Continuous Subcutaneous Infusion of Treprostinil, a Prostacyclin Analogue, in Patients with Pulmonary Arterial Hypertension

A Double-blind, Randomized, Placebo-controlled Trial

GERALD SIMONNEAU, ROBYN J. BARST, NAZZARENO GALIE, ROBERT NAEIJE, STUART RICH, ROBERT C. BOURGE, ANNE KEOGH, RONALD OUDIZ, ADAANI FROST, SHELMER D. BLACKBURN, JAMES W. CROW, and LEWIS J. RUBIN, for the Treprostinil Study Group

Division of Pulmonary and Critical Care Medicine, Antoine Béclère Hospital, Clamart, Paris-Sud University, Clamart, France; Department of Pediatrics, Columbia Presbyterian Medical Center, New York, New York; Division of Cardiology, University of Bologna, Bologna, Italy; Departments of Pathophysiology and Cardiac Surgery, Erasme University Hospital, Brussels, Belgium; Division of Cardiology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois; Division of Cardiology, University of Alabama, Birmingham, Alabama; Department of Medicine, St. Vincent's Hospital, Sydney, Australia; Division of Cardiology, Harbor-UCLA Medical Center, Torrance, California; Pulmonary Section, Lung Transplant Program, Baylor College of Medicine, Houston, Texas; United Therapeutic Corporation, Research Triangle Park, North Carolina; and Division of Pulmonary and Critical Care Medicine, University of California, San Diego, California

Pulmonary arterial hypertension is a life-threatening disease for which continuous intravenous prostacyclin has proven to be effective. However, this treatment requires a permanent central venous catheter with the associated risk of serious complications such as sepsis, thromboembolism, or syncope. Treprostinil, a stable prostacyclin analogue, can be administered by a continuous subcutaneous infusion, avoiding these risks. We conducted a 12-week, double-blind, placebo-controlled multicenter trial in 470 patients with pulmonary arterial hypertension, either primary or associated with connective tissue disease or congenital systemic-to-pulmonary shunts. Exercise capacity improved with treprostinil and was unchanged with placebo; the between treatment group difference in median six-minute walking distance was 16 m ($p = 0.006$). Improvement in exercise capacity was greater in the sicker patients and was dose-related, but independent of disease etiology. Concomitantly, treprostinil significantly improved indices of dyspnea, signs and symptoms of pulmonary hypertension, and hemodynamics. The most common side effect attributed to treprostinil was infusion site pain (85%) leading to premature discontinuation from the study in 8% of patients. Three patients in the treprostinil treatment group presented with an episode of gastrointestinal hemorrhage. We conclude that chronic subcutaneous infusion of treprostinil is an effective treatment with an acceptable safety profile in patients with pulmonary arterial hypertension.

Keywords: treprostinil; prostacyclin analogue; primary pulmonary hypertension; pulmonary arterial hypertension associated with connective tissue disease; pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts

Despite recent major therapeutic advances, pulmonary arterial hypertension remains a life-threatening disorder (1, 2). Continuous intravenous infusion of epoprostenol (prostacyclin) has been shown to improve exercise capacity, hemodynamics, and quality of life in primary pulmonary hypertension (3, 4) as well as in other forms of pulmonary arterial hypertension complicating scleroderma (5, 6) and congenital systemic-to-pulmonary shunts (7, 8). In addition, improved survival with epoprostenol has been demonstrated in one unblinded, randomized study of patients with severe primary pulmonary hypertension (3). However, despite these favorable outcomes, continuous intravenous infusion of epoprostenol is far from ideal as a treatment for severe pulmonary arterial hypertension due to its very short half-life (one to two minutes) requiring a continuous intravenous infusion. This delivery method is associated with frequent severe and potentially serious side effects (3, 5, 9). In addition, it is very costly (10). Thus, other modes of prostacyclin delivery are being considered using stable prostacyclin analogues administered orally (11, 12), subcutaneously (13), or by inhalation (14, 15).

Treprostinil, a stable prostacyclin analogue, shares pharmacological actions similar to epoprostenol (16, 17), with similar acute hemodynamic effects (18). However, in contrast to epoprostenol, treprostinil is chemically stable at room temperature and neutral pH and has a longer half-life (three to four hours) permitting continuous subcutaneous infusion rather than continuous intravenous infusion, avoiding the risks of severe infection and thrombosis (19). The objective of this study was to assess the effects of subcutaneous treprostinil on exercise capacity, disease symptoms, hemodynamics, and quality of life in patients with severe pulmonary arterial hypertension, including primary pulmonary hypertension as well as pulmonary arterial hypertension associated with connective tissue disease and congenital systemic-to-pulmonary shunts.

METHODS

Patients

Between November 1998 and October 1999, 470 patients were randomized from 24 centers in North America (Canada, Mexico, and the United States), and from 16 centers in the rest of the world (Australia, Austria, Belgium, France, Germany, Israel, Italy, Poland, Spain, UK). Eligible patients had pulmonary arterial hypertension in accordance with the inclusion and exclusion criteria summarized in Table 1. Patients with connective tissue disease had no pulmonary parenchymal disease as evidenced by lung function tests and a high-resolution computed tomography (CT) scan. Patients with congenital heart disease (left-to-right shunts) had either pulmonary arterial hypertension that developed a variable number of years after surgical correction, or presented with an inversion of the shunt due to the development of

(*Received in original form June 18, 2001; accepted in final form December 6, 2001*)

This study was supported by United Therapeutics Corporation, Research Triangle Park, North Carolina.

Correspondence and requests for reprints should be addressed to Gerald Simonneau, Division of Pulmonary and Critical Care Medicine, Hopital Antoine Béclère, 157 rue de la Porte de Trivaux, 92141, Clamart, France. E-mail: gerald.simonneau@abc.ap-hop-paris.fr

The members of the Treprostinil Study Group are listed in the online data supplement.

This article has an online data supplement, which is accessible from this issue's table of contents online at www.atsjournals.org

Am J Respir Crit Care Med Vol 165. pp 800–804, 2002
DOI: 10.1164/rccm.2106079
Internet address: www.atsjournals.org

TABLE 1. MAIN INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria
Primary pulmonary hypertension or pulmonary hypertension associated with connective tissue diseases or associated with congenital systemic to pulmonary shunts
Age between 8 and 75 yr
New York Heart Association (NYHA) functional class II, III, or IV
Significant pulmonary hypertension defined by
Mean pulmonary arterial pressure ⩾ 25 mm Hg at rest
Mean pulmonary capillary wedge pressure ⩽ 15 mm Hg
Pulmonary vascular resistance > 3 mm Hg/L/min
Ventilation perfusion lung scan or pulmonary angiography not indicative of thromboembolic disease
Exclusion criteria
Significant parenchymal pulmonary disease as evidenced by pulmonary function tests or high resolution CT scan
Porto pulmonary hypertension or HIV-associated pulmonary hypertension
Uncontrolled sleep apnea
History of left side heart disease
Other diseases associated with pulmonary hypertension (e.g., sickle cell anemia, shistosomiasis)
Baseline exercise capacity of less than 50 m or greater than 450 m walked in 6 min
Any new type of chronic therapy for pulmonary hypertension added within the last month
Any pulmonary hypertension medication discontinued within the last week except anticoagulants
Any use of prostaglandin derivatives within the past 30 d

Definition of abbreviations: CT = computed tomography; HIV = human immunodeficiency virus.

pulmonary hypertension and associated increase in pressures of the right heart (Eisenmenger complex). All patients gave written informed consent. The protocol was approved by the local ethics committee at each participating center.

Randomization and Treatment

Patients were randomly assigned to receive either continuous subcutaneous infusion of treprostinil (Remodulin; United Therapeutics Corporation, Research Triangle Park, NC) plus conventional therapy or continuous infusion of placebo (vehicle solution without treprostinil) plus conventional therapy. All patients had conventional therapy optimized for at least one month before enrollment. Conventional therapy could include oral vasodilators, oral anticoagulants, diuretics, and/or digitalis (20). Randomization was based on a permuted block design stratified on the basis of baseline exercise capacity and etiology of pulmonary arterial hypertension.

Treprostinil or placebo was administered using a positive pressure, microinfusion pump (MiniMed, Sylmar, CA). The infusion catheter was placed by the patient in the subcutaneous tissue of the abdominal wall. Chronic study drug infusion was initiated at the dose of 1.25 ng/kg/min. During the 12-week study, doses were increased to a maximum dose at which pulmonary hypertension signs and symptoms were improved while achieving an acceptable side effect profile. At Week 12, the maximum allowable dose was 22.5 ng/kg/min. These doses were selected on the basis of approximately equipotent pulmonary hemodynamic effects compared with those of prostacyclin (18).

Outcome Measures

The primary measure of efficacy was exercise capacity as defined by the maximum distance a patient could walk in six minutes (21). The unencouraged six-minute walk test was administered by a "blinded" tester not involved in the patient's daily care and unaware of the patient's treatment assignment. Each patient performed at least one practice walk test before the baseline assessment conducted before randomization. The walk test was then repeated at Weeks 1, 6, and 12.

Principal reinforcing endpoints of efficacy were signs and symptoms of pulmonary hypertension using a composite score including 16 signs or symptoms recorded at baseline and Weeks 1, 6, and 12; the Dyspnea Fatigue Rating (22) assessed at baseline and Weeks 1, 6, and 12; and the number of deaths, lung transplantations, or discontinuations for clinical deterioration. Secondary endpoints were assessment of shortness of breath immediately after the six-minute walk test using the Borg Dyspnea Scale (23) at baseline and Weeks 1, 6, and 12; cardiopulmonary hemodynamics measured by right heart catheterization at baseline and Week 12; global, physical, and emotional quality of life using the "Minnesota Living with Heart Failure Questionnaire" (24) assessed at baseline and Weeks 6 and 12.

Safety was assessed by comparison of adverse experiences in the two treatment groups and by laboratory assessments (including hemoglobin level, platelet count, leukocyte count, serum creatinine concentration, blood urea nitrogen, alkaline phosphatase, and alanine aminotransferase) at baseline and Week 12. An independent data safety monitoring board reviewed serious adverse events and deaths after 20%, 40%, and 60% of patients had completed the study.

Statistical Analysis

Changes in the distance walked in six minutes from baseline to Week 12 were compared between treatment groups using an intention-to-treat, nonparametric analysis of covariance, prespecified as the primary analysis. A least squares regression analysis was applied to calculate the six-minute walk distances as linear functions of baseline walk, vasodilator use, etiology, and study center. The standardized mid-ranks of the residuals from these linear regression analyses were then determined. Patients who discontinued the study due to death, clinical deterioration, or transplantation before Week 12 were assigned a standardized rank of 0. For patients who discontinued before Week 12 for any other reason, the standardized mid-rank from the last available assessment was carried forward. The ranks were then compared between treatment groups using the extended Cochran–Mantel–Haenszel test. Changes from baseline to Week 12 in the composite score of signs and symptoms of pulmonary hypertension, Dyspnea-Fatigue Rating, Borg Dyspnea Score, and Quality of Life scores were compared between treatment groups using the Wilcoxon rank sum test without imputation. Between treatment group changes in hemodynamic variables were compared using parametric analysis of covariance adjusting for baseline value without imputation. In analyses of possible treatment interactions, a significance level of $\alpha = 0.1$ was considered suggestive of a treatment effect.

RESULTS

Baseline Characteristics and Patient Disposition

Baseline demographic and hemodynamic characteristics of the two groups are shown in Tables 2 and 3, respectively. The two groups were well matched with respect of severity of pulmonary hypertension, duration of illness, and etiology of

TABLE 2. DEMOGRAPHIC CHARACTERISTICS AT BASELINE

Characteristic	Treprostinil (*n = 233*)	Placebo (*n = 236*)
Age, yr	44.6 ± 1.0	44.4 ± 0.9
Sex, n (%)		
Male	36 (16)	51 (22)
Female	197 (85)	185 (78)
Ethnic group, n (%)		
Black	13 (6)	8 (3)
White	198 (85)	198 (84)
Other	22 (9)	30 (13)
NYHA functional class, n (%)		
II	25 (11)	28 (12)
III	190 (82)	192 (81)
IV	18 (8)	16 (7)
6-min walk distance, m	326 ± 5	327 ± 6
Etiology of pulmonary hypertension, n (%)		
Primary pulmonary hypertension	134 (58)	136 (58)
Connective tissue disease	41 (17)	49 (20)
Congenital systemic to pulmonary shunts	58 (25)	51 (22)
Years since pulmonary hypertension diagnosis	4.3 ± 0.5	3.3 ± 0.5

Definition of abbreviation: NYHA = New York Heart Association.

TABLE 3. HEMODYNAMIC VARIABLES AT BASELINE

Variables	Treprostinil (*N = 233*)	Placebo (*N = 236*)
Heart rate, beats/min	82 ± 1	82 ± 1
Mean right atrial pressure, mm Hg	10 ± 0.4	10 ± 0.4
Mean pulmonary artery pressure, mm Hg	62 ± 1	60 ± 1
Mean pulmonary capillary wedge pressure, mm Hg	10 ± 0.3	9 ± 0.2
Cardiac index, L/min/m^2	2.4 ± 0.1	2.3 ± 0.1
Pulmonary vascular resistance index, units/m^2	26 ± 1	25 ± 1
Mean systemic artery pressure, mm Hg	90 ± 1	91 ± 1
Systemic vascular resistance index, units/m^2	38 ± 1	39 ± 1
Mixed venous oxygen saturation, %	62 ± 1	60 ± 1
Arterial oxygen saturation	92 ± 0.5	91 ± 0.5

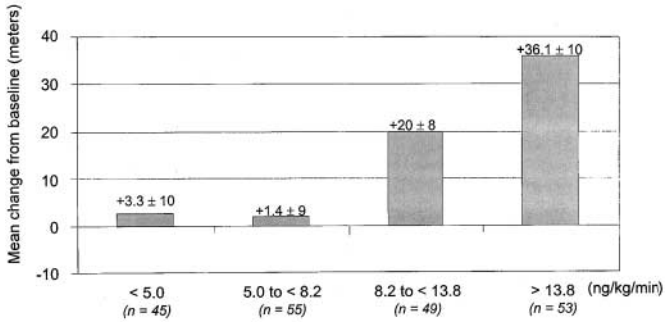

Figure 1. Mean change in the six-minute walk distance from baseline to Week 12 versus Week 12 trepostinil dose quartile.

pulmonary hypertension; 233 patients were randomized to treprostinil and 237 patients to placebo.

Primary Endpoint

Exercise capacity. All but one of the 470 randomized patients were included in the analysis of the primary endpoint; this patient, assigned to receive placebo, did not receive any study drug. The distance walked in six minutes improved at Week 12 in the treprostinil group by a median change of 10 m (−24 to +47 m; 25th–75th percentile) and remained essentially unchanged in the placebo group with a median change of 0 m (−44 to +32 m; 25th–75th percentile). The difference in median distance walked between the two groups at Week 12 was 16 m (95% CI, 4.4 m to 27.6 m, Hodges–Lehmann estimate of the median difference, $p = 0.006$).

Neither baseline demographic covariates nor disease etiology showed significant interaction with the change in exercise capacity. In contrast, a treatment interaction was observed with the baseline walking distance ($p = 0.03$), baseline New York Heart Association (NYHA) functional class ($p = 0.11$), and baseline mixed venous oxygen saturation ($p = 0.07$). Patients who were more compromised at baseline had a greater improvement in exercise capacity from baseline to Week 12. Severely ill patients who walked less than 150 m at baseline had an estimated treatment effect of +51 ± 16 m ($p = 0.002$) and less sick patients who walked more than 351 m at baseline had no substantial estimated treatment effect (−2 ± 12 m, $p = 0.869$). In addition, there was a relationship between the treprostinil dose achieved at Week 12 and the change in the 6-min walk distance. When patients were grouped by quartile of the dose achieved at Week 12, the highest quartile dose had the greatest improvement in six-minute walk distance, and the first and second quartile dose had small improvements ($p = 0.03$) (Figure 1).

Principal Reinforcing Endpoints

Signs and symptoms of pulmonary arterial hypertension. The signs and symptoms composite score improved in the treprostinil group from 7.6 ± 0.5 at baseline to 8.5 ± 0.5 at Week 12 compared with the placebo group, in which it worsened from 7.5 ± 0.4 at baseline to 7.4 ± 0.2, $p < 0.0001$ for the comparison between the treatment groups.

Dyspnea-Fatigue Rating. The Dyspnea-Fatigue Rating improved from 4.2 ± 0.1 at baseline to 5.4 ± 0.2 at Week 12 in the treprostinil group, whereas it worsened in the placebo group from 4.4 ± 0.1 to 4.3 ± 0.1, $p = 0.0001$ for the comparison between the treatment groups.

Death, transplantation, or clinical deterioration. Fourteen patients died while receiving the study drug (seven in each group). Five additional patients (two in the treprostinil group and three in the placebo group) died during the 12-week study period but after withdrawal of the study drug. Six patients in each group discontinued the study due to clinical deterioration; five patients receiving treprostinil and four receiving placebo were transitioned to continuous intravenous epoprostenol therapy. One placebo patient underwent lung transplantation and was alive at the end of the 12-week study period. The total number of deaths, transplantations, or discontinuations due to clinical deterioration was 13 patients in the treprostinil group versus 16 patients in the placebo group.

Secondary Endpoints

Borg Dyspnea Score. In the treprostinil group, patients had an improvement in the Borg Dyspnea Score from 4.3 ± 0.2 at baseline to 3.2 ± 0.2 at Week 12, versus an improvement in the placebo group from only 4.4 ± 0.2 to 4.2 ± 0.2, $p < 0.0001$ for the comparison of the treatment groups.

Cardiopulmonary hemodynamics. Changes in hemodynamic variables are shown in Table 4. Comparison of treatment groups showed that treprostinil-treated patients had significant improvement in mean right atrial pressure, mean pulmonary artery pressure, cardiac index, pulmonary vascular resistance, and mixed venous oxygen saturation.

Quality of life. Patients treated with treprostinil experienced a significant improvement in their physical dimension score at Week 12 ($p = 0.0064$) with a trend toward improvement in the global dimension score ($p = 0.17$) as compared with the placebo group.

Tolerability, Dose, Safety

No clinically significant changes in hematologic or biochemical variables were observed in either group. The most common adverse events are shown in Table 5. Infusion site pain was common in both treatment groups but was more common in the treprostinil group, 85% versus 27%, respectively. Eighteen patients (8%) in the treprostinil group discontinued their study treatment due to intolerable abdominal infusion site pain versus one in the placebo group. Adverse events classically related to the use of prostacyclin, such as diarrhea, jaw pain, flushing, and lower limb edema occurred more often in the treprostinil group. There were no reports of infusion site infections in either group.

By the end of the 12-week study period, the mean dose of the study drug received was 9.3 ng/kg/min versus 19.1 ng/kg/min in the placebo group ($p < 0.001$). Infusion system malfunctions were common, reported in 55 patients of the treprostinil group (24%) and in 77 patients of the placebo group (33%). Adverse events resulting from these dysfunctions were rare (four patients in each group) and had no clinically serious adverse consequences.

In addition, three patients in the treprostinil group presented with a gastrointestinal hemorrhage; each patient experienced

TABLE 4. CARDIOPULMONARY HEMODYNAMICS: CHANGE FROM BASELINE TO WEEK 12

	Treprostinil	Placebo	p Value
Heart rate, beats/min	−0.5 ± 0.8	−0.8 ± 0.7	ns
Mean right atrial pressure, mm Hg	−0.5 ± 0.4	+1.4 ± 0.3	0.0002
Mean pulmonary artery pressure, mm Hg	−2.3 ± 0.5	+0.7 ± 0.6	0.0003
Cardiac index, L/min/m^2	+0.12 ± 0.04	−0.06 ± 0.04	0.0001
Pulmonary vascular resistance index, units/m^2	−3.5 ± 0.6	+1.2 ± 0.6	0.0001
Mean systemic artery pressure, mm Hg	−1.7 ± 0.9	−1.0 ± 0.9	ns
Systemic vascular resistance index, units/m^2	−3.5 ± 0.9	−0.8 ± 0.8	0.0012
Mixed venous oxygen saturation, %	+2.0 ± 0.8	−1.4 ± 0.7	0.0001

melena and one patient experienced a small hematemesis and rectal bleeding. Two of these patients presented with excessively increased INR (4.0 and 3.14), one of whom had taken naproxen, a nonsteroidal antiinflammatory drug. Two of these patients required transfusion of one and three units of packed red blood cells, respectively. All three gastrointestinal hemorrhage episodes subsided spontaneously without adverse clinical consequences.

DISCUSSION

This study is the first double-blind, placebo-controlled trial conducted in pulmonary arterial hypertension; it is also the largest clinical trial with worldwide participation. The results show that continuous subcutaneous infusion of treprostinil, a stable prostacyclin analogue, is effective therapy in patients with primary pulmonary hypertension as well as in patients with pulmonary arterial hypertension associated with either connective tissue disease or congenital systemic-to-pulmonary shunts. Compared with continuous subcutaneous infusion of placebo, treprostinil consistently improved exercise capacity, indices of dyspnea, signs and symptoms of pulmonary arterial hypertension, cardiopulmonary hemodynamics, and the physical dimension of quality of life.

The distance walked in six minutes has been previously shown to be an independent predictor of mortality in primary pulmonary hypertension (3, 25). After 12 weeks, the difference in median distance walked between the two treatment groups was 16 m. Although significant, this difference appears moderate compared with previous results obtained with intravenous epoprostenol (3, 5). The relatively limited increase in the six-minute walk distance after three months of subcutaneous treprostinil may be explained by the inclusion of less compromised patients, and by the fact that the most important improvement in exercise capacity was observed in the sickest patients. Actually, in the sicker patients, the magnitude of the exercise capacity improvement was similar to that obtained with epoprostenol therapy (3, 5). In addition, in a proportion of patients, only a relatively low dose of treprostinil was achieved by Week 12 due to local infusion site pain. This likely limited the improvement in the six-minute walking distance, as the present results also show a relationship between the dose of treprostinil achieved and increase in six-minute walk distance. However, although limited in magnitude, the increase in the six-minute walk distance in treprostinil-treated patients really reflected clinical improvement as supported by the improvements in the Dyspnea-Fatigue Rating, signs and symptoms scores, and the Borg Dyspnea Score measured at the end of the exercise test indicating increased exercise with less dyspnea. The effectiveness of treprostinil is further supported by a significant improvement in the hemodynamic variables previously shown to be associated with mortality in primary pulmonary hypertension (26). These hemodynamic changes observed after 12 weeks of treprostinil therapy, although small, with average differences between study groups of only 3 mm Hg in mean pulmonary artery pressures and 0.3 L/min/m^2 in cardiac index, were of the same order of magnitude as those previously reported in randomized controlled trials of 12 weeks of intravenous epoprostenol in patients with primary pulmonary hypertension (3) or with pulmonary hypertension secondary to connective tissue disease (5). Chronic epoprostenol or treprostinil may induce more important improvements in exercise hemodynamics, accounting for the observed clinical improvement in patients with pulmonary arterial hypertension.

The large placebo-control group in the present trial offered a unique opportunity to observe the spontaneous evolution, over a period of three months, of stable NYHA class III patients with pulmonary arterial hypertension under optimal medical treatment but without prostacyclin therapy. It appears that such patients are remarkably stable, at least over a three-month period of time, with modest changes in exercise capacity, and a mortality of only 3%. This mortality rate after a relatively short observation period of only three months was actually expected on the basis of both the six-minute walk distances (25) and the hemodynamic profile (26) of the included patients. Much larger numbers of patients with the same disease severity and longer periods of observation would be necessary to show a treatment effect on mortality. The mortality rates in the present study are similar to those reported in a recent randomized, controlled trial of intravenous epoprostenol in patients with pulmonary arterial hypertension secondary to connective tissue disease (5). Intravenous epoprostenol was previously reported to decrease mortality in a randomized, controlled trial that differed from the present study by the inclusion of a smaller number of more severely ill patients, with lower exercise capacity and worse NYHA functional class (3).

In terms of safety, continuous subcutaneous infusion of treprostinil presents several advantages over continuous intravenous infusion of epoprostenol. Due to its short half-life (one to two minutes) and chemical instability, epoprostenol can be given only intravenously, and requires a permanently implanted cen-

TABLE 5. MOST FREQUENT ADVERSE EVENTS

Event	Treprostinil (*n = 233*) n (%)	Placebo (*n = 236*) n (%)	p Value
Infusion site pain	200 (85)	62 (27)	< 0.0001
Infusion site reaction	196 (83)	62 (27)	< 0.0001
Infusion site bleeding/bruising	79 (34)	102 (44)	ns
Headache	64 (27)	54 (23)	ns
Diarrhea	58 (25)	36 (16)	0.009
Nausea	52 (22)	41 (18)	ns
Rash	32 (14)	26 (11)	ns
Jaw pain	31 (13)	11 (5)	0.001
Vasodilatation	25 (11)	11 (5)	0.01
Dizziness	21 (9)	19 (8)	ns
Edema	21 (9)	6 (3)	0.002
Vomiting	12 (5)	14 (6)	ns

tral venous catheter and a portable infusion pump, as well as refrigeration during administration. Sepsis, thrombosis, paradoxical embolism, and interruptions of treatment due to accidental occlusions, perforations, and dislodgments of the catheter, and pump malfunction all have been reported under intravenous epoprostenol. Additionally, any interruption of intravenous delivery of epoprostenol may be associated with syncope, and even death, from an acute pulmonary hypertensive crisis (3–8). None of these life-threatening complications of intravenous epoprostenol therapy was observed in the present study.

Infusion site pain was the most common side effect attributed to treprostinil. Its mechanism remains unclear. It did not appear to be dose-related but seems correlated to the rate of dose increase. It often improved after several months of treatment and could be minimized by moving the infusion site every three days as opposed to every day. Topical cold and hot packs, topical and oral analgesics, and antiinflammatory drugs were variably effective.

There were three episodes of gastrointestinal hemorrhage reported in the treprostinil group. These serious adverse events were attributed to concomitant administration of anticoagulant therapy as indicated in severe pulmonary hypertension (2) in two patients, and the use of a nonsteroidal antiinflammatory drug in one patient with the known platelet antiaggregatory effects of prostacyclin. All of these gastrointestinal hemorrhage episodes rapidly resolved without adverse clinical consequences, after adjustment of anticoagulant therapy, and withdrawal of the antiinflammatory drug, but required a transfusion in two patients.

During the 12-week study period, five patients receiving subcutaneous treprostinil and discontinuing the study due to clinical deterioration were transitioned to intravenous epoprostenol.

In conclusion, chronic subcutaneous treprostinil is an effective therapy with an acceptable safety profile in patients with pulmonary arterial hypertension. Further clinical experience with chronic subcutaneous treprostinil will define its place as an alternative to intravenous epoprostenol in patients with pulmonary arterial hypertension.

References

1. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Koerner SK, *et al*. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* 1987;107:216–223.
2. Rubin LJ. Primary pulmonary hypertension. *N Engl J Med* 1997;336:111–117.
3. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, *et al*. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med* 1996;334:296–302.
4. McLaughlin VV, Genthner DE, Panella MM, Rich S. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. *N Engl J Med* 1998; 338:273–277.
5. Badesch DB, Tapson VF, McGoon MD, Brundage BH, Rubin LJ, Wigley FM, Rich S, Barst RJ, Barrett PS, Kral KM, *et al*. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease: a randomized, controlled trial. *Ann Intern Med* 2000;132:425–434.
6. Sanchez O, Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary hypertension secondary to connective tissue disease. *Thorax* 1999;54:273–277.
7. Rosenzweig EB, Kerstein D, Barst RJ. Long term prostacyclin for pulmonary hypertension associated congenital heart defects. *Circulation* 1999;99:1858–1865.
8. McLaughlin VV, Genthner DE, Panella MM, Hess DM, Rich S. Compassionate use of continuous prostacyclin in the management of secondary pulmonary hypertension: a case series. *Ann Intern Med* 1999; 130:740–743.
9. Fishman AP. Epoprostenol (prostacyclin) and pulmonary hypertension. *Ann Intern Med* 2000;132:500–502.
10. Higenbottam T, Stenmark K, Simonneau G. Treatments for severe pulmonary hypertension. *Lancet* 1999;353:338–340.
11. Okano Y, Yoshioka T, Shimouchi A, Satoh T, Kunieda T. Orally active prostacyclin analogue in primary pulmonary hypertension. *Lancet* 1997;349:1365.
12. Nagaya N, Uematsu M, Okano Y, Satoh T, Kyotani S, Sakamaki F, Nakanishi N, Miyatake K, Kunieda T. Effect of orally active prostacyclin analogue on survival of outpatients with primary pulmonary hypertension. *J Am Coll Cardiol* 1999;34:1188–1192.
13. McLaughlin V, Barst RJ, Rich S, Rubin LJ, Horn E, Gaine SP, Blackburn SD, Crow JW. Efficacy and safety of UT-15, a prostacyclin analogue for primary pulmonary hypertension (abstract). *Eur Heart J* 1999;20:486.
14. Olschewski H, Ghofrani HA, Schemhl T, Winkler J, Hoeper MM, Behr J, Kleber FX, Seeger W. Inhaled iloprost to treat severe pulmonary hypertension. *Ann Intern Med* 2000;132:451–459.
15. Hoeper MM, Schwarze M, Ehlerding S, Adler-Schuermeyer A, Spiekeroetter E, Niedermeyer J, Hamm M, Fabel H. Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. *N Engl J Med* 2000;342:1866–1870.
16. Steffen RP, de la Mata M. The effects of 15AU81, a chemically stable prostacyclin analogue, on the cardiovascular and renin-angiotensin systems of anesthetized dogs. *Prostaglandins Leukot Essent Fatty Acids* 1991;43:277–286.
17. McNulty MJ, Sailstad JM, Steffen RP. The pharmacokinetics and pharmacodynamics of prostacyclin analogue 15AU81 in anesthetized beagle dog. *Prostaglandins Leukot Essent Fatty Acids* 1993;48: 159–166.
18. Gaine SP, Oudiz R, Rich S, Barst R, Roscigno R. Acute hemodynamic effects of 15AU81, a stable prostacyclin analogue, in severe primary pulmonary hypertension (abstract). *Am J Respir Crit Care Med* 1998; 157:A595.
19. Graham DR, Kelermans MM, Klemm LW, Semenza NJ, Shafer RM. Infectious complications among patients receiving home intravenous therapy with peripheral, central, or peripherally placed central venous catheters. *Am J Med* 1991;91:95S–100S.
20. Rich S, editor. Primary pulmonary hypertension: Executive Summary from the World Symposium-Primary Pulmonary Hypertension available from the World Health Organization via the internet (http://www.who.int/ncd/cvd/.pph.html), 1998.
21. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, Berman LB. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J* 1985; 132:919–923.
22. Feinstein AR, Fisher MB, Pigeon JG. Changes in dyspnea-fatigue ratings as indicators of quality of life in the treatment of congestive heart failure. *Am J Cardiol* 1989;64:50–55.
23. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exercise* 1982;14:377–381.
24. Rector RS, Kubo SH, Cohn JN. Patients self-assessment of their congestive heart failure. *Heart Failure* 1987;1:198–209.
25. Miyamoto S, Nagaya N, Satoh T, Kyotani S, Satamaki F, Fujita M, Nakanishi N, Miyatake K. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2000;161:487–492.
26. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT, *et al*. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991;115:343–349.