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One-year experience with intravenous treprostinil for pulmonary arterial hypertension

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BACKGROUND: Intravenous (IV) epoprostenol has been the mainstay of therapy in advanced pulmonary arterial hypertension (PAH). Continuous IV treprostinil has several potential advantages over IV epoprostenol; however, there has been a lack of published long-term efficacy and safety data on IV treprostinil in PAH.

METHODS: We conducted a 48-week, multicenter, prospective, open-label, uncontrolled, study of continuous IV treprostinil in 16 patients on no prior PAH specific therapy at baseline (de novo), or 31 patients transitioned at baseline from IV epoprostenol (transition). The primary end point was change in exercise capacity assessed by the 6-minute walk distance (6MWD) test.

RESULTS: In de novo patients, IV treprostinil increased the mean ± standard error 6MWD by 125 m from 332 ± 21 m at baseline to 457 ± 26 m at Week 48. There were also improvements in the secondary end points of Naughton-Balke treadmill time, Borg Dyspnea Score, and hemodynamics at Week 48 compared with baseline. In 23 patients transitioned from IV epoprostenol with 48-week follow-up data, 6MWD, hemodynamic measures, and World Health Organization functional class at Week 48 were all stable compared with baseline. Side effects were generally mild and consistent with those reported with prostacyclin treatment. During the study, 5 patients died of causes not considered related to the therapy, and 7 discontinued due to adverse events.

CONCLUSIONS: In this open-label trial, continuous IV treprostinil for 1 year appears to be safe and effective in de novo PAH patients and those transitioned from IV epoprostenol.

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Before 2001, approved pharmacotherapy for pulmonary arterial hypertension (PAH) consisted of continuous intravenous (IV) epoprostenol sodium (Flolan; GlaxoSmithKline, Research Triangle Park, NC).[1] Since 2001, oral, inhaled, and alternatively infused medications have been approved based on improved exercise capacity.[2–5] Even with many new therapies, PAH remains a life-threatening disease.[6–8] The expanded treatment armamentarium has many advantages to individualizing treatment but also increases the complexity of choosing the most appropriate therapy.

Although prostacyclin therapy is deemed the most effective treatment available for moderate to severe PAH, current data suggest a sub-optimal use of parenteral therapy in high-risk patients.[9] Recent data from the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) registry indicate that 40% of patients who died with World Health Organization (WHO) Functional Class IV limitations were never treated with a parenteral

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prostanoid. Although these data cannot fully be explained, they underscore the need to consider initiation of prostacyclin therapy in high-risk patients and to overcome barriers to their use.[10]

Traditionally, intravenous (IV) epoprostenol has been considered the most effective treatment, particularly for advanced PAH, despite requiring a daily mixing regimen and cooling with ice packs. Treprostinil sodium (Remodulin; United Therapeutics Corp, Research Triangle Park, NC) was subsequently developed as an alternative to epoprostenol due to increased stability. Treprostinil sodium is available for sub-cutaneous (SC) or IV administration and has anti-platelet aggregation and pulmonary and systemic vascular bed vasodilatory properties, similar to those of epoprostenol. Bioequivalence and linearity of dosing exists between IV and SC treprostinil.[11,12] In previous studies, SC treprostinil increased exercise capacity, improved indices of dyspnea, reduced signs and symptoms of PAH, and improved cardiopulmonary hemodynamics in patients with PAH, but may have a more favorable safety and convenience profile compared with IV epoprostenol.[5,13] As with epoprostenol, these beneficial effects are dose-related and independent of PAH etiology.[14–17] For patients unable to tolerate SC treprostinil infusion, IV administration is an option.

Although the pharmacodynamics of epoprostenol* and treprostinil may be qualitatively similar, they differ in their pharmacokinetic profile. Treprostinil has a longer half-life (elimination $t_{½}$ of 4.5 hours; distribution $t_{½}$ of 40 minutes vs $t_{½}$ of 2 to 3 minutes for epoprostenol); thereby, it may avoid abrupt hemodynamic effects in the event of infusion disruption and may impart greater safety. Treprostinil also demonstrates chemical stability at physiologic pH and at an ambient temperature of up to 104°F, thus alleviating the need for ice packs as required by Flolan, the available epoprostenol at the time of this study. The 48-hour infusion interval for IV administration allows for drug preparation and cassette replacement every other day. These characteristics make treprostinil favorable for IV use and suggest that it may have safety and convenience advantages over some forms of epoprostenol for appropriate PAH patients.[11,18–20] Parenteral prostanoid therapy is considered appropriate for advanced PAH patients at higher risk of death.[21]

In a 12-week open label observational trial, we previously reported that IV treprostinil appears to be safe and effective in treatment-naïve patients as initial therapy[22] and in patients transitioned from IV epoprostenol monotherapy to IV treprostinil monotherapy.[23] The 48-week safety and efficacy results of the open-label IV treprostinil extension trial are presented here to inform physicians treating PAH that this form of parenteral prostacyclin does provide a lasting effect, as measured by traditional end points, and to report the long-term tolerability of the drug.

*Flolan and Veletri are 2 available epoprostenols today. At the time that this study was done, only Flolan was available.

Methods and materials

The clinical study was approved by each investigator's respective Investigational Review Board. All patients provided written informed consent.

Patient population

This is an update of the previously published 12-week study. The extension study, with data updated to 48 weeks, consisted of patients aged 12 to 65 years with symptomatic PAH that was idiopathic, heritable, related to connective-tissue disease, or related to underlying congenital heart disease despite treatment with anticoagulants, cardiac glycosides, diuretics, supplemental oxygen, and calcium channel blockers, as described for the original 12-week report.[22,23] Newly diagnosed WHO Functional Class II, III, or IV patients not previously treated with specific targeted PAH therapies (de novo) with a baseline 6-minute walk distance (6MWD) $>$ 50 m who were clinically stable for $>$ 1 month before study enrollment were eligible. Transition patients receiving IV epoprostenol at baseline (minimum treatment period of 3 months) had to have been on a stable epoprostenol dose for 1 month and have WHO Functional Class II or III disease status at baseline. Exclusion criteria were similar to those in the 12-week study.[22]

Study design

All patients were hospitalized at the start of the 48-week study. A central catheter was placed in de novo patients for continuous IV treprostinil (initial dose of 2.0 ng/kg/min). Transition patients had 2 separate IV catheters, and treprostinil was up-titrated as the epoprostenol (Flolan) dose was down-titrated, with vital sign monitoring over a 24- to 48-hour period. Investigators increased the treprostinil doses as tolerated by the treatment-related side effects to manage dyspnea as effectively as possible throughout the study.

Outcome measures

The primary efficacy end point was exercise capacity as assessed by the 6MWD test, the standard at the time this study was done. The test was repeated at Weeks 6, 12, 24, 36, and 48. Secondary efficacy end points included time on the Naughton-Balke treadmill test, Borg Dyspnea Score, and WHO functional classification, assessed at Weeks 6, 12, 24, 36, and 48. Hemodynamic assessments were performed at baseline, Week 12, and Week 48. Adverse events (AEs) and standard laboratory hematology and blood chemistry assessments were made at baseline and at Weeks 12 and 48.

Statistical analysis

Continuous data are presented as mean ± standard deviation (or standard error) and categorical data are presented in frequency and percentage. All paired changes from baseline to Weeks 12 and 48 for each end point are summarized with descriptive statistics. The Kaplan-Meier method was used to estimate overall survival and treatment success defined as free from death, lung transplantation, atrial septostomy, or discontinuation of IV treprostinil. To avoid the potential of biasing the results of this uncontrolled study with a small sample size, no imputation for missing values was used.