Subcutaneous Treprostinil for Pulmonary Hypertension in Chronic Lung Disease of Infancy

abstract

Pulmonary arterial hypertension (PAH) associated with chronic lung disease of infancy can be a life-threatening disease affecting an increasing number of former premature infants. There is a need for improved delivery of targeted PAH therapies for this subgroup of patients who have severe and persistent PAH despite standard respiratory care for chronic lung disease. Currently infants who have severe PAH despite oral or inhaled therapy receive continuous intravenous prostanoid therapy (mostly epoprostenol), which is complicated because of the need for central venous access and associated catheter-related complications.

We present a series of 5 infants who were successfully treated with a continuous infusion of subcutaneous treprostinil, which is a longer-acting prostanoid with similar hemodynamic effects. There were improvements in echocardiographic assessment of right ventricular function and estimated pulmonary hypertension, and in respiratory support required within weeks of therapy. Unlike commonly in adults, these 5 infants had no instances of severe site erythema, bleeding, bruising, or infection. In our experience with 5 former extremely preterm infants who had PAH associated with chronic lung disease, subcutaneous treprostinil was safe, efficacious, and well tolerated. We believe that subcutaneous treprostinil can be beneficial in a select group of former premature infants who have chronic lung disease and severe pulmonary arterial hypertension who have not responded adequately to conservative therapies. Pediatrics 2014;134:e274–e278

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KEY WORDS
extreme prematurity, pulmonary arterial hypertension, chronic lung disease of infancy, treprostinil

ABBREVIATIONS
iNO—inhaled nitric oxide
IV—intravenous
PAH—pulmonary arterial hypertension
PAH-CLD—pulmonary arterial hypertension associated with chronic lung disease
RV—right ventricle
SC—subcutaneous
SCTre—subcutaneous treprostinil

Dr Krishnan conceptualized and designed the case study, supervised the treatment protocols, and revised the final manuscript; Dr Rosenzweig conceptualized and designed the case study, supervised the treatment protocols, and revised and reviewed the final manuscript; Dr Ferdman drafted the initial manuscript and collected the data; Dr Zuckerman supervised the treatment protocols and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Pulmonary arterial hypertension (PAH) is a life-threatening disease of progressive pulmonary vasoconstriction and vascular remodeling, leading to right ventricular (RV) failure. PAH associated with chronic lung disease (PAH-CLD) of infancy (formerly known as bronchopulmonary dysplasia) is thought to have elements of both Group I (PAH) and Group III (lung disease-related) pulmonary hypertension. Initial treatment includes adequate respiratory management, treatment of aspiration and reactive airway disease, and control of exacerbating factors, such as systemic hypertension and left ventricular diastolic dysfunction. Despite these measures, however, some patients may require targeted pulmonary vasodilator therapy to demonstrate clinical improvement, either oral medications used alone or in combination with prostanoids. Continuous intravenous (IV) epoprostenol is added in severe and refractory PAH, but this is complicated in infants and small children owing to the need for central venous access and associated catheter-related complications, including infections, catheter breakage, loss of venous access, and thrombosis. Furthermore, the short half-life of epoprostenol increases the risk associated with infusion interruptions attributable to line breakage or inadvertent bolus, especially in young children. There is a need for an alternate delivery system to potentially reduce these complications.

Treprostinil is an alternative prostanooid formulation delivered either IV or subcutaneously (SC), has a longer half-life (4 hours) than epoprostenol (minutes), and is stable at room temperature. In the past, pediatric PAH specialists were reluctant to use subcutaneous treprostinil (SCTre) in young children because of the significant infusion site pain described in older patients. This is the first reported use of SCTre in select infants who have PAH-CLD.

**PATIENT CHARACTERISTICS**

Five patients were identified as appropriate for SCT therapy at our institution in the past year. All were former premature infants, born at a gestational age of 23 to 26 weeks, birth weight of 470 to 653 g (Table 1), and who had already required the addition of targeted PAH treatment to conservative management for PAH-CLD. Patients 1 to 4 were younger than 1 year of age when started on SCTre, after failure of oral and inhaled therapies. Patient 5 was already on IV epoprostenol via an indwelling catheter and was electively transitioned to SCTre because of multiple hospitalizations for line breakages and infection. All the infants required prolonged respiratory support and had multiple gut and respiratory infections. Patients 1 through 4 had multiple brief cardiorespiratory arrests secondary to PAH crises needing resuscitation and inotropic support during their hospital stay. None of the patients had systemic hypertension at the time of SCTre initiation; rather, several continued to require inotropes for hypotension. Echocardiograms done because of increasing need for respiratory support revealed severe pulmonary hypertension, RV dysfunction, and right-to-left atrial and dural shunts. Cardiac catheterization was performed in 4 patients under general anesthesia (Table 1). Because of severe desaturation, 3 infants were already on nitric oxide (iNO) during their baseline hemodynamics. Patient 2 had a concern for pulmonary vein stenosis on echocardiogram and so underwent angiography of all 4 pulmonary veins demonstrating a mild narrowing of the left lower pulmonary vein with the remainder unobstructed.

**OUR TREATMENT PROTOCOL**

At initial presentation of acute PAH crises, iNO was started along with milrinone infusion to support the failing RV. Oral (or IV) sildenafil (followed by bosentan in patients 1 and 5) was added to the therapy, with attempts at weaning iNO. In patients 1 through 4, inhaled iloprost was initiated at 1 to 5 (median 3) mcg every 1 to 4 (median 2) hours, before starting SCTre. Patient 5, who had been on IV epoprostenol, was initially transitioned to IV treprostinil and subsequently converted to SCTre.

SCTre was initiated at 1.25 ng/kg/min via an in-house pump at a concentration of 0.1 mg/mL. The dose was titrated up by 1.25 ng every 12 to 48 hours as tolerated. They were monitored closely for adverse effects, including increasing oxygen requirement or ventilator support, hypotension, irritability, feeding intolerance, and diarrhea. Patients 1 through 4 were already receiving sedation owing to their ventilator support and did not require additional medication. Patient 5 did not require any use of analgesic medication. Once the target dose of 20 ng/kg/min was reached, the increase was slowed to 1.25 ng/kg/once weekly until discharge or side effects. Concentration was increased as needed up to 1 mg/mL. Patient caregivers were trained on medication preparation, sterile techniques, pump use, and subcutaneous delivery, and educated on the side effects. Patients were discharged only after training was complete. As outpatients, the dose titration is every 3 to 4 weeks, with the assistance of specialty pharmacy and home nursing. There were no local reactions, evidence of pain or tenderness at the infusion site (Fig 1A and B), and no systemic side effects. The infusion sites were changed every 2 to 4 weeks to prevent local reactions or if the infusion cannula inadvertently came off. Infusion sites included the back of the arms, over the thighs, and abdomen.

**FOLLOW-UP DATA**

All patients had improvements in respiratory and inotropic support and echocardiogram parameters after SCTre initiation (Table 2). They were monitored...
for ventilation perfusion mismatch and none had worsening of respiratory status acutely or throughout treatment initiation. Patients 1 and 2 were both ventilator-dependent initially and now are home breathing room air. Patient 3 had ongoing necrotizing enterocolitis and sepsis, and although he initially improved hemodynamically, he died of septic shock 3 weeks after starting SCTre. Patient 4 was discharged to a chronic care facility on 35% FiO\(_2\) (via tracheostomy) after 4 months on SCTre. Patient 5 had been on 1/2 L oxygen via nasal cannula at home. Soon after transition from IV epoprostenol to SCTre she was weaned to room air with no right-to-left shunting at the patent ductus arteriosus. iNO was weaned off 3 weeks after SCTre initiation in patients 1 and 2, and by 6 weeks in patient 4. Patients 2 and 4 were on inhaled iloprost, and were weaned off within 2 weeks after initiation.

**DISCUSSION**

Very low birth weight infants are at risk for severe lung injury and CLD, secondary to hypoalveolarization and prolonged ventilation. A subset of these patients develop associated PAH. When PAH becomes severe, these infants are at high risk for death.\(^5\) Currently no clear guidelines exist for the treatment of these infants. Targeted PAH therapies available include endothelin-receptor antagonists, phosphodiesterase type-5 inhibitors, and prostanoids. Often patients who have severe PAH are on a combination of drugs from multiple categories.\(^6\) Although none of these therapies are FDA-approved for use in infants and children, PAH specialists judiciously use these therapies in managing sick children.

Aside from iNO, intravenous prostacyclin (epoprostenol), was the first targeted

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**TABLE 1** Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case No.</th>
<th>Case No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td>653</td>
<td>470</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>Gender</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>Age at PAH diagnosis (wk)</td>
<td>15</td>
<td>31</td>
</tr>
<tr>
<td>Diagnostic catheterization</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Age (wk)</td>
<td>20</td>
<td>36</td>
</tr>
<tr>
<td>Baseline rest state FiO(_2) 35% iNO 4 ppm</td>
<td>FiO(_2) 60% iNO 16 ppm</td>
<td></td>
</tr>
<tr>
<td>SAPm (mm Hg) 69</td>
<td>58</td>
<td>FiO(_2) 21%</td>
</tr>
<tr>
<td>PAPm (mm Hg) 31</td>
<td>35</td>
<td>FiO(_2) 40%</td>
</tr>
<tr>
<td>PCPm (mm Hg) 9</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Mean RAP (mm Hg) 6</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>CI (L/min/m(^2)) 3.09</td>
<td>3.8</td>
<td>50</td>
</tr>
<tr>
<td>Qp:Qs 1.1</td>
<td>1.2:1*</td>
<td>11</td>
</tr>
<tr>
<td>PVRI (WU(^{m^{-2}}) 7.8</td>
<td>9</td>
<td>3.9</td>
</tr>
<tr>
<td>PVRI (WU(^{m^{-2}}) on AVT on 4.3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Atrial septal defect yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Comorbidities CLD, NEC</td>
<td>CLD, NEC, recurrent sepsis</td>
<td>CLD, intestinal perforation</td>
</tr>
<tr>
<td>H/o cardiopulmonary arrest yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ASD, atrial septal defect; AVT, acute vasoreactivity testing with iNO 80 ppm; CI, cardiac index; CLD, chronic lung disease; NEC, necrotizing enterocolitis; Fap, right atrial pressure; PAPm, mean pulmonary artery pressure; PCPm, mean pulmonary capillary wedge pressure; PDA, patent ductus arteriosus; PVRI, pulmonary vascular resistance index Qp/Qs, ratio of pulmonary to systemic blood flow; SAPm, mean systemic artery pressure; WU, Woods units.

* Baseline data collected on 5 ppm iNO, and AVT 80 ppm. > (could not be weaned lower on FiO\(_2\) or iNO).

\(^b\) All values obtained under general anesthesia.

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**FIGURE 1**

Infusion sites over the A, thigh and B, arm in patient 1.
PAH therapy with demonstrated efficacy in children; however, there are many potential complications of continuous intravenous therapy. Adult data have shown the effectiveness of SCTre. Transition from IV epoprostenol to SCTre has been reported without clinical deterioration in adults and children. Adverse effects of the SC infusion include site pain in 89% to 92% of adults, and site reactions in 81% to 100%. In adults, 23% discontinued SCTre owing to adverse effects, mainly site pain. Typically this is managed with the use of a preferred site, frequent site changes, oral and topical analgesics, and rapid increases in dosage to goal.

Levy et al reported on 8 children (ages 1.5 to 10 years, median 4 years) who were started on SCTre after failure of oral medications. A total of 5/8 patients had congenital heart defects and 3 had idiopathic PAH. All had suprasystemic pulmonary artery pressure. There was no mention of prematurity in any patients. Follow-up ranged from 6 to 18 months; at last follow-up, 6 improved and 2 died. Unlike our experience, they had significant local site pain requiring analgesics. One child required narcotics, and transitioned to IV epoprostenol after 6 months of SC therapy. There were no serious adverse events related to the treprostinil.

In our single-center experience, all 5 patients tolerated initiation of SCTre and demonstrated clinical and echocardiographic improvement (Table 2). All patients were former premature infants who were critically ill and refractory to conventional therapies. Because of the novel administration of the medication, extra training was required for the intensive care nursing staff. There were no instances of severe site erythema, bleeding, bruising, or infection. The patients were not irritable or noted to withdraw the limb with the infusion site, even when the limb was examined or handled. This has

<table>
<thead>
<tr>
<th>TABLE 2: Patient Characteristics at Initiation of SCTre and Latest Follow-Up</th>
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<tbody>
<tr>
<td>Case No.</td>
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<tr>
<td>---------</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
</tbody>
</table>

Echo parameters:
- RV systolic dysfunction: Mild
- Estimated PH: Normal
- TR jet (mm Hg): Normal
- Inotrope support: None
- Other PAH meds: Sildenafil
- Respiratory support: Ventilator
- Oxygen: 80%

- Milrinone
- Epoprostenol
- Iloprost
- PDA, patent ductus arteriosus; PH, pulmonary hypertension; RV, right ventricular; TR, tricuspid regurgitation; n/a, not applicable; dagger, not sufficient to quantify right ventricle pressure.

- Insufficient tricuspid regurgitation to obtain an accurate TR gradient estimate.
been the experience with other centers managing these patients as well. This suggests pain perception and development of local inflammation may be different in the premature infant compared with the term infant, and certainly is different than in adults. Preterm infants with chronic lung disease may be more suited to tolerate SC infusions than older patients. Anand et al suggest that immature cortical nociceptive response circuitry make them better suited to tolerate SC infusions than older infants. Additionally, the soft and loose subcutaneous tissue in infants may prevent the local accumulation and reaction seen in adults. This makes this subgroup of former preterm infants who have PAH-CLD ideal candidates for SCTre therapy if indicated.

As neonatal intensive care centers are becoming more skilled at caring for extremely premature infants who have improved overall survival, the population who have severe PAH-CLD may increase. Currently there are no long-term, randomized, controlled studies involving targeted PAH therapies for these patients. In our experience, SCTre was safe, efficacious, and well tolerated, and may enable safer delivery of a prostanoid to critically ill infants. As with any systemic pulmonary vasodilator, monitoring is critical for ventilation-perfusion mismatch in children who have lung disease, and therapy must be altered appropriately. We suggest this therapy should be considered for early use in infants who have severe PAH in centers with experience in the use of SCTre. Further study of SCTre is warranted in larger pediatric cohorts.

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