Eur Respir J 2006; 28: 1195–1203
DOI: 10.1183/09031936.06.00044406

Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil

R.J. Barst*, N. Galie#, R. Naeije¶, G. Simonneau+, R. Jeffs§, C. Arneson§ and L.J. Rubinƒ

ABSTRACT: Pulmonary arterial hypertension (PAH) is fatal if untreated. Intravenous epoprostenol improves exercise capacity and haemodynamics in PAH, and increases survival in idiopathic PAH (IPAH). To evaluate the effects of subcutaneous (SC) treprostinil, a longer-acting prostacyclin analogue, followed by the addition of other PAH therapies if needed, 860 PAH patients treated with SC treprostinil for up to 4 yrs were followed.

Survival is reported as Kaplan–Meier estimates. For 332 IPAH patients with baseline haemodynamics, observed survival is also compared with predicted survival using the National Institute of Health formula.

Out of the 860 patients, 199 (23%) discontinued due to adverse events, 136 (16%) died, 117 (14%) discontinued due to deterioration, 29 (3%) withdrew consent and 11 (1%) underwent transplantation. In total, 97 patients (11%) switched from SC treprostinil to an alternative prostacyclin analogue; bosentan was added in 105 patients (12%) and sildenafil in 25 (3%).

In conclusion, survival was 87–68% over 1–4 yrs for all 860 patients and 88–70% over 1–4 yrs with subcutaneous treprostinil monotherapy. For the idiopathic pulmonary arterial hypertension subset with baseline haemodynamics (n=332), survival was 91–72% over 1–4 yrs. In contrast, predicted survival was 69–38% over 1–4 yrs. The safety profile for long-term subcutaneous treprostinil was consistent with previous short-term trials with no unexpected adverse events.

KEYWORDS: Idiopathic pulmonary arterial hypertension, prostacyclin analogue, pulmonary arterial hypertension, survival, treprostinil

Pulmonary arterial hypertension (PAH) is a disease that leads to a progressive increase in pulmonary vascular resistance and right heart failure [1, 2]. In 1980, the National Institute of Health established an idiopathic PAH (IPAH) registry (previously termed primary pulmonary hypertension), which described the characteristics of IPAH and its natural history over a 5-yr period. The median survival was 2.8 yrs, with survival rates of 68, 48, and 34% at 1, 3 and 5 yrs, respectively [3]. Despite therapeutic advances, PAH remains a life-threatening disorder without a cure. In 1995, *i.v.* epoprostenol was approved by the Food and Drug Association for the treatment of severe IPAH, and was subsequently approved in 2000 for PAH related to the scleroderma spectrum of disease [4, 5]. The first oral therapy, bosentan, an endothelin receptor antagonist, was approved in 2001 [6] and the prostacyclin analogue treprostinil was approved for continuous subcutaneous (SC) infusion in 2002 [7]. In 2004, the prostacyclin analogue iloprost was approved *via* inhalation [8], and in 2005 the oral phosphodiesterase inhibitor sildenafil was approved [9].

Treprostinil is a prostacyclin analogue that possesses similar pharmacological actions to epoprostenol, including vasodilatation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation [10, 11]. However, epoprostenol therapy is associated with problems due to its short half-life (3–6 min) [12], necessitating continuous *i.v.* infusion *via* a central venous catheter. Treprostinil, unlike epoprostenol, is stable at room temperature and has a neutral pH with an elimination half-life of 4.5 h (with a distribution half-life of approximately

For editorial comments see page 1073.

This article has supplementary material accessible from www.erj.ersjournals.com

AFFILIATIONS
*Columbia University College of Physicians and Surgeons, New York, NY,
§United Therapeutics Corporation, Research Triangle Park, NC, and,
ƒUniversity of California, San Diego, School of Medicine, La Jolla, CA, USA.
#Institute of Cardiology, University of Bologna, Bologna, Italy.
¶Erasmus University Hospital, Brussels, Belgium, and
+Hospital Antoine Beclere, Clamart, France.

CORRESPONDENCE
R.J. Barst
Columbia University College of Physicians and Surgeons
3959 Broadway
BHN 2-255
New York
NY 10032
USA
Fax: 1 2123421443
E-mail: rjb3@columbia.edu

Received:
March 30 2006
Accepted after revision:
July 25 2006

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

40 min) [13]. These properties permit the delivery of treprostinil *via* SC infusion. However, SC treprostinil therapy can be limited by pain at the SC infusion site.

A placebo-controlled pilot study, evaluating the safety and efficacy of SC treprostinil infusion in 26 PAH patients [13], found favourable trends in exercise capacity, dyspnoea and haemodynamics. Subsequently, two double-blind, randomised, placebo-controlled 12-week studies in a total of 470 patients demonstrated that SC treprostinil therapy improves exercise capacity and haemodynamics [7]. Patients who participated in these controlled studies were eligible to enrol in an open-label extension study. In addition, *de novo* patients were also eligible to enrol in the open-label study. Subjects who participated in these studies received SC treprostinil therapy for up to 4 yrs. The objectives of the present open-label study were to retrospectively analyse the effects of SC treprostinil monotherapy (as well as SC treprostinil therapy with the addition of other PAH therapies if needed) on outcomes in PAH. In a subset of patients with IPAH in whom baseline haemodynamic measurements were available, the current authors also compared observed survival with predicted survival, determined using the formula by D'ALONZO *et al.* [3] based on the National Institute of Health (NIH) Registry data.

METHODS

Patients

Patients evaluated in these analyses were enrolled in the three placebo-controlled trials of SC treprostinil in PAH [7, 13]. *De novo* patients were also eligible if they met the following entry criteria: 1) New York Heart Association (NYHA) functional class II, III or IV; 2) PAH, either idiopathic or associated with connective tissue disease; 3) congenital heart disease; 4) portal hypertension; or 5) HIV. Additional entry criteria included: 1) aged $\geqslant$8 yrs; 2) mean pulmonary artery pressure $\geqslant$25 mmHg; 3) mean pulmonary capillary wedge pressure $\leqslant$15 mmHg; 4) pulmonary vascular resistance >3 units (measured or calculated by right heart catheterisation); and 5) 6-min walk distance 50–450 m. Patients had no previous exposure to prostaglandins or their analogues. Background PAH therapies, *e.g.* anticoagulants, oral vasodilators, cardiac glycosides, diuretics and supplemental oxygen, were administered at the discretion of the treating physicians. Treprostinil was administered as a continuous SC infusion *via* an ambulatory micro-infusion pump. Patients randomised to treprostinil in a prior controlled study continued receiving treprostinil at the same dose they were receiving at the end of the prior study, with subsequent dose adjustments based on investigator discretion. Patients receiving placebo in previous controlled studies and *de novo* patients started treprostinil at a dose of 1.25 $ng \cdot kg^{-1} \cdot min^{-1}$ with dose increases based on PAH signs and symptoms, and side effects.

All studies were conducted in accordance with the Amended Declaration of Helsinki in the North America, Europe, Australia and Israel sites. Studies were approved by local ethics review committees. Written informed consent (and assent as indicated) was obtained from all patients (and/or parents).

In addition to treatment with chronic SC treprostinil, the use of additional PAH treatments was at the discretion of the treating physicians. Patients continued in the study until one of the following: 1) death; 2) transplantation; 3) initiation of *i.v.* inhaled or oral prostaglandins or their analogues; or 4) an intolerable adverse event (AE).

Data on vital status, safety and additional or alternative treatments were collected from June 25, 1998 to December 1, 2003 (data cut-off).

Statistical analyses

Baseline parameters were recorded at the start of treprostinil treatment. Survival was assessed from the start of treprostinil to death or data cut-off. All treprostinil-treated PAH patients were included in the analyses (intent to treat). The Kaplan–Meier method was used to estimate the proportion of patients surviving at each time point. The date of initial treprostinil dosing was used as the index date for determining survival. Patients were censored if they underwent transplantation or discontinued treprostinil. Survival rates were also estimated for patients treated with SC treprostinil monotherapy, censoring patients when additional PAH treatment was added. A separate analysis of survival was performed for the subgroup of patients with IPAH with available baseline haemodynamics. Expected survival was calculated for each IPAH patient based on the NIH formula [3]. Possible predictors of survival were tested using a proportional hazards model. All variables were fit simultaneously to estimate hazard ratios. Sensitivity analyses were carried out to determine whether patients who discontinued due to AEs differed from the remainder of the cohort with respect to baseline demographic and clinical characteristics, including known PAH risk factors, *e.g.* PAH aetiology, NYHA class, haemodynamic parameters, or the time from diagnosis to the initiation of SC treprostinil therapy.

Safety was evaluated by AEs and laboratory values. Laboratory values were summarised descriptively at baseline and every 6 months thereafter. Baseline was defined as the measurement just prior to the first dose of treprostinil in either the controlled studies or open-label study. AEs were recorded throughout the study. An AE was considered ''treatment emergent'' if it first occurred or worsened following treprostinil initiation, and ''treatment related'' if it was considered by the investigator to be possibly or reasonably attributable to treprostinil treatment.

RESULTS

Patient population

In total, 860 patients were included in the analyses. Of these: 653 (76%) patients were female; 711 (83%) were Caucasian; 63 (7%) were Hispanic; 48 (6%) were of African origin; 23 (3%) were Asian; 11 (1%) were other of races; and four (<1%) were Native American. The mean (range) age was 46 (5–84) yrs. In total, 32 (4%) patients were $\leqslant$16 yrs of age and 21 (2%) patients were $\geqslant$75 yrs of age.

PAH history at time of enrolment for the 860 patients is summarised in table 1. The initial PAH diagnosis was made an average of 42 months before enrolment. The most common diagnosis for the 860 patients was IPAH (48%; n=412). In total, 13 (2%) patients were HIV positive, with HIV status being unknown for an additional 41 (5%) patients. Patients had been at their current NYHA class for a mean 15 months before enrolment. The majority of patients were NYHA class III (76%; n=654) at baseline.

TABLE 1 Pulmonary arterial hypertension history

Subjects n	860
IPAH	412 (48)
IPAH associated with	
Congenital systemic to pulmonary shunts	177 (21)
Diffuse cutaneous systemic sclerosis	72 (8)
Thromboembolic disease	49 (6)
Portopulmonary hypertension	43 (5)
Systemic lupus erythematosus	35 (4)
Limited cutaneous systemic sclerosis	28 (3)
Mixed connective tissue disease	27 (3)
HIV	13 (2)
Overlap syndrome	4 (<1)
Months since diagnosis	42±74
HIV	
No	806 (93)
Yes	13 (2)
Unknown	41 (5)
NYHA functional class at baseline	
II	128 (15)
III	654 (76)
IV	78 (9)
Months at baseline NYHA functional class	15±31

Data are presented as n (%) or mean±SD, unless otherwise stated. IPAH: idiopathic pulmonary arterial hypertension; NYHA: New York Heart Association.

TABLE 2 Patient disposition

Subjects	860
Total in previous controlled study	423 (49)
Randomised to receive treprostinil in previous study	205
Randomised to receive placebo in previous study	218
De novo patients	437 (51)
Completed#	331 (38)
Prematurely discontinued	506 (59)
Ongoing as of December 1, 2003	23 (3)
Reason for premature discontinuation	
Death	136 (16; 27)
Transplantation	11 (1; 2)
Clinical deterioration/rescue therapy	117 (14; 23)
Withdrew consent	29 (3; 6)
Adverse event	199 (23; 39)
Protocol violation	10 (1; 2)
Lost to follow-up	4 (<1; 1)

Data are presented as n, n (%) or n (% total; % discontinuations). #: transitioned to commercial drug.

Patient disposition

Patient disposition is summarised in table 2. In total, 860 patients were treated with SC treprostinil, including 423 (49%) who entered from controlled clinical studies and 437 (51%) *de novo* patients. Of the 423 patients who had previously participated in a controlled clinical study, 205 patients had received treprostinil and 218 patients had received placebo.

As of December 1, 2003, 354 (41%) of the 860 treated patients had remained on treprostinil and 506 (59%) had discontinued (table 2). The mean±SD duration of exposure for the 354 patients was 135±41 weeks. Out of the 860 treated patients, 23% (199 out of 860) discontinued due to AEs, 16% (136 out of 860) died, 14% (117 out of 860) discontinued due to deterioration, 3% (29 out of 860) withdrew consent, 1% (11 out of 860) underwent transplantation, 1% (10 out of 860) were withdrawn due to a protocol violation, and <1% (four out of 860) were lost due to follow-up. The 199 AEs that led to discontinuation were predominantly related to the study drug, *i.e.* infusion site pain and/or reaction (n=196). However, the dropout rate for site pain (fig. 1) demonstrates that if the patient discontinued treatment with SC treprostinil due to site pain, it was most likely to occur during the first year of treatment (fig. 2). In addition, sensitivity analyses did not demonstrate any significant differences between the patients who dropped out due to site pain *versus* those who did not.

Concomitant PAH medications

While all patients were started on SC treprostinil as PAH monotherapy, the addition of other PAH treatments was at the discretion of the treating physician. In total, 98 patients were started on alternative prostacyclin analogues during the study, *i.e. i.v.* epoprostenol (n=84), inhaled iloprost (n=8) and oral beraprost (n=6). Of these, 97 patients were transitioned off SC treprostinil to the alternative prostacyclin analogue and one patient had inhaled iloprost added during the study. However, it was discontinued after 8 days. In addition, during the study, bosentan was initiated in 12% (105 out of 860) of patients and sildenafil was added in an additional 3% (25 out of 860) of patients. None of the patients were treated with both bosentan and sildenafil in addition to SC treprostinil.

Duration of exposure and changes in mean doses over time

Continuous SC treprostinil was administered to 538 (63%) patients, 312 (36%) patients, 135 (17%) patients and 13 (2%) patients for 1, 2, 3 and 4 yrs respectively. As of December 1, 2003, 860 patients had received treprostinil for a total of 1,419 patient-yrs, with exposure of up to 4.5 yrs. The average dose increased from 1.25 $ng \cdot kg^{-1} \cdot min^{-1}$ at initiation to 26, 36, 42 and 42 $ng \cdot kg^{-1} \cdot min^{-1}$ at 1, 2, 3 and 4 yrs, respectively.

Survival analyses

Kaplan–Meier survival rates for the 860 treated patients, including 412 with IPAH and 448 with PAH related to other conditions, were 87, 78, 71 and 68% at 1, 2, 3 and 4 yrs, respectively (fig. 3). Survival rates with SC treprostinil monotherapy, censoring patients when additional targeted PAH therapy was added (130 out of 860 patients, *i.e.* 15% of the total cohort received additional PAH treatment), were 88, 79, 73 and 70% at 1, 2, 3 and 4 yrs, respectively (fig. 4), and not significantly different than for the entire cohort. In addition, due to the significant drop-out rate due to site pain during the first year of treatment, survival rates were estimated for patients treated with SC treprostinil for ⩾1 yr. Survival rates 90, 82 and 79% at 2, 3 and 4 yrs, respectively (fig. 5).

Out of the 412 IPAH patients, baseline haemodynamics were available for 332 patients as follows: mean pulmonary artery pressure 59±13 mmHg; mean right atrial pressure

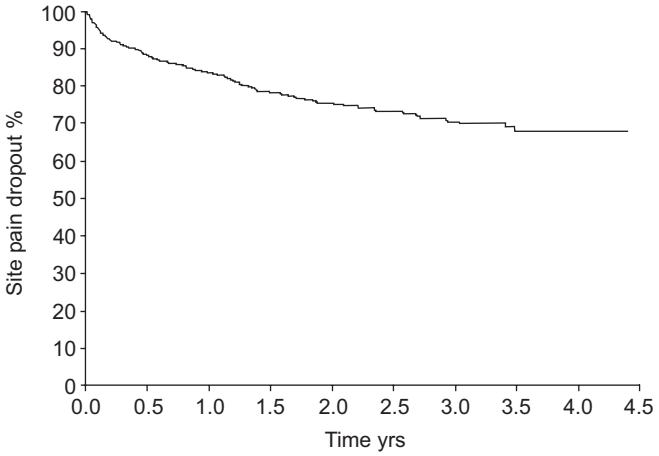

FIGURE 1. Kaplan–Meier time to discontinuation due to site pain in 860 subcutaneous treprostinil-treated pulmonary arterial hypertension patients. Discontinuation estimates (95% confidence intervals) were 83% (81–86) at 1 yr, 75% (72–78) at 2 yrs, 70% (66–74) at 3 yrs and 67% (62–72) at 4 yrs. The number patients at risk were 538, 312, 135 and 13 at 1, 2, 3 and 4 yrs, respectively.

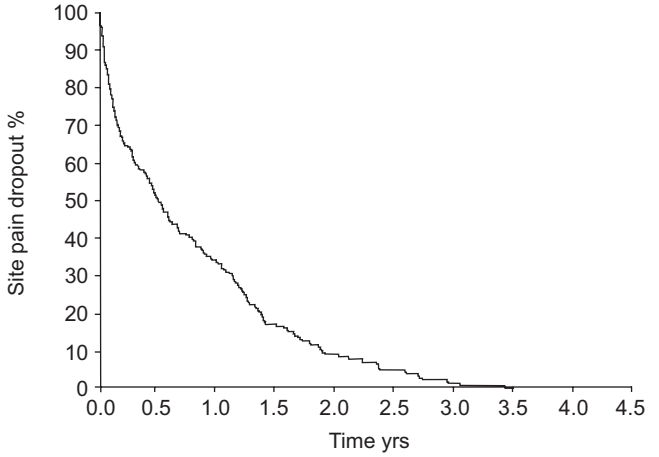

FIGURE 2. Kaplan–Meier estimate of time to discontinuation due to site pain in 196 patients who discontinued subcutaneous treprostinil. The time to discontinuation estimates (95% confidence intervals) were 34% (27–40) at 1 yr, 9% (6–14) at 2 yrs and 1.5% (0.4–4) at 3 yrs. The numbers of patients at risk were 66, 18, 3 and 0 at 1, 2, 3 and 4 yrs, respectively.

10 ± 5 mmHg; and cardiac index 2.2 ± 0.7 L·min^{-1}·m^{-2}. Baseline clinical characteristics and demographics for these 332 IPAH patients are shown in table 3. Observed survival rates for the 332 IPAH patients were 91, 82, 76 and 72% at 1, 2, 3 and 4 yrs, respectively. In contrast, expected survival rates (calculated for each patient based on the NIH formula) were 69, 56, 46, and 38% at 1, 2, 3 and 4 yrs, respectively (fig. 6).

Survival rates were highest for NYHA class II patients (n=128) at study entry, with survival rates of 91, 84, 79 and 74% at 1, 2, 3 and 4 yrs, respectively. Survival rates for NYHA class III patients (n=654) were 88, 79, 72 and 70% at 1, 2, 3 and 4 yrs, respectively; while survival rates for NYHA class IV patients (n=78) were 71, 62 and 52% at 1, 2 and 3 yrs, respectively (fig. 7).

Predictors of survival

Complete baseline demographic and clinical characteristics and haemodynamics were available in 432 PAH patients. Although the associations of both mixed venous oxygen saturation and pulmonary vascular resistance with survival were statistically significant (p=0.01, hazard ratio (95% confidence) 0.98 (0.96–0.99); and p=0.04, 1.03 (1.002–1.05), respectively), the magnitude of these associations was small. However, in the IPAH subset (baseline parameters available in 265 patients), the association between NYHA class and survival was significant statistically and in magnitude (NYHA class IV *versus* NYHA class III p=0.001, 5.35 (1.96–14.56); and NYHA class IV *versus* NYHA class II p=0.002, 8.74 (2.23–34.21)).

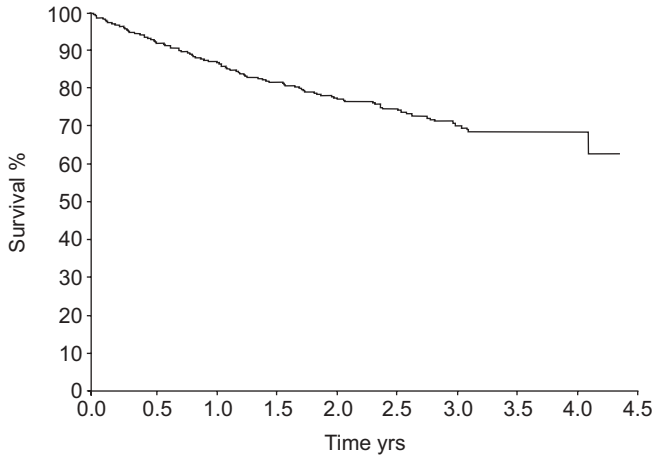

FIGURE 3. Observed survival in 860 subcutaneous treprostinil-treated pulmonary arterial hypertension patients. Survival estimates (95% confidence intervals) were 87% (84–89) at 1 yr, 78% (75–81) at 2 yrs, 71% (67–75) at 3 yrs and 68% (63–73) at 4 yrs. The numbers of patients at risk were 538, 312, 135 and 13 at 1, 2, 3, and 4 yrs, respectively.

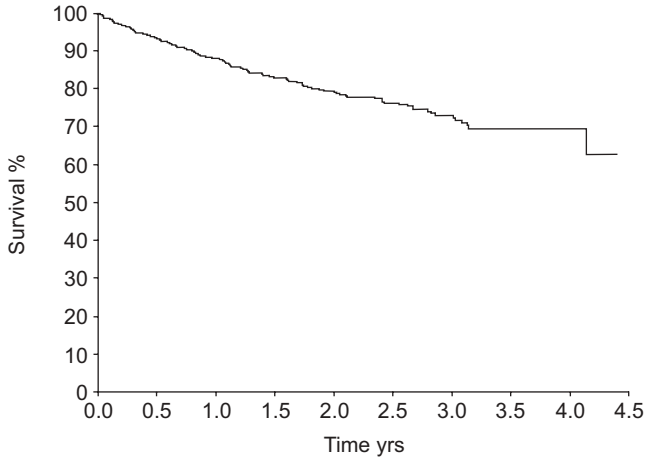

FIGURE 4. Observed survival with subcutaneous treprostinil monotherapy. Patients were censored when additional pulmonary arterial hypertension therapies were initiated. Survival estimates (95% confidence intervals) were 88% (85–90) at 1 yr, 79% (76–82) at 2 yrs, 73% (69–77) at 3 yrs and 70% (64–74) at 4 yrs. The numbers of patients at risk were 859, 525, 298, 118 and 11 at 0, 1, 2, 3 and 4 yrs, respectively.

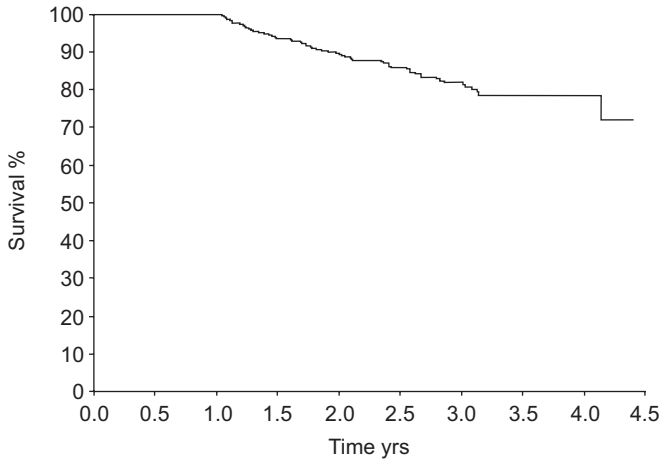

FIGURE 5. Observed survival for 538 patients who were treated with subcutaneous treprostinil for ⩾1 yr. Survival estimates (95% confidence intervals) were 90% (86–92) at 2 yrs, 82% (77–86) at 3 yrs and 79% (73–83) at 4 yrs. The numbers of patients at risk were 538, 312, 135 and 13 at 1, 2, 3 and 4 yrs, respectively.

Clinical laboratory values

All mean chemistry, haematology, coagulation and urinalysis values were within normal ranges throughout the 4 yrs of treatment.

Adverse events

A total of 168 patients died during the study or within 30 days of study discontinuation. One death was attributed to treprostinil by the investigator. The cause of this death was reported as progressive PAH. The patient had been receiving treprostinil for 1,123 days and was receiving 45 $ng \cdot kg^{-1} \cdot min^{-1}$ at the time of death.

A total of 415 patients had at least one serious AE, with 62 (7%) having a serious AE attributable to treprostinil. Overall, the reported serious AEs were typical of patients with PAH and included heart failure (14%; n=122), pulmonary hypertension (9%; n=76), syncope (4%; n=38), pneumonia (4%; n=37) and dyspnoea (3%; n=28). Serious AEs attributable to treprostinil included site infection (n=9), systemic hypotension (n=8), site pain (n=7), dyspnoea (n=4), syncope (n=4) and heart failure (n=4).

The AEs experienced by the study patients are shown in table 4. The most frequently reported AEs were infusion site pain in 792 (92%) patients and site reaction in 700 (81%) patients. Infusion site reactions were defined as any local AE other than pain, bleeding or bruising at the infusion site and were most often erythema, swelling, induration or rash. There were no reported episodes of catheter-related sepsis. Other less frequently observed treatment-related site events were bleeding/bruising in 170 (20%) patients and infection in 35 (4%) patients.

The treatment-related events rated as severe in intensity for ⩾1% of patients were: headache (1.7%; n=15); pain (1.4%; n=12); diarrhoea (1.3%; n=11); and nausea (1.2%; n=10). Headache was the only treatment-related AE, other than site events, that led to discontinuation for five (0.6%) patients.

TABLE 3 Baseline demographics and clinical characteristics in idiopathic pulmonary arterial hypertension patients[#]

Subjects	332
Age yrs	45±15
Sex	
Male	74 (22)
Female	258 (78)
Months from diagnosis	28±45
NYHA functional class at baseline	
II	53 (16)
III	262 (79)
IV	17 (5)
Months at baseline NYHA functional class	13±21
P_{pa} mmHg	59±13
P_{ra} mmHg	10±5
CI $L \cdot min^{-1} \cdot m^{-2}$	2.2±0.7

Data are presented as n, mean±SD or n (%). NYHA: New York Heart Association; P_{pa}: mean pulmonary artery pressure; P_{ra}: mean right atrial pressure; CI: cardiac index. [#]: idiopathic pulmonary arterial hypertension patients with baseline haemodynamic parameters.

Treatment-related events leading to a dose reduction in ⩾1% of patients were: diarrhoea (6.6%; n=57); headache (6.3%; n=54); nausea (6.2%; n=53); vomiting (2.7%; n=23); pain (2.4%; n=21); vasodilatation (2.4%; n=21); dizziness (2.3%; n=20); jaw pain (1.7%; n=15); systemic hypotension (1.6%; n=14); and anorexia (1.0%; n=9).

All treatment-emergent AEs reported in ⩾10% of the 860 patients were well-characterised side effects of prostacyclin and its analogues, *e.g.* diarrhoea (42%; n=365), nausea (27%;

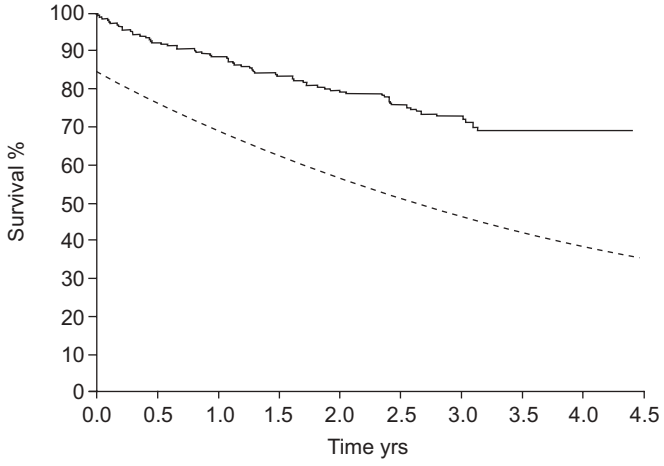

FIGURE 6. Observed survival (——) in 332 subcutaneous treprostinil-treated IPAH patients (with baseline haemodynamic parameters available) *versus* predicted survival (- - -) by the National Institute of Health equation. Survival estimates (95% confidence intervals) were 91% (87–94) at 1 yr, 82% (76–86) at 2 yrs, 76% (69–81) at 3 yrs and 72% (65–78) at 4 yrs *versus* predicted survival rates of 69, 56, 46 and 38% at 1, 2, 3 and 4 yrs, respectively. The numbers of patients at risk were 231, 149, 82 and 10 at 1, 2, 3 and 4 yrs, respectively.

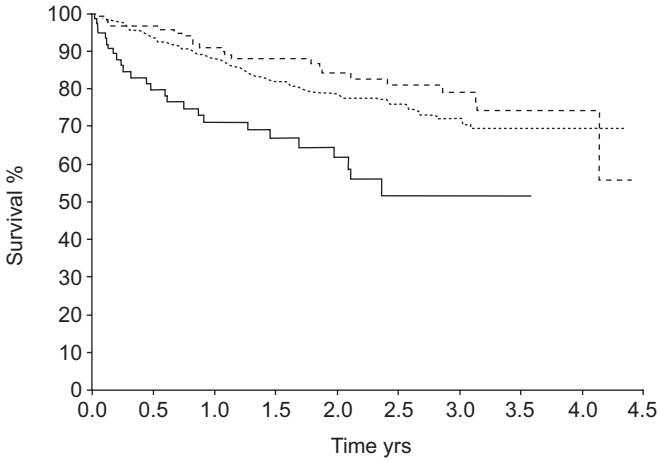

FIGURE 7. Observed survival in 860 subcutaneous treprostinil-treated pulmonary arterial hypertension patients, based on the New York Heart Association (NYHA) functional class at time of treprostinil initiation. NYHA class II: - - -; NYHA class III: · · · ·; NYHA class IV: ——. Survival rates for 128 NYHA class II patients (95% confidence intervals (CI)) were 91% (84–95), 84% (75–90), 79% (68–86) and 74% (62–83) at 1, 2, 3 and 4 yrs, respectively. Survival rates for 654 NYHA class III patients (95% CI) were 88% (85–91), 79% (75–82), 72% (67–76) and 70% (64–75) at 1, 2, 3 and 4 yrs, respectively. Survival rates for 78 NYHA class IV patients (95% CI) were 71% (58–81), 62% (48–73) and 52% (36–66) at 1, 2 and 3 yrs, respectively. The number of patients at risk in NYHA class II was 91, 59, 34, and 5 at 1, 2, 3 and 4 yrs, respectively; NYHA class III was 409, 230, 96 and 8 at 1, 2, 3 and 4 yrs, respectively; and NYHA class IV was 38, 23, 2 and 0 at 1, 2, 3 and 4 yrs, respectively.

n=235), headache (25%; n=214), jaw pain (23%; n=195), pain (16%; n=139), vasodilatation (13%; n=115), anorexia (10%; n=89) and rash (10%; n=88).

Delivery system complications were reported in 255 (30%) out of the 860 patients. These complications were most often due to pump malfunction, which was reported in 222 (26%) out of the 860 patients, or infusion set complications which were reported in 74 (9%) of the study patients. Pump failures were managed by correcting the alarm condition and/or substituting the backup pump, with no reported incidences of clinically significant deterioration occurring in association with the drug delivery system malfunction.

Overdoses were reported due to programming errors (n=3), accidental bolus infusions (n=4), concentration increases without rate decreases (n=6), and infusion set replacement following catheter dislodgement (n=1).

Haemorrhagic events not related to the infusion site were epistaxis (2%), ecchymosis (1%), haemoptysis (1%) and haemorrhage (<1%). These events did not appear to be related to the treprostinil dose. One patient was hospitalised for gastrointestinal haemorrhage and one patient for epistaxis. Both of these events resolved without sequelae. These were the only haemorrhagic events rated as severe in intensity. The gastrointestinal haemorrhage was the only haemorrhagic event leading to discontinuation.

Thrombocytopaenia was reported as a treatment-related event in six (0.7%) patients with one (0.1%) patient requiring hospitalisation and two (0.2%) reporting thrombocytopaenia as a severe event; all events resolved. One out of the six patients had PAH associated with portopulmonary hypertension. This patient reported a single, mild episode of thrombocytopaenia, which resolved in 31 days.

Renal (n=12) and hepatic failure (n=3) were infrequent and appeared not to be associated with treprostinil.

DISCUSSION

In the present study, the observed survival rates over 1–4 yrs were 87–68% for the entire cohort of 860 PAH patients treated with SC treprostinil. Survival rates with SC treprostinil monotherapy were 88–70% over 1–4 yrs, which is not significantly different than for the entire cohort, or for the cohort of patients excluding those who received combination therapy, in whom survival rates were 84–63% over 1–4 yrs (data not shown). For the IPAH patients, observed survival rates over 1–4 yrs were 91–72% compared with predicted survival rates of 69–38% [3]. Survival was also evaluated in this study by NYHA class at treatment initiation. This analysis was performed because poor survival has been associated with NYHA class in various studies, *e.g.* IPAH patients from the NIH Registry, IPAH patients treated with *i.v.* epoprostenol, and IPAH patients treated with oral bosentan [3, 14–16]. Historically, survival for NYHA class III and IV patients from the NIH Registry was 32 and 6 months, respectively [3]. The results of the present study were consistent with the NIH Registry with improved survival rates for patients who were NYHA class II (n=128) at study entry (observed survival was 91, 84, 79 and 74% at 1, 2, 3 and 4 yrs, respectively) *versus* NYHA class III (88, 79, 72 and 71% at 1, 2, 3 and 4 yrs, respectively; n=654) or NYHA class IV (71, 62 and 52% at 1, 2 and 3 yrs, respectively; n=78).

Observational studies have demonstrated a survival benefit in IPAH with warfarin [17, 18], and with chronic calcium-channel blockers in the small subset of IPAH patients who demonstrate acute pulmonary vasoreactivity [19]. In the 12-week randomised open-label trial of 81 NYHA class III and IV IPAH patients, survival was improved in patients treated with *i.v.* epoprostenol compared with patients treated with conventional therapy alone [4]. Since that study, several observational studies have confirmed a long-term survival benefit in NYHA class III and IV IPAH patients treated with *i.v.* epoprostenol when compared with either historical controls or predicted survival based on the NIH Registry equation [14, 15]. In a recently published review from 1992–2002, survival rates were reported for IPAH patients treated with conventional therapy alone *versus* *i.v.* epoprostenol plus conventional medical therapy. The 1, 2 and 3 yr survival rates were 72, 53 and 48%, respectively, for patients who did not receive *i.v.* epoprostenol *versus* 82, 74 and 62%, respectively, for patients who did receive *i.v.* epoprostenol [2]. The observed and predicted survival rates from the observational epoprostenol studies are similar to the observed and predicted survival rates for the IPAH patients in the present study. However, life-threatening AEs associated with *i.v.* epoprostenol, such as sepsis and drug interruption, are unlikely to occur with SC treprostinil.

TABLE 4 Adverse events

Subjects	860
Serious adverse events	415 (48)
Heart failure	122 (14)
Pulmonary hypertension	76 (9)
Syncope	38 (4)
Pneumnoia	37 (4)
Dyspnoea	28 (3)
Serious adverse events attributable to treprostinil	62 (7)
Site infection	9 (1)
Systemic hypotension	8 (1)
Site pain	7 (1)
Dyspnoea	4 (<1)
Syncope	4 (<1)
Heart failure	4 (<1)
Adverse events	
Infusion site pain	792 (92)
Site reaction	700 (81)
Bleeding/bruising	170 (20)
Infection	35 (4)
Treatment-related events	
Headache	15 (2)
Pain	12 (1)
Diarrhoea	11 (1)
Nausea	10 (1)
Treatment-related events leading to dose reduction	
Diarrhoea	57 (7)
Headache	54 (6)
Nausea	53 (6)
Vomiting	23 (3)
Pain	21 (2)
Vasodilatation	21 (2)
Dizziness	20 (2)
Jaw Pain	15 (2)
Systemic hypotension	14 (2)
Anorexia	9 (1)
Prostacyclin-related effects	
Diarrhoea	365 (42)
Nausea	235 (27)
Headache	214 (25)
Jaw pain	195 (23)
Pain	139 (16)
Vasodilation	115 (13)
Anorexia	89 (10)
Rash	88 (10)
Delivery system complications	255 (30)
Pump malfunction	222 (26)
Infusion set complications	74 (9)
Overdose	
Programming error	3 (<1)
Accidental bolus	4 (<1)
Concentration increase without rate decrease	6 (1)
Infusion set replacement following catheter dislodgement	1 (<1)
Haemorrhagic events	
Epistaxis	14 (2)
Ecchymosis	11 (1)
Haemoptysis	10 (1)
Haemorrhage	1 (<1)
Thrombocytopenia	6 (1)
Thrombocytopenia-related hospitalisation	1 (<1)
Severe thrombocytopenia	2 (<1)
Renal failure	12 (1)
Hepatic failure	3 (<1)

Data are presented as n or n (%).

Subsequently, MCLAUGHLIN *et al.* [16] reported improved survival in 169 IPAH patients treated with oral bosentan. The 1, 2 and 3 yr observed survival rates were 96, 89 and 86%, respectively, compared with NIH predicted survival rates of 69, 57 and 48%, respectively. In addition, survival in IPAH patients treated with first-line bosentan has been compared with first-line *i.v.* epoprostenol [20]. Thus, while these survival rates are similar to those with SC treprostinil reported in the present study, clinical trials cannot be directly compared with each other (table 5).

More recently, PROVENCHER *et al.* [21] reported that in an IPAH cohort treated with bosentan, many patients required the addition of another targeted PAH therapy during long-term follow-up. In addition, OPITZ *et al.* [22] also reported the need to add another PAH therapy in a cohort of IPAH patients treated with first-line inhaled iloprost. Both studies are not inconsistent with the observations made in the present study.

In the SC treprostinil 12-week randomised clinical trials, although 84% of patients receiving the active drug reported site pain, 27% of patients receiving placebo also reported site pain. Site pain is a major drawback with SC treprostinil therapy. In this open-label extension study, 23% of the patients discontinued due to AEs, with 98% of discontinuations due to site pain. However, almost 70% of these dropouts occurred within the first year. For those patients who remained on SC treprostinil for 1 yr, survival rates were 90–79% at 2–4 yrs. For the majority of patients, long-term SC treprostinil therapy was well tolerated in patients who had minimal site pain. Prostacyclin-related side effects were controlled by dose adjustment, and no clinically significant changes in laboratory values were observed. The longer half-life of treprostinil makes an exacerbation of PAH symptoms resulting from abrupt cessation of drug less likely to occur with treprostinil than with epoprostenol. In addition, serious complications associated with a continuous *i.v.* infusion, *e.g.* sepsis or thromboembolic events, are unlikely to occur with a SC infusion treatment. In 2004, treprostinil was also approved by the Food and Drug Association for continuous *i.v.* administration, an alternative option for patients intolerant to SC treprostinil as well as an alternative to *i.v.* epoprostenol. Potential advantages of *i.v.* treprostinil over *i.v.* epoprostenol include better stability, easier drug preparation and longer duration of activity [23, 24].

There are several important limitations to the current observational study. The use of the NIH Registry equation as opposed to a parallel placebo-treated or historical control group is a significant limitation. The NIH equation is based on data from the 1980s and background practice patterns have changed over the past 20 yrs. In addition, the 23% discontinuation rate during the study due to AEs (predominantly site pain) cannot exclude a selection bias. However, analysing the patients who dropped out due to site pain *versus* those who did not, did not demonstrate any significant differences between the two groups with respect to known PAH risk factors, such as NYHA class, PAH aetiology or haemodynamic parameters at the time of SC treprostinil initiation. Additional limitations in the present observational study include the doses of treprostinil the patients received were lower than the overall current doses patients receive. Whether higher doses may have affected outcome remains to be studied. In addition, with

TABLE 5 Baseline characteristics of survival and predicted survival in idiopathic pulmonary arterial hypertension patients treated with *i.v.* epoprostenol, oral bosentan or subcutaneous (SC) treprostinil based on the National Institute of Health Registry

	i.v. epoprostenol[#,f]	Oral bosentan[¶,##]	SC treprostinil[+]	*i.v.* epoprostenol[§,¶¶]	Oral bosentan[§,¶¶]
P_{pa} mmHg	61±13	57±16	59±13	59±15	57±15
P_{ra} mmHg	14±6	10±6	10±5	10±5	10±5
CI L·min^{-1}·m^{-2}	1.8±0.6	2.4±0.8	2.2±0.7	2.1±0.6	2.2±0.6
NYHA class					
I/II		15 (9)	53 (16)		
III	75 (46)	139 (82)	262 (79)	83 (100)	83 (100)
IV	87 (54)	15 (9)	17 (5)		
Survival rates yrs					
1	88, 59	96, 69	88, 69	93[++]	95[++]
2	76, 46	89, 57	80, 56	89[++]	87[++]
3	63, 35	86, 48	74, 46	78[++]	82[++]
4 yrs	56, NA	NA	69, 38	NA	NA

Data are presented as mean±SD, n (%). For survival rates data are presented as % observed, % predicted, unless otherwise stated. P_{pa}: mean pulmonary artery pressure; P_{ra}: mean right atrial pressure; CI: cardiac index; NYHA: New York Heart Association; NA: not available. [#]: n=162; [¶]: n=169; [+]: n=332; [§]: n=83; [f]: from reference [14]; [##]: from reference [16]; [¶¶]: from reference [20]; [++]: % observed.

either bosentan or sildenafil initiated in 15% of patients, the current study cannot adequately address the effects of SC treprostinil monotherapy on survival in PAH.

In conclusion, having multiple therapeutic options available for pulmonary arterial hypertension patients should improve the efficacy in treating pulmonary arterial hypertension. The selection of an ''optimal'' medical regimen for an individual patient should be based on a risk–benefit assessment of all treatment options available. While subcutaneous treprostinil may not be the drug of first choice for most pulmonary arterial hypertension patients, having subcutaneous treprostinil as a therapeutic option may improve outcome in pulmonary arterial hypertension.

ACKNOWLEDGEMENTS

The authors would like to thank the following investigators for their contributions. R. Bourge (Birmingham, AL, USA); D. Ross and S. Shapiro (Los Angeles, CA, USA); R. Channick (San Diego, CA, USA); T. DeMarco (San Francisco, CA, USA); R. Doyle (Stanford, CA, USA); R. Oudiz (Torrance, CA, USA); D. Badesch (Denver, CO, USA); D. Ivy (Denver, CO, USA); C. Lawrence (Atlanta, GA, USA); S. Rich (Chicago, IL, USA); B. deBoisblanc (New Orleans, LA, USA); J. Wirth (Portland, ME, USA); S. Gaine (Baltimore, MD, USA); A. Waxman (Boston, MA, USA); M. Rubenfire (Ann Arbor, MI, USA); M. McGoon (Rochester, MN, USA); V. Tapson (Durham, NC, USA); R. Schilz and A. Arroliga (Cleveland, OH, USA); J. Edleman (Portland, OR, USA); S. Murali (Pittsburgh, PA, USA); N. Hill (Providence, RI, USA); I. Robbins (Nashville, TN, USA); A. Frost (Houston, TX, USA); F. Shardonofsky (Houston, TX, USA); G. Elliott (Salt Lake City, UT, USA); D. Zwicke (Milwaukee, WI, USA); A Keogh (Sydney, Australia); M. Kneussl (Wein, Austria); M. Delcroix (Leuven, Belgium); D. Langleben (Montreal, Canada); J. Granton (Toronto, Canada); D. Ostrow (Vancouver, Canada); M. Hoeper (Hannover, Germany); N. Berkman (Jerusalem, Israel); M. Kramer (Petach Tikvah, Israel); I. Ben-Dov (Tel-Hashomer, Israel); J. Sandoval (Mexico City, Mexico); A. Boonstra Amsterdam, the Netherlands); A. Torbicki (Warsaw, Poland); M. Gomez-Sanchez (Madrid, Spain); J. Pepke-Zaba (Cambridge, UK); C. Black, S. Gibbs and D. Kiely (London, UK); T. Higenbottam (Sheffield, UK); A. Peacock (Glasgow, UK); P. Corris (Newcastle-upon-Tyne, UK).

REFERENCES

1 Proceeding of the 3rd World Symposium on Pulmonary Arterial Hypertension. Venice, Italy, June 23-25, 2003. *JACC* 2004; 43: Suppl. 12, 1S–90S.
2 Diagnosis and management of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004; 126: S1–S92.
3 D'Alonzo GE, Barst RJ, Ayres SM, *et al.* Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991; 115: 343–349.
4 Barst RJ, Rubin LJ, Long WA, *et al.* A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996; 334: 296–302.
5 Badesch DB, Tapson VF, McGoon MD, *et al.* Continuous intravenous epoprostenol for pulmonary hypertension secondary to the scleroderma spectrum of disease. A randomized controlled trial. *Ann Int Med* 2000; 132: 425–434.
6 Rubin LJ, Badesch DB, Barst RJ, *et al.* Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002; 346: 896–903.
7 Simonneau G, Barst RJ, Galiè N, *et al.* Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2002; 165: 800–804.

8 Olschewski H, Simonneau G, Galie N, *et al.* Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002; 347: 322–329.

9 Galie N, Ghofrani HA, Torbicki A, *et al.* Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005; 353: 2148–2157.

10 Steffen RP, de la Mata M. The Effects of 15Au81, a chemically stable prostacyclin analogue, on the cardiovascular and rennin-angiotensin systems of anesthetized dogs. *Prostaglandins Leukot Essent Fatty Acids* 1991; 43: 277–286.

11 McNulty MJ, Sailstad JM, Steffen RP. The pharmacokinetics and pharmacodynamics of prostacyclin analogue 15AU81 in anesthetized beagle dog. *Prostaglandins Leukot Essent Fatty Acids* 1993; 43: 159–166.

12 Epoprostenol package insert. GlaxoWellcome, Inc., Research Triangle Park, NC 27709, USA. May, 1998.

13 McLaughlin VV, Gaine SP, Barst RJ, *et al.* Efficacy and safety of treprostinil: an epoprostenol analogue for primary pulmonary hypertension. *J Cardiovasc Pharmacol* 2003; 41: 293–299.

14 McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2002; 106: 1477–1482.

15 Sitbon O, Humbert M, Nunes H, *et al.* Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002; 40: 780–788.

16 McLaughlin VV, Sitbon O, Badesch DB, *et al.* Survival with first-line bosentan therapy in patients with primary pulmonary hypertension. *Eur Respir J* 2005; 25: 244–249.

17 Fuster V, Steele PM, Edwards WD, *et al.* Primary pulmonary hypertension: natural history and the importance of thrombosis. *Circulation* 1984; 70: 580–587.

18 Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992; 327: 76–81.

19 Sitbon O, Humbert M, Jais X, *et al.* Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation* 2005; 111: 3105–3111.

20 Sitbon O, McLaughlin VV, Badesch DB, *et al.* Survival in patients with class III idiopathic pulmonary arterial hypertension treated with first-line oral bosentan compared with an historical cohort of patients started on *i.v.* epoprostenol. *Thorax* 2005; 60: 1025–1030.

21 Provencher S, Sitbon O, Humbert M, Cabrol S, Jais X, Simonneau G. Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. *Eur Heart J* 2006; 27: 589–595.

22 Opitz CF, Wensel R, Winkler J, *et al.* Clinical efficacy and survival with first-line inhaled iloprost therapy in patients with idiopathic pulmonary arterial hypertension. *Eur Heart J* 2005; 26: 1895–1902.

23 Tapson VF, Gomberg-Maitland M, *et al.* Safety and efficacy of intravenous treprostinil for pulmonary arterial hypertension: a prospective, multicenter, open-label 12-week trial. *Chest* 2006; 129: 683–688.

24 Gomberg-Maitland M, Barst RJ, Benza R, *et al.* Transition from intravenous epoprostenol to intravenous treprostinil in patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2005; 172: 1586–1589.