Safety and Efficacy of IV Treprostinil for Pulmonary Arterial Hypertension*

A Prospective, Multicenter, Open-Label, 12-Week Trial

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Background: Pulmonary arterial hypertension (PAH) is a life-threatening disease for which both continuous IV epoprostenol and continuous subcutaneous treprostinil have proven effective. With continuous IV treprostinil having potential advantages over both of the above therapies, we investigated the safety and efficacy of this regimen in patients with PAH.

Methods: We conducted a 12-week, prospective, open-label, uncontrolled, multicenter study of continuous IV treprostinil in 16 patients with PAH that was idiopathic (n = 8), related to connective tissue disease (n = 6), or related to congenital heart disease (n = 2). The primary end point was change from baseline to week 12 in exercise capacity assessed by the 6-min walk (6MW) test.

Results: Continuous IV treprostinil increased 6MW distance (mean ± SE) by 82 m from baseline (319 ± 22 m) to week 12 (400 ± 26 m) [n = 14; p = 0.001]. There were also significant improvements in the secondary end points of Naughton-Balke treadmill time (p = 0.007), Borg dyspnea score (p = 0.008), and hemodynamics (mean pulmonary artery pressure, p = 0.03; cardiac index, p = 0.002; pulmonary vascular resistance, p = 0.001) at week 12 compared with baseline. Side effects were mild and consistent with those reported with prostacyclin treatment. One death, unrelated to study drug, occurred during the 12-week study in a patient who received 3 days of treprostinil and died 2 weeks later.

Conclusions: Long-term IV infusion of treprostinil is safe and appears to be effective for the treatment of patients with PAH.

(CHEST 2006; 129:683–688)

Key words: idiopathic pulmonary arterial hypertension; prostacyclin analog; pulmonary arterial hypertension related to congenital heart disease; pulmonary arterial hypertension related to connective tissue disease; treprostinil

Abbreviations: PAH = pulmonary arterial hypertension; 6MW = 6-min walk; WHO = World Health Organization

Although recent therapeutic advances have significantly improved the long-term outcome for pulmonary arterial hypertension (PAH), this disease remains life threatening.1,2 Continuous IV epoprostenol (prostacyclin) improves exercise capacity, hemodynamics, and quality of life in patients with idiopathic pulmonary arterial hypertension (PAH).3,4 PAH related to connective tissue disease,5,6 and PAH related to congenital heart disease.7,8 Epoprostenol is the only PAH therapy demonstrating im-

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This investigator-initiated study was supported by United Therapeutics Corporation, Research Triangle Park, NC.

Manuscript received May 7, 2005; revision accepted September 18, 2005.

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proved survival in a randomized controlled trial.\textsuperscript{3} In
two large retrospective series\textsuperscript{9,10} of patients with
idiopathic PAH followed up at 3 years and 5 years,
observed survival of epoprostenol-treated patients
was significantly greater compared to predicted sur-
vival based on historical data.

Trexprostinil, a stable prostacyclin analog, has sim-
lar pharmacologic effects to epoprostenol.\textsuperscript{11–13} However,
in contrast to epoprostenol, treprostinil is chemically stable at room temperature and neutral
pH and has a longer half-life (elimination half-life of 4.5 h with distribution half-life of 40 min, compared
with 2 to 3 min for epoprostenol) permitting contin-
uous subcutaneous infusion.\textsuperscript{14} Long-term subcuta-
neous infusion of treprostinil improves exercise ca-
pacity, indexes of dyspnea, symptoms and signs of
PAH, and hemodynamics, compared with place-
bo.\textsuperscript{15,16} Similar to epoprostenol, these beneficial
effects are dose related and independent of PAH
etiology. However, infusion site pain is common with
continuous subcutaneous infusion and limits its use.\textsuperscript{15} Based on the potential advantages over
epoprostenol, we conducted a 12-week, open-label
trial with continuous IV treprostinil to assess its
safety and efficacy in patients with PAH.

**Materials and Methods**

**Patient Population**

Patients with PAH that was idiopathic, related to connective
tissue disease,\textsuperscript{17} or related to underlying congenital heart disease
who were at least 12 years of age with symptomatic PAH despite
treatment with anticoagulants, cardiac glycodies, diuretics, sup-
plemental oxygen, and calcium-channel blockers (if indicated), in
whom treatment with continuous IV epoprostenol was consid-
ered, were eligible for study participation if they met the
following criteria: (1) a baseline 6-min walk (6MW) distance \(\geq\) 50
m; and (2) clinically stable for \(>1\) month prior to study
enrollment. Exclusion criteria were as follows: (1) investigational
drug therapy or participation in an investigational drug study
within the past month; (2) addition of a new long-term therapy
for PAH during the past month (including but not limited to
oxygen, a different category of vasodilator, a diuretic, or cardiac
glycodies); or (3) PAH medication (except for anticoagulants)
discontinued within the week prior to study entry. All patients
gave written, informed consent. The protocol was approved by
local institutional review boards and ethics committees.

**Study Design**

The study was a 12-week, prospective, uncontrolled, open-
label, multicenter trial. Patients were hospitalized for initiation of
continuous IV treprostinil via a dedicated central venous catheter
with an infusion pump (CADD-Legacy; Deltec; St. Paul, MN).

Trexprostinil was diluted with normal saline solution or sterile
water for IV infusion and initiated at a dose of 2.0 ng/kg/min.
During the 12-week study, the dose was escalated to optimize
improvement in PAH symptoms and signs, unless side effects
precluded a dose increase.

**Outcome Measures**

The primary efficacy end point was the effect of IV treprostinil
on exercise capacity as assessed by the 6MW test.\textsuperscript{19} Each patient
performed at least one practice 6MW test prior to the baseline
assessment. The walk test was repeated at week 6 and week 12.
Secondary efficacy end points included time on the Naughton-
Balke treadmill test, Borg dyspnea score, World Health Organiza-
tion (WHO) functional classification, and hemodynamic pa-
rameters. These studies were performed at week 6 and week 12,
with the exception of repeat hemodynamic assessment, which
was performed only at week 12. Safety was assessed by adverse
events and by laboratory assessments (including hemoglobin
level, platelet count, leukocyte count, serum creatinine, BUN,
alanine phosphatase, and alanine aminotransferase) at baseline
and week 12.

**Statistical Analysis**

Changes in baseline to week 12 for each study end point were
summarized for all patients with nonmissing values at each of
these assessments. All paired changes from baseline to week 12
were tested using the Wilcoxon signed-rank test. To avoid the
potential of biasing the results of this uncontrolled, small-sample-
size study, no imputation for missing values was used. Data at
week 6 were analyzed in the same manner. Data are presented as
mean \(\pm\) SE. All reported \(p\) values are two sided. A \(p\) value of
< 0.05 was considered statistically significant.

**Results**

** Patients and Treprostinil Dosing**

Sixteen patients with PAH were enrolled between
February 2003 and September 2004. Fourteen of the
16 patients completed the 12-week protocol. One
patient received drug for 3 days and died 2 weeks
later. A second patient completed the 6-week study
but was hospitalized and could not return for the
12-week studies. Thus, 16 patients are included in
the baseline characteristics, 16 in the safety table,
and 14 in the 12-week data table. Baseline demo-
graphic and hemodynamic characteristics are shown
in Table 1. No patient received other investigational
drugs during the 12-week trial period; one patient
had been receiving bosentan for 18 months prior to
starting treprostinil.

The mean dose of IV treprostinil at discharge (1 to
7 days) was 5 ng/kg/min (range, 2 to 8 ng/kg/min).
During the course of the study, it became evident
that relief of dyspnea with exertion was greater with
more rapid dose escalations and with higher doses
than previously reported with continuous subcuta-
neous treprostinil. While there were no specific guide-
lines on how quickly to titrate up, the dose was
increased approximately three times per week in 1 to
2 ng/kg/min increments (approximately 3 to 6 ng/kg/
min per week). At week 12, the mean dose was
41 \(\pm\) 4 ng/kg/min (range, 20 to 62 ng/kg/min) in the
14 patients completing the 12-week study.
Exercise Capacity

**6MW Test:** In the 14 patients completing the 12-week evaluation, the mean 6MW distance increased by 82 m from 319 ± 22 m at baseline (median, 331 m) to 400 ± 26 m (median, 407 m) at week 12; p = 0.001 (Fig 1). There was also an increase in 6MW distance of 59 ± 19 m (n = 14; p = 0.008) by week 6. There was no significant difference in the treatment effect based on the etiology of PAH.

**Naughton-Balke Treadmill Test:** In the 14 patients who completed the 12-week evaluation, the mean Naughton treadmill time increased by 146 s from 309 ± 33 s (median, 376 s) at baseline to 454 ± 51 s (median, 472 s) at week 12 (p = 0.007), as shown in Figure 2. There was no significant difference in the treatment effect based on the etiology of PAH. There was also an increase in treadmill time of 81 ± 25 s (n = 15; p = 0.006) by week 6.

**Borg Dyspnea Score:** Borg dyspnea score decreased, *ie*, improved, from 4.3 ± 0.6 at baseline to 2.5 ± 0.4 at week 12 (n = 14; p = 0.008), with this change paralleling the improvement observed with the 6MW test.

**WHO Functional Class:** Of the 16 patients enrolled in the trial, 14 patients (88%) were WHO class III and 2 patients (13%) were class IV at baseline, while of the 14 patients who completed the 12-week evaluation, 13 patients (93%) were class III and 1 patient (7%) was class IV. At week 12, there were nine class III patients, four class II patients, and one class I patient; one patient improved from class IV to class III, four patients improved from class III to class II, one patient improved from class III to class I, and eight patients remained class III. Of the eight patients remaining in class III, four patients had a lower Borg dyspnea score at week 12. None of the 14 patients completing the 12-week study deteriorated to class IV (Fig 3).

**Hemodynamics:** Treprostinil decreased mean pulmonary artery pressure by 9% (59 ± 4 mm Hg at baseline and 54 ± 4 mm Hg at week 12; n = 14; p = 0.03). Cardiac index increased 29% (1.7 ± 0.1 L/min/m² at baseline and 2.2 ± 0.1 L/min/m² at week 12; n = 14; p = 0.002), and pulmonary vascular resistance decreased 33% (30 ± 3 U × m² at baseline and 20 ± 3 U × m² at week 12; n = 14; p = 0.001) [Table 2].

**Safety:** One patient died during the 12-week trial. In this class IV patient, treprostinil was discontinued after 3 days of therapy when an altered mental status developed and (preexisting) subdural hematoma was diagnosed; the patient died 2 weeks later. A second patient (functional class III) hospitalized for urosep-

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**Table 1—Baseline Demographic and Hemodynamic Characteristics (n = 16)*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range), yr</td>
<td>45 (26–59)</td>
</tr>
<tr>
<td>White race, No. %</td>
<td>11 (69)</td>
</tr>
<tr>
<td>Female gender, No. (%)</td>
<td>16 (100)</td>
</tr>
<tr>
<td>Etiology of PAH, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>6 (38)</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Borg dyspnea score</td>
<td>4.4 ± 2.3</td>
</tr>
<tr>
<td>WHO functional class, No. (%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>14 (88)</td>
</tr>
<tr>
<td>IV</td>
<td>2 (13)</td>
</tr>
<tr>
<td>6MW, m</td>
<td>307 ± 115</td>
</tr>
<tr>
<td>Naughton treadmill time, s</td>
<td>319 ± 125†</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>58 ± 15</td>
</tr>
<tr>
<td>Mean RAP, mm Hg</td>
<td>12 ± 5</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>1.7 ± 0.4</td>
</tr>
<tr>
<td>PVR, U × m²</td>
<td>29 ± 10</td>
</tr>
</tbody>
</table>

*Data are expressed as mean ± SD unless otherwise indicated. PAP = pulmonary artery pressure; RAP = right atrial pressure; PVR = pulmonary vascular resistance. †n = 15.

**Figure 1.** Change in 6MW distance from baseline. The baseline 6MW distance (matched to 12-week outcomes), *ie*, 319 ± 22 m, increased by 82 m to 400 ± 26 m at week 12 (p = 0.001; n = 14). At week 6, the 6MW distance had increased by 59 ± 19 m from baseline (p = 0.008; n = 14).
sis completed 12 weeks on IV treprostinil but due to the hospitalization at a local hospital did not complete the 12-week evaluation. Thus, although 16 patients were enrolled and 12-week data were only available for 14 patients, the 2 patients not completing the 12-week evaluation were included in the safety assessments.

The most frequent adverse events were extremity pain and jaw pain; both were reported in 69% of patients. Extremity pain was only described as severe in one case. Additional adverse events included nausea, headache, flushing, and diarrhea, ie, side effects frequently reported in patients receiving IV epoprostenol or subcutaneous treprostinil (Table 3). There were no serious adverse events attributable to treprostinil. While the mean systemic BP decreased by a mean of 16.2 ± 4.3 mm Hg over the 12-week period only one patient reported dizziness (not considered severe by either the patient or the investigator).

<table>
<thead>
<tr>
<th>Table 2—Effects of Continuous IV Treprostinil on Hemodynamic Parameters: Change from Baseline to Week 12*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameters</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
</tr>
<tr>
<td>Mean RAP, mm Hg</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
</tr>
<tr>
<td>PVR, U × m²</td>
</tr>
<tr>
<td>Mean SAP, mm Hg</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
</tr>
</tbody>
</table>

*Data expressed as mean ± SE. SAP = systemic arterial pressure.
See Table 1 for expansion of abbreviations.
†Fourteen of 16 patients completed the 12-week study.
‡p = 0.030.
§p = 0.002.
¶p = 0.001.

Figure 2. Change in Naughton-Balke treadmill time from baseline. The baseline treadmill time (matched to 12-week outcomes) was 309 ± 33 s, increasing by 146 s to 454 ± 51 s (p = 0.007; n = 14) by week 12. At week 6, the treadmill time had increased 81 ± 25 s from baseline (p = 0.006; n = 15).

Figure 3. Effects of continuous IV treprostinil on WHO functional class: change in number of patients from baseline to week 12. Eight of the patients who were class III at baseline, remained class III (of these, four patients had a lower Borg dyspnea score at week 12). No patient deteriorated to class IV, although two patients (one class III and one class IV; not shown) did not complete the study. The class IV patient shown above improved to class III (n = 14).

Table 3—Most Frequent Adverse Events (n = 16)

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td></td>
</tr>
<tr>
<td>Extremity pain*</td>
<td>11 (69)</td>
</tr>
<tr>
<td>Jaw pain</td>
<td>11 (69)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Flushing</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Loose stools</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
</tr>
<tr>
<td>Fluid overload</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Mental status change†</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Subdural hematoma†</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Urosepsis</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

*Includes foot, arm, leg, and toe.
†Same patient.
**Discussion**

This is the first prospective evaluation of treprostinil, a stable prostacyclin analog, administered by the continuous IV route in patients with PAH. We demonstrated that IV treprostinil improved exercise capacity (assessed by the 6MW test and by the Naughton-Balke treadmill test), Borg dyspnea score, WHO functional class, and hemodynamics at week 12 compared to baseline. The most frequent side effects were those commonly attributed to prostacyclin therapy.

Potential advantages of IV treprostinil over IV epoprostenol include the following: (1) its longer half-life, which could reduce life-threatening crises in the event of sudden infusion interruption; (2) unlike epoprostenol, room temperature stability renders ice packs unnecessary with IV treprostinil enhancing patient convenience; and (3) the treprostinil cassette can be prepared every 48 h rather than every 24 h as is required with epoprostenol. An advantage over subcutaneous treprostinil is the lack of infusion site pain.

Although the study was open label in design and included a small number of patients, the efficacy of treprostinil has already been demonstrated in a large multicenter randomized clinical trial evaluating subcutaneously infused treprostinil. In addition, the bioequivalence of subcutaneous and IV treprostinil has already been demonstrated.

In the large, double-blind, randomized, placebo-controlled clinical trial evaluating the safety and efficacy of subcutaneous treprostinil in PAH, the median improvement in 6MW distance at week 12 compared with placebo was 16 m (p = 0.006). The mean dose at the end of the 12-week study period was only 9 ng/kg/min, but the highest dose quartile had a 36-m treatment effect in 6MW distance. In this IV study, the much higher mean dose of treprostinil achieved at week 12 (41 ng/kg/min) may explain the greater improvement in 6MW distance with IV treprostinil, ie, a mean increase of 82 m, compared with the subcutaneous treprostinil study.

The mean walk distance improvement demonstrated in this study was also high relative to other clinical trials. Another potential explanation for the relative improvement is that patients with lower baseline 6MW distances (sicker patients) may have a tendency to improve more with regard to this parameter than less severely ill patients. The mean baseline walk distance of 307 ± 29 m in the 16 patients we enrolled was even lower than in the pivotal trial by Barst and colleagues (316 ± 18 m for the epoprostenol group), although importantly, the small size of our study and the SE noted preclude any firm conclusions. In the 14 patients with complete 12-week data, the baseline 6MW distance was 319 ± 22 m. Furthermore, baseline pulmonary vascular resistance index was higher in our IV study. The fact that improvement was significant correlates with the other improvements in these patients and reinforces the efficacy of this mode of treprostinil administration. Larger studies will be useful.

In conclusion, the data from this prospective, multicenter trial suggests that continuous IV treprostinil is a safe and effective treatment option for patients with PAH. The long-term effect on survival with continuous IV treprostinil, however, remains unknown. Long-term data are needed in order to determine optimal therapeutic regimens for individual patients, based on overall risk/benefit considerations.

**Acknowledgment:** We thank Abby Krichman, RBT (Duke University Medical Center) for contributing to the study design and development of the protocol. We also thank the study coordinators from each of the centers involved: Ginger Ward, RN (Duke University Medical Center), Daniela Brady, RN (Columbia University College of Physicians & Surgeons), and Susie McDevitt, RN (University of Michigan), as well as Carl Arnesson, MStat, for statistical advice.

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