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Long-term treatment, tolerability, and survival with sub-cutaneous treprostinil for severe pulmonary hypertension

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KEYWORDS:
pre-capillary pulmonary hypertension;
sub-cutaneous treprostinil;
prostanoid therapy;
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long-term treatment

BACKGROUND: Randomized controlled trials have resulted in improved outcomes in pulmonary arterial hypertension; however, they are biased by stringent inclusion criteria, pre-specified patient sub-sets, and study durations. In addition, common practice is to start oral therapies ahead of the more potent and titratable prostanoid therapies, despite advanced disease states at diagnosis. The objectives of our prospective registry were to evaluate long-term effects on functional class, 6-minute walking distance, hemodynamics, and survival, and also long-term tolerability of first-line sub-cutaneous treprostinil, a prostacyclin analog, in patients with severe pulmonary hypertension.

METHODS: Data were collected from patients with functional class III/IV pre-capillary pulmonary hypertension (Dana Point groups 1 and 4; mean right arterial pressure $\geq$ 10 mmHg, and/or cardiac index $\leq$ 2.2 liters/min/m^2). Treprostinil dose adjustments were driven by clinical symptoms and side effects.

RESULTS: The study included 111 patients (1999 to 2010). Of these, 13 (12%) stopped treatment prematurely because of drug side effects, 11 (9.9%) underwent double lung transplantation, and 49 (44.1%) died of any cause (41 on treatment, 8 after early drug discontinuation). Overall survival rates at 1, 5, and 9 years were 84%, 53%, and 33%. In patients who were able to tolerate treatment $>$ 6 months, survival rates were 57% at 9 years.

CONCLUSION: First-line treatment of severe pre-capillary pulmonary hypertension with sub-cutaneous treprostinil is safe and efficacious over many years. If up-titration beyond 6 months is tolerated, effective doses are reached and outcomes are good.

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Pre-capillary pulmonary hypertension (PH) is a severe condition. According to the National Institutes of Health (NIH) registry,[1] idiopathic and heritable pulmonary arterial hypertension (PAH) have a median untreated time to death of 2.8 years. Although these conditions are rare,[2] the associated forms of PAH[3] and chronic thromboembolic PH (CTEPH)[4] may be more common. The pathogenesis of PH is poorly understood, but imbalances between vasoconstrictive/proliferative (eg, endothelin) and vasodilator/antiproliferative mediators (eg, prostacyclin and nitric oxide) have been identified,[5] indicating occlusive pulmonary vascular remodeling.

Currently approved PH-targeted drugs are primarily vasodilators and fall into 3 classes: prostanoids, endothelin-receptor antagonists, and phosphodiesterase type-5 inhibitors. These treatments improve symptoms, quality

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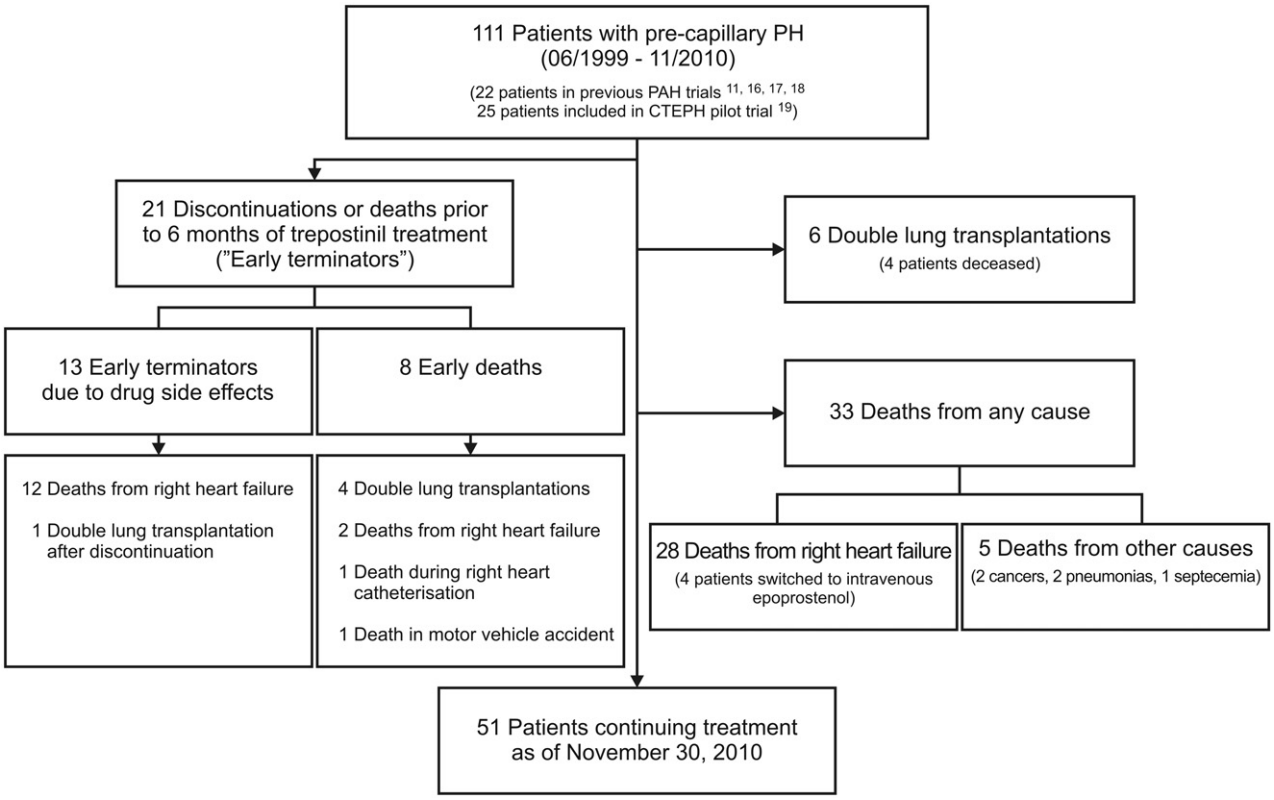

Figure 1 Patient disposition. CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

of life,[6] exercise capacity, hemodynamics, and outcomes,[7] but the disease still carries annual mortality rates of 10% to 15%.[8,9]

More than 66% of newly diagnosed PH patients present in World Health Organization functional classes (WHO FC) III and IV.[8,10] According to our current understanding of the disease pathology, most of the pulmonary vessels are dysfunctional or occluded at these stages. Although current evidence-based guidelines do not specify first-line treatments, we have pursued an aggressive treatment strategy.

Treprostinil is a stable prostacyclin analog (Remodulin®, United Therapeutics, Research Triangle Park, NC) with an elimination half-life of 4.6 hours. Treprostinil has similar acute hemodynamic effects as epoprostenol, exerting vasodilatation of pulmonary and systemic arteries and inhibition of platelet aggregation. Treprostinil can be given sub-cutaneously (SC), thus avoiding risks inherent with chronic intravenous drug administration.

A double-blind, randomized, placebo-controlled trial documented that treprostinil improved exercise capacity, indices of dyspnea, signs and symptoms of PH, cardiopulmonary hemodynamics, and quality of life. However, because local side effects limited dose up-titration, the benefit of SC treprostinil over 12 weeks was modest.[11]

Practical and psychologic support is an essential component of individualized care for patients receiving SC infusion therapy because it takes time for them to learn how best to manage their pain and cope with the infusion pump system.

The objectives of our registry were to evaluate in patients with severe pre-capillary PH the long-term effects on WHO FC, 6-minute walking distance (6MWD), hemodynamics, and survival, as well as long-term tolerability of first-line SC treprostinil.

Patients and methods

The database used in this study has been under the auspices of the Ethics Committee of the Medical University of Vienna (#972/2009). Patients provided written informed consent. Patient disposition is shown in Figure 1.

Study design

This prospective registry included patients (aged ≥ 18 years) with advanced pre-capillary PH who received first-line treatment with SC treprostinil. Inclusion criteria were (1) pre-capillary PH[10] Dana Point groups I or IV, (2) WHO FC III or IV, and (3) a mean right atrial pressure (mRAP) ≥ 10 mmHg and/or a cardiac index (CI) ≤ 2.2 liters/min/m^2. Diagnoses were established according to guidelines.[12] Date of diagnosis and baseline corresponded to the date of the first diagnostic right heart catheterization, which was 3 days to 3 months before treatment initiation. Patients were stable on therapies that included anti-coagulants, cardiac glycosides, diuretics, and supplemental oxygen.

Assessments

Patients were seen every 3 to 6 months as outpatients, parallel to monthly consultations at their primary care physicians. We counted

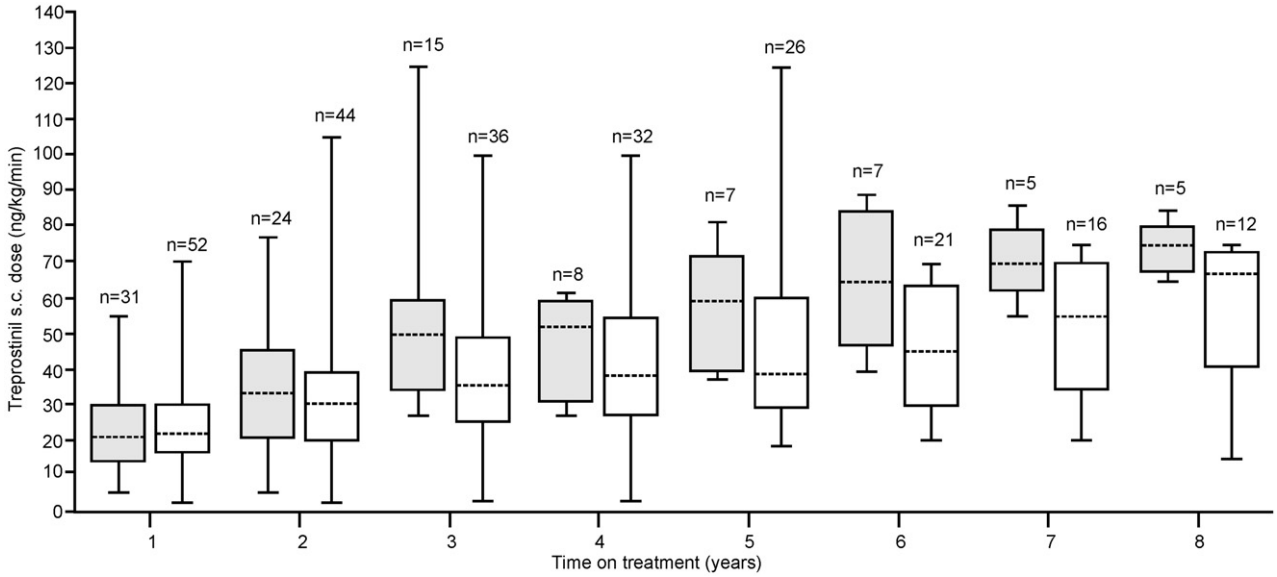

Figure 2 Box and whisker plots show stable sub-cutaneous (SC) doses of treprostinil by 1-year periods since individual treatment started. The grey boxes represent doses in patients who died, and white boxes represent doses for patients who were alive within the respective treatment year. Patient numbers (*n*) are indicated. The horizontal line in the middle of each box indicates the median; the top and bottom borders of the box mark the 75th and 25th percentiles, respectively; and the whiskermark the 90th and 10th percentiles.

350 ambulatory visits and 132 hospital admissions. Reasons for hospital admissions were clinical worsening, defined as a $>$ 20% decrease in 6MWD combined with a more than 2-fold rise in N-terminal prohormone brain natriuretic peptide (NT-proBNP) or an increase of $>$ 1 in WHO FC, need for intravenous diuretics, vasopressors, or inotropes, and evaluation for double lung transplantation.

For hemodynamic assessment, a 7F Swan-Ganz catheter (Baxter, Irvine, CA) was inserted from a femoral or jugular approach. Mean pulmonary arterial pressure (mPAP), mRAP, pulmonary capillary wedge pressure (PCWP), and respective oxygen saturations, including the inferior and superior vena cava, were measured in every patient. Cardiac output (CO) was assessed by thermodilution and by the Fick method. Patients underwent a median of 2 right heart catheterizations (range, 1–7), with an evaluation at baseline, at 6 months, and yearly thereafter, if deemed necessary.

Tolerability and safety

Treprostinil was administered SC, first through the MiniMed 407C insulin infusion pump (Medtronic, Minneapolis, MN), and starting in 2004, the CADD-MS3 (Smith Medical MD Inc, St. Paul, MN) was used. Treprostinil was started at a dose of 1.25 ng/kg/min, and dose adjustments were done weekly for 6 months, and then at a mean of every 4.5 months (range, 3–6 months). The arbitrary goal was to reach 30 ng/kg/min after 1 year. Dose increases were driven by clinical symptoms, objective criteria (6MWD, WHO FC, NT-proBNP measurements), and patient and physician consensus.[13] The dose adaptations per patient amounted to 47 $\pm$ 17 (Figure 2). Bosentan was added in 2 patients and sildenafil in 3. Intravenous prostacyclin is rarely used at our center; for example, in cases where rapid dose escalations are necessary such as in pregnancy or other selected cases. Adverse events were adjudicated by our multidisciplinary PH team, including patients' primary care physicians.

Statistical analyses

The analysis included all patients who met the inclusion criteria and received treatment with first-line SC treprostinil at our institution before the database lock on November 30, 2010. Time to clinical worsening was defined as time to first hospitalization or death without hospitalization. Whichever of those occurred first was censored.

Continuous variables are reported as means $\pm$ standard deviations. Categoric variables are expressed as counts and percentages. Hemodynamic parameters, 6MWD, and the Borg dyspnea score (BDS) values are provided as means $\pm$ standard deviations if normally distributed, and not normally distributed variables are reported as medians and interquartile ranges (IQR). In addition to a descriptive data analysis, the Wilcoxon test for paired data was used for comparison of baseline and follow-up for ordinal variables or not normally distributed metric variables, and a quantification of follow-up values was derived from the reverse Kaplan-Meier curve by medians and quartiles.[14]

Analysis of overall survival and event-free status was performed using Kaplan-Meier curves, Cox regression, and life tables. The log-rank test was used to compare groups of survival times. Survival curves were defined by PH sub-groups, by 6MWD higher and lower than the median at baseline, and by WHO FC at the start of SC therapy. Predicted survival was calculated for patients with IPAH, drug-induced PAH, and heritable PAH using the NIH equation,[1] the French equation,[8] and the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) equation.[9]

Univariable analysis and multivariable analyses based on the proportional hazard model were used to find predictors of outcome. The effect of the cumulative treprostinil dose on overall survival was analyzed in a Cox model for time-dependent covariates. Results are expressed as hazard ratios with 95% confidence intervals and 2-tailed *p*-values. All statistical computations were done with SPSS 17.0.1 software (SPSS Inc, Chicago, IL) and SAS 9.2 software (SAS Institute, Cary, NC).

Relative survival functions[15] were obtained by relating the survival probabilities of treprostinil-treated patients to those of the Austrian reference population matched by age and sex. This analysis was based on life tables published by Statistics Austria (http://www.statistik.at/web_de/statistiken/bevoelkerung/demographische_masszahlen/sterbetafeln/index.html#index6). The departure of

mortality of study patients from that of the reference population was analyzed by a chi-square test.

Results

Patient characteristics

Between June 1, 1999, and November 30, 2010, SC treprostinil was started in 111 patients with severe pre-capillary PH (Table 1). There was an 11.7% discontinuation rate due to side effects throughout the median observation time of 56 months (IQR, 31–91 months). At baseline by the WHO FC, 62 patients (56%) were classified as III and 49 (44%) as IV. PAH was present in 69 patients (62%), categorized by a diagnosis of IPAH in 33 (29.7%), PAH associated with congenital heart disease in 21 (18.9%), PAH associated with connective tissue diseases in 7 (6.3%), drug and toxin-induced PAH in 4 (3.6%), portopulmonary PAH in 2 (1.8%), and heritable PAH in 2 (1.8%). Because our center is the national referral center for pulmonary endarterectomy (PEA), 42 CTEPH patients (38%) represent the largest subgroup; of whom 37 (88.1%) were classified as non-operable by our PEA surgeon (W.K.). Five patients (11.9%) had developed persistent/recurrent PH within a median of 2 years after PEA (range, 1-8 years).

Effects of treprostinil on FC, exercise capacity, and hemodynamics

The treatment effects at 1, 3 and 5 years on exercise capacity and hemodynamics over baseline are shown at median treprostinil doses (in ng/kg/min) of 21.25 (IQR, 16.25–30), 37.5 (IQR, 27.5–55), and 42.55 (IQR, 30–61, Table 2), respectively. Improvements of 6MWD, BDS, WHO FC, mPAP, and CI over baseline were sustained at 5 years.

Effects on clinical worsening

The median time to clinical worsening was 18 months (range, 0–30 months). Total event-free survival was 49%, 20%, and 16% at 1, 5 and 8 years, respectively.

Survival

Deaths from any cause occurred in 49 patients (16 deaths $<$ 6 months on treatment and 33 deaths $>$ 6 months on

Table 1 Baseline Clinical and Hemodynamic Characteristics

	Patient groups			
Variables[a]	All	Treated ≥ 6 months	PAH[b]	CTEPH
Clinical data	(n = 111)	(n = 85)	(n = 39)	(n = 42)
Age, year	52 ± 17	53 ± 17	49 ± 18	61 ± 15
Sex				
Male	34 (31)	27 (32)	9 (23)	15 (36)
Female	77 (69)	58 (68)	30 (77)	27 (64)
Etiology of PH				
PAH	69 (62)	54 (64)		
CTEPH	42 (38)	31 (36)		
WHO FC				
III	62 (56)	51 (60)	21 (54)	20 (48)
IV	49 (44)	34 (40)	18 (46)	22 (52)
6MWD, meters	288 ± 108	293 ± 108	289 ± 119	269 ± 97
Borg Dyspnea Score	6 ± 2	6 ± 2	6 ± 2	7 ± 2
Time to				
Diagnosis, months	16 (3–276)	14 (2–276)	13 (3–276)	30 (6–96)
Treatment start, months	0.1 (0.1–3)	0.1 (0.1–1.2)	0.1 (0.1–1)	0.1 (0.1–3)
Hemodynamics				
Heart rate, beats/min	83 ± 18	83 ± 17	84 ± 15	81 ± 14
mRAP, mmHg	11 ± 5	11 ± 6	12 ± 6	11 ± 4
mPAP, mmHg	60 ± 16	60 ± 15	59 ± 15	56 ± 13
PCWP, mmHg	10.4 ± 4.2	10.3 ± 3.3	9.4 ± 3.3	11.2 ± 3.2
Cardiac output, liters/min	3.7 ± 1.0	3.8 ± 1.0	3.5 ± 1.0	3.6 ± 0.7
Svo_2, %	55.8 ± 8.3	59.8 ± 10.2	55.1 ± 8.1	56.1 ± 8.5
CI, liters/min/m^2	2.0 ± 0.4	2.1 ± 0.4	2.1 ± 0.4	2.0 ± 0.3
PVR, dyn/sec/cm^5	1,103 ± 519	1,075 ± 539	1,038 ± 499	1,000 ± 367

6MWD, 6-minute walking distance; CI cardiac index; CTEPH, chronic thromboembolic pulmonary hypertension; mPAP, mean pulmonary arterial pressure; mRAP, mean right arterial pressure; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; Svo_2, mixed venous saturation; WHO FC, World Health Organization functional class.

[a]Continuous data are shown as mean ± standard deviation or as median (range); categoric data are shown as number (%).

[b]Includes idiopathic pulmonary arterial hypertension, drug-induced pulmonary arterial hypertension, and heritable pulmonary arterial hypertension.

Table 2 Effects of Sub-cutaneous Treprostinil on Exercise Capacity, World Health Organization Functional Class and Hemodynamics

Variables[a]	Absolute values (baseline)	Treprostinil dose at follow-up interval (ng/kg/min)					
		TE1 year	*n*	TE3 years	*n*	TE5 years	*n*
		21.25 (16.25–30)		37.5 (27.5–55)		42.55 (30–61)	
6MWD, meters	293 ± 108	+71 (88; 55)[b]	90	+100 (+120; +81)[b]	61	+109 (+141; +78)[b]	29
BDS	6 ± 2	−2 (0; −4)[b]	90	−3 (0; −5)[b]	61	−4 (0; −6)[c]	29
WHO FC	3.0 ± 0.5	−0.8 (−0.7; −0.9)[b]	90	−0.7 (−0.6; −0.8)[b]	61	−0.8 (−0.6; −1.0)[b]	29
mRAP, mmHg	11 ± 6	−1.2 (−0.1; −2.4)[c]	69	−1.8 (0.8; −4.5)	20	−0.8 (+2.3; −4.0)	11
mPAP, mmHg	60 ± 15	−5.2 (−3; −7.4)[b]	69	−8.6 (−1.7; −15.4)[c]	20	−7.4 (−3; −11.8)[c]	11
CI, liters/min/m^2	2.1 ± 0.4	+0.5 (+0.6; +0.3) [b]	69	+0.55 (+0.9; +0.2) [c]	20	+0.47 (+0.8; +0.1)[c]	11
PVR, dyn/sec/cm^5	1075 ± 539	−220 (−126; −314) [b]	69	−296 (−93; −501) [c]	20	−230 (+32; −492) [d]	11

6MWD, 6-minute walking distance; BDS, Borg Dyspnea Score; CI, cardiac index.

mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; PVR, pulmonary vascular resistance; TE, treatment effect; WHO FC, World Health Organization functional class.

[a]Data for variables are shown as mean ± standard deviation, treatment effects are shown as medians (95% confidence interval), and treprostinil doses are shown as median (interquartile range).

[b]$p < 0.001$, [c]$p < 0.05$, [d]$p < 0.1$, for effects of sub-cutaneous (SC) treprostinil at 1, 3, and 5 years, compared with the respective baseline, after at least 6 months on treatment with SC treprostinil. The data that are shown only refer to patients who are alive, to illustrate the median treatment effect.

treatment, Figure 1), with 41 on and 8 off treprostinil since the preceding 3.6 months (range, 1–36 months). Four further deaths occurred after lung transplantation.

Overall survival rates, including all patients ever started on SC treprostinil, were 84%, 53%, and 33% at 1, 5, and 9 years. Patients treated at least 6 months had excellent survival rates of 96%, 78% and 57% at 1, 5 and 9 years (Figure 3). The average annual mortality rate was 8.7% in patients treated ≥ 6 months.

Although patients were newly diagnosed at the time of treatment start (ie, were classified as incident cases),[8] patients in our registry reached a 70% survival rate at 3 years, which was better than predicted by the NIH[1] and the French equations, indicating that treprostinil effectively delays disease progression.

Overall survival in PAH was not significantly different from CTEPH ($p = 0.679$, log-rank test; Figure 4). WHO FC IV patients had a poorer overall survival than FC III patients

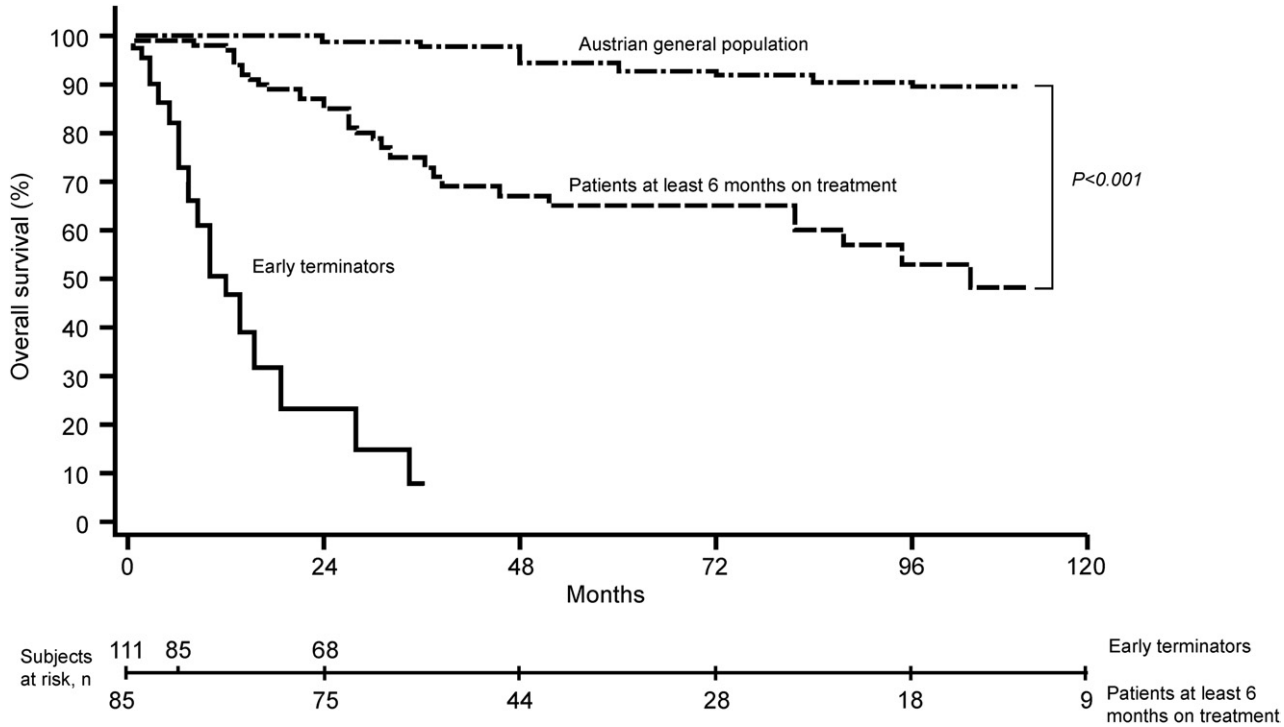

Figure 3 Relative survival rates of patients receiving subcutaneous treprostinil. Patients who stopped treatment had a survival rate of 32% at 1 year (solid line) compared with patients > 6 months on subcutaneous treprostinil (dashed line): 96%, 78% and 57% survival at 1, 5, and 9 years, respectively. The 2002 Austrian reference population matched for age and sex is shown as the dashed-dotted line, with 99%, 97% and 93% survival at 1, 5, and 8 years, respectively ($p < 0.001$).

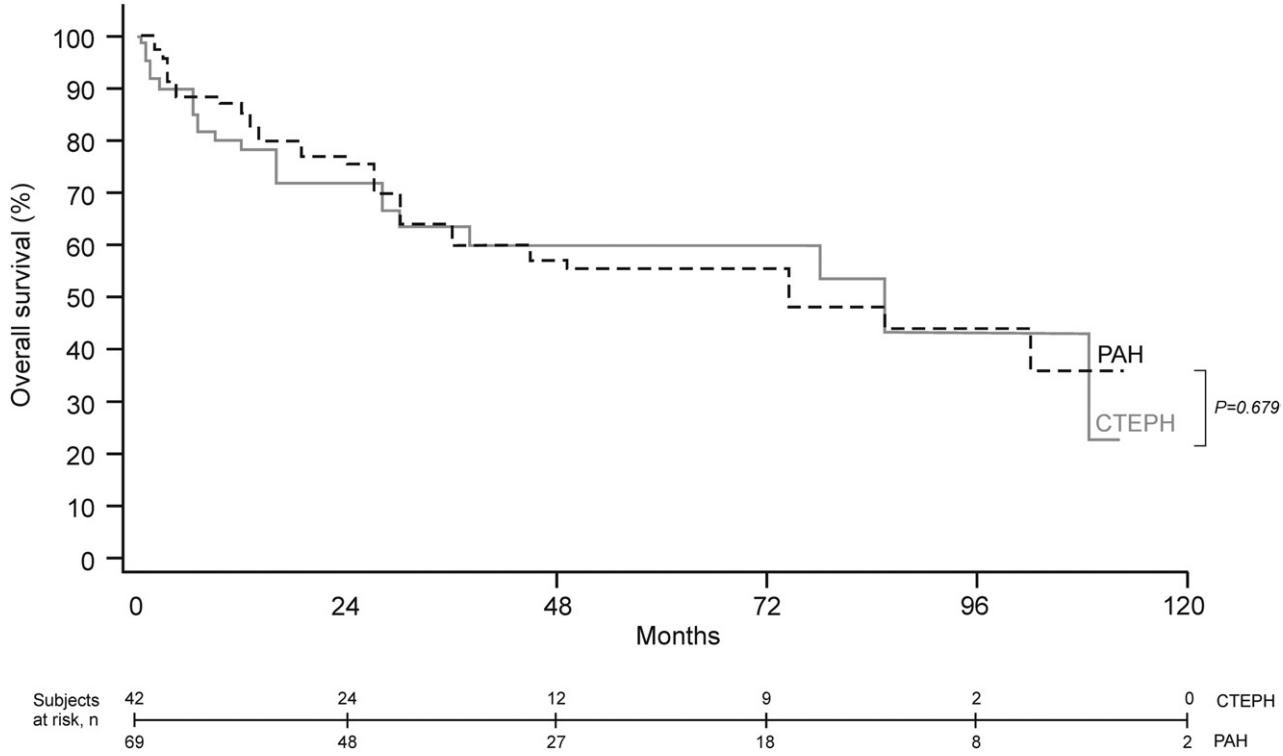

Figure 4 Overall survival rates by disease etiology of chronic thromboembolic pulmonary hypertension (CTEPH) vs pulmonary arterial hypertension (PAH). Kaplan-Meier overall survival rates in CTEPH patients (79%, 60% and 42%; solid line) are compared with PAH patients (86%, 56% and 38%; dashed line; $p = 0.679$, log-rank test) at 1, 5 and 9 years, respectively.

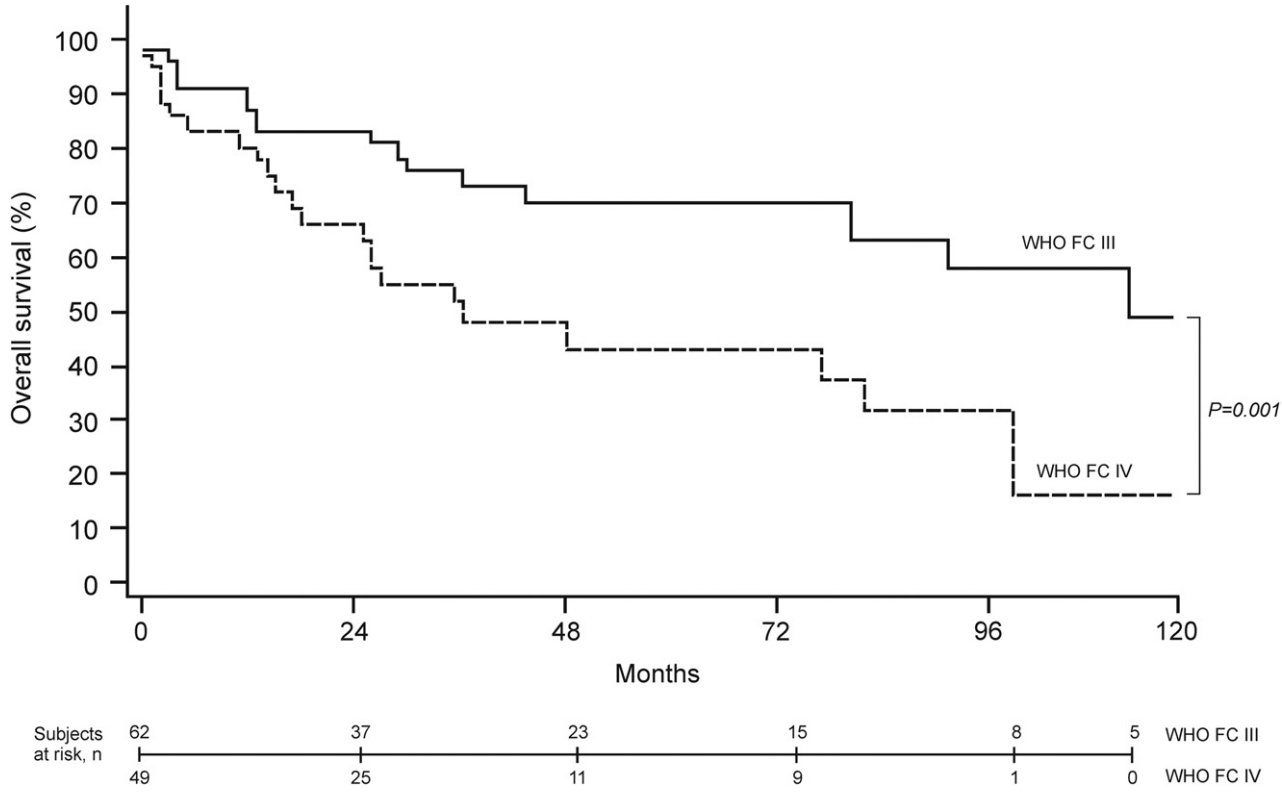

Figure 5 Overall survival rates by World Health Organization functional class (WHO FC). Kaplan-Meier overall survival estimates by baseline WHO FC III (83%, 72% and 59%; solid line) or IV (79%, 41% and 18%; dashed line; $p = 0.001$, log-rank test) at 1, 5 and 9 years, respectively.

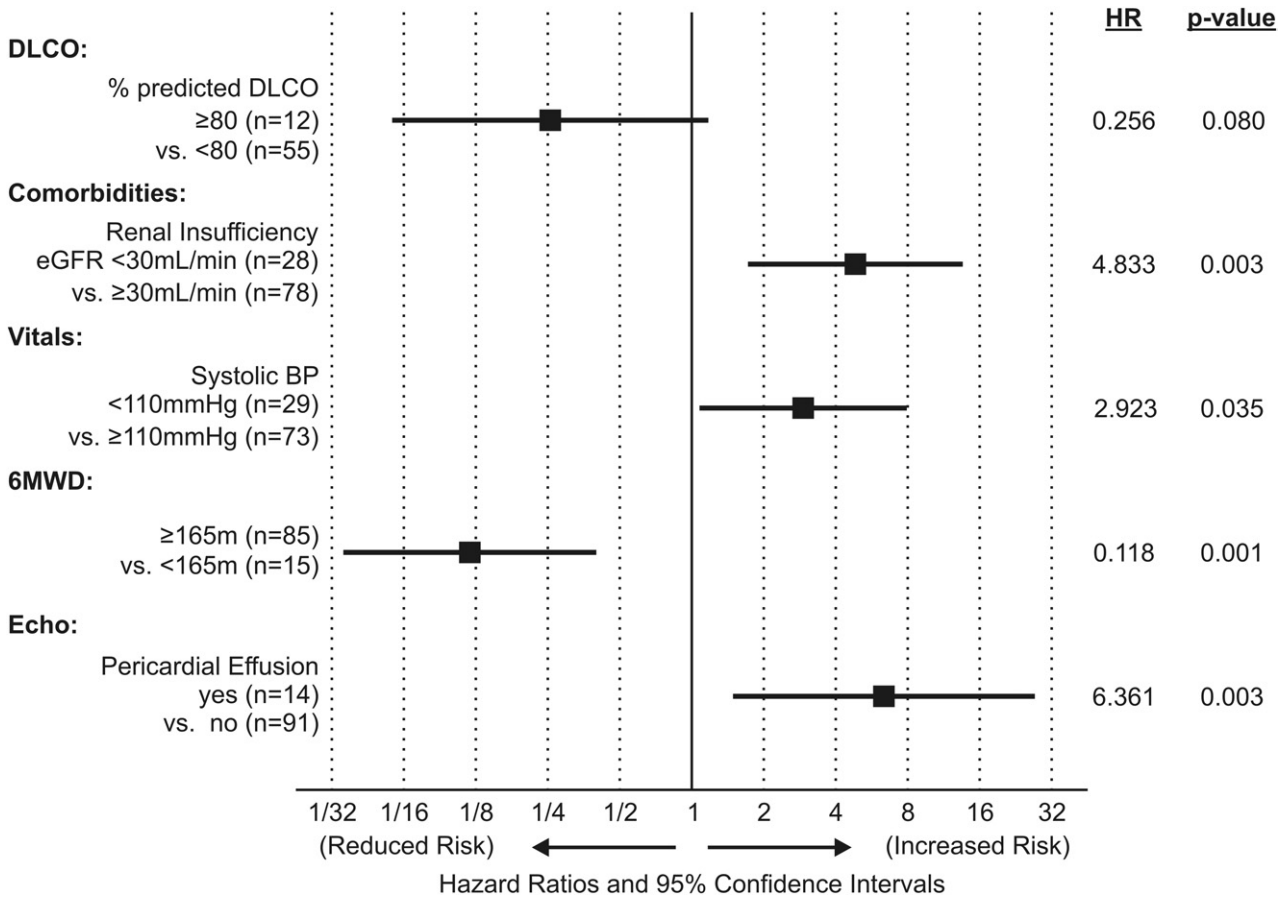

Figure 6 Cox proportional-hazards estimates are shown for multivariable model of survival. 6MWD, 6-minute walking distance; BP, blood pressure; DLCO, diffusion capacity of the lung for carbon monoxide; Echo, echocardiogram; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

($p = 0.001$, log-rank test; Figure 5). Patients with a baseline walking distance $\geq$ 300 meters survived longer than patients with a median baseline 6 MWD $<$ 300 meters ($p = 0.004$ by log-rank test; data not shown).

Outcomes for early terminators

In our center, we allow 6 months for up-titration of SC prostanoids. Ten early terminators (47.6%) were recorded during the first 5 years of the study, and 11 patients (52.4%) discontinued in the second 5-year period. The pattern of dose escalation and early drug termination did not change over the years. Treatment in 21 patients (18.9%) was stopped at a median of 3.3 months (range, 0.5–5 months) for various reasons (Table 1 and Figure 1). Early treatment terminations in 13 patients (11.7%) due to intolerable drug side effects, such as infusion site reaction and infusion site pain, occurred at $<$ 6 months of treatment at a median dose of just 14 ng/kg/min (IQR, 6.25–23.75 ng/kg/min). Of the 21 early terminators, 13 were off-treatment at the time of death (Figure 1).

Baseline predictors of outcome

Systolic blood pressure $<$ 110 mmHg, estimated glomerular filtration rate $<$ 30 mL/min, pericardial effusion, and a 6MWD $<$ 165 meters were negative predictors of outcome (Figure 6). The dose of treprostinil inversely affected overall survival in a Cox model for time-dependent covariates ($p = 0.0034$). Patients who died or received a transplant were characterized by the need for a higher dose since the second year of their treatments (Figure 2).

Treprostinil adverse events

Infusion site reactions were observed in all patients, and 89 patients (80%) reported infusion site pain (Table 3). In 31 patients (27.9%), right heart decompensation required 2.2 hospitalizations per patient (range, 1–5) for intravenous diuretic treatment and/or vasopressors. Twenty-five patients (22.5%) were surviving other adverse events (Table 3). Delivery system complications included primary pump failure and infusion line obstruction and occurred in 4 patients (3.6%). Interruption of medication resulted in sudden-onset dyspnea within 6 hours of the interruption.

Discussion

The ability to conduct large, prospective randomized controlled trials over years with morbidity and death as primary

end points for PH is limited by patient numbers, economic constraints, and ethical constraints to using a placebo. Therefore, all information and evidence leading to novel drug approval have been based on 12- to 24-week studies and their open-label phases. This is a particular shortfall for SC treprostinil, demonstrating a between-treatment group difference in median 6MWD of only 16 meters in the pivotal 12-week study,[11] whereas 6MWD increased by 65 meters from baseline in a subsequent 3-year open-label trial.[16]

The main differences in this registry compared with previously published studies in SC treprostinil were the inclusion of patients with CTEPH and a higher percentage of patients in WHO FC IV (44% in our registry vs 8.0%[11] or 5%[17]), a lower CI (2.0 vs 2.4[11] and 2.2 liters/min/m^2),[17] a low proportion of additional targeted PAH treatments (4.5% in our series vs 15%),[17] and a longer observation time of 10 years compared with 12 weeks[11] or 4 years.[17] Since these publications[11,16–19] it has become clear that SC treprostinil requires up-titration, followed by dose adjustments over time. An average of 6 months is required before an effective and stable dose is reached. For example, the change in 6MWD in the pivotal trial was 10 meters at 12 weeks compared with an absolute increase of 109 meters after 5 years on treatment in our registry. The key strategy for keeping patients on treatment has been minimizing site changes and maintaining sites for a minimum of 4 weeks (range, 4–10 weeks) because the initial pain subsides after ~5 days.

Stable median doses > 37.5 ng/kg/min were achieved in 27 patients (71%) by Year 3 of treatment, in 24 patients (92.3%) by Year 5, and in 20 patients (91%) by Year 6 (Figure 2). The high annual mortality rate in those patients who met the study criteria but did not receive SC treprostinil in a sufficient dose illustrates the overall high attrition rate of patients within this registry.

Still, our data illustrate a very favorable survival rate compared with other contemporary registries. For example, in the recently published REVEAL registry, 2,700 patients receiving various targeted treatments[9] had 1-year survival of 91% with a mean baseline 6MWD of 370 meters, a BDS of 2.9, CI of 2.6 L/min/m^2, and only 5.5% of patients were in New York Heart Association (NYHA) class IV. For comparison, patients in the current registry were 44% in WHO FC IV, had a mean baseline 6MWD of 288 meters, a BDS of 6, CI of 2.1 liters/min/m^2, and reached a 1-year survival of 96% if under treatment for > 6 months. Humbert et al[20] investigated survival in patients with idiopathic, familial, and anorexigen-associated PAH and found a 1-year survival on contemporary treatments of 86%, with only 14% of patients in NYHA class IV.

This study has a few limitations. We have practiced a first-line SC treprostinil strategy in patients with severe PH at our center since 1999, at which time serial BNP levels were not available. We allow 6 months for up-titration and patient adjustment to the therapy and analyzed this majority sub-group of 91 patients (81%) remaining on therapy > 6 months separate from those dropping out earlier.

An important limitation of our database is that dose adjustments were not pre-specified, and the time-dependent dose appeared as a negative predictor of survival, which is in apparent disagreement with recent data suggesting that a treprostinil dose of ≥ 40 ng/kg/min and every 10 ng/kg/min–dose increase resulted in improved long-term survival.[18]

Although the current study was at a single-center, uncontrolled, naturally biased, and involved a small population with PH of various etiologies, the treatment protocol was uniform and sustained over a decade, despite the appearance of oral therapies. The rationale for using vasodilator therapy in CTEPH patients was derived from the observation that CTEPH represents a combination of major-vessel thromboembolic obstruction and a small-vessel disease that resembles classical pulmonary arteriopathy.

The use of a functional collaboration of measures to group patients ("severe PH") is of potential debate, both pro and con. Because treatment of patients with advanced disease aims at maintaining right ventricular function, and survival differences for specific sub-sets have not been demonstrated in advanced stage disease,[21,22] we submit that data derived from a more homogenous population would not be different.

In conclusion, 3 simple messages derived from our data are that:

1. SC treprostinil therapy is safe and improves functional status, exercise capacity, hemodynamics, and survival in patients with PAH and CTEPH. It is essential to up-titrate against a high attrition rate and a 12% drug intolerance rate within the first 6 months, providing high-quality supportive care to the patient.
2. Sustained dose increases are beneficial, and patients who are on treatment beyond the third year have an excellent prognosis.
3. Although an effective dose of SC treprostinil appears to be ~40 ng/kg/min, the higher the dose that is required to maintain a stable condition the worse is prognosis.

Disclosure Statement

R.S.-K. has served as a paid consultant for AOPOrphan Pharmaceuticals AG and has received compensation for scientific symposia from Actelion, GlaxoSmithKline, and AOPOrphan Pharmaceuticals AG. N.S.-S. has served as a paid consultant for Actelion, Nycomed, Pfizer, GlaxoSmithKline, United Therapeutics Corporation, and AOPOrphan Pharmaceuticals AG and has received educational grants and compensations for scientific symposia from Actelion, Nycomed, Pfizer, GSK, United Therapeutics Corporation, and AOPOrphan Pharmaceuticals AG. D.B. has served as a paid consultant for Bayer, Actelion, Nycomed, Pfizer, GlaxoSmithKline, United Therapeutics Corporation, and AOPOrphan Pharmaceuticals AG, and has received educational grants and compensations for scientific symposia from Actelion, Bayer, Nycomed, Pfizer, GSK, United Therapeutics Corporation, and AOPOrphan Pharmaceuticals AG. W.K. has served as a paid consultant to the sponsor,

Table 3 Adverse Events

Adverse event relationship with underlying disease or treatment	No. (%)[a]
Likely	
Infusion site reaction	111 (100)
Infusion site pain	89 (80)
Diarrhea	24 (21.6)
Facial flushing	15 (13.5)
Local abscesses	3 (2.7)
Painful swelling of inguinal lymph nodes	3 (2.7)
Persistent lower limb pain	2 (1.8)
Hospitalizations for IV diuretics and/or vasopressors	31 (27.9)
Unlikely	
Major surgeries	
Urologic surgery	4 (3.6)
Hip replacement	2 (1.8)
Other orthopedic surgeries	2 (1.8)
Aortic valve replacement	1 (0.9)
Hepatic surgery	1 (0.9)
Minor surgeries	16 (14.4)
Cytostatic chemotherapy	1 (0.9)

IV, intravenous.
[a]Number of affected patients of the total number.

Bayer, and Actelion. J.G. is an employee of AOPOrphan Pharmaceuticals AG. I.M.L. has served as a paid consultant to the sponsor, Gilead, Bayer, Actelion, Nycomed, Pfizer, GlaxoSmithKline, Astra Zeneca, Servier, United Therapeutics Corporation, and AOPOrphan Pharmaceuticals AG. I.M.L. is a paid speaker for the sponsor, GlaxoSmithKline, Pfizer, Bayer, and Actelion, United Therapeutics Corporation, and serves on advisory board committees for Actelion, Gilead, Bayer, Nycomed, Pfizer, GlaxoSmithKline, Astra Zeneca, Servier, United Therapeutics Corporation, and AOPOrphan Pharmaceuticals AG.

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