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

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**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.

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**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 disease7,8 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-
Tinil, a chemically stable prostacyclin analog with a longer half-life, administered as a long-term subcutaneous infusion. 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 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 undosing 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.

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 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**

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

*PPH = primary pulmonary hypertension; VSD = ventricular septal defect; PDA = patent ductus arteriosus; CTD = connective tissue disease.*
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 ery-
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\(^4\),\(^5\),\(^6\) 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 platelet aggregate effects of prostacyclins. Infusion site problems, including irritation, infection, bleeding and pain, have also been reported in patients receiving continuous IV epoprostenol.\(^2\),\(^3\),\(^4\),\(^6\),\(^8\),\(^9\)

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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REFERENCES