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Efficacy and Safety of Treprostinil: An Epoprostenol Analog for Primary Pulmonary Hypertension

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Summary: Intravenous epoprostenol is currently FDA approved for management of primary pulmonary hypertension, but it requires intravenous infusion and is associated with adverse effects. The objective of this study was to evaluate the effects of an epoprostenol analog, treprostinil, for management of pulmonary hypertension. Ten tertiary care academic institutions with pulmonary hypertension programs participated in these pilot trials. In the first trial, intravenous epoprostenol and intravenous treprostinil were compared. In the second trial, intravenous treprostinil and subcutaneous treprostinil were compared. In the third trial, subcutaneous treprostinil was compared with placebo infusion during an 8-week period. Intravenous epoprostenol and intravenous treprostinil resulted in a similar reduction in pulmonary vascular resistance acutely (22% and 20%, respectively). Intravenous treprostinil and subcutaneous treprostinil also demonstrated comparable short-term decrease in pulmonary vascular resistance (23% and 28%, respectively). The placebo-controlled 8-week trial demonstrated a mean improvement of 37 ± 17 m as measured by the 6-minute walk distance in patients receiving treprostinil compared with a 6 ± 28 m reduction in those receiving placebo. There were trends toward an improvement in cardiac index and pulmonary vascular resistance index in the treprostinil group. Subcutaneous treprostinil has favorable hemodynamic effects when given acutely and in the short term. Treprostinil can be given safely to an ambulatory patient with a novel subcutaneous delivery pump system. **Key Words:** Pulmonary arterial hypertension—Hemodynamics—Epoprostenol—Prostacyclin.

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Management of primary pulmonary hypertension (PPH) is problematic. Intravenous epoprostenol (Flolan®, Glaxo-SmithKline, Research Triangle Park, NC, U.S.A.) is currently FDA approved for patients with advanced PPH. Epoprostenol is a potent vasodilator of the systemic and pulmonary arteries and is a potent inhibitor of platelet aggregation. Previous studies have demonstrated that in the short term (12 weeks), epoprostenol improves exercise tolerance, symptoms, hemodynamics, and survival in patients with PPH who are functional class III and IV and refractory to conventional therapy (1,2). Longer-term therapy with epoprostenol has been demonstrated to lower pulmonary vascular resistance beyond the level achieved in the short term (3).

Despite its benefits, epoprostenol therapy is associated with a number of obstacles. Since the drug is unstable at pH values below 10.5, it cannot be given orally, and continuous intravenous infusion is necessary due to its short half-life. Serious complications, particularly catheter-related infections and temporary interruption of the infusion due to malfunction of the pump or dislodgment of the central venous catheter, have been reported (1,3). These complications can be potentially life threatening and underscore the need for an alternative mode of drug delivery.

More recently, bosentan (Tracleer) has been approved by the FDA for management of pulmonary arterial hypertension (4). A 16-week placebo-controlled trial demonstrated an improvement in exercise tolerance and an increased time to clinical worsening. Treprostinil (Remodulin, United Therapeutics, Research Triangle Park, NC, U.S.A.) is an epoprostenol analog with a half-life of 3 hours and is stable at room temperature (5). Animal studies suggest that its hemodynamic effects appear similar to epoprostenol (6,7). We chose to take advantage of these properties and evaluate the feasibility for continuous subcutaneous infusion of treprostinil in patients with PPH.

This article reports a series of clinical trials designed to assess the utility of the chronic subcutaneous administration of treprostinil. The objective of the first trial was to compare the immediate hemodynamic effects of intravenous treprostinil with those of intravenous epoprostenol in patients with PPH who were functional class III or IV. The objective of the second trial was to compare the short-term hemodynamic effects of intravenous treprostinil with those of subcutaneous treprostinil in patients with PPH. Based on the results of these studies indicating comparable efficacy with subcutaneous and intravenous treprostinil, a third study was undertaken. This study was a multicenter, double-blinded, placebo-controlled chronic pilot trial. The objectives of this third trial were to assess the safety of chronically administered continuous subcutaneous infusion of treprostinil in patients with PPH and to assess the efficacy of treprostinil on exercise capacity and hemodynamics.

METHODS

All three trials enrolled patients with PPH based on the criteria of the National Institutes of Health Registry on PPH (8). For all three trials, the inclusion criteria were New York Heart Association functional class III or IV despite conventional therapy, a mean pulmonary artery pressure greater than or equal to 25 mm Hg, a pulmonary capillary wedge pressure or left ventricular end diastolic pressure of less than or equal to 15 mm Hg, and a pulmonary vascular resistance of greater than 3 Wood units. Right heart catheterization was performed with a triple-lumen flow-directed catheter via the internal jugular or femoral vein and left in place for monitoring (trials 1 and 2). Standard hemodynamic measures were evaluated at select times throughout the study. All patients (or parents for patients aged less than 18 years) provided informed consent approved by the Institutional Review Board of each of the participating institutions.

TRIAL DESIGNS

Trial 1

This was a multicenter, open-label, acute trial designed to compare the effects of intravenous epoprostenol and intravenous treprostinil. Following right heart catheterization, epoprostenol was administered intravenously beginning at 2 ng/kg/min and increased every 15 to 30 minutes in 2-ng/kg/min increments to a maximum tolerated dose while serial hemodynamic measurements were obtained. Following a 90-minute epoprostenol-free washout period, intravenous treprostinil was initiated at 5 ng/kg/min for 30 minutes and increased every 30 minutes to 10, 20, 30, 40, and 60 ng/kg/min. The dose-ranging procedure was continued until a dose was achieved that produced side effects that warranted reduction or discontinuation of the infusion; this was considered the nontolerated dose. A 90-minute maintenance infusion was continued at 10 to 20 ng/kg/min below the nontolerated dose and followed by a 120-minute treprostinil-free washout period. The catheters were removed, and the patients were observed for 24 hours in a post-treatment phase.

Trial 2

This was a multicenter, open-label, acute trial designed to compare the effects of intravenous treprostinil

and subcutaneous treprostinil. Following right heart catheterization, patients received a 10 ng/kg/min intravenous dose of treprostinil for 75 min, followed by a 150-minute washout period. Baseline measurements were again obtained. Patients then received subcutaneous treprostinil in fixed doses of 5, 10, and 20 ng/kg/min (cohorts 1, 2, and 3, respectively) for 150 minutes. This was followed by a 150-minute washout period. The catheters were removed, and the patients were observed in the hospital for 24 hours following completion of the treatment. Serial plasma samples (5 ml each) were collected at baseline, 15, 30, 60, and 75 minutes during the intravenous treprostinil infusion, at 5, 10, 15, 30, 60, 90, and 120 minutes during the washout, at baseline, 15, 30, 60, 90, 120, and 150 minutes during the subcutaneous treprostinil infusion, and at 5, 10, 15, 30, 60, 90, 120, and 150 minutes during the washout for pharmacokinetic determinations.

Trial 3

This was a multicenter, double-blinded, parallel, placebo-controlled, 2:1 randomized, 8-week trial. Patients underwent a screening practice and baseline 6-minute walk test during which they had to walk 50 to 450 m to be included. Borg Dyspnea Score and Dyspnea Fatigue Rating were obtained in conjunction with the 6-minute walk. Right heart catheterization was performed within 2 days of the walk test at baseline and at the end of 8 weeks. After baseline evaluation, patients were randomized in a 2:1 fashion to receive either subcutaneous treprostinil or placebo. The dose of treprostinil was initiated at 2.5 to 5.0 ng/kg/min and was adjusted in increments of 2.5 to 5.0 ng/kg/min every 24 hours based on response to therapy and side effects to a maximum dose of 20 ng/kg/min. Patients were observed in the hospital during initiation of therapy and were trained by a clinical nurse specialist on preparation of the study medication and operation of the ambulatory infusion pump. After hospital discharge, the dose was increased by no more than 5 ng/kg/min each week. Right heart catheterization and the 6-minute walk were repeated after 8 weeks.

Statistical analysis

Data are presented as mean ± SE. All patients having a baseline cardiac catheterization are included in the analyses of demographics and baseline characteristics. Patients completing the epoprostenol and treprostinil dose-ranging segments in trial 1 were considered in the evaluation of changes in hemodynamic measurements from baseline to maximum tolerated dose ($n = 14$). In trial 2, the patients completing the 150-minute subcutaneous treprostinil dosing segment were considered for the analysis of changes in hemodynamics from baseline ($n = 20$). The percent change in hemodynamics from baseline was calculated after intravenous treprostinil administration, and then a second baseline measure was obtained after the washout period and was used to calculate the percent change with subcutaneous treprostinil administration.

Also in trial 2, individual patient pharmacokinetic parameters during intravenous treprostinil and subcutaneous treprostinil dosing were determined from the corresponding plasma treprostinil concentration versus time profile. The noncompartmental routine in WinNonlin was used for the pharmacokinetic analysis. All pharmacokinetic parameters were determined from treprostinil concentration values based on actual blood sampling times (not nominal times as described in the protocol). In trial 3, 6-minute walk data were analyzed in an intention-to-treat analysis of all randomized patients utilizing a parametric analysis of variance (ANOVA). Patients who died, exited the study prematurely due to clinical deterioration, or underwent transplantation were assigned a value of 0 m; patients who did not have a week 8 walk due to an adverse event, withdrawal of consent, or who were lost to follow-up evaluation were assigned the last observation carried forward as their 8-week value. Other efficacy parameters (Borg dyspnea score, dyspnea fatigue score, and hemodynamic measurements) were analyzed utilizing available data, and treatment group differences in the changes from baseline were assessed using the Wilcoxon rank sum test.

RESULTS

Baseline demographics for each of the trials are displayed in Table 1. Baseline hemodynamic measurements for trials 1 and 2 are shown in Table 2, and for trial 3 in Table 3.

Trial 1

Fourteen patients were enrolled. The maximum tolerated doses of intravenous epoprostenol and intravenous treprostinil were 6.4 ± 0.8 ng/kg/min and 24.6 ± 4.0 ng/kg/min, respectively. Dose-limiting adverse effects were similar for epoprostenol and treprostinil and included headache, nausea, chest pain, jaw pain, backache, and restlessness. Epoprostenol and treprostinil produced similar increases in cardiac output and decreases in the mean pulmonary artery pressure. There was a 22% reduction in pulmonary vascular resistance with epoprostenol and a 20% reduction with treprostinil ($p = NS$ for epoprostenol vs. treprostinil). There were no serious adverse events related to treprostinil during the dose-

TABLE 1.
Baseline demographics

	Trial 1 IV epoprostenol vs. IV treprostinil	Trial 2 IV treprostinil vs. SC treprostinil	Trial 3 SC treprostinil vs. placebo
Centers, n	4	10	3
Patients, n	14	25	26
Age, years	35 ± 12	42 ± 11	37 ± 17
Age range, years	12–57	22–71	12–73
Female, %	10 (71)	20 (80)	21 (81)
Male, %	4 (29)	5 (20)	5 (19)
NYHA III, %	13 (93)	19 (76)	25 (96)
NYHA IV, %	1 (7)	6 (24)	1 (4)

NYHA = New York Heart Association.

ranging segment of the study. One patient experienced a serious adverse event during the maintenance infusion. Having successfully completed the dose-ranging study, the patient was maintained at 16 ng/kg/min. Forty-five minutes into the maintenance infusion, the patient experienced an increase in pulmonary artery pressure and severe hypoxia, possibly related to an increase in right-to-left flow through a documented patent foramen ovale. The infusion was terminated, and the patient subsequently recovered.

Trial 2

Twenty-five patients were enrolled. The changes in hemodynamic parameters with intravenous treprostinil infusion at 10 ng/kg/min and subcutaneous treprostinil at 5, 10, and 20 ng/kg/min (cohorts 1, 2, and 3) are shown in Table 4. Five patients were prematurely withdrawn from this study due to intolerable local side effects from the subcutaneous treprostinil infusion: 1 in cohort 1, 1 in cohort 2, and 3 in cohort 3. There were 5 patients in cohort 1, 12 in cohort 2, and 3 in cohort 3. As the 20-ng/kg/min dose in cohort 3 was poorly tolerated, additional patients were enrolled in cohort 2 to better define the hemodynamic effects of the maximal tolerated dose. Data reported are for those 20 patients who completed the subcutaneous treprostinil infusion. A dose of 10 ng/kg/min was identified as the maximal tolerated subcutaneous dose acutely. Dose-limiting side effects of subcutaneous treprostinil were similar to intravenous treprostinil and included nausea, vomiting, headache, dizziness, and anxiety. Changes in hemodynamic measures were similar for intravenous treprostinil and subcutaneous treprostinil at the maximal tolerated dose (co-

TABLE 2.
Baseline hemodynamics

	Trial 1 IV epoprostenol vs. IV treprostinil (n = 14)	Trial 2 IV epoprostenol vs. SC treprostinil (n = 25)
RAPm, mm Hg	10 ± 1	10 ± 1
PAPm, mm Hg	56 ± 5	63 ± 4
PCWPm, mm Hg	12 ± 1	12 ± 2
CO, l/min	4.6 ± 0.5	3.8 ± 0.3
CI, l/min/m^2	2.5 ± 0.2	2.1 ± 0.1
PVR, Units	11.0 ± 1.7	15.5 ± 2.2
PVRI, Units/m^2	19.2 ± 2.5	28.1 ± 3.7
SAPm, mm Hg	9.38 ± 2.9	92.8 ± 2.8
MV Sat, %	66 ± 3	59 ± 2
SaO_2, %	95 ± 1	95 ± 1

CI, cardiac index; CO, cardiac output; MV Sat, mixed venous saturation; PAPm, mean pulmonary artery pressure; PCWPm, mean pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; PVRI, pulmonary vascular resistance index; RAPm, mean right atrial pressure; SAPm, mean systemic arterial pressure; SaO_2, systemic arterial saturation.

TABLE 3.
Baseline hemodynamics and exercise capacity, trial 3 (sc treprostinil vs. placebo)

	Placebo (n = 9)	Treprostinil (n = 17)	p
RAPm, mm Hg	10 ± 1	9 ± 1	NS
PAPm, mm Hg	64 ± 6	59 ± 4	NS
PCWPm, mm Hg	10 ± 1	8 ± 1	NS
CI, l/min/m^2	2.4 ± 0.2	2.3 ± 0.2	NS
MV Sat, %	61.7 ± 2.8	62.1 ± 3.0	NS
PVRI, Units/m^2	24.7 ± 3.0	24.8 ± 2.6	NS
Exercise, meters	384 ± 27	373 ± 25	NS
Borg dyspnea score	+2.4 ± 0.7	+3.2 ± 0.3	NS

CI, cardiac index; MV Sat, mixed venous saturation; PAPm, mean pulmonary artery pressure; PCWPm, mean pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index; RAPm, mean right atrial pressure.

TABLE 4.
Percent change from baseline, Trial 2 (IV treprostinil vs. SC treprostinil)

	IV 10 ng/kg/min	5 Cohort 1 SC 5 ng/kg/min	10 Cohort 2 SC 10 ng/kg/min	20 Cohort 3 SC 20 ng/kg/min
n	20	5	12	3
RAPm, %	−11 ± 31	+27 ± 68	−20 ± 46	13 ± 63
PAPm, %	−7 ± 12	+4 ± 7	−13 ± 12	−8 ± 8
PCWPm, %	3 ± 30	+3 ± 9	−1 ± 24	−20 ± 8
CI, %	+15 ± 17	+6 ± 16	+20 ± 22	+7 ± 3
PVRI, %	−22 ± 15	+2 ± 27	−26 ± 21	−15 ± (NA)
SAPm, %	−4 ± 8	+1 ± 3	−3 ± 9	−9 ± 11
MVO_2, %	+9 ± 21	−3 ± 9	+6 ± 8	+6 ± 19
SaO_2, %	−3 ± 11	−1 ± 2	0 ± 2	−1 ± 2

Values shown as mean ± SD.

CI, cardiac index; MV Sat, mixed venous saturation; PAPm, mean pulmonary artery pressure; PCWPm, mean pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index; RAPm, mean right atrial pressure; SAPm, mean systemic arterial pressure; SaO_2, systemic arterial saturation.

hort 2). In the intravenous treprostinil and subcutaneous treprostinil 10-ng/kg/min cohort, there was a 6% and 13% decrease in mean pulmonary artery pressure and a 23% and 28% decrease in pulmonary vascular resistance, respectively. Pharmacokinetic data were available for 4 patients in cohort 1, 8 patients in cohort 2, and 3 patients in cohort 3, and are displayed in Table 5.

Trial 3

Twenty-six patients were enrolled. There were no statistically significant differences in baseline hemodynamics or walk distance between the placebo and the treprostinil groups (Table 3). Two patients in the treprostinil group did not complete the study due to intolerable side effects. One patient had hypotension with the initiation of treprostinil and was withdrawn from the study and treated with intravenous epoprostenol. The other patient had intolerable pain at the site of the subcutaneous infusion. Of the remaining patients, 15 were on a mean dose of 13.0 ± 3.1 ng/kg/min of treprostinil (range, 2.5–50), while the 9 patients receiving placebo were on 38.9 ± 6.7 ng/kg/min (range, 20–75) at the end of the 8-week period. Clinically significant adverse effects and local adverse effects related to the subcutaneous infusion were common (Table 6). In general, these effects occurred with the initiation of the drug and were short lived. Treprostinil had a favorable effect on hemodynamics and exercise tolerance (Table 7). While none of these favorable effects associated with treprostinil reached statistical significance, there was a 20% decrease in pulmonary vascular resistance index during the 8-week period. There was a trend toward improvement of 37 ± 17 m in the 6-minute walk distance in patients receiving treprostinil for 8 weeks (from 373 m to 411 m) compared with a 6 ± 28 m decrease in those receiving placebo (379 m at week 8 compared with 384 m at baseline; p = NS). In addition, there was a trend toward improvement in the Borg Dyspnea Scale from 3.2 to 3.1 in the treprostinil

TABLE 5.
Plasma half-life of treprostinil, trial 2

	Cohort 1 (n = 4)		Cohort 2 (n = 8)		Cohort 3 (n = 3)	
	IV dosing	SC dosing	IV dosing	SC dosing	IV dosing	SC dosing
$T_{1/2}$ min						
Mean	41.7	65.1	35.4	117.2	25.6	55.1
SD	60.8	48.0	31.7	89.4	12.1	20.1

TABLE 6.
Clinically significant adverse effects, trial 3 (sc treprostinil vs. placebo)

	Placebo n (%)	Treprostinil n (%)	p
Vomiting	0 (0)	4 (24)	NS
Hypotension	0 (0)	4 (24)*	NS
Bradycardia	0 (0)	2 (12)	NS
Vasovagal	2 (22)	0 (0)	NS
Syncope	3 (33)	1 (6)	NS
Insomnia	3 (33)	1 (6)	NS
Infusion site erythema/induration	2 (22)	16 (94)	0.0004
Infusion site pain	2 (22)	15 (88)*	0.0016

Placebo, n = 9; treprostinil n = 17.

*One patient was withdrawn from the study.

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