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ORIGINAL ARTICLE

Initial experience using continuous intravenous treprostinil to manage pulmonary arterial hypertension in patients with end-stage liver disease

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Summary

Treprostinil is a prostacyclin analog and has been used on idiopathic pulmonary arterial hypertension (PAH). There is only limited clinical experience using treprostinil to manage PAH in patients with end-stage liver disease (ESLD). We report three ESLD patients with PAH, who were treated with continuous intravenous treprostinil. A 59-year-old woman with ESLD secondary to alcoholic hepatitis had portopulmonary hypertension with mean pulmonary arterial pressure (mPAP) of 44 mmHg and transpulmonary gradient (TPG) of 23 mmHg. Treprostinil at 45 ng/kg/min for 6 months decreased mPAP to 23 (TPG to 8). A 53-year-old man had ESLD secondary to alcoholic hepatitis with PAH caused by multiple pulmonary embolisms (mPAP of 32 and TPG of 23). Treprostinil at 36 ng/kg/min for 3 months decreased mPAP to 23 and TPG to 14. Both patients underwent uneventful liver transplantation. A 48-year-old man had ESLD secondary to hepatitis C and portopulmonary hypertension with mPAP of 60 and TPG of 44. Two years after intravenous treprostinil at 106 ng/kg/min, his mPAP decreased to 44 and TPG to 30. These results demonstrate that for a selected group of ESLD patients with PAH, a continuous intravenous infusion of treprostinil appears to be safe and effective.

Introduction

Pulmonary arterial hypertension (PAH) in patients with end-stage liver disease (ESLD) can affect the outcome of these patients. Portopulmonary hypertension (PPH), which is found in 2–8% of candidates for liver transplantation (LT) [1], has a significant impact on the fitness of the candidate for undergoing the transplantation procedure and remains a significant risk factor for mortality and morbidity after LT [2–4].

Continuous intravenous (IV) epoprostenol (prostacyclin) has been successfully used as a preparatory step to transplantation in patients with concurrent ESLD and PPH [5]. Indeed, epoprostenol has improved survival in a randomized controlled trial of patients with idiopathic PAH [6].

Treprostinil, a stable prostacyclin analog, has pharmacologic effects similar to epoprostenol [7,8]. Treprostinil can be administered by continuous subcutaneous infusion because it is chemically stable at room temperature at a neutral pH and has a longer elimination half-life (4.5 h, compared with 2–3 min for epoprostenol) [9]. Long-term subcutaneous infusion of treprostinil has also been shown to be effective over placebo in patients with PAH [10,11]. The effectiveness of treprostinil is dosage-related and is independent of the etiology of PAH as is the case with epoprostenol. Unfortunately, infusion site pain is common with continuous subcutaneous infusion and limits

its use [10]. Continuous IV treprostinil may have theoretical advantages over subcutaneous infusion of treprostinil to eliminate the problem.

In this report, we evaluated three adult ESLD patients with PAH who were treated with continuous IV infusion of treprostinil. To the best of our knowledge, this is the first report of the use of continuous IV treprostinil in this patient population.

Patients and methods

The institutional review board of the University of Pittsburgh (Pittsburgh, Pennsylvania, USA) approved this retrospective study. Three adult patients who had ESLD with PAH being treated with IV infusion of treprostinil for the last 3 years (February 1, 2005–January 31, 2008) were identified. The clinical data were recorded in a prospective manner in all these patients and reviewed and analyzed retrospectively. IV treprostinil was initiated when a diagnosis of PAH was made on patients being considered for LT or in patients who were functionally limited. Right heart catheterization (RHC) was performed before the initiation of treatment. Follow-up RHC was performed at 3-month intervals or greater if the patient was clinically stable. The goal of the therapy was to bring the mean pulmonary arterial pressure (mPAP) below 30–35 mmHg and the transpulmonary gradient (TPG) under 15–20 mmHg with a normal cardiac output. When a patient underwent LT, intra-operative and postoperative hemodynamics were recorded using a Swan–Ganz catheter (8-Fr CCOmbo V; Edwards Lifesciences, Irvine, CA, USA), and RHC was repeated at 3 months or more post-transplantation to assess response to therapy.

Results

Case A

A 59-year-old woman with ESLD secondary to alcohol use underwent a RHC for pre-LT assessment because of Doppler echocardiography results that had revealed an estimated systolic pulmonary arterial pressure (PAP) of 59 mmHg [12]. RHC confirmed PPH; PAP was 65/26(mean 44) mmHg with a TPG of 23 mmHg and a cardiac index (CI) of 4.04 l/min/m^2 (Table 1). The increased

Table 1. Case A: Hemodynamic measurements by right heart catheterizations, right heart function by transthoracic echocardiograms, and liver function tests.

After initial evaluation (months)	0	4		10	15	26
Therapy	None	Preiloprost	Postiloprost	IV treprostinil	IV treprostinil	Sildenafil
Dosage (ng/kg/min)				45	45	
LT candidacy	No	No	No	Yes	During LT*	Post-LT
PAP (mean) (mmHg)	65/26(44)	58/21(39)	53/19(34)	36/−1(23)	35/21(26)	67/23(41)
PVR (dyn·s/cm^5)	249	344	201	69	–	387
PCWP (mmHg)	21	13	15	15	–	16
TPG (mmHg)	23	26	19	8	–	25
CO (l/min)	7.39	6.04	7.58	9.25	10.5	5.17
CI (l/min/m^2)	4.04	3.41	4.28	5.35	6.1	2.37
RA (mmHg)	11	11	10	6	11	1
PA sat (%)	75	59	60	72	90	64
HR (b.p.m.)	80	84	87	87	100	89
SBP (mmHg)	153/73	135/59	106/48	114/60	123/58	115/78
RV size	Mild dil.	Mod. dil.	–	Normal	Normal	Normal
RV wall thickness	Normal	Increased	–	Normal	Normal	Normal
RV function	Normal	Normal	–	Normal	Normal	Normal
LVEF (%)	70					
CAG	Normal					
T. Bil. (mg/dl)	2.6	2.6	–	1.4	1.3	0.4
ALT (units/l)	26	39	–	17	22	26
AST (units/l)	39	82	–	26	20	19
INR	1.3	1.3	–	1.2	1.2	1.0

IV, intravenous infusion; LT, liver transplantation; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure; TPG, transpulmonary gradient; CO, cardiac output; CI, cardiac index; RA, right atrial pressure; HR, heart rate; SBP, systolic blood pressure; RV, right ventricular; Mod., moderate; dil., dilatation; LVEF, left ventricular ejection fraction; CAG, coronary angiography; T. Bil., total bilirubin; ALT, alanine aminotransferase; ASL, aspartate aminotransferase; INR, international normalized ratio.

–Not determined.

*No postreperfusion syndrome[50] was noted.

pulmonary capillary pressure (21 mmHg) was recorded on this occasion; however, this case was considered as PPH because of the high TPG and was treated as such [13]. During RHC, the effect of inhaled iloprost revealed only modest improvement in PAP; therefore, a continuous IV infusion of treprostinil was initiated via a Hickman catheter and maintained at a rate of 45 ng/kg/min. In the sixth month of infusion, the PAP decreased to 36/−1(23) with a TPG of 8 and a CI of 5.35, and the patient was placed on the LT list. In the eighth month of IV treprostinil treatment, the patient presented to the emergency room (ER) because her Hickman catheter accidentally fell out. IV treprostinil was off for 5 h until a central line was placed, and the patient was stable throughout this period. A new Hickman catheter was later inserted and the patient underwent a deceased donor LT [Model for ESLD (MELD) score of 22] in the 11th month of the infusion. The initial PAP during LT was 35/21(26) with a CI of 6.1. IV treprostinil was continued during the entire LT procedure and the postoperative period and perioperative hemodynamic status was stable (PAP ranged from 29/14–45/25). During the reperfusion of the graft, the hemodynamic parameters were stable, including the systemic blood pressure (baseline 120/45 mmHg to 115/45 after the reperfusion), the cardiac output (11.1 l/min to 10.7), the PAP (32/17 mmHg to 36/19), and the right ventricular size and function by trans-esophageal echocardiography. There was no episode of pulmonary hypertension either during or after the LT, therefore, no additional pulmonary vasodilators were required. The treprostinil infusion was weaned off 2 months after LT and sildenafil citrate 20 mg p.o. t.i.d. was started. One year after LT, RHC revealed persistent PPH with PAP of 67/23(41) with a TPG of 25 and a CI of 2.37. The recurrence of the pulmonary hypertension is concerning and a close monitoring of the pulmonary hemodynamics will be needed. The patient is clinically well with a functioning allograft 2 years after LT.

Table 2. Case B: Hemodynamic measurements by right heart catheterizations, right heart function by transthoracic echocardiograms, and liver function tests.

After initial evaluation (months)	0	5		5	8	12	15	24
		GA	1 l*					
Therapy	No	No	No	No	IV Trpro.	IV Trepro.	IV Trepro.	Sildenafil
Dosage (ng/kg/min)					36	36	36	
LT candidacy	Yes	No	No	No	Yes	During LT†	Post-LT	
PAP(mean) (mmHg)	23/8(12)	56/24(33)	60/36(44)	53/15(32)	42/9(23)	35/14(21)	46/15(27)	37/‡
PVR (dyn·s/cm^5)	85	–	–	304	191	–	165	–
PCWP (mmHg)	6	–	–	9	9	–	14	–
TPG (mmHg)	6	–	–	23	14	–	13	–
CO (l/min)	5.6	7.0	7.0	6.0	5.85	13	6.3	–
CI (l/min/m^2)	2.9	3.6	3.6	3.18	3.11	7.2	3.54	–
RA (mmHg)	4	6	10	7	6	4	7	–
PA sat (%)	72	88	90	69	75	96	–	–
HR (b.p.m.)	58	60	60	72	62	80	48	–
SBP (mmHg)	96/55	120/55	122/58	120/72	120/69	105/50	147/81	–
RV size	Normal	–	–	–	–	Normal	–	Normal
RV wall thickness	Normal	–	–	–	–	Normal	–	Normal
RV function	Normal	–	–	–	–	Normal	–	Normal
LVEF (%)	55							
CAG	Normal							
T. Bil. (mg/dl)	1.6	2.6	–	2.3	1.9	6.5	0.6	0.9
ALT (Units/l)	–	49	–	48	35	32	18	36
AST (Units/l)	–	54	–	40	39	21	16	42
INR	–	1.3	–	1.4	1.5	1.9	1.2	1.2

GA, general anesthesia; IV, intravenous infusion; LT, liver transplantation; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure; TPG, transpulmonary gradient; CO, cardiac output; CI, cardiac index; RA, right atrial pressure; HR, heart rate; SBP, systolic blood pressure; RV, right ventricular; LVEF, left ventricular ejection fraction; CAG, coronary angiography; T. Bil., total bilirubin; ALT, alanine aminotransferase; ASL, aspartate aminotransferase; INR, international normalized ratio.

–Not determined.

*****After 1 l volume challenge during general anesthesia.

†No postreperfusion syndrome[50] was noted.

‡Estimated pulmonary systolic pressure by transthoracic echocardiogram.

Case B

A 53-year-old man with ESLD secondary to alcohol use with no known history of PAH was found to have elevated PAP pretransplantation after induction of general anesthesia. The initial measurement of the PAP was 56/24(33) with a CI of 3.6 l/min/m^2 (Table 2). After 1 l of volume challenge based on the low right atrial pressure (6 mmHg) [14], the PAP rose to 60/36(44) and trans-esophageal echocardiogram showed moderate right ventricular dysfunction. Given the unexpected PAH, LT was cancelled. A ventilation/perfusion lung scan showed multiple perfusion defects, strongly suggesting multiple pulmonary thromboembolisms and a Greenfield filter was placed in the inferior vena cava. None of the anticoagulants were prescribed. Repeated RHC revealed an mPAP of 32, a TPG of 23 with a CI of 3.18. A continuous IV infusion of treprostinil was initiated at a rate of 24 ng/kg/min and increased to 36 ng/kg/min. In the third month of treprostinil infusion, the PAP decreased to 42/9(23) with a TPG of 14 and a CI of 3.11, and the patient was made active again on the LT list. In the fourth month of the treprostinil infusion, he presented to the ER for repair of his Hickman catheter which was damaged during a dressing change. The catheter was repaired and IV treprostinil was reinstituted after 5–6 h. He stayed over night in a telemetry unit in stable condition. In the sixth month following the initiation of treprostinil infusion, the patient underwent a deceased donor LT (MELD of 33). The initial PAP after induction of general anesthesia was 35/14(21) with a CI of 7.2. Treprostinil infusion was continued during the entire transplant procedure and also in the postoperative period. Perioperative hemodynamic status was stable (range of PAP, 25/8 to 44/21). During the reperfusion of the donor liver, the hemodynamic parameters were stable, including the systemic blood pressure (baseline 100/60 mmHg to 120/60 after the reperfusion), the cardiac output (13.3 l/min to 12.7), the PAP (27/8 mmHg to 25/8), and the right ventricular size and function by trans-esophageal echocardiography. There was no episode of pulmonary hypertension during and after the LT, therefore, no additional pulmonary vasodila-

Table 3. Case C: Hemodynamic measurements by right heart catheterizations, right heart function by transthoracic echocardiograms, and liver function tests.

After initial evaluation (months)	0	11	16	20	31	45
Treprostinil therapy	None	SC	IV	IV	IV	IV
Dosage (ng/kg/min)		39	57	90	106	106
LT candidacy	No	No	No	No	No	No
PAP(mean) (mmHg)	90/45(60)	77/29(49)	70/21(44)	68/25(45)	72/27(44)	76/*
PVR (dyn·s/cm^5)	718	446	349	239	279	–
PCWP (mmHg)	16	13	11	12	14	–
TPG (mmHg)	44	36	33	33	30	–
CO (l/min)	4.9	6.46	7.56	11.03	8.23	–
CI (l/min/m^2)	1.9	2.91	3.45	5.18	4.00	–
RA (mmHg)	15	10	9	10	12	–
PA sat (%)	63	–	68	73	72	–
HR (b.p.m.)	–	67	67	80	65	–
SBP (mmHg)	140/92	134/93	122/80	134/86	132/76	–
RV size	Mod. dil.	Mod. dil.	–	–	Mod. dil.	Mod. dil.
RV wall thickness	Increased	Normal	–	–	Increased	Normal
RV function	Normal	Mod. increase	–	–	Mild decrease	Mild decrease
LVEF (%)	55					
CAG	Normal					
T. Bil. (mg/dl)	4.2	–	2.8	1.9	1.8	2.6
ALT (Units/l)	235	–	45	18	29	26
AST (Units/l)	287	–	44	24	25	39
INR	1.2	–	1.2	1.3	1.3	1.4

SC, subcutaneous infusion; IV, intravenous infusion; LT, liver transplantation; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure; TPG, transpulmonary gradient; CO, cardiac output; CI, cardiac index; RA, right atrial pressure; HR, heart rate; SBP, systolic blood pressure; RV, right ventricular; Mod., moderate; dil., dilatation; LVEF, left ventricular ejection fraction; CAG, coronary angiography; T. Bil., total bilirubin; ALT, alanine aminotransferase; ASL, aspartate aminotransferase; INR, international normalized ratio.
–Not determined.
*Estimated pulmonary systolic pressure by transthoracic echocardiogram.

tors were required. Three months after LT, RHC revealed residual PAH with a PAP 46/15(27) and a TPG of 13 on IV treprostinil. Treprostinil infusion was slowly weaned off and sildenafil citrate 20 mg p.o. t.i.d. was started. The patient is in excellent condition with good graft function 2 years after LT.

Case C

A 48-year-old man with ESLD secondary to hepatitis C had PPH with PAP of 90/45(60), a TPG of 44 and a CI of 1.9 (Table 3). After 11 months of continuous subcutaneous infusion of treprostinil, RHC revealed elevated PAP [77/29(49)] with a TPG 36 and a CI 2.91. At this point, the route of the administration of treprostinil was switched to a continuous IV infusion. At the 19th month of IV treprostinil treatment, the patient had an episode of Hickman catheter infection by *Enterobactor cloacae,* which was treated with intravenous antibiotics and replacement of the catheter. Twenty months after the IV treprostinil at a rate of 106 ng/kg/min, he had persistent PAH [PAP of 72/27(44)] with a TPG 30 and a CI 4.0. The follow-up study demonstrated a mildly decreased right ventricular function on a trans-thoracic echocardiography. Therefore, the patient was not listed as a candidate for LT.

Discussion

Various classes of drugs have been used for the treatment of PAH associated with ESLD [15–20] Among available options, the following three classes of drugs appear to be the current choices: endothelin-receptor antagonists (bosentan) [21–27], phospodiesterase-5 inhibitors (sildenafil) [28–32], and prostacyclin (epoprostenol) and its analogs (iloprost, beraprost, and treprostinil).

Epoprostenol, a metabolite of arachidonic acid, is a naturally occurring prostaglandin with potent vasodilatory activity as well as anti-thrombotic, anti-inflammatory, and anti-proliferative properties. Kuo *et al.* [33] reported the effectiveness of IV epoprostenol to treat PPH in LT candidates, and this finding was further supported by Krowka *et al.* [34]. The first successful LT after continuous IV epoprostenol treatment of PPH was reported in 1998 [35]. Since then, the successful perioperative management of PPH with IV epoprostenol alone [36–41] or combined with nitric oxide [42–44] has been reported. Fix *et al.* reported a long term follow-up (a median of 15.4 months) of a cohort of moderate and severe PPH. Out of a total of 36 patients, 19 patients who received IV epoprostenol demonstrated significant improvements in mean pulmonary pressure, pulmonary vascular resistance and cardiac output. Two of the 19 patients improved sufficiently to undergo LT [45]. Based on the favorable effect, several synthetic analogs of epoprostenol including iloprost, beraprost and treprostinil were tested in randomized controlled trials. There is, however, very limited reported experience using prostacyclin analogs for the treatment of PPH [46].

Treprostinil is a stable, long-acting prostacyclin analog, which has been shown to improve the clinical state, functional class, exercise capacity and quality of life in patients with idiopathic PAH [47,48]. The drug can be administered as a continuous subcutaneous infusion using a portable miniature delivery system or as an intravenous infusion. Based on the clinical efficacy of IV treprostinil on idiopathic PAH [48] and the theoretical benefit over subcutaneous route administration for prevention of site pain [10], we elected to treat three patients, having ESLD and also concurrently PAH, with IV treprostinil in our institution.

This case series suggests that continuous IV treprostinil is reasonably effective in controlling mild to moderate PAH in adult patients with ESLD. Two patients had significantly decreased PAP 3 months after continuous IV treprostinil and became candidates for and successfully underwent LT. We consider listing the patients for LT if the mPAP measures under 30–35 mmHg and the TPG under 15–20 mmHg with normal or supra-normal cardiac output. The third patient had an initial response to continuous subcutaneous infusion of treprostinil, but switching to a continuous IV route did not further improve PAH, though he remained clinically stable for 2 years on IV treprostinil. The dosage of treprostinil in our cases ranged from 24–106 ng/kg/min, and these dosages were within the published linearity of IV treprostinil between 15 and 125 ng/kg/min [49].

There were no hemodynamic derangements associated with continuous use of IV treprostinil during the preoperative period in our two patients who underwent LT. Especially, there was no hemodynamic instability (or reperfusion syndrome) [50] noted during the donor liver reperfusion period. There was no episode of worsening pulmonary hypertension throughout the perioperative period. No additional pulmonary vasodilatation regimen, including inhaled nitric oxide, was required. We believe that continuation of IV treprostinil at the pre-LT dosage may prevent a rebound pulmonary hypertension which often occurs in patients who have had the treatment discontinued during this critical period.

Intravenous treprostinil in the first and the second patients was successfully switched to oral sildenafil [31] 3 and 2 months after LT respectively. Careful monitoring of PAH and patients' symptoms should allow physicians to successfully and safely switch IV treprostinil to oral medications [51]. As there are no data to guide specific timing of the switch at this moment, we tried the switch gradually watching carefully for any hemodynamic

compromise. Endothelin-receptor antagonist therapy was avoided because of the potential for hepatic injury and a possible drug-drug interaction with calcinuerin inhibitors [52]. There is a new oral formulation of treprostinil that is currently in Phase III development.

Our second patient (Case B) had PAH resulting from chronic multiple pulmonary embolisms, instead of PPH, and the effectiveness of treprostinil on thromboembolic PAH has also been reported recently [53].

Complications related to IV treprostinil therapy were found in the three study patients, all of whom had unexpected cessation of the continuous IV infusion because of catheter malfunction (Case A and B) and an episode of catheter-related infection (Case C). In the first two cases, both patients were able to tolerate 4–6 h of cessation of treprostinil because of the longer elimination half-life of the drug, until new IV access was restored. Treprostinil has a long elimination half-life (4.4 h with IV infusion) and, therefore, may minimize the chance of rebound PAH in case of accidental cessation of continuous infusion.

One of our three patients (Case C) had an initial decrease of PAP after continuous subcutaneous infusion of treprostinil but did not achieve further improvement in pulmonary hemodynamics upon switching to continuous IV treprostinil at maximum dosage. Such a refractory case to IV treprostinil therapy should be acknowledged and alternative therapy including combination of two [54] or even three [55] different classes of pharmacological therapies should be considered with the goal of listing these patients for LT. The cost of this therapeutic regimen, especially IV treprostinil, is a significant issue; however, we believe it is not a prohibitive factor to use these therapeutic options on a patient if the pulmonary hemodynamics is the determinant of transplant candidacy.

In conclusion, a continuous IV infusion of treprostinil was used to control PAH in three adult patients with ESLD. Two patients successfully underwent LT, and continuous IV treprostinil infusion during LT was safe. Further studies are necessary to confirm the effectiveness of IV treprostinil in the treatment of PAH in patients with ESLD who require LT.

Authorship

TS, RMP and RV: designed study. RMP, MAM, MEDV and RV: performed study, reviewed paper. TS: collected data, wrote paper.

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