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Safety, efficacy and Management of subcutaneous treprostinil infusions in the treatment of severe pediatric pulmonary hypertension

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ABSTRACT

Background: Continuous intravenous epoprostenol was the first treatment approved for pulmonary arterial hypertension (PAH) but administration through a central venous line carries risks of thrombosis and sepsis, particularly in children. We sought to evaluate the safety, efficacy and management of subcutaneous (SC) treprostinil in children with PAH.
Methods: Fifty-six children (median age 65, range 1–200 months) were treated with SC treprostinil. Clinical status, echocardiography, NT-proBNP, and site pain and infection were evaluated. Right heart catheterization was performed in 54 patients before starting SC treprostinil infusion and was repeated at 6 months in 31 patients.
Results: Treatment was well tolerated in 79% of patients. Site pain resistant to simple analgesics occurred in 12 patients (21%), but could be managed in 9/12 children. At 6 months, 3 patients had died, 4 had received a Potts shunt and 1 underwent lung transplantation. Among the 48 treated patients, 40 (83%) showed significant improvement in WHO functional class, 6 minute walk distance, NT-proBNP and pulmonary vascular resistance ($p < 0.01$ for all parameters). At last follow-up (median 37 months), ten patients had died, 2 underwent a lung transplantation and 8 underwent a Potts shunt. In 30 of the 36 remaining treated patients, improvement of clinical status was sustained. No children developed sepsis and 12 had minor site infections.
Conclusion: Subcutaneous treprostinil infusion is an effective therapy without serious side effects in children with PAH. Site pain can be managed with simple analgesics in most children.

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1. Introduction

Pulmonary arterial hypertension (PAH) is a life-threatening disease characterized by progressive pulmonary vasculopathy [1]. Severe PAH is treated with epoprostenol continuously infused through a central venous catheter [2–6]. In infants and children, complications of long-term intravenous infusions have been reported in up to 60% of patients [7,8]. Frequent inhalations, bronchoconstriction, inadequate fluctuating blood levels and the inability of young children to coordinate the use of the delivery device limit use of inhaled prostanoids [9]. Subcutaneous treprostinil results in equipotent drug levels as intravenous drug delivery [10–12]. The major drawback of SC treprostinil therapy has been infusion site pain. Changes in the management of SC trepostinil therapy have resulted in a renewed interest in SC therapy [13,14]. There remains a paucity of information to inform the management of continuous SC treprostinil infusions in infants and children despite recent favorable single center case series reports [13–16]. Therefore, we sought to describe the efficacy, tolerability and clinical management from a multicenter review of children treated with continuous SC treprostinil infusions.

2. Methods

We undertook a four-center retrospective cohort study conducted with Research Ethics Board approval. We reviewed all available clinical, echocardiographic and hemodynamic data on children with PAH who were treated with a continuous SC infusion of treprostinil between 2009 and 16.

We defined pulmonary arterial hypertension as a mean pulmonary arterial pressure ≥25 mm Hg and a pulmonary arterial wedge pressure <15 mm Hg according to internationally defined criteria for children [17].

Abbreviations: ERA, endothelin receptor antagonist; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; PDE, phosphodiesterase; SC, subcutaneous; 6MWT, 6-minute walk test.

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2.1. Patient characteristics

We diagnosed 23 patients with idiopathic PAH, 13 with heritable PAH (4 BMPR2 mutation, 3 TBX4 mutation, 2 ALK1 mutation, one EIF2KF4 and 3 familial PAH without known mutation), 20 patients with PAH associated with a congenital heart defect (one Eisenmenger, 4 left-to-right shunt but PVRI >8 WUm^2, 7 small shunt (Qp:Qs ≤1.3:1) and 8 post-operative PAH), 17 patients with pulmonary hypertension associated with lung disease (10 with broncho-pulmonary dysplasia, and 7 with congenital diaphragmatic hernia) and 3 patients in group 5 of the Nice classification (Table 1). Only the 56 group 1 PH patients were considered for this study.

Fifty-four patients underwent cardiac catheterization at diagnosis. Two patients were considered too sick and were diagnosed by echocardiography alone. All patients were in WHO-FC III-IV at initiation of SC treprostinil except 4 stable patients in FC II who were switched from IV to SC prostanoids.

First line therapy was either bosentan (2 mg/kg b.i.d) ($n = 13$) or sildenafil (1 to 2 mg/kg t.i.d) ($n = 20$) or both ($n = 16$) or triple therapy with SC treprostinil ($n = 7$) according to PAH treatment algorithm [18]. The interval between PAH diagnosis and starting SC treprostinil was 39.3 ± 43 months (range 0–151 months).

We began SC treprostinil administration through a subcutaneously inserted catheter in hospital. Families and children, if developmentally able to do so, were taught how to mix the drug, insert the cannula, prime, run and change doses on the pump. The SC sites used were the outer thigh, the abdomen and the posterior upper arm. We used Cleo (Smiths Medical), or the Silhouette (Medtronics) SC cannulas and Smiths Medical CADD-MS™ 3 microinfusion pumps. We used treprostinil sodium concentrations of 1, 2.5, 5 and 10 mg/ml. We started the infusion at the lowest dose (1.25 ng/kg/min) deliverable by the pump. The infusion rate was titrated by 0.002 ml/h. We increased the dose every 8–12 h until the patient reported benefit or side effects. Doses were increased by 1.25 to 2.5 ng/kg/min. The average dose was 20 ng/kg/min at hospital discharge. Treprostinil concentrations were adjusted to keep the infusion at the smallest volume. The syringe containing the treprostinil solution was changed every 3 days but the subcutaneous cannula remained in situ providing there was no redness, swelling, drug leakage or crystallization around the insertion site. The syringe of treprostinil was placed in a portable pocket and attached to the waist and the catheter tubing was securely fixed.

If patients were hemodynamically unstable, we started IV prostacyclin or treprostinil, and transitioned to SC treprostinil at an equivalent dose over 24 h. The patients were discharged home, albeit with close telephone contact and visits by the PH clinic staff, once they were stable and the family had attained a good understanding of the pump, cannula insertion technique and drug preparation.

Site pain was evaluated using standard scales of pain adapted to age. Site pain was reported as maximal during the first 2–5 days of starting the infusion at a new site. Redness and tenderness during the first 5 days were not regarded as an indication to change the site and subsided gradually. Site pain was treated individually with cold packs, acetaminophen, non-steroidal anti-inflammatory drugs, anti-histamines, and gabapentin.

SC treprostinil dose was adjusted at outpatient visits or by telephone consultation. Specialized nurses trained in the management of PAH patients provided domiciliary technical assistance.

2.2. Data collection

Study data were collected and managed at the Université Paris Descartes.

Baseline data at time of initiation of triple therapy are shown in Tables 1 and 2.

Table 2
Clinical, hemodynamic and outcome data at initiation of subcutaneously delivered treprostinil therapy, after 6 months and at last follow-up.

	Pre-treatment	6 months	Last follow-up median 37 months
WHO FC I–II	4/56 (7%)	40/48 (83%)****	30/36 (83%)****
WHO FC III–IV	52/56 (93%)	8/48 (17%)	6/36 (17%)
Death		3 (5.3%)	10 (18%)
Potts shunt		4	11[a] (19.6%)
Lung transplantation		1	3 (5.3%)
6MWT (meters)[b]	335 ± 140	448 ± 102****	455 ± 102***
	$n = 39$	$n = 36$	$n = 21$
TAPSE (mm)[b]	15 ± 4	17 ± 4***	19 ± 5***
NT-proBNP[b] ($n = 33$)	3293 ± 142	223 ± 388***	876 ± 340***
Syncope[b]	25 (49%)	2 (6%)****	1 (5%)***
Mean PAP[b] (mm Hg)	63 ± 20	50 ± 28**	
	$n = 52$	$n = 31$	
PVRI (WU ∗ m^2)[b]	16 ± 10	12 ± 10***	
CI (L/min/m^2)[b]	3.7 ± 1.4	3.7 ± 1 ns	
RAP (mm Hg)[b]	7 ± 3	6 ± 2.6 ns	

Abbreviations: WHO FC=World Health Organization Functional Class, 6MWT = 6 min walk test, TAPSE = Tricuspid annular plane systolic excursion, NT-proBNP = N terminal pro brain natriuretic peptide, PAP = pulmonary artery pressure, PVRI = Pulmonary vascular resistance index, CI = Cardiac index, RAP = Right atrial pressure.

[a] Includes 3 deaths.

[b] Comparisons made only in FC III–IV patients (the 4 FCII excluded).

** $p < 0.01$.

*** $p < 0.001$.

**** $p < 0.0001$ vs Pre-SC treprostinil condition using Chi2 or paired t-test analyses with a Bonferroni correction for multiple variables.

During follow-up, efficacy was assessed by evaluation of WHO-FC, 6-minute walk distance, NT-proBNP, and echocardiographic parameters of right ventricular function. Right heart catheterization was repeated at 6 months in 25 children (see Table 2).

Treatment tolerance was evaluated at each visit and between visits by telephone contact with the families. A number of families took photographs of the subcutaneous site with their mobile phones and sent them for review.

2.3. Statistical analysis

Data are presented as mean ± SD or median and range for nonparametric data. Differences in outcome parameters before and after starting SC treprostinil infusions were compared using the paired Student *t*-test or Chi2 analysis when appropriate using XLStat 2014 (Addinsoft, New York, USA). Significance threshold was corrected for multiple variables to $p = 0.005$. Variables not following a normal distribution were log transformed and the normal distribution was then checked before statistical analysis.

Table 1
Characteristics of patients at diagnosis and initiation of subcutaneous treprostinil therapy.

Patients $n = 56$	Total	Female	Male	P value
Sex (F/M)	35/21	35	21	
Age at diagnosis (median)	65 ± 60 months (41)	77 ± 62 months (60)	45 ± 53 months (25)	<0.01
Weight at diagnosis (median)	21 ± 16 kg (15 kg)	23 ± 16 kg (18 kg)	16 ± 17 kg (8.5 kg)	<0.01
IPAH	23	13	10	
aPAH-CHD	20	14	6	
hPAH	13	8	5	
Age in months at SC treprostinil (median)	96.8 ± 68 (84)	102.8 ± 69 (92.8)	86.6 ± 68 (66)	NS
Interval (months) between diagnosis and SC treprostinil	39.3 ± 43	34.8 ± 34	46.6 ± 54	NS
WHO FC (I–II/III–IV)%	7%/93%	6%/94%	10%/90%	
Syncope	25	17	8	
Increased NT-proBNP[a]	33	21	12	
Mean PAP mm Hg[b]	63 ± 20	66 ± 20	59 ± 21	NS
PVRI Wood U·m^2	16 ± 10 (15)	18 ± 11 (15.6)	13 ± 7 (12)	<0.01
Cardiac Index L/min/m^2	3.7 ± 1.4	3.6 ± 1.4	3.9 ± 1.5	NS
RAP mm Hg	7 ± 3	7.7 ± 3	5.1 ± 2.5	NS

Abbreviations: F = female, M = male, IPAH = Idiopathic pulmonary arterial hypertension, aPAH-CHD = pulmonary arterial hypertension associated with congenital heart disease, hPAH = heritable pulmonary arterial hypertension, PHT = pulmonary hypertension, BPD = bronchopulmonary dysplasia, CDH = congenital diaphragmatic hernia, SC = subcutaneous, FC = Functional class, NT-proBNP = N terminal pro brain natriuretic peptide, PAP = pulmonary artery pressure, PVRI = pulmonary vascular resistance indexed to body surface area, RAP = right atrial pressure.

[a] Measurements obtained in 51/56 and increased in 33.

[b] 54/56 underwent heart catheterization before SC treprostinil initiation.

The survival distributions and Kaplan–Meier curves were compared using a *p*-value calculated from a log-rank test. The median survival time was estimated as the amount of time after which 50% of the patients have died, i.e., the time when the Kaplan–Meier curve for survival has reached a probability of survival of 50% by fitting the survival curve with a Weibul distribution.

3. Results

We identified 56 children (median age 65 months, range 1–16.5 years, median weight 15 kg, range 3–65 kg) who received SC treprostinil.

We started SC treprostinil therapy in 45 patients because of failure to improve despite optimal therapy with PDE5i and ERA. Seven patients were started on SC treprostinil therapy as well as dual oral therapy at diagnosis. Four patients stabilized in WHO FC II were switched from IV epoprostenol to SC treprostinil because of repeated central venous line infections ($n = 2$) and patient request (n = 2).

After discharge, SC treprostinil doses were increased depending upon patient tolerance and symptoms, reaching a median dose of 43 ng/kg/min (range 15–350 ng/kg/min).

The effect of the treatment at 6 months on WHO-FC, recurrence of syncope, 6-minute walk distance, changes in NT-proBNP, TAPSE, and hemodynamics is reported in Table 2.

At 6 months there were 48 treated patients and 40/48 (83%) had sustained clinical improvement (Fig. 1, Table 2) reflected by WHO-FC ($p < 0.0001$), the 6MWT (mean + 113 m, $p < 0.0001$) and the decrease of 92% of NT-proBN*P* values at baseline, at 6 months ($p < 0.001$).

Right heart catheterization 6 months after treprostinil initiation was performed in 25/48 subjects. Pulmonary artery pressure decreased significantly ($p = 0.02$) in 18/25 (72%) by 30–60% in 15 patients and 10–20% in 3 patients. Pulmonary vascular resistance decreased significantly ($p = 0.001$), with a decrease of 30–60% ($n = 15$) and 10–20% ($n = 3$).

3.1. Death

Ten patients died during follow-up. Three died shortly after diagnosis 1 to 2 months after initiation of SC treprostinil. Seven patients died after an initial improvement with treprostinil (1 to 5 years).

3.2. Transplantation

Three patients were transplanted 5, 7 and 48 months after SC treprostinil initiation. One died 10 days after the lung transplantation.

3.3. Potts shunt

Eleven patients underwent a Potts procedure: four shortly after SC treprostinil initiation, six for clinical deterioration despite optimal doses of SC treprostinil after a follow-up of 1 to 7 years, and one patient who did not tolerate SC treprostinil and refused IV treatment. Three patients died immediately after the Potts procedure performed 3, 12 and 36 months after SC treprostinil initiation. The remaining eight patients are in WHO-FC I or II and could be weaned slowly off SC treprostinil treatment.

Four children who were switched from IV eproprostenol to SC treprostinil treatment remained in WHO-FC II. These patients were not considered in statistical analyses.

The median follow-up after SC treprostinil initiation was 37 months (range 6 to 98 months). Data at last follow-up are shown in Table 2.

Fig. 2 A shows transplantation and Potts-free survival in the 45 prevalent patients. Probability of survival at 6 months, 1, 3 and 5 years were 94%, 88%, 85% and 85%, respectively. Fig. 2 B shows event-free survival of a composite endpoint consisting of death, lung-transplantation and switch from SC treprostinil to IV epoprostenol for treatment failure. Event-free survival probability at 6 months, 1, 3 and 5 years were 92%, 86%, 84% and 81% respectively. Fig. 2 C shows event-free survival including patients who underwent a Potts shunt. At last follow-up (median 37 months 1–8.5 years) event-free survival was 69%. Fig. 2D shows event-free survival of the 7 incident patients. For these patients, event-free survival at 6 months, 1, 3 and 5 years were 71%, 57%, 43% and 29%, respectively.

Management of infusion site pain was straightforward in 44/56 patients using lidocaine patches, cold packs, and acetaminophen. Nonsteroidal anti-inflammatory drugs were required in 12 patients. Opioids were used transiently in 3 patients but only at treatment initiation.

The severity of infusion site pain was maximal in the first 2–5 days after starting a new site. Site pain varied markedly both between

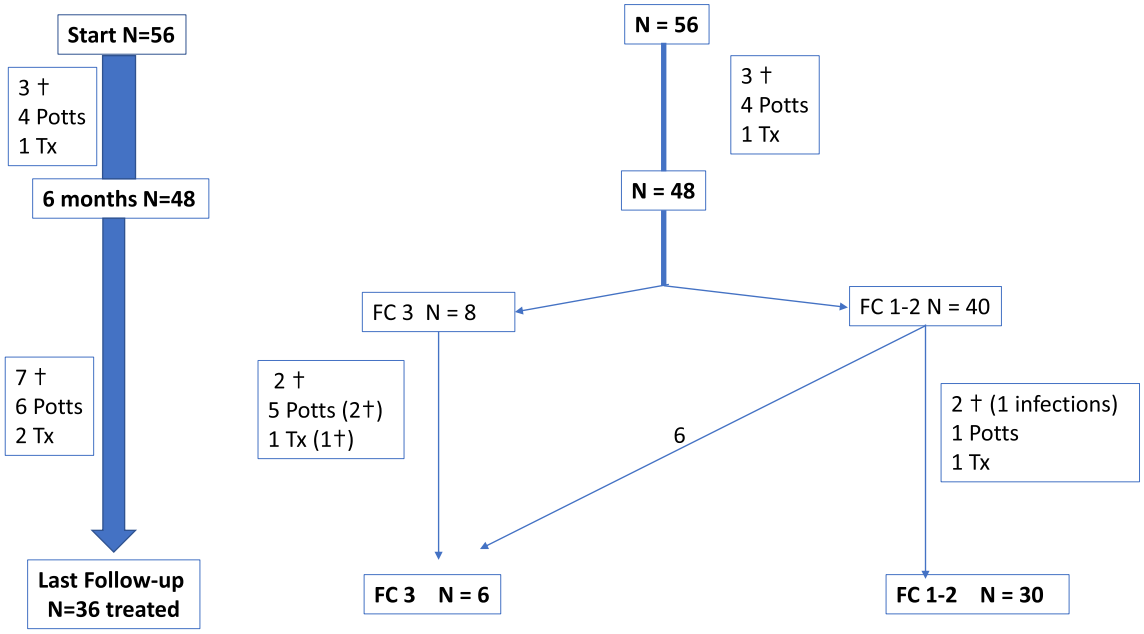

Fig. 1. Flow diagram showing the outcome of the 56 treated patients during the study. At 6 months 48 patients were treated with SC treprostinil (3 early deaths, 1 transplantation and 4 Potts weaned from SC treprostinil). At last follow-up, 36 patients were still treated (10 deaths, 2 transplantations, 8 Potts alive and weaned from SC treprostinil). †: death; Tx: transplantation.

patients and from one infusion site to another in the same patient. It appeared to be unrelated to sex, dose or concentration of treprostinil. We strove to concentrate the infusion to the smallest possible volume compatible with available infusion pumps especially once a stable dose was reached. Infusion sites were maintained for a median duration of four weeks (2–28 weeks).

After dose adjustment, the SC infusion site tolerance was good in all except 3 of the patients who were switched to IV epoprostenol.

One child developed severe leg pain with lymphedema resistant to usual treatments one month after the catheter was placed on the upper leg. The pain resolved with transient use of opioids. This child has been tolerating treatment well for 7 years and the site is usually changed every 2 to 3 months.

Local infection of the infusion sites requiring antibiotic therapy occurred in 12 with surgical drainage in 2.

Minor effects have been observed, including headache, jaw pain with chewing, local edema at site, diarrhea, and epistaxis that are features of all PAH medications.

In case of accidental dislodging of the needle or tubing, parents were taught to change the site with the support from PH clinic staff as required.

4. Discussion

The main findings of our multicenter review of 56 infants and children with refractory PAH are that following the addition of SC treprostinil therapy the majority of patients (83%) derived important improvements in functional class, exercise tolerance and hemodynamics. Furthermore, SC infusions of SC treprostinil were well tolerated in 79% and easily managed in 94% of subjects without the complications of a longterm central venous line. For the most part SC infusion sites lasted an average of 4 weeks and the local site pain was only of concern in the first 3–4 days of a new site. All school-aged children were able to return to full time school.

In our experience SC treprostinil was intolerable in 3 patients (5%). Local complications that occurred in 12 patients were managed easily. We suggest that management of site pain at treatment initiation is crucial and the families require the support of a specialized PH clinic. Parents are taught to maintain the site as long as possible. Each site change may be painful for 3 days. Thereafter the pain resolves. It is, therefore, important to invest maximally in pain control rather than changing the site because the infusion site pain will regress after the 3rd to 5th days. In some patients, if the infusion site change is elective,

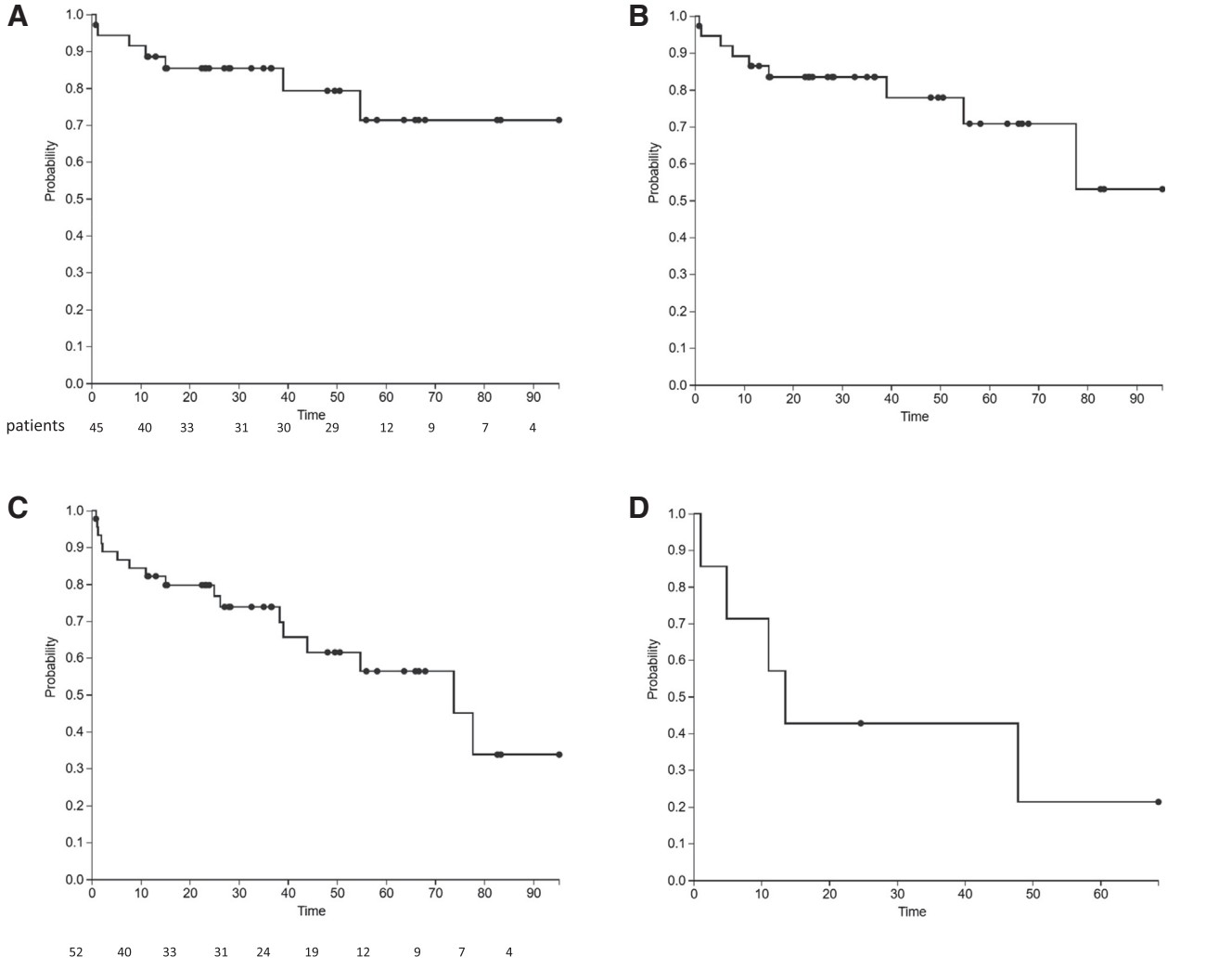

Fig. 2. A: Kaplan Meier survival curve for prevalent patients initially in WHO- FC III/IV who received SC treprostinil ($n = 52$). Survival rates at 6 months, 1, 3 and 5 years were 94%, 88%, 85% and 85% respectively. x axis probability of freedom from event. y axis time in months. B: Kaplan Meier curve showing event-free survival of a composite endpoint consisting of death, lung-transplantation and switch from SC treprostinil to IV epoprostenol for treatment failure for prevalent patients in FC III-IV at start of therapy. Event-free survival at 6 months, 1, 3 and 5 years were 92%, 86%, 84% and 81% respectively. x axis probability of freedom from event. y axis time in months. C: Kaplan Meier curve shows event-free survival (death, lung-transplantation, switch from SC treprostinil to IV epoprostenol and Potts shunt). At last follow-up (median 37 months 1–8.5 years) event-free survival was 69%. x axis probability of freedom from event. y axis time in months. D: Kaplan Meier curve shows event-free survival (death, lung-transplantation, switch from SC treprostinil to IV epoprostenol and Potts shunt) of the 7 incident patients. Event-free survival rates at 6 months, 1, 3 and 5 years were 71%, 57%, 43% and 29% respectively.

the pain may be reduced at the new site by running saline for 24 h before beginning the infusion of treprostinil.

If interruption of the infusion occurs there is less urgency to prime the backup pump and insert a new cannula because treprostinil has a half-life of approximately 4 h and there is reservoir of treprostinil contained subcutaneously, compared with just a few minutes for prostacyclin infusions. Furthermore, a new site may be inserted at home and the infusion continued without the need for hospitalization. In contrast continuous intravenous infusions if interrupted require urgent insertion of a temporary peripheral intravenous line, which often in children requires considerable skill and may be a challenge in hospitals in remote areas with little experience dealing with children. Children treated with SC treprostinil may bathe using a custom-made scuba suit to fit the arm and protect the site thus obviating the need for a new site after bathing.

In PAH, treatment "failure" is difficult to assess because the disease is intrinsically progressive. This is particularly true in infants and young children, in whom functional class assessment is subjective and deterioration cannot routinely be measured with the 6MWT in the youngest patients. In our series 58% of patients could perform a walk test at initiation and at follow-up with significant improvement (see Table 2). Treatment was efficacious in 83% with clinical and hemodynamic improvement and well tolerated in 80% of the patients with active management of site pain.

The mean final dose achieved was 55 ng/kg/min with a range of 15–350 ng/kg/min.

We have not compared the efficacy of continuous SC treprostinil infusions versus intravenously delivered prostanoid therapy. However, we have found that in most children SC treprostinil provides a feasible alternative mode of drug delivery while avoiding the complications of a long-term central venous catheter.

In summary, we have found that continuous infusion of SC treprostinil is an effective treatment in children with PAH refractory to orally administered medications. The reported treatment limiting drawbacks of site pain and need for frequent site changes were not observed. Further research is required to elucidate if pediatric subjects have a different tolerability profile of SC treprostinil compared with adults.

We suggest that with close and frequent observation in an experienced pediatric pulmonary hypertension center that SC treprostinil provides hemodynamic, and clinical benefit in most children without the complications of prolonged central venous access. SC treprostinil may, therefore, be a useful adjunct in the therapeutic algorithm for infants and children with severe PAH. It remains an ongoing question if triple therapy with the earlier use of parenteral prostanoid therapy would be of benefit. The demonstration that SC treprostinil therapy is safe, efficacious and well tolerated, if adapted to suit young children, is important information for practitioners, children and their families if earlier use of parenteral prostanoids to improve outcomes is considered.

Conflict of interest

No conflict of interest to disclose except for Dr Bonnet who has received honorarium from Actelion, Bayer Health Care and Novartis.

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