Transitioning From IV Epoprostenol to Subcutaneous Treprostinil in Pulmonary Arterial Hypertension*

Jean-Luc Vachiéry, MD; Nicholas Hill, MD, FCCP; Diane Zwicke, MD, FCCP; Robyn Barst, MD; Shelmer Blackburn, MD; and Robert Naeije, MD

Objective: **Continuous IV epoprostenol (prostacyclin) therapy improves survival and quality of life in patients with pulmonary arterial hypertension (PAH). IV epoprostenol therapy may be limited by serious complications related to the need for an implanted central venous catheter, and its chemical instability and short half-life. Treprostinil is a longer-acting prostacyclin analog, chemically stable, and suitable for continuous subcutaneous administration. We report successful transitioning to subcutaneous treprostinil of patients who presented with life-threatening complications of IV epoprostenol delivery.**
Design: **Open, uncontrolled study.**
Setting: **ICUs and departments of cardiology at academic hospitals.**
Patients: **Eight patients with PAH treated with continuous IV epoprostenol.**
Intervention: **Transition to subcutaneous treprostinil following an empiric protocol.**
Results: **Transition to treprostinil was achieved successfully in 21 to 96 h, with no major adverse side effects, and no change in the improved clinical status achieved with IV epoprostenol. Doses of epoprostenol before transition ranged from 3.5 to 75 ng/kg/min (mean, 27 ng/kg/min). Doses of treprostinil at completion of the transition ranged from 3 to 65 ng/kg/min (mean, 22 ng/kg/min). Four to 11 months later, the patients remained clinically improved. In spite of mild-to-moderate infusion site pain, all patients reported an improved sense of comfort and well-being.**
Conclusion: **Patients with PAH can be safely transitioned from treatment with IV epoprostenol to subcutaneous treprostinil.** ***(CHEST 2002; 121:1561–1565)***

Key words: anorexigens; congenital heart disease; connective tissue disease; epoprostenol; HIV infection; portal hypertension; primary pulmonary hypertension; pulmonary arterial hypertension; treprostinil

Abbreviations: NYHA = New York Heart Association; PAH = pulmonary arterial hypertension

Continuous IV epoprostenol (prostacyclin) therapy improves functional state, exercise capacity, pulmonary hemodynamics, and survival in patients with primary pulmonary hypertension.[1–6] Similar clinical effects of epoprostenol have been reported in patients with pulmonary hypertension associated with connective tissue disease[7,8] and congenital heart defects.[9] The treatment therefore appears indicated in pulmonary arterial hypertension (PAH) as recently defined by a World Health Organization-sponsored consensus conference.[10] However, due to its short half-life and chemical instability, long-term epoprostenol therapy requires a permanently implanted central venous catheter and a portable infusion pump, exposing the patients to a series of complications including catheter-related embolism or thrombosis, infection, and delivery system malfunctions resulting in poorly tolerated, rapid overdosing or underdosing.[1–9] Accordingly, alternative modes of administration and longer acting prostacyclin derivatives are currently under investigation. Favorable results have been reported with trepros-

*From the Departments of Cardiology (Dr. Vachiéry) and Pathophysiology (Dr. Naeije), Erasme University Hospital, Brussels, Belgium; Rhode Island Hospital (Dr. Hill), Providence, RI; St Luke's Medical Center (Dr. Zwicke), Milwaukee, WI; the Department of Pediatrics (Dr. Barst), Columbia Presbyterian Medical Center, New York, NY; and United Therapeutics Corporation (Dr. Blackburn), Research Triangle Park, NC.
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Correspondence to: Robert Naeije, MD, Laboratory of Physiology, Erasmus Campus, CP 604, Route de Lennik 808, B-1070 Brussels, Belgium; e-mail: rnaeije@ulb.ac.be

tinil, a chemically stable prostacyclin analog with a longer half-life, administered as a long-term subcutaneous infusion.[11] This report describes the successful first transition to subcutaneous treprostinil of eight patients with PAH who presented with life-threatening complications of long-term IV epoprostenol therapy.

Materials and Methods

Eight patients with severe PAH who had initial clinical improvement (improved symptoms, exercise capacity) with long-term IV epoprostenol administration, but presented with life-threatening complications of this treatment, gave written informed consent to the study. All patients were followed up at centers experienced in long-term IV epoprostenol therapy, and which had participated in a randomized controlled trial[11] of long-term subcutaneous treprostinil therapy in New York Heart Association (NYHA) class III and IV patients with PAH.

An empiric transition protocol was agreed on and approved by the local institutional review boards. Patients were hospitalized throughout the transition process. The transitions were performed in an intensive care or telemetry setting, with continuous monitoring of clinical status, including ECG and BP. While in the hospital and receiving a prescribed dose of epoprostenol, each patient was initiated on a dose of treprostinil (generally ≤ 5 ng/kg/min) equal to not more than one half of the current epoprostenol dose. Treprostinil was maintained at this dose for at least 6 h. During this time, the dose of epoprostenol was reduced slowly, in not more than 2-ng/kg/min decrements, based on appearance of prostacyclin-related signs and symptoms. With the patient in clinically stable condition, treprostinil was increased further, by no more than one half of the current dose, and maintained for at least 6 h while epoprostenol was further reduced based on prostacyclin-related events. Symptoms of insufficient or excess prostacyclin were managed with adjustments to the IV epoprostenol dose. This process was continued until epoprostenol was discontinued. Symptoms of prostacyclin overdosing were facial flush, headache, jaw pain, abdominal cramping, diarrhea, and hypotension. Symptoms of prostacyclin underdosing were fatigue, dyspnea, chest pain, and pallor. Clinical state, NYHA functional class, and exercise capacity were evaluated before and after the transition, and then at least every 3 months. Exercise capacity was evaluated using a standard unencouraged 6-min walk test.[12]

Treprostinil, available in a ready-to-use parenteral solution, was administered subcutaneously using a positive-pressure microinfusion pump (MiniMed; Sylmar, CA). The catheter was placed by the patient in the subcutaneous tissue of the abdominal wall, changing the infusion site location every 3 days. Epoprostenol, provided as a lyophilized powder for dilution with glycine buffer, was administered through a permanently implanted central venous catheter, using a portable infusion pump. Conventional therapy included coumarin derivatives with doses adapted for an international normalized ratio between 1.5 and 2.5, and diuretics and/or digitalis as needed.

The results are expressed individually or as mean ± SE. Student's paired *t* tests were used for statistical analysis.

Results

The baseline characteristics of the patients are summarized in Table 1. Five of the patients had primary pulmonary hypertension, which was associated with fenfluramine ingestion in three patients and associated with HIV infection in one patient. One patient had pulmonary hypertension associated with portal hypertension, one patient had a congenital left-to-right cardiac shunt, and one patient had scleroderma. All patients had been severely ill, NYHA class III or IV, before the institution of IV epoprostenol therapy. Mean pulmonary artery pressure ranged from 31 to 88 mm Hg (mean ± SE, 58 ± 8 mm Hg). After 3 to 15 months of epoprostenol therapy, seven patients were NYHA class II and one patient had improved from NYHA class IV to class III. Severe complications justifying transition to subcutaneous treprostinil included recurrent central venous catheter-related sepsis in five patients; severe headache, jaw pain, abdominal cramping, and diarrhea preventing an increase in epoprostenol dose in the presence of clinical deterioration in one patient; recurrent cerebral air emboli with residual left paralysis in one patient; and several episodes of syncope due to the short half-life and accidental disconnections of the IV line in one patient.

The doses of epoprostenol at transition, the initial treprostinil dose, the treprostinil dose at completion of transition, and the time needed to complete the transition are presented in Table 2. The dose

Table 1—*Patient Characteristics

Patient No.	Age, yr	Gender	Diagnosis	Initial NYHA Class	Time Receiving IV Epoprostenol, mo	Current NYHA Class	Epoprostenol Complications
1	39	Female	PPH	IV	39	II	Sepsis
2	54	Female	PPH	IV	21	III	Headache
3	35	Male	PPH	IV	31	II	Sepsis
4	30	Female	VSD, PDA	III	4.5		Cerebral emboli, hemiplegia
5	32	Male	Portal hypertension	IV	36	II	Sepsis
6	48	Female	PPH/HIV	III	29	II	Recurrent syncope
7	54	Female	CTD	III	25	II	Sepsis
8	52	Female	PPH	III	21	II	Sepsis

*PPH = primary pulmonary hypertension; VSD = ventricular septal defect; PDA = patent ductus arteriosus; CTD = connective tissue disease.

Table 2—*Doses of Epoprostenol and Treprostinil, and Duration of Transition in Eight Patients With Severe PAH*

Patient No.	Epoprostenol Dose, ng/kg/min	Initial Treprostinil Dose, ng/kg/min	Final Treprostinil Dose, ng/kg/min	Time to Transition, h
1	15	4	7	23
2	13	4	10	22
3	18	6	16	21
4	3.5	1	3	24
5	75	5	65	96
6	26	5	16	56
7	26	4.2	23	50
8	40	5.45	36.6	54

of epoprostenol at transition ranged from 3.5 to 75 ng/kg/min (mean, 27 ng/kg/min), and the dose of treprostinil at completion of transition ranged from 3 to 65 ng/kg/min (mean, 22 ng/kg/min). Moderate symptoms of excess prostacyclin delivery were promptly relieved by reduction of the IV epoprostenol infusion rate. There were no other side effects of the transition. Clinical status and NYHA functional class were unchanged after the transition. Heart rate (from 75 ± 3 to 76 ± 4 beats/min), mean systemic BP (from 79 ± 4 to 82 ± 4 mm Hg), and distance walked in 6 min (from 496 ± 45 to 486 ± 29 m, n = 5) were unchanged posttransition from the improvement experienced with IV epoprostenol (Table 3; p = not significant 6 to 8 weeks posttransition vs within 1 week prior to transition, Student's paired *t* test). The 6-min walk test could not be performed in patient 4, was refused by one patient because of local infusion site pain, and one patient did not have a pretransition test.

All patients experienced varying degrees of erythema, swelling, and pain at the treprostinil infusion site at the completion of the transition. The maximum pain rating was mild in one patient with the lowest dose of epoprostenol, but was moderate to severe in the seven other patients. The pain was treated with topical cooling and corticosteroid or nonsteroidal anti-inflammatory drug ointments, oral paracetamol (acetaminophen), and/or other oral nonsteroidal anti-inflammatory drugs. Two patients received paracetamol-codeine preparations, briefly. Two other patients were treated with short courses (2 mg/kg/d) of oral prednisolone, which appeared to be very effective. The local pain markedly improved after a few weeks in six patients. The only other side effect of subcutaneous treprostinil therapy reported was minor infusion site hematoma, occurring in four patients.

Table 3—*NYHA Classification and 6-min Walk Test Prior to and After Transition**

Patient No.	NYHA Class Prior to Transition	NYHA Class After Transition	6-min Walk Prior to Transition, m†	6-min Walk After Transition, m‡
1	II	II	528	496
2	III	III	325	404
3	II	II	563	555
4	NA	NA	NA	NA
5	II	II	NA	639
6	II	II	482	449
7	II	II	583	525
8	II	II	242	NA

*NA = not assessed.
†6-minute walk test was conducted within 1 week prior to transition.
‡6-minute walk test follow-up ranged from 6 to 8 weeks after transition.

Follow-up after transition to treprostinil ranged from 4 to 11 months. Clinical state, NYHA functional class, and 6-min walk distances remained unchanged, except in one NYHA class III patient who slowly deteriorated in spite of continuous increases of treprostinil, but improved moderately after an atrial septostomy. This patient had been deteriorating while receiving IV epoprostenol.

Discussion

The present results demonstrate that the transition from IV epoprostenol to subcutaneous treprostinil is safe, with excellent intermediate (4 to 11 months) results, in patients with severe PAH in whom epoprostenol therapy is effective but complicated by life-threatening side effects.

Severe PAH is a rapidly progressive and fatal disease that remains incurable.[13] However, patient outcome has been improved in recent years by several therapeutic advances.[13] The most significant advance has unquestionably been in the introduction of long-term IV epoprostenol therapy.[1–10,13] However, this treatment is not without complications. Due to its short half-life (1 to 2 min) and chemical instability, epoprostenol can only be administered via IV, and thus requires a permanently implanted central venous catheter and a portable infusion pump, as well as refrigeration during administration. This carries risks of sepsis, thrombosis, paradoxical embolism, and interruptions of treatment due to accidental occlusions, perforations and dislodgments of the catheter, and pump malfunction.[2–4,6–9] Additionally, any interruption of delivery may be associated with syncope, and even death, from an acute pulmonary hypertensive crisis.[2–4,6–9] The present series of patients illustrates how patients who have had life-threatening complications such as recurrent

sepsis, paradoxical embolism, and interruptions of drug delivery while receiving IV epoprostenol may be transitioned to therapy with longer acting prostacyclin analogs administered by an alternative delivery route, with a reduction in the risk of life-threatening complications.

Treprostinil is a stable prostacyclin analog with pharmacologic actions[14,15] and acute pulmonary vasodilating properties[16] similar to prostacyclin. In contrast to prostacyclin, treprostinil is chemically stable at room temperature and neutral pH, has a longer half-life (3 to 4 h), and is thus suitable for subcutaneous administration. A recent multicenter, randomized, double-blind, placebo-controlled trial in 470 patients has shown that long-term subcutaneous treprostinil therapy improves exercise capacity, symptoms of pulmonary hypertension, hemodynamics, and quality of life, and is safe and well tolerated in patients with PAH (primary or associated with congenital cardiac shunts or connective tissue disease).[11] However, as also noted in the present study, the treatment is frequently associated with local infusion site erythema, swelling, and pain. This side effect profile occasionally can be severe enough to alter quality of life and exercise capacity, but most often is controlled by topical cold packs, corticosteroid or anti-inflammatory ointments, and oral anti-inflammatory and analgesic drugs. Two patients in the present study reported severe local pain that was satisfactorily controlled by a short course of high-dose corticosteroids. Infusion site reactions also tend to abate over time, generally after a few months. Of interest, all but one of the eight patients felt an improved sense of comfort and well-being soon after transition to subcutaneous treprostinil, despite the infusion site pain.

The only other notable side effect of long-term subcutaneous treprostinil was the occurrence of hematomas at the infusion site. Four of eight patients experienced such hematomas, none of which were severe enough to preclude continuation of the treatment. These infusion site hematomas are explained by the combination of mechanical trauma, anticoagulation, and possibly the antiplatelet aggregate effects of prostacyclins. Infusion site problems, including irritation, infection, bleeding and pain, have also been reported in patients receiving continuous IV epoprostenol.[2–4,6–9]

In one patient, transition to treprostinil was elected due to clinical deterioration that could not be treated with increased epoprostenol doses due to intolerable prostacyclin-related side effects including headache and diarrhea. Subcutaneous treprostinil allowed better control of the clinical state by progressive increases in dose with no or only mild signs and symptoms of prostacyclin intolerance.

In summary, subcutaneous treprostinil can be safely considered as an alternative option to IV epoprostenol therapy in patients with severe PAH who experience life-threatening complications while receiving IV epoprostenol or in patients who cannot tolerate dose increases. Transition to subcutaneous treprostinil can be safely achieved using an empirical protocol that accomplishes the transition over a brief time period with minimal adverse side effects.

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