Current and Emerging Therapies in Pulmonary Arterial Hypertension: Focus on Treprostinil

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Abstract: Pulmonary arterial hypertension (PAH) is a progressive disease process with a high morbidity and mortality. Until the advent of epoprostenol, a continuous prostacyclin infusion therapy, PAH was uniformly fatal but for those few who responded to calcium channel blockers. The development of PAH specific oral therapies including endothelin antagonists and phosphodiesterase-5 inhibitors provide effective alternatives to intravenous epoprostenol for mild to moderately symptomatic persons. But while effective, a significant number of patients fail oral therapy and require combination oral therapy and progression to prostacyclins. While epoprostenol improves quality of life and average life span in PAH, a short 4 minute half life places patients at high risk for rapid decompensation with even short interruptions of the infusion. Additionally, epoprostenol requires a complicated delivery system including a large pump and an indwelling central line that carries risk of infection and sudden occlusion. The second prostanoid developed was treprostinil which has the advantage of a 4 hr half life, stability at room temperature, and the ability to be continuously administered subcutaneously with a small pump. Subsequently, treprostinil was demonstrated to be safe and effective given intravenously and by inhalation. We will review the pharmacokinetics, dosing, metabolism, and side effects of treprostinil in its various forms and overall place in the treatment of PAH.

Keywords: pulmonary arterial hypertension, treprostinil, prostacyclins
Introduction

Pulmonary arterial hypertension (PAH) encompasses a group of diseases characterized by a pulmonary arteriopathy and unique plexiform lesions that lead to an increase in pulmonary artery pressure and pulmonary vascular resistance and progressive right ventricular failure and death. The most recent expert consensus classification of pulmonary hypertension was published from the Dana Pointe meeting in 2008 (see Table 1, Simonneau et al)\(^1\). The diagnosis of PAH (Group 1) pulmonary hypertension requires a thorough clinical evaluation that excludes other causes of pulmonary hypertension (PH) including left heart and valvular heart disease, chronic lung disease or hypoxemia, pulmonary thromboembolism, and other rare causes with undefined mechanisms.\(^1\)

The prevalence of PAH is approximately 30–50 persons per million but there are certain high risk groups for which the incidence is considerably higher including familial PAH, connective tissue diseases, congenital heart disease, HIV, and portal hypertension. When PAH is suspected, a heart catheterization is necessary to assess the severity of pulmonary hypertension, vasodilator response to inhaled nitric oxide, detect intra-cardiac shunts, and exclude PH due to left heart disease. The hemodynamic criteria for PAH include a mean pulmonary arterial pressure (mPA) elevation $\geq 25$ mmHg in the setting of a pulmonary capillary wedge pressure $\leq 15$ mmHg or left ventricular end-diastolic pressure $\leq 15$ mmHg.

The most common causes of pulmonary hypertension are left heart failure and chronic lung disease and the treatment is that of the underlying heart or lung disease. Group 1 pulmonary hypertension or PAH affects less than 200,000 people in the US, which qualifies it as one of the orphan diseases. In the US and several other countries, orphan disease status provides the pharmaceutical industry financial incentives (tax loss) for performing clinical trials and 7 years of marketing exclusivity. That designation has resulted in FDA approval of several PH specific drugs over the past 15 years. The first PH specific drug, epoprostenol, was approved in 1995 based upon a 12 week open label study that compared epoprostenol to conventional care.

Table 1. Classification of Pulmonary Hypertension (Dana Point, 2008).

<table>
<thead>
<tr>
<th>1. Pulmonary arterial hypertension (PAH)</th>
</tr>
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<tbody>
<tr>
<td>a. Idiopathic PAH</td>
</tr>
<tr>
<td>b. Heritable</td>
</tr>
<tr>
<td>c. Drug- and toxin-induced</td>
</tr>
<tr>
<td>d. Associated conditions:</td>
</tr>
<tr>
<td>i. Connective tissue diseases</td>
</tr>
<tr>
<td>ii. HIV</td>
</tr>
<tr>
<td>iii. Portal hypertension</td>
</tr>
<tr>
<td>iv. Congenital heart disease</td>
</tr>
<tr>
<td>v. Chronic hemolytic anemia</td>
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</tbody>
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<table>
<thead>
<tr>
<th>2. Pulmonary hypertension secondary to left heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Systolic dysfunction</td>
</tr>
<tr>
<td>b. Diastolic dysfunction</td>
</tr>
<tr>
<td>c. Valvular disease</td>
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</tbody>
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<table>
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<tr>
<th>3. Pulmonary hypertension secondary to lung diseases and/or hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>b. Interstitial lung disease</td>
</tr>
<tr>
<td>c. Mixed restrictive and obstructive pattern</td>
</tr>
<tr>
<td>d. Sleep-disordered breathing</td>
</tr>
<tr>
<td>e. Alveolar hypoventilation disorders</td>
</tr>
<tr>
<td>f. Chronic exposure to high altitude</td>
</tr>
<tr>
<td>g. Developmental abnormalities</td>
</tr>
</tbody>
</table>

| 4. Chronic thromboembolic pulmonary hypertension               |

| 5. Pulmonary hypertension secondary to unclear mechanisms      |
| a. Hematologic disorders: eg, myeloproliferative disorders, splenectomy |
| b. Systemic disorders: eg, sarcoidosis, vasculitis, chronic renal failure on dialysis |
| c. Metabolic disorders: eg, hypo- or hyperthyroidism            |


Figure 1. Targets for current or emerging therapies in PAH. Reprinted with permission from Humbert, M et al. Treatment of Pulmonary Arterial Hypertension. NEJM 2004; 351:1425–1436.
in primary pulmonary hypertension (PPH, now idiopathic or IPAH). Subsequent trials have been randomized and controlled with primary endpoints improved distance in a standardized 6-minute walk, and secondary endpoints improvement in functional status (expressed as World Health Organization functional class I-IV) and hemodynamic indices. The trials have been limited to pulmonary arterial hypertension with the majority being idiopathic, familial, connective tissue diseases (particularly scleroderma), anorexigens, and congenital heart disease. Most trials have excluded patients with portal pulmonary hypertension and HIV.

Prior to the introduction of epoprostenol, the mean survival from the time of diagnosis of PPH was 2.5 years. Therapy included diuretics, systemic vasodilators, digoxin, oral anticoagulation, and in some centers lung or heart/lung transplantation, and atrial septostomy. In the mid-1980s, calcium channel blockers (CCB) were introduced, though in practice only a small percentage of patients with pulmonary hypertension benefit from long-term treatment.

As our understanding of the pathobiology of PAH has progressed, so have the number of available pharmacotherapies. Today there are 3 PAH specific FDA drug classes approved: oral endothelial antagonists, oral phosphodiesterase-5 inhibitors, and parenteral (intravenous, subcutaneous, inhaled) prostanoids (see Figure 1). The mean survival has dramatically improved in the modern era. The goal of this review is to summarize the clinical profile of treprostinil and how it fits into the spectrum of therapies available for the treatment of PAH.

Pathobiology of PAH and Therapeutic Targets

Pulmonary arterial hypertension (PAH) is a complex disorder with multiple contributing pathologic pathways. Vascular wall remodelling (thickening), pulmonary vasoconstriction, endothelial and smooth muscle cell dysfunction, and in situ thrombosis each contribute to the development of PAH. In the normal pulmonary vasculature, vasodilation and anti-proliferation are mediated by endothelial derived prostacyclin and nitric oxide, whereas vasoconstriction is stimulated by endothelial derived endothelin-1. Each of these identified mediators has been targeted for pharmacologic therapy in PAH.

Prostacyclin and prostacyclin synthase are reduced in pulmonary vascular endothelial cells in PAH. Endogenous pulmonary vascular prostacyclin (PGI₂) effects include vasodilation, inhibition of platelet aggregation, anti-inflammatory, and antiproliferative by decreasing secretion of extracellular matrix.

The endothelin antagonists (ETA) inhibit the vasoconstrictive and proliferative effects of endothelin. Both the non-selective ETA bosentan (Tracleer®) and selective ETA ambrisentan (Letairis®) are FDA approved and effective treatments for PAH. Each has been associated with improved 6-minute walk distance, functional status, and hemodynamics in placebo controlled trials, and improved survival compared to historical controls. Phosphodiesterase-5 inhibitors (PDE-5i) enhance the effect of pulmonary vascular nitric oxide by inhibiting the metabolism of cyclic GMP. The FDA approved PDE-5i’s [sildenafil (Revatio®) and tadalafil (Adcirca®)] have an efficacy comparable to the ETA’s.

Epoprostenol

Epoprostenol sodium (Flolan®, GlaxoSmithKline, Research Triangle Park, North Carolina, Veletrï®, Actelion Pharmaceuticals, San Francisco, California, and generic epoprostenol sodium, Teva Pharmaceuticals, North Wales, Pennsylvania) (see Figure 2) is an intravenous formulation of prostacyclin (PGI₂) which stimulates adenylate cyclase and increases production

![Chemical structures of epoprostenol and treprostinil.](image-url)
of cAMP leading to potent vasodilation of systemic and pulmonary vascular beds. Continuous intravenous prostacyclin therapy was introduced in the mid-1990s and revolutionized the treatment and survival of patients with IPAH. Because of the long term experience, relative safety when administered to critically ill patients with PAH, and as the only PAH therapy in which there was a demonstrated mortality benefit, epoprostenol has been the gold standard for severe PAH.

In 1982, the acute hemodynamic effect of intravenous epoprostenol was tested in seven patients with PPH. A mean dose of 5.7 ng/kg/min resulted in a reduction in pulmonary vascular resistance and an increase in cardiac output. Long term infusions (1–25 months) improved hemodynamics, exercise capacity, provided clinical stabilization, and became useful as a bridge to lung transplantation for patients with severe PAH. The hemodynamic effects of long term epoprostenol in IPAH and PAH with associated conditions include a decrease in mPA (mean 15 mmHg or 22%) and PVR (mean 8.8 RU or 53%), and more robust increase in cardiac output (mean 2.53 L/min or 67%). The increase in cardiac output may be related to a decrease in right ventricular (RV) afterload, but possibly is also attributable to increased right heart inotropy via improvement of flow in the RV microcirculation.

The first randomized trial in 23 patients demonstrated improvement in functional class, exercise capacity, and pulmonary vascular resistance in the 10 patients in the treatment arm. Epoprostenol received FDA approval in 1995 after a 12 week multicenter randomized trial of 81 patients with PPH comparing epoprostenol to standard care. Epoprostenol was associated with improved survival, quality of life score, functional class, 6-minute walk distance, and hemodynamics. Soon thereafter, a pivotal twelve week study was conducted in 111 patients with PAH related to the scleroderma spectrum of diseases (SSc). Epoprostenol had a similarly favourable clinical outcome in SSc, though there was no change in mortality. Initial approval of epoprostenol was limited to PPH and SSc spectrum of diseases, but is currently used in all Group 1 PAH with advanced symptoms as well as Group 4 or chronic thromboembolic pulmonary hypertension (CTEPH). The benefits of epoprostenol have been demonstrated in observational studies in PAH related to congenital heart disease, HIV, portopulmonary hypertension, systemic lupus erythematosus, sarcoidosis, and CTEPH. Significant improvement in survival has been reported in two observational studies. McLaughlin et al reported that with epoprostenol therapy, the observed survival at 1, 2, and 3 years was 88%, 76%, and 63% compared to the expected survival predicted by the National Institute of Health (NIH) registry which was 59%, 46%, and 35%.

While highly effective in World Health Organization (WHO) functional class (FC) III and IV PAH, intravenous epoprostenol is difficult to administer and has important safety issues. As a constant intravenous infusion, for long term use it must be delivered through a permanent single-lumen, tunneled and cuffed central venous access device line (ie, Hickman catheter). Epoprostenol has a very short half-life of less than 5 minutes and even short interruptions can lead to cardiovascular collapse. It needs to be at a high pH after reconstitution (10.2–10.8) and must be mixed daily. Patients carry a relatively heavy ambulatory portable battery operated infusion pump, ie, the CADD-Legacy pump (Simms-Deltex). Because Flolan® and generic epoprostenol are unstable at room temperature, they must be prepared every 8 hours or daily and kept cold, necessitating ice packs. Veletri® is a novel epoprostenol that is stable at room temperature thus not requiring ice packs and for which several days of drug can be prepared in advance with changing of cassettes daily.

Eligibility for IV epoprostenol includes the approval of insurance for the specific indication, availability of a significant other to assist in preparation of the drug, ability to understand the patient’s responsibilities, and reasonable facile coordination for preparing and maintaining the treatment and care of the insertion site. Patients require an average of 3 days of hospitalization for initiation of therapy which includes insertion of the Hickman or other percutaneous access device, monitoring initial dose titration, and continuing education regarding sterile preparation of the medication, operation of the pump, and care of the Hickman catheter. Home education prior to the hospitalization helps shorten length of stay and improves patient confidence.

The FDA package insert (2008) recommends initial dosing start at 2 ng/kg/min with increases by 2 ng/kg/min every 15 minutes or longer as tolerated.
Treprostinil review

Treprostinil

Despite the advances and hope offered by epoprostenol, the complicated method of delivery, risk of interruptions to the constant infusion pump, risks of line infections, as well as rare events associated with the central venous catheter such as pneumothorax, venous thrombosis, and paradoxical embolus via a PFO or ASD, limit its use and motivated research and development of other agents such as treprostinil. The major advantages of this prostacyclin analog are its longer half-life and stability at room temperature, and ability to be given subcutaneously as a continuous infusion. Subcutaneous (SC) treprostinil received a provisional FDA approval in 2002 for patients with WHO functional class II-IV symptoms and full approval in 2006. Early animal studies suggested similarities between treprostinil and epoprostenol, but final approval was based on data from a clinical trial by Rubenfire et al that demonstrated short term equivalency to IV epoprostenol in patients with PAH.

Mechanism

Treprostinil sodium (Remodulin®) is a tricyclic benzidine prostacyclin analog (see Figure 2), which has a similar mechanism of action to epoprostenol. All prostacyclins cause vasodilation by activating membrane-bound adenylate cyclase which increases cyclic adenosine monophosphate (cAMP), and smooth muscle relaxation. All prostanoids reduce pulmonary smooth muscle cell remodelling, secretion of extracellular matrix, platelet aggregation and thrombosis, and enhance endothelial cell function. Perhaps one of the most significant actions of prostacyclins for patients with PAH is the potential for increasing inotropy of the right ventricle, as has been demonstrated with treprostinil in an in vitro study of rat ventricular cardiomyocytes.

Metabolism

Treprostinil is metabolized by the liver, although the exact enzymes have not been identified. Patients with hepatic insufficiency have up to an 80% decrease in metabolism of treprostinil. Caution is recommended when administering treprostinil to patients with severe hepatic insufficiency, though no specific trial has addressed dosing in these patients. Patients with mild or moderate hepatic insufficiency should be started at a lower initial dose with more cautious titration. Treprostinil has not been specifically studied in patients with renal insufficiency. There is no known interference with the metabolism of digoxin, warfarin, or acetaminophen.

Pharmacokinetics

Absorption of subcutaneous treprostinil is rapid, complete, and 100% bioavailable. A study of healthy volunteers demonstrated that a dose of 10–15 ng/kg/min led to a rapid rise in plasma concentration with a peak occurring within 2 to 3 hours post infusion. Steady state pharmacokinetics of SC treprostinil in patients with PAH is dose proportional from 10 to 125 ng/kg/min. The average elimination half-life of intravenous treprostinil is 4.4 hours and subcutaneous treprostinil is 4.6 hours; these formulations are considered bioequivalent at steady state. Treprostinil is chemically stable in 0.9% sodium chloride and 5% dextrose solution or in sterile water, at room temperature, and close to neutral pH. Early comparisons of intravenous epoprostenol and intravenous treprostinil

Table 2. Average prostacyclin dosing in our pulmonary hypertension clinic.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mean dose (Standard deviation)</th>
<th>Median dose [Interquartile range]</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>ng/kg/min</td>
<td>ng/kg/min</td>
</tr>
<tr>
<td>IV epoprostenol</td>
<td>42.5 (22.2)</td>
<td>38 [31–51]</td>
</tr>
<tr>
<td>IV treprostinil</td>
<td>82.4 (49.4)</td>
<td>70.5 [58–102]</td>
</tr>
<tr>
<td>SC treprostinil</td>
<td>74.4 (33.1)</td>
<td>76 [43–93.5]</td>
</tr>
</tbody>
</table>
revealed a similar reduction in pulmonary vascular resistance acutely (22% and 20% respectively) at short term maximal tolerated doses. Since it is chemically stable at room temperature, treprostinil does not need ice-packs after mixing. The neutral pH of treprostinil and its solubility at physiological pH allows it to be administered subcutaneously with excellent bioavailability.

Clinical Studies and Efficacy
The pivotal study of subcutaneous treprostinil was a placebo-controlled, double-blind, randomized trial conducted in 24 centers in the United States, Europe, and Australia. Four hundred and seventy patients with PAH (idiopathic, associated with connective tissue disease or congenital systemic-to-pulmonary shunts) were followed for 12-weeks. The primary end point was improvement in exercise capacity as measured by the 6-minute walk distance. In the treatment arm, the placebo-corrected median improvement was a modest 16 meters, whereas there was no improvement in the placebo arm. However, patients in the highest quartile of dosing had the most significant improvement in exercise capacity with a 36 meter increase in 6-minute walk distance (doses greater than 13.5 ng/kg/min to a maximal trial dose of 22.5 ng/kg/min). Compared to placebo, there was also improvement in hemodynamics (mean right atrial pressure, mean PA, cardiac index, PVR, and mixed venous oxygen saturation) and Borg dyspnea scores. In comparison to the initial trials of epoprostenol in which patients with PPH improved 103 meters (placebo-corrected) and SSc related PAH improved 94 meters (placebo-corrected), the 16 meter improvement reported with treprostinil was notably inferior. However, there are several reasons for these findings. Perhaps most importantly, the average treprostinil dosing was inadequate since patients at higher doses had more improvement. The treprostinil study also had broader entry criteria that included WHO functional class II patients, greater baseline 6-minute walk distances, and congenital heart disease patients who had not previously been enrolled in the placebo controlled 12 weeks studies. In a subset of patients with connective tissue disease, treatment with treprostinil led to a 21-meter placebo-corrected improvement in 6-minute walk distance.

An observational study of 860 patients with PAH treated with subcutaneous treprostinil was reported by Barst et al in 2006. Patients were followed for 4 years; 23% discontinued the medication due to adverse events; 11% were switched to an alternative prostacyclin analogue; and 15% had a second PAH therapy added. The Kaplan-Meier estimates of survival at 1, 2, 3, and 4 years were 87%, 78%, 71%, and 68%, respectively. Among patients with IPAH and documented baseline hemodynamic assessment, survival estimates were 91%, 82%, 76%, and 72% versus the predicted survival of 69%, 56%, 46%, and 38% based on the NIH registry.

Administration
Treprostinil is stable at room temperature with a neutral pH. The drug comes in premixed syringes obviating the need for daily mixing. It is supplied in 20 mL vials at four strengths: 1 mg/mL, 2.5 mg/mL, 5 mg/mL, or 10 mg/mL and infused via a small, lightweight pump such as the MiniMed (Sylmar, CA). Patients self-administer the medication by inserting a small catheter under their skin, typically in the abdomen, upper thighs (rarely tolerated), or high buttocks for continuous infusion. Approximately 10% of patients experience severe pain and may need to switch to IV or inhaled prostanoids. There is no way to predict who will have significant pain, and the symptoms are not dose-related. Historically, based upon clinical trials patients were recommended to change sites every 3 to 4 days. But after extensive clinical patient experience, it became clear that site pain tends to decrease with time, and patients can keep certain sites for several weeks. SC treprostinil is typically started at home with assistance of the experienced home health care nurses and the guidance of the pulmonary hypertension specialist.

Place in Therapy
FDA approval for subcutaneous treprostinil treatment in PAH includes WHO functional class II to IV symptoms. In our practice, treprostinil is frequently used for newly diagnosed patients who are WHO FC class III and high risk based upon hemodynamics, limited 6-minute walk distance, reduced kidney function, and those who fail to improve or deteriorate despite oral therapy with or without inhaled prostanoids. We also use subcutaneous treprostinil in patients with more than one infection on IV prostanoids, WHO FC IV patients with moderate hemodynamic compromise,
those not capable of compliance with or who refuse the indwelling catheter, and those who live a long distance from emergency services. The choice between intravenous prostanooids and SC treprostinil is made based upon extensive clinical experience, and an informed patient/family preference.

**Dosing and Titration**

No specific dosing schedule is widely agreed upon. Institutions have specific protocols which frequently differ from the recommendations on the package labeling. In general, treprostinil is started at a low dose and then up-titrated to balance an improvement in symptoms with limited side effects. The FDA approved recommendation is 1.25 ng/kg/min as the initial starting dose, with increases by 1.25 ng/kg/min per week for the first 4 weeks, and 2.5 ng/kg/min per week thereafter in patients without hepatic insufficiency. This recommendation is based on the pivotal trials in which the maximum dose achieved was 22.5 ng/kg/min.

Dose was thought to be related to the severity of infusion site pain, and therefore early studies adhered to a low dose, slow-titration regimen. Subsequent studies have shown that pain severity is not dose dependent. A study of 23 patients by Skoro-Sajer and colleagues compared slow- and rapid-escalation dosing regimens. The slow-escalation regimen began at 2 ng/kg/min with weekly dose increments of 1.25–2 ng/kg/min. The rapid-escalation group started at 2.5 ng/kg/min with dose increase of 2.5 ng/kg/min on days 2 and 4 and further increments of 2.5 ng/kg/min at weekly or biweekly intervals. By 12 weeks, the rapid-escalation group was on an average dose of 20.3 ng/kg/min versus the slow-escalation group at 12.9 ng/kg/min, and rapid-escalation was associated with more significant improvement in functional status and exercise capacity. The authors concluded that it was safe and effective to reach a target dose of 12–15 ng/kg/min within 4–6 weeks. All patients had infusion site erythema and induration, but patients in the rapid-dose escalation group actually reported less pain. Several studies have shown that higher doses of treprostinil are associated with greater improvement in 6-minute walk distance, while most clinical trials used relatively low doses. Regardless of the specific prostanoid or infusion site, potential serious errors in medication administration include incorrect cassette placement in the pump, incorrect pump programming, incorrect drug dosing, and inadvertent cessation of the pump (each of which is increased in IV administration and hospitals with little experience with the prostacyclin therapies).

**Safety**

The complexity of continuous infusions of parenteral prostacyclin greatly increases the risk of errors that place patients at risk of morbidity and even death. While no clinical trials have been performed to assess the relative safety of IV versus subcutaneous prostanooids, the latter are not associated with bacteremia (1/1000 patient days with IV and can be fatal), and sudden loss of catheter function by fracture, kinking, or thrombosis and the need for emergent IV access. A recent survey of PH experts concluded that serious errors occur because of variability in hospital policies, use of home versus hospital infusion pumps, and variation in the use and storage of back-up medications. Regardless of the specific prostanoid or infusion site, potential serious errors in medication administration include incorrect cassette placement in the pump, inaccurate pump programming, incorrect drug dosing, and inadvertent cessation of the pump (each of which is increased in IV administration and hospitals with little experience with the prostacyclin therapies).

**Side Effects**

All prostacyclin analogs (intravenous epoprostenol, inhaled iloprost, and both intravenous and SC formulations of treprostinil) have similar side effects
including nausea, diarrhea, flushing, jaw pain, vomiting, headache, dizziness, foot pain, and anxiety. Thrombocytopenia (range 50–100K) occurs in about 10% of those on epoprostenol and is less common with treprostinil. The most common adverse effects of SC treprostinil are infusion site pain and inflammation, erythema/induration, and bleeding/bruising.

### Site Pain

Subcutaneous treprostinil results in site pain which can be severe. Between 5 and 23% of patients started on SC treprostinil discontinue the medication due to intolerable site pain.\(^{45,46,48,51}\) Infusion sites are typically the subcutaneous abdominal fat, outer hips and much less commonly thighs and underside of the upper arm, which can all be associated with mild-to-moderate erythema and inflammation, warmth, mild bleeding, and induration. Among patients studied by McLaughlin et al in 2003,\(^{45}\) 88% had infusion site pain and 94% had infusion site erythema versus 22% in the placebo arm. With improvements in managing site pain, most patients are able to tolerate treprostinil.\(^{48,50}\) There is no way to determine which patients will have severe reactions and intolerable pain.

Pain remedies include topical application of heat or cold, topical analgesics, anti-inflammatory agents, and oral analgesics (ie, NSAIDS). In early trials, sites were changed every 1 to 3 days, but as discussed site pain tends to improve after the infusion has continued for several days in the same location. Generally, pain at a new infusion site is maximal after 2 to 5 days, improving after 5 to 7 days. In a group of 24 patients followed closely for site pain, the pain had largely abated 9 days after a site change\(^{54}\) which reinforces the concept that keeping sites in longer makes the infusion pain more tolerable. Patients may have the most success when a site is maintained for 4 or more weeks.\(^{50,51}\)

Furthermore, as patients are treated for longer periods of time, site pain and erythema tends to improve over several months of therapy. It is unknown if this is related to subjective patient tolerability or the development of an organic biochemical tolerance.

The cause of infusion site pain is not completely understood. Prostanoids are known to both inhibit and promote inflammation, and can intensify the reactions that are induced by bradykinin and histamine.\(^{45}\) They can act both centrally and peripherally to increase pain sensation,\(^{39}\) which may also explain other side effects such as jaw pain, headache, and extremity pain which may be neuropathic, muscular, and joint mediated.

A variety of pain management techniques are utilized at centers that specialize in pulmonary hypertension (see Table 3). Pluronic lecithin organogel (PLO gel) has been developed for both prevention and treatment of site pain and is provided in 4 graduated strengths. Other topical therapies such as ice or heat and lidocaine patches are also first-line therapies. Oral agents include acetaminophen, gabapentin, and tramadol. Using a dry needle-catheter to initiate an infusion site is believed to be helpful by separating the local trauma of the catheter placement from the vasodilatory and inflammatory effects of the medication infusion. Ensuring the needle has no drug on the tip after priming can reduce local inflammation. One study utilized a technique that involved a thin Duoderm (ConvaTec Inc, Skillman, NJ) patch with PLO gel, as well as oral agents and psychological support to achieve a 100% compliance rate among 12 patients over a 16-week period.\(^{57}\) For the most effective pain management plan, several techniques will often need to be used in concert with support and advice by nurses and other health care professionals.

### Table 3. Methods of improving site pain.

| Maintain sites as long as possible (4 or more weeks) |
| Abandon unfavorable sites quickly |
| Every 72 hours: change medication, syringe, and tubing to improve sterility |
| Rapid dose titration |
| Removing medication droplets from the needle tip after priming |
| Low pump rate (less than 0.020 mL/h) to decrease volume of infusion |
| Pretreatment with anti-inflammatory agents (local medication and oral H1 and H2 antagonists) |
| Preplacement of a dry catheter: separation of local trauma of the needle/catheter from the medication effects (vasodilation, inflammation) |
| Topical therapies: eg, ice, PLO gel, lidocaine patches, Duoderm patches |
| Oral anti-inflammatory agents: eg, H1 and H2 antagonists |
| Oral pain medication: acetaminophen, gabapentin, narcotics as last-line |
| Alternative nonpharmacologic therapies: massage, acupuncture, acupressure, relaxation techniques, psychological support |
Treprostinil review

Intravenous Treprostinil

Intravenous and SC treprostinil have the same formulation with the same pharmacology, bioavailability, and hemodynamic effects. Due to intolerable site pain, some patients who start on SC treprostinil may switch to intravenous therapy, and those on successful intravenous therapy can switch to SC for safety and convenience. SC treprostinil would be preferred over IV in the setting of an atrial septal defect or functional patent foramen ovale because of the potential risk of paradoxical thromboemboli.

A recent study demonstrated that during 12 weeks of treatment with intravenous treprostinil, patients had an improvement in exercise capacity, increasing the 6-minute walk distance an average of 83 meters, reducing the Borg dyspnea score by a median of 2 units, and improving NYHA functional class from III to II. There was also a decrease in plasma angioptoin-2 levels in patients treated with treprostinil. An earlier multicenter study of 14 de novo patients with PAH treated with intravenous treprostinil for 12 weeks also showed an improvement in 6-minute walk distance, Borg dyspnea score, and hemodynamics. Intravenous treprostinil is initiated in a monitored hospital setting by physicians experienced in the diagnosis and treatment of PAH with appropriate inpatient and outpatient nursing and pharmacy support. The dosing and adverse effects are similar to that for subcutaneous treprostinil, with the exception of subcutaneous site pain. Intravenous prostanoids are associated with a risk of bacteremia, which may be fatal. The reported prevalence is 0.15 per 1000 days of therapy. An increase in bacteremia, particularly gram negative, was reported in association with treprostinil. One potential explanation suggests the alkaline pH of the diluent used for epoprostenol, Sterile Diluent for Flolan (SDF), may have better antimicrobial properties than sterile saline or water, which have been used for treprostinil. Changing the treprostinil diluent to SDF led to improved antimicrobial activity against gram negative bacteria.

Transition from Epoprostenol to Treprostinil

In 2007 a study showed that patients receiving intravenous epoprostenol could be safely transitioned to subcutaneous treprostinil. This was a small, multicenter trial of 22 patients, WHO functional class II-III on stable doses of epoprostenol who were transitioned to SC treprostinil or placebo during a 2 week hospital stay and monitored for 8 weeks for signs of clinical deterioration. It was concluded that patients could be safely transitioned from IV epoprostenol to SC treprostinil without clinical worsening. The study was not powered to compare the two medications directly, though the authors described secondary end points of 6-minute hall walk and Borg dyspnea scores and found the two groups were comparable. They also reported that the mean maximum dose of treprostinil was 153% of the epoprostenol dose, on the basis of nanograms per kilogram per minute. Subsequent to this study, the US FDA approved the use of treprostinil for patients transitioning off of epoprostenol therapy. Another study of 27 patients successfully transitioned from IV epoprostenol to IV treprostinil in an open label 12 week study. Vachiery and colleagues reported that transition between epoprostenol and treprostinil can be done

Table 4. Cost comparison of pulmonary arterial hypertension therapies.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Labeled indication</th>
<th>Dose</th>
<th>Drug cost/year/pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV epoprostenol (Flolan)</td>
<td>WHO FC III and IV</td>
<td>30–40 ng/kg/min</td>
<td>$48,027 to $63,620a</td>
</tr>
<tr>
<td>SC/IV treprostinil (Remodulin)</td>
<td>WHO FC II-IV</td>
<td>60–70 ng/kg/min</td>
<td>$142,350c 75</td>
</tr>
<tr>
<td>Inhaled treprostinil (Tyvaso)</td>
<td>WHO FC III</td>
<td>18–54 mcg INH 4x daily</td>
<td>$176,880 (40 ng/kg/min)74</td>
</tr>
<tr>
<td>Inhaled iloprost (Ventavis)</td>
<td>WHO FC III and IV</td>
<td>2.5–5 mcg INH 6–9x daily  (10 mcg/mL)</td>
<td>$104,755b 78</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5–5 mcg INH 6–9x daily (20 mcg/mL)</td>
<td>$162,67074</td>
</tr>
</tbody>
</table>

Notes: a For drug and diluent alone; b For first year, add $980 for start-up costs which cover device and back-up; c For first year, add $3350 for start-up costs which cover device, medication chambers, and back-up.
in the hospital over a short period of time by physicians experienced in the use of these medications. A “rapid switch” protocol was assessed by Sitbon and colleagues in a small uncontrolled trial where the infusion pump containing epoprostenol was swapped out for a cassette containing treprostinil, without any gradual dose changes. This technique of switching IV epoprostenol to IV treprostinil was found to be safe and efficacious over 12 weeks.

When using IV treprostinil at our Pulmonary Hypertension Center, we use similar dosing as with SC treprostinil for initiation, uptitration, and long-term maintenance. Transition from IV epoprostenol to subcutaneous or IV treprostinil or from treprostinil to epoprostenol is individualized and conducted in the hospital unit experienced with prostacyclins and PAH. A dosing protocol is written for each patient prior to starting with notation of specific times and doses. Dosing changes are only made during daytime hours and can take anywhere from hours to a few days depending on the dose. If there are any symptoms of prostacyclin excess (hypotension, or severe nausea, vomiting or headache), epoprostenol is decreased by at least 2 ng/kg/min. Our average dose of treprostinil is about 1.85 times higher than epoprostenol.

**Combination Therapy**

Treprostinil is frequently used in combination with oral therapies including PDE-5i and ETA’s, although relatively few trials have studied combination therapy. A retrospective study of 38 patients treated with subcutaneous treprostinil showed improved functional class, 6-minute walk distance, Borg dyspnea score, and hemodynamics. Nineteen patients had bosentan added and were found to have additional improvement in pulmonary arterial pressure, 6-minute walk distance, and Borg dyspnea scale compared to baseline. Among 20 patients with PAH in a multicenter open-label 12 week study who were treated with oral therapy (a PDE-5i, ETA, or both) who had continuous IV or SC treprostinil sodium added to their treatment, there was a 35 meter improvement in 6-minute walk distance by week 12 with a trend toward improvement in Borg dyspnea score. Of the 20 patients, three discontinued therapy prematurely; one had a central line infection, one died due to worsening PAH, and one was lost to follow-up. Combination therapy was well-tolerated.

**Inhaled Treprostinil**

Inhaled treprostinil (Tyvase®, United Therapeutics Corporation, Research Triangle Park, North Carolina) became available in 2009 after FDA approval for patients with PAH and functional class III symptoms. The first inhaled prostacyclin analog, iloprost (Ventavis®, Actelion, San Francisco, California) was approved in December 2004 for PAH patients with WHO FC class III or IV symptoms and in other countries it is also approved for patients with CTEPH. The advantage of an inhaled therapy is selective pulmonary vasodilation with less systemic effects, as well as the absence of indwelling catheters and continuous infusions. There have been no studies comparing the efficacy of inhaled prostanooids to IV epoprostenol or IV or SC treprostinil. Because of the limited ability to achieve very high blood levels with inhaled prostanooids, the therapeutic efficacy is lower than with continuous infusions. While an attractive option, the safety and efficacy of transitioning patients from continuous infusions to inhaled prostanooids has not been established.

**Pharmacokinetics**

The half-life of inhaled treprostinil is 44–52 minutes as compared to inhaled iloprost which is 20–30 minutes. When administered at a dose of 30 ug, the time to maximum concentration was 15 minutes, and at a dose of 45 ug was 45 minutes. Inhaled treprostinil was reported to have sustained improvement in PVR reduction for 3 hours after administration, with a near-maximal acute PVR decrease at a dose of 30 ug. It can be safely and effectively administered with a metered dose inhaler.

**Clinical Studies: Efficacy**

The safety and efficacy of inhaled treprostinil was studied in 12 patients with PAH who were functional class III on bosentan monotherapy. The mean PVR improved by 26% and the mPA decreased by 10%, with improvement in 6-minute walk distance of 49 meters. Nine of 11 patients had improvement in functional class from III to II. A small open label study reported acute improvement in hemodynamics (lower mPA and PVR and increased cardiac output) when inhaled treprostinil was administered 1 hour after sildenafil in patients with PAH and chronic CTEPH; however, no significant improvement occurred in...
patients with pulmonary fibrosis associated pulmonary hypertension.72

The TRIUMPH I study evaluated 233 patients with PAH on treatment with oral bosentan (70%) or sildenafil (30%) who were functional class III or IV (>95% class III). Patients were randomized to inhaled treprostinil or inhaled placebo four times daily. The primary endpoint was improvement in 6-minute walk distance; the placebo-corrected median difference from baseline was 19 meters at 6 weeks and 20 meters at 12 weeks. There was improvement in quality of life measures and NT-proBNP, but no improvement in time to clinical worsening, Borg Dyspnea Score, functional class, or PAH signs and symptoms.73 Somewhat surprisingly, patients receiving concomitant bosentan had a greater improvement in 6-minute walk distance (22 meters at 6 weeks and 25 meters at 12 weeks) than those receiving sildenafil (11 meters at 6 weeks and 9 meters at 12 weeks). Fewer patients were enrolled in the sildenafil arm with varying doses.73 Since this trial was not designed to compare sildenafil and bosentan, further study of combination oral sildenafil and inhaled treprostinil is warranted.

Adverse Effects
The most commonly reported side effects of inhaled treprostinil include cough, throat irritation, headache, nausea, flushing, and syncope.

Dosing
Inhaled treprostinil is typically started at 3 breaths (6 ug/per breath) four times a day and up-titrated by 3 breaths every one to two weeks to a maximum dose of 9 breaths (54 ug) four times daily. Each treatment time averages approximately 3 minutes.

Cost Considerations
Oral PDE5-i are the least costly PAH therapies, ranging from $14,910 to $18,788 annually.74 ERAs are estimated to cost $79,278 annually.74 Intravenous and subcutaneous medication is even more costly. The average dosing of intravenous epoprostenol is 30–39 ng/kg/min which costs $63,620 annually (for the drug and diluent alone). Typical equipotent dosing of treprostinil is 60–69 ng/kg/min which costs $142,350 annually.75 These estimates can be much higher when factoring in additional costs of intravenous therapy including hospitalization for initiating treatment, education of patients and family members, placement of Hickman catheter, and treatment of adverse events from the central line such as sepsis. Taking these costs into consideration, two cost comparison studies determined that intravenous epoprostenol was more expensive than SC treprostinil, which avoids the costs associated with a central line.76–77 Narine et al76 estimated the annual cost of epoprostenol as $123,005 and SC treprostinil as $100,304, assuming both doses were 25 ng/kg/min, though in practice treprostinil doses are usually at least 1.5–2 times higher than epoprostenol. Similarly, a Canadian study by Highland et al77 estimated the annual cost of epoprostenol (at 9.2 ng/kg/min) as $88,897 and SC treprostinil as $59,339 (at 9.3 ng/kg/min) (in 2003 Canadian dollars).

Inhaled therapies are even more expensive than continuous infusions. Inhaled iloprost has been estimated to cost up to $155,578 to $244,404 annually at the highest dose, and inhaled treprostinil costs $104,755 to $162,670 annually.74,78 Insurance approval is typically obtained prior to initiation of any PAH therapy (see Table 4).

Future Directions and Emerging Therapies
While the development of treprostinil has been an important advancement in PAH therapy, the treatment landscape continues to evolve. A variety of areas are being actively explored including gene therapy, stem cell therapy, and multiple novel pharmacotherapies.79 Several agents including serine elastase inhibitors, tyrosine kinase inhibitors, Rho-kinase inhibitors, serotonin transporter inhibitors, and caveolin-1 peptide are potential therapeutic agents.79 Thus far studies have been limited to animal models or small trials of monotherapy or combination therapy with established pulmonary hypertension medications. Gene therapies include extracellular superoxide dismutase gene, plasmid inhibiting MCP-1, prostacyclin synthase gene, and the interleukin-10 gene. Cell therapy is being explored primarily in experimental rat models using smooth muscle cells, endothelial progenitor cells, mesenchymal stem cells over expressing endothelial nitric oxide synthase (eNOS), and fibroblasts transfected with eNOS or VEGF. One study of autologous endothelial progenitor cell infusion to patients with idiopathic PAH showed beneficial
effects and appeared to be safe and feasible, but further studies are needed.

Conclusions
PAH remains a disabling condition with a high mortality rate and no cure. Advances in therapy have increased the survival in PAH from 2 years to a mean of 4 years in patients with SSC and 6 years in IPAH. Management of patients with PAH remains challenging and many relatively simple questions remain unanswered. Since PAH is relatively rare, multicenter trials are necessary, which makes clinical trials very costly. Research in PAH is further complicated by the fact that commonly used clinical endpoints are not necessarily good predictors of survival. Furthermore, the relative efficacy of the continuous prostanooids, the optimal dosing, and value of single versus multiple drug targets is not known. Patient selection for each of the therapeutic options requires extensive experience in the diagnosis and management of PAH. Use of the prostanooids alone or in combination with other PH specific drugs should be limited to clinicians with extensive experience, preferably in PH centers of excellence.

Disclosures
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References


