Clinical Investigations

Respiration

Respiration 2016;92:362–370
DOI: 10.1159/000450759

Received: August 13, 2016
Accepted after revision: September 13, 2016
Published online: October 27, 2016

Safety, Tolerability and Clinical Effects of a Rapid Dose Titration of Subcutaneous Treprostinil Therapy in Pulmonary Arterial Hypertension: A Prospective Multi-Centre Trial

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Key Words

Treprostinil · Pulmonary arterial hypertension · Subcutaneous infusion

Abstract

Background: Subcutaneous treprostinil has dose-dependent beneficial effects in patients with severe pulmonary arterial hypertension, but adverse effects like infusion site pain can lead to treatment discontinuation. ***Objectives:*** The objective of this study was to evaluate safety, tolerability and clinical effects of a rapid up-titration dosing regimen of subcutaneous treprostinil using proactive infusion site pain management. ***Methods:*** Effects of rapid up-titration dosing regimen on tolerability and clinical parameters were evaluated in this 16-week, open-label multi-centre study. ***Results:*** Thirty-nine patients with idiopathic or heritable pulmonary arterial hypertension on stable treatment with oral pulmonary arterial hypertension-approved drugs (90% on dual combination therapy) were included. Patients achieved a median treprostinil dosage of 35.7 ng/kg/min after 16 weeks. A good overall safety profile was demonstrated with 3 patients (8%) withdrawing due to infusion site pain, which occurred in 97% of patients. After 16 weeks, median 6-min walking distance, cardiac index, pulmonary vascular resistance, and tricuspid annular plane systolic excursion improved. ***Conclusions:*** Rapid up-titration of subcutaneous treprostinil was well tolerated, achieving a clinically effective dose associated with improvement of exercise capacity and haemodynamics after 16 weeks. A rapid dose titration regimen and proactive infusion site pain management may improve the handling of this therapy and contribute to better treatment outcome.

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0025–7931/16/0926–0362$39.50/0

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Introduction

Pulmonary arterial hypertension (PAH) is a rare, life-threatening condition that is characterised by a progressive increase in pulmonary vascular resistance (PVR), resulting in chronic right heart failure and premature death. The loss of endogenous prostacyclin plays an important role in the pathogenesis of PAH. Prostacyclin has vasodilatory, anti-proliferative, anti-inflammatory and antithrombotic properties and is therefore an important target substance in PAH-specific therapy [1]. Epoprostenol was the first specific therapy approved for the treatment of PAH, after showing a positive effect on survival [2]. Epoprostenol is chemically unstable with a short biological half-life of 3–5 min, and must be continuously administered by intravenous (IV) infusion using an external pump and indwelling central venous catheter.

Treprostinil, which can be administered by either subcutaneous (SC) or IV infusion, has improved stability with a terminal elimination half-life of ~4 h [3]. A permanent central venous catheter can be avoided by using SC therapy. The medication is continuously administered via a micro-infusion pump using a small-bore catheter and SC cannula which can be self-inserted by the patient. Treatment with SC treprostinil has been shown to improve exercise capacity, symptoms and haemodynamics in patients with PAH in a dose-dependent manner [4], and may improve long-term outcome [5–7]. Local adverse reactions, including infusion site pain, mild bleeding and swelling, can lead to discontinuation of treatment [5, 6] and may cause a slow and reluctant dose titration, prolonging the time until treatment is clinically effective. There is, however, no apparent correlation between local adverse reactions and treprostinil dose rate [3, 8]. By contrast, rapid dose escalation has been reported to cause less frequent site pain (58 vs. 82%, $p = 0.04$) and a significantly greater improvement of 6-min walk distance (6MWD; $p = 0.03$) compared with slow dose escalation [3]. Treprostinil dose rate has also been found to be an independent prognostic on-treatment predictor of survival in a retrospective analysis of 811 patients treated with SC treprostinil [9]. A slow dose titration is therefore a potential cause of sub-therapeutic dosages [10], which may provoke premature discontinuation of treatment. A thorough medical management of SC treprostinil therapy, including multidisciplinary patient support and proactive infusion site pain management, is necessary to achieve a clinically effective dosing regimen [10]. Importantly, infusion site pain can be minimised by avoidance of infusion site replacement until clinically indicated. A rapid treatment initiation of epoprostenol has already been shown to significantly improve haemodynamics and clinical outcome compared to a slow titration regimen [11, 12].

Up to now, a rapid dosing regimen of treprostinil has only been investigated in a small group of 12 patients [3]. It is not clear whether this regimen, together with a proactive approach to infusion site pain management, can be well tolerated and effective in a larger patient cohort. Therefore, the aim of this study was to investigate prospectively the safety and tolerability of a rapid dose titration regimen together with proactive infusion site management of SC treprostinil in a larger cohort of patients with severe PAH. Furthermore, the clinical effects after a treatment period of 16 weeks were to be evaluated.

Materials and Methods

Study Design

This was an open-label, single-territory, multi-centre study designed to evaluate the safety, tolerability and clinical effects of a rapid dose titration regimen of SC treprostinil in subjects with severe PAH.

Patients/Setting

Subjects were either treatment naïve or receiving an approved endothelin receptor antagonist (ERA) and/or an approved phosphodiesterase (PDE)-5 inhibitor for at least 60 days and maintained on a stable dose for at least 30 days prior to providing informed consent. Thirty-nine patients were enrolled across 10 centres throughout Germany from 16 April 2012 to 20 March 2014 to ensure a minimum of 30 completing patients [6]. Thirty completing patients were believed to be the minimum requirement to show tolerance to the rapid titration regimen. The main entry criteria for the study are summarised in table 1.

Enrolment and Treprostinil Treatment

SC treprostinil was initiated on an in-patient basis (minimum of 72 h) and under medical supervision at approximately 2 ng/kg/min with dose increments of 1–2 ng/kg/min approximately every 12 h according to tolerability. The length of hospital stay was determined by subject competency to administer SC treprostinil using a micro-infusion pump (Crono 5; Canè Medical Technology), coupled with either the Cleo (Smiths Medical) or Quickset (Medtronic) infusion set. The SC infusion cannula remained in situ for as long as clinically appropriate because infusion site pain has been shown to diminish over ~5 days following the insertion of each new cannula [7]. To avoid regular insertion site changes, site pain was managed by proactive application of topical and systemic analgesics, and patients were taught how to maintain a sterile site.

Following discharge from hospital, dose increases of 1–2 ng/kg/min were permitted every 24 h. Once a dose rate of 20 ng/kg/min had been achieved, the dose increments could be up to 4 ng/kg/min separated by at least 24 h based on tolerability. The aim was to achieve a target dose of 10, 20 and 30 ng/kg/min by the end of weeks 1, 4 and 12, respectively, and a dose rate by the end of 16 weeks that achieved and maintained the pre-defined treatment goals, as follows:

Table 1. Main inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1 Minimum 18 years of age and written informed consent	1 Pregnant or lactating
2 Weight at least 40 kg and body mass index less than 40	2 Received epoprostenol, treprostinil, IV iloprost, or beraprost within 30 days prior to screening[a]
3 Using two effective forms of contraception required for females, and males to use a condom throughout the study and for 64 days following treatment cessation	3 Previous intolerance or significant lack of efficacy to treatment with prostacyclin or prostacyclin analogues
4 Diagnosed with symptomatic idiopathic or heritable PAH	4 Any disease associated with pulmonary hypertension or an atrial septostomy
5 6MWD at least 150 and no more than 550 m	5 WHO-FC IV
6 Treatment naïve or receiving an approved PDE-5 inhibitor and/or an approved ERA for at least 60 days and on a stable dose for at least 30 days prior to screening	6 Uncontrolled sleep apnoea
7 Optimally treated with conventional pulmonary hypertension therapy with no changes for at least 14 days prior to screening	7 AST and ALT more than 3 times the upper limit of the laboratory reference range and/or an international normalised ratio more than 3 units at screening
8 Right heart catheterisation conducted within 8 weeks prior to or during the screening period with: a Mean pulmonary artery pressure at least 25 mm Hg b Pulmonary capillary wedge pressure (PCWP) no more than 15 mm Hg c PVR more than 3 Wood units[b]	8 Clinically significant bleeding episode within the previous 6 months, or any other condition that would either jeopardise subject safety and/or interfere with interpretation of assessments
9 Echocardiography with evidence of clinically normal left ventricular function, absence of left-sided heart disease and unrepaired congenital heart disease	9 History of ischaemic heart disease within the previous 6 months of screening, or history of left-sided myocardial disease as evidenced by a PCWP greater than 15 mm Hg or left ventricular ejection fraction less than 40%
10 Ventilation perfusion lung scan, high-resolution computerised tomography scan of the chest and/or pulmonary angiography consistent with the diagnosis of PAH	10 Uncontrolled systemic hypertension as evidenced by: a Systolic blood pressure above 160 mm Hg b Diastolic blood pressure above 100 mm Hg
11 Pulmonary function tests conducted within previous 9 months demonstrating: a Total lung capacity at least 60% b FEV_1/FVC ratio at least 50%	11 Musculoskeletal disorder or other disease that would limit ambulation or was connected to a machine that was not portable
	12 Unstable psychiatric condition or any condition which would constitute an unacceptable risk to subject safety
	13 Any investigational drug, investigational device in place or participation in an investigational study 30 days prior to screening

Entry criteria taken from the latest protocol version. [a] Subjects who had administered inhaled prostacyclins prior to entry were now permitted provided usage ceased prior to enrolment. Due to the short wash-out period of these agents, their use prior to study enrolment was believed to have no impact on efficacy outcomes of the study. [b] Study-defined timelines for pre-screening right heart catheter was extended from 4 to 8 weeks. Little or no change in parameters was expected over this extended period, and this timeline was believed to be more ethical for study subjects.

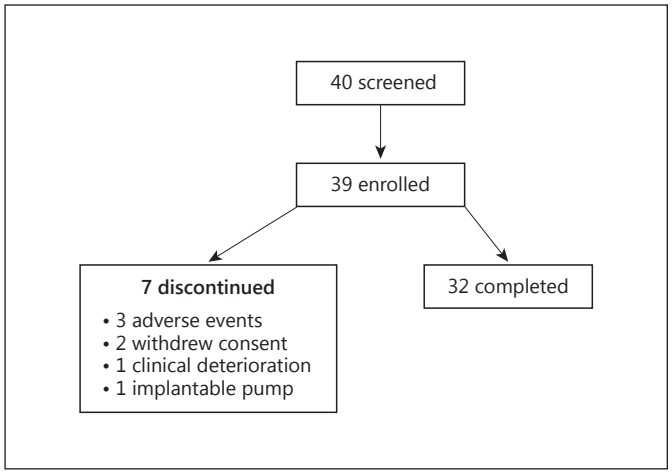

Fig. 1. Flowchart of study patients.

1 World Health Organisation (WHO) functional class (FC) II
2 6MWD greater than 400 m (or increase of more than 30 m if baseline 6MWD was greater than 400 m or if 400 m could not be reached)
3 Tricuspid annular plane systolic excursion (TAPSE) as measured by echocardiography greater than 2 cm. Patients achieving one or more goals were considered to be treatment responders.

Outcome Measures and Safety

The primary objective to evaluate safety and tolerability was assessed throughout the study by monitoring adverse events (AEs), vital signs, severity of PAH symptoms (including fatigue, dyspnoea, oedema, dizziness, syncope, chest pain and orthopnoea) and physical examination. Overall tolerability of the rapid up-titration regimen was quantified by assessing the number of subjects who remained on treprostinil therapy for 16 weeks without experiencing a treprostinil-related serious AE (SAE).

The secondary efficacy endpoints included the changes from baseline to week 16 in exercise capacity (assessed using the 6MWD [13] and the Borg dyspnoea score), N-terminal pro-brain natriuretic peptide (NT pro-BNP) plasma concentration, WHO-FC, TAPSE and tricuspid regurgitant jet velocity (TRJV) (assessed by echocardiography), symptoms of PAH, and cardiopulmonary haemodynamics measured by right heart catheterisation (RHC). Subject quality of life was assessed using the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) questionnaire.

Statistical Analysis

The study population was defined as all subjects enrolled into the study. In general, the data were summarised by scheduled assessment. For continuous variables, the summary statistics included the mean, standard deviation, standard error, median, lower and upper quartile, and minimum and maximum values. For the purposes of describing the difference between baseline and follow-up assessments, p values from Wilcoxon signed-rank test (for continuous variables) were included, but were not intended to test formal hypotheses. All values that were missing or deemed unknown were omitted from any analysis. No pre-defined co-variates were used in the analysis of the data.

Table 2. Summary of demographic and other baseline characteristics

Baseline parameter	Baseline value/ number (n = 39)
Age, years	
Mean (median)	52.7 (50)
Range	25–82
Gender, n (%)	
Female	29 (74.4)
Male	10 (25.6)
PAH aetiology, n (%)	
Idiopathic/heritable	39 (100)
Background oral PAH therapy, n (%)	
None	1 (2.6)
ERA only	1 (2.6)
PDE-5 inhibitor only	2 (5.1)
ERA and PDE-5 inhibitor	35 (89.7)
Baseline 6MWD, m	
Mean ± SD	355±93.1
Range	163.0–547.0
Median (Q1, Q3)	352 (288.0, 423.0)
Borg dyspnoea score (1–10)	
Mean ± SD	4.5±1.9
Median (Q1, Q3)	5.0 (3.0, 6.0)
WHO-FC, n (%)	
II	6 (15.4)
III	33 (84.6)

6MWD = Six-min walk distance; ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase-5; SD = standard deviation; WHO = World Health Organization; Q1 = first quartile; Q3 = third quartile.

Ethical Standards

The study was conducted in compliance with Good Clinical Practice guidelines and in accordance with the principles defined in the amended Declaration of Helsinki. The protocol was approved by the German regulatory authority (BfArM) and the central and local ethics committees of the Universities of Heidelberg, Cologne, Dresden, Regensburg, Leipzig, Munich and Saarbrucken, and of the medical council Hamburg, Munich and Dusseldorf. Written informed consent was obtained from all subjects prior to the conduct of any study-specific activities.

Results

Baseline Characteristics and Patient Disposition

Patient disposition and baseline demographics are summarised in figure 1 and table 2, respectively. A total of 40 subjects were screened for the study. Thirty-nine

Table 3. AEs experienced by at least 20% of patients

Preferred term	Subjects, n (%) (n = 39)	Events, n
Any adverse event	39 (100)	374
Infusion site pain	38 (97.4)	39
Diarrhoea	30 (76.9)	30
Headache	27 (69.2)	29
Nausea	20 (51.3)	20
Vomiting	15 (38.5)	16
Infusion site erythema	10 (25.6)	10
Dyspnoea	9 (23.1)	9
Pain in jaw	9 (23.1)	9
Dizziness	8 (20.5)	8
Vertigo	8 (20.5)	8

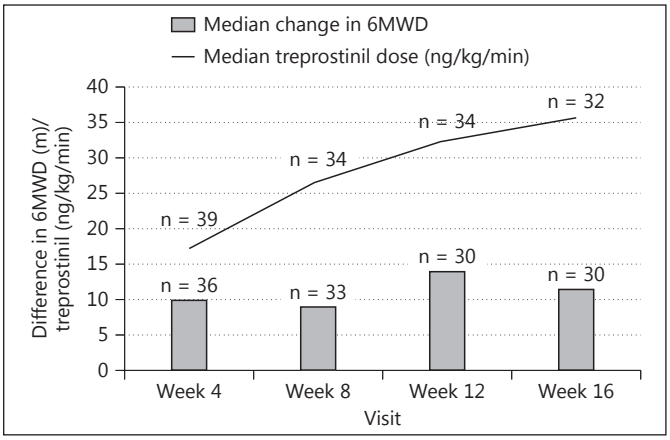

Fig. 2. Change of median 6MWD and treprostinil dosage throughout the study.

subjects fulfilled the entry criteria and were enrolled and commenced on SC treprostinil therapy. Seven subjects (18%) prematurely terminated the study before completion of the 16-week treatment period: 3 withdrew due to treatment-related AEs (infusion site pain, diarrhoea and nausea), 2 withdrew consent, 1 discontinued due to clinical deterioration, and 1 subject transitioned to IV treprostinil and was withdrawn from the study.

The proportion of female subjects (74%) was almost three times that of the males (26%) enrolled. Thirty-five subjects (90%) were on dual oral background therapy (PDE-5 inhibitor and ERA), 3 subjects were on monotherapy (2 subjects on a PDE-5 inhibitor, 1 on an ERA) and 1 subject was treatment naïve. The median baseline 6MWD was 352 m with a median Borg dyspnoea score of 5.0. The majority of subjects (33/39; 85%) were in WHO-FC III, with the remainder (6/39; 15%) in WHO-FC II.

Primary Objective: Safety and Tolerability

AEs experienced by at least 20% of the patients are outlined in table 3. A total of 374 AEs were recorded. All subjects experienced at least one event during the study. The most frequently recorded AE reported by 38/39 subjects (97%) was infusion site pain. Infusion site pain was reasonably well tolerated, and was associated with study drug discontinuation in only 3 (8%) subjects. In general, AEs were well tolerated, with symptomatic treatments prescribed at the discretion of the investigators. Opioids were prescribed 35 times in the form of oral treatment, including morphine on five occasions. Mainly hydromorphone and oxycodone were used. Most of the patients received non-steroidal analgesics (e.g., ibuprofen, paracetamol, diclofenac). There were 27 SAEs reported by 11/39 subjects (28%). Thirteen SAEs, which occurred in 7/39 subjects (18%), were considered to be related to treprostinil. Three of those related SAEs, diarrhoea, nausea and infusion site pain, occurred in more than 1 subject.

Secondary Objective: Efficacy

Exercise Capacity

Table 4 provides a summary of the median 6MWD together with the median dose of treprostinil achieved by all patients remaining on therapy at each time point. The effects seen during the treatment period are illustrated in figure 2. The results of the Wilcoxon signed-rank test indicate that the week 12 and week 16 6MWD ranks were statistically significantly higher than the baseline 6MWD ranks ($p = 0.0409$ and $p = 0.0086$, respectively). Median changes from baseline of 14.0 and 11.5 m were observed at weeks 12 and 16, respectively. This indicates that there was an improvement in exercise capacity for the 32 subjects (82%) who were able to tolerate the rapid up-titration of SC treprostinil therapy to 30 ng/kg/min and completed the 16-week treatment period. The targeted dosage of at least 30 ng/kg/min was achieved by 25 (78%) of the 32 patients who completed the 16-week treatment period of the study.

Other Clinical Parameters

There were beneficial and statistically significant changes in other important clinical parameters assessed during the 16-week treatment period (table 5). A median change from baseline in plasma NT pro-BNP of –182 pg/

Table 4. Summary of 6MWD and treprostinil dose rate achieved during the study

Visit	Week 4 (n = 36)	Week 8 (n = 33)	Week 12 (n = 30)	Week 16 (n = 30)
Median baseline 6MWD, m	353	352	348	351
Q1	291	294	288	294
Q3	427	420	423	420
Median visit 6MWD, m	395	360	402	419
Q1	297	300	320	309
Q3	460	453	462	468
Median change in 6MWD from baseline, m	10	9	14	11.5
p value	0.0113	0.2368	0.0409	0.0086
Treprostinil dose rate, ng/kg/min				
Median	17.2	26.8	32.6	35.7
Q1	14.5	22.5	27.0	31.1
Q3	22.4	30.7	36.2	41.0
Patients, n[a]	39	34	34	32

6MWD = Six-min walk distance; Q1 = first quartile; Q3 = third quartile. [a] Number of patients completing the given assessment at the visit outlined.

ml, and an improvement in WHO-FC at week 16 compared to baseline in 25% of subjects was observed. Only 2 patients (6.3%) worsened, one from WHO-FC II to III, and the other from WHO-FC III to IV. Median changes from baseline in the cardiac index of 0.3 l/min/m^2 ($p < 0.0001$) and PAPm of –4.0 mm Hg were associated with a median change from baseline in PVR index of –2.7 mm Hg/min/m^2/l ($p < 0.0001$), suggesting an overall improvement in cardiopulmonary haemodynamics. This was further supported by median changes from baseline to week 16 of 0.1 cm and –0.3 m/sec in the TAPSE and TRJV, respectively, which are consistent with an improvement in right ventricular performance. After 16 weeks, there was a significant improvement in patient outcome assessed by the CAMPHOR questionnaire ($p = 0.0040$), which could also be seen in a significant improvement of the two subscales, Symptoms ($p = 0.0105$) and Activity ($p = 0.0094$). The CAMPHOR subscale score 'quality of life' also improved, although this was not statistically significant ($p = 0.0845$). There was no clear change in the severity of PAH symptoms recorded during the study. However, the overall effects observed during the study indicate that a rapid up-titration dosing regimen for SC treprostinil therapy administered to subjects with severe PAH can improve exercise capacity, functional performance and cardiopulmonary haemodynamics.

Treatment Goals

Analysis of the pre-defined, protocol-specified treatment goals achieved by those patients who remained on treprostinil therapy for the 16-week treatment period of the study is summarised in table 6. The number of patients who achieved each of the individual criteria is shown together with the number of patients that met multiple goals. In line with the criteria for defining a treatment responder, a total of 20/39 (51%) of the enrolled subjects achieved at least one pre-defined treatment goal on SC treprostinil therapy when administered in accordance with the rapid up-titration dosing regimen. In 18 of the 20 aforementioned patients, achievement of treatment goals was due to improvement of clinical parameters during the study: the remaining 2 subjects remained WHO-FC II from baseline through to week 16.

Discussion

To the best of our knowledge, this is the first prospective multicentre study investigating the effect of rapid dose titration of SC treprostinil, together with a proactive approach to infusion site management and RHC performed at baseline and after 16 weeks. Rapid dose titration was generally well tolerated and led to a clinically effective dosage, as demonstrated by an improvement in exercise capacity and haemodynamics during the 16-week study period. A rapid dose titration and proactive infusion site management may therefore improve the management of this therapy and contribute to an improved treatment outcome.

Clinically effective dosages could be reached by rapid dose titration and were generally tolerable. Compared to the rapid dose titration scheme used by Skoro-Sajer et al. [3], the mean dosages achieved after 4, 8 and 12 weeks were considerably higher in this study, with 32.0 com-

Table 5. Summary of changes in clinical assessments from baseline

Parameter	Baseline	Week 16	Change from baseline	p value
Borg dyspnoea score (1–10)				
Median	5.0	3.5	0.0	0.1937
Q1	3.0	3.0	–1.0	
Q3	6.0	5.0	0.5	
Patients, n	39	30[a]		
WHO-FC, n (%)				
II	6 (15.4)	12 (30.8)	II–II: 4 (12.5)	n.a.
III	33 (84.6)	19 (48.7)	II–III: 1 (3.1)	
IV	0 (0)	1 (3)	III–II: 8 (25.0)	
			III–III: 18 (56.3)	
			III–IV: 1 (3.1)	
Patients, n	39	32[a]	32	
NT pro-BNP, pg/ml (n = 32)				
Median	999	702	–182	0.0081
Q1	522	376	–985	
Q3	2,538	1,377	51	
Haemodynamics				
PAPm, mm Hg (n = 29)[a]				
Median	52.0	49.0	–4.0	0.1115
Q1	47	44	–10	
Q3	62	60	1	
Cardiac index, l/min/m^2 (n = 29)[a]				
Median	2.2	2.6	0.3	<0.0001
Q1	2	2	0	
Q3	3	3	1	
PVRI, mm Hg/min/m^2/l (n = 29)[a]				
Median	20.7	16.3	–2.7	<0.0001
Q1	16	12	–6	
Q3	25	22	–1	
SVRI, mm Hg/min/m^2/l (n = 25)[a]				
Median	36.1	29.7	–5.5	<0.0001
Q1	31	25	–8	
Q3	42	36	–2	
Echocardiography				
TAPSE, cm				
Median	1.6	1.8	0.1	0.0174
Q1	1.4	1.6	0.0	
Q3	1.9	2.0	0.3	
Patients, n	39	31[a]		
TRJV, m/s				
Median	4.40	3.90	–0.3	0.0068
Q1	4.00	3.40	–0.6	
Q3	4.74	4.53	0.1	
Patients, n	38	27[a]		

WHO = World Health Organisation; NT pro-BNP = N-terminal pro-brain natriuretic peptide; PAPm = mean pulmonary artery pressure; PVRI = pulmonary vascular resistance index; SVRI = systemic vascular resistance index; TAPSE = tricuspid annular plane systolic excursion; TRJV = tricuspid regurgitant jet velocity.

[a] Number of patients completing each assessment at week 16.

Table 6. Treatment goals achieved at the end of the study (n = 39)

	Subjects, n (%)
Treatment goal	
Completed 16-week treatment period	32 (82)
WHO-FC II	12 (31)[a]
6MWD greater than 400 m	11 (28)[b]
TAPSE greater than 2 cm	6 (15)[c]
Number of treatment goals achieved	
0	19 (49)
1 or more goals	20 (51)
1	12 (31)
2	7 (18)
3	1 (3)

[a] Four subjects were WHO-FC II at baseline and remained WHO-FC II at week 16, [b] Three subjects had a baseline walk greater than 400 m, all increased by more than 30 m at week 16, [c] Two subjects had a TAPSE of greater than 2 cm at baseline and retained a value of greater than 2 cm at week 16.

pared to 20.3 ng/kg/min after 12 weeks. AEs, especially infusion site pain, did not differ substantially from previous studies, even though higher dosages were achieved within the 16-week study period.

Infusion site pain occurred in 97% of the patients, which is comparable to the rate reported by Barst et al. [6], but higher than the rate of 82% that was detected by Lang et al. [5] and by Skoro-Sajer et al. [3]. In our patient cohort, the finding of a significantly lower incidence (58%) of infusion site pain when using a rapid dose titration regimen [3] was not confirmed. The study by Skoro-Sajer et al. [3] only included 12 patients performing rapid dose titration, which may have limited the reliability of the results. In addition, only site pain experienced by patients from Vienna was systematically assessed by a visual analogue scale, which may have led to less frequent reporting of site pain compared to a systematic assessment in all of our study patients. Furthermore, in up to 20% of patients investigated by Skoro-Sajer et al. [3], infusion site pain required drug interruption. In our patient cohort, only 8% of patients discontinued treatment due to infusion site pain, which is comparable to the frequency of discontinuation due to site pain reported by Barst et al. [6]. In that study, out of a cohort of 860 patients, 196 discontinued treatment due to infusion site pain (23%) during a mean duration of exposure of 2.6 ± 0.8 years. Within the first 6 months, 50% of the patients who discontinued due to site pain had already stopped treatment and had a comparable dropout rate to our cohort after 16 weeks of treatment [6]. Different pain treatments, including local/topical options and systemic analgesics, are available and may be used for different intensities of infusion site pain [10]. In our cohort, mostly non-opioid an-

algesics were used. However, opioids were also prescribed on 35 occasions throughout the study, including morphine in 5 cases. Up to now, little is known about the best point in time that pain treatment should begin. Whether a prophylactic pain management regimen that coincides with the start of the infusion may influence the intensity of infusion site pain and the overall tolerability of the treatment remains to be investigated. Other side effects included systemic adverse reactions typical of those associated with prostacyclin use, such as diarrhoea, headache, nausea and vomiting.

Our study results are consistent with previous reports of clinical improvements in 6MWD [4, 5, 14] and haemodynamics [4] measured by RHC with a significant improvement of cardiac index and reduction of PVR. More than half of the patients in our cohort (51%) were considered to be treatment responders who achieved at least one of the pre-defined treatment goals at the end of the study period. Out of 20 patients showing a treatment response, 18 improved until the end of the 16-week study period to reach at least one treatment goal, whilst 2 remained stable from baseline. It is important to recall that these subjects had severe PAH, with 85% in WHO-FC III at baseline. Furthermore, the majority of patients enrolled (90%) were established on dual oral background therapy, and the additional treatment response following 16 weeks of SC treprostinil indicates the effectiveness of a triple combination intervention. As early treatment for PAH improves long-term outcomes, the impact of such a triple therapy combination targeting the individual therapeutic targets of vascular pathology merits further investigation.

The main limitations of our study are the small sample size and the study duration of 16 weeks. The patients of our study cohort were hospitalised for at least 72 h for the initial up-titration phase every 12 h. However, we assume that rapid, patient-triggered up-titration may also be feasible in an ambulatory setting.

As this study was intended to investigate the safety and tolerability of a rapid dose titration regimen, the main focus was on the titration phase. Thus, a long-term follow-up was not performed. As the titration phase occurs principally during the first 3–4 months of treatment, the study allowed evaluation of safety and tolerability over the most crucial time period. Patients are more likely to discontinue SC treprostinil during the initiation of therapy [6]. All patients who completed the 16-week study period tolerated SC treprostinil well. Therefore, a significant deviation from discontinuation rates due to medication intolerance already reported in the literature is not expected.

A further option to avoid SC infusion site pain and minimise the risk of blood stream infections associated with the presence of an in-dwelling central venous catheter is to deliver IV treprostinil via an implanted infusion pump device, which has been successfully used both in neurology for intrathecal or epidural therapy and for the treatment of patients with PAH [15–17]. The application, safety and tolerability of implantable pumps for IV treprostinil therapy in PAH patients is currently being investigated.

Conclusion

Though many new agents have been developed for disease-specific therapy of PAH, prostanoids remain one of the most potent treatment options associated with improvement of exercise capacity, PAH symptoms and cardiopulmonary haemodynamics. In this study, rapid dose titration led to earlier attainment of clinically effective dosages of SC treprostinil than is usually achieved during the titration phase, as described by the current European labelling for treprostinil [18]. In combination with a proactive approach to infusion site pain management, an accelerated titration scheme can be well tolerated, whilst more rapidly improving exercise capacity and haemodynamics in patients with severe PAH already established on dual oral background therapy. A rapid dose titration regimen together with proactive infusion site pain management may therefore improve the management of this therapy and contribute to a better treatment outcome.

Acknowledgements

The study was funded by United Therapeutics Limited.

Financial Disclosure and Conflicts of Interest

E.G. reports research grants to his institution from United Therapeutics during the conduct of the study; received speaker fees and honoraria as advisory board member from Bayer, Actelion, GSK and United Therapeutics.

N.B. reports research grants to her institution from United Therapeutics during the conduct of the study; received speaker fees from Bayer and Actelion.

T.J.L. reports grants and non-financial support from United Therapeutics during the conduct of the study; personal fees and non-financial support from Actelion, personal fees and non-financial support from Bayer, personal fees and non-financial support from GlaxoSmithKline, personal fees and non-financial support

from Pfizer, personal fees from United Therapeutics, outside the submitted work.

U.K. reports research grants to his institution from United Therapeutics during the conduct of the study.

H.K. reports research grants to his institution from United Therapeutics during the conduct of the study; reports personal fees from Pfizer, grants and personal fees from GSK, personal fees from Bayer, personal fees from United Therapeutics, grants and personal fees from Actelion, outside the submitted work.

C.N. reports research grants to his institution from United Therapeutics during the conduct of the study.

H.W. reports study fees from United Therapeutics during the conduct of the study; grants and personal fees from Actelion, personal fees from Bayer, personal fees from GSK, personal fees from Pfizer, personal fees from Biotest, personal fees from Roche, outside the submitted work.

M.H. reports grants from Actelion, honoraria for lectures from Actelion, Bayer Healthcare, Berlin Chemie, Boehringer Ingelheim, GSK, Novartis, Pfizer, honoraria for advisory board activities from Actelion, Bayer Healthcare, GSK, during the conduct of the study; and participation in clinical trials of Actelion, Bayer, GSK, Pfizer, United Therapeutics.

H.-J.S. reports personal fees from Actelion Deutschland GmbH and personal fees from GlaxoSmithKline GmbH & Co KG, outside the submitted work.

M.H. reports research grants to his institution from United Therapeutics during the conduct of the study; reports personal fees for lectures and for advisory board activity and congress travel support from Actelion, AstraZeneca, Bayer, GlaxoSmithKline, Pfizer and Novartis outside the submitted work.

A.T. is an employee of the sponsor.

M.P. was an employee of the sponsor during the conduct of the study.

R.G. is an employee of the sponsor.

B.E. has nothing to disclose.

F.G. reports research grants to his institution from United Therapeutics during the conduct of the study; he has received remunerations for lectures and advisory boards from Actelion, Bayer and GSK His institution has received research grants from Actelion, Bayer, Novartis, Pfizer and United Therapeutics.

T.V. received honoraria for lectures from Actelion, GSK, UT, Vifor, Bayer; grants for participation in clinical trials from Bayer, UT, Actelion, GSK, and is an employee of Bayer.

S.R. reports research grants to his institution from United Therapeutics during the conduct of the study; he has received remunerations for lectures and advisory boards from Actelion, Bayer, Gilead, GSK, Novartis, Pfizer and United Therapeutics. His institution has received research grants from Actelion, Bayer, Novartis, Pfizer and United Therapeutics.

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