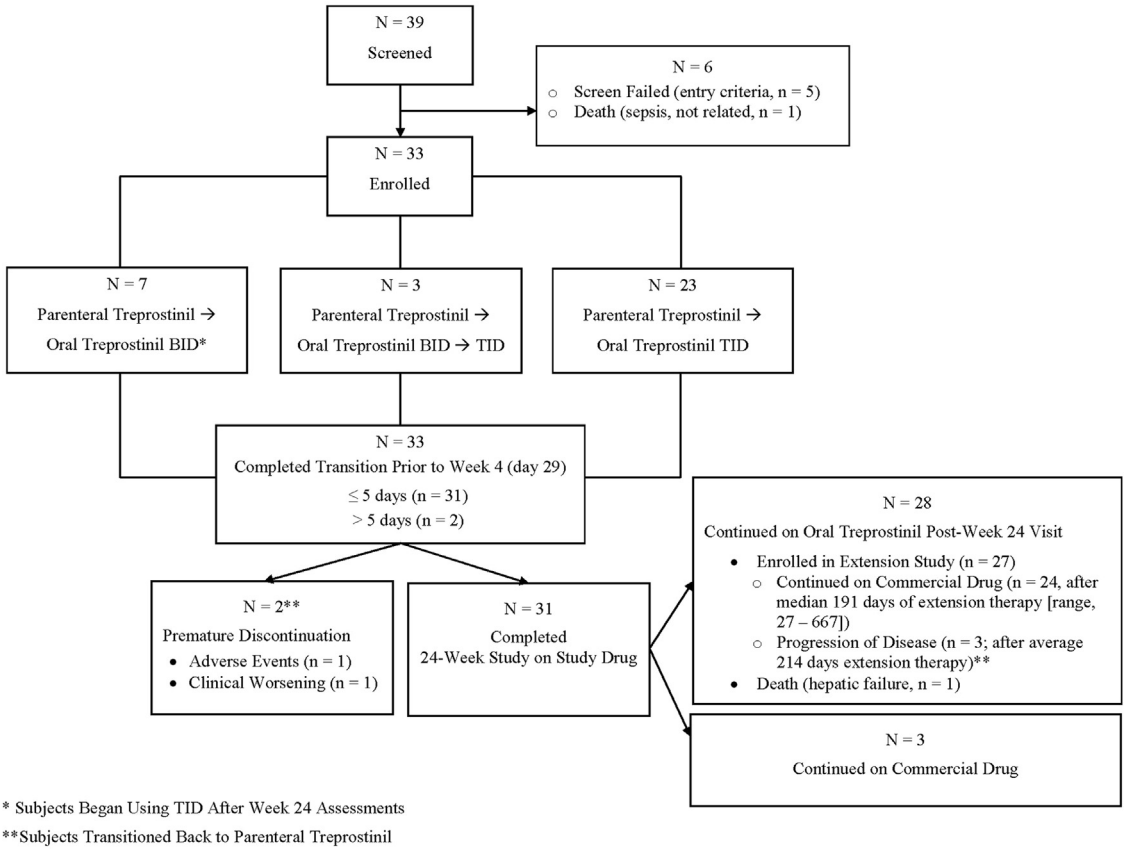

Figure 1 Patient disposition. Of the 33 subjects who enrolled, 2 returned to parenteral treprostinil before Week 24. Of the 31 subjects who completed Week 24, 3 immediately began commercial therapy with oral treprostinil (Orenitram) and did not have further follow-up. One subject died of chronic hepatic failure 145 days after completing Week 24, but this occurred before enrollment in the formal extension study. The remaining 27 subjects enrolled in the extension study and were followed for a median of 206 (range 27 to 667) days. Three subjects (of these 27) had late deterioration; thus, 24 of the 30 participants for whom we had longer term follow-up remained on oral treprostinil at the close of formal observation.