Clinical Medicine Reviews in Vascular Health

Libertas Academica
FREEDOM TO RESEARCH

CMR
Clinical Medicine Reviews

REVIEW

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

Melinda B. Davis and Melvyn Rubenfire

Division of Cardiovascular Medicine, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA.
Corresponding author email: davismb@med.umich.edu; mrubenfi@med.umich.edu

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

Clinical Medicine Reviews in Vascular Health 2011:3 39–52

doi: 10.4137/CMRVH.S3397

This article is available from http://www.la-press.com.

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]

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

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

As modified from Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol.* Jun 30 2009;54(1 Suppl):S43–54.

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 ≥ 25 mmHg in the setting of a pulmonary capillary wedge pressure ≤15 mmHg or left ventricular end-diastolic pressure ≤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

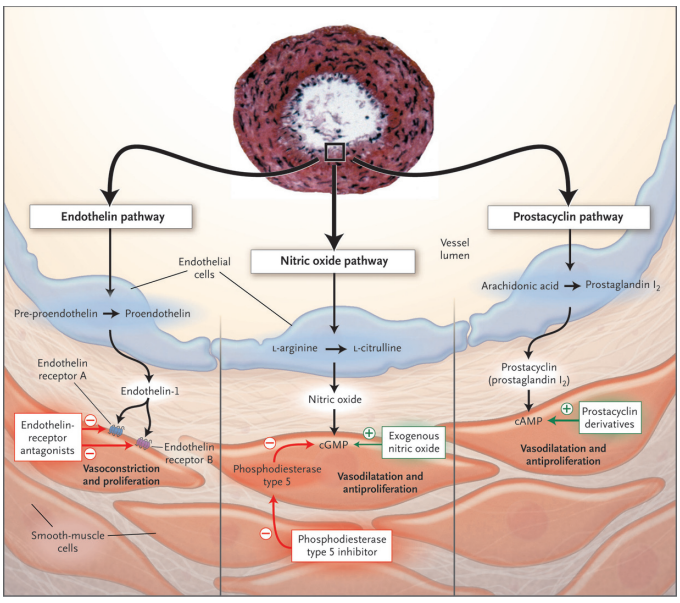
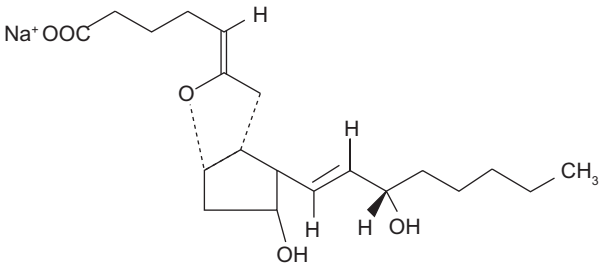
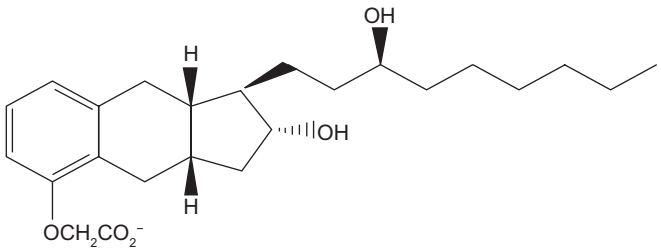


Figure 1. Targets for current or emerging therapies in PAH. Reprinted with permission from Humbert, M et al. Treatment of Pulmonary Arterial Hypertension. NEJM 2004; 351:1425–1436



Epoprostenol



Treprostinil

Figure 2. Chemical structures of epoprostenol and treprostinil.

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.[2] 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.[3]

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 phopshodiesterase-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.[4] 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.[5] Endogenous pulmonary vascular prostacyclin (PGI_2) 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.[6,7] 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.[8,9]

Epoprostenol

Epoprostenol sodium (Flolan®, GlaxoSmithKline, Research Triangle Park, North Carolina, Veletri®, Actelion Pharmaceuticals, San Francisco, California, and generic epoprostenol sodium, Teva Pharmaceuticals, North Wales, Pennsylvania) (see Figure 2) is an intravenous formulation of prostacyclin (PGI_2) which stimulates adenylate cyclase and increases production

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.[10] 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.[11] 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%).[12] 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.[13] 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.[14] 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.[15] 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.[16–25] Significant improvement in survival has been reported in two observational studies.[26,27] McLaughlin et al[27] 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, tunnelled 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-Deltec). 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

by side effects. At our Pulmonary Hypertension Center, the initial dose is 2 ng/kg/min with an increase by 1–2 ng/kg/min over the first few days with most patients discharged on 4–8 ng/kg/min. Subsequent titration is about 2 ng/kg/min every 1–2 weeks until improvement to WHO FC I-II or limited by side effects. The mean dose after 6 months in our program is about 42.5 ng/kg/min (see Table 2).

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 epopoprostenol,[28,29] 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.[30]

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.[31] All prostanoids reduce pulmonary smooth muscle cell remodelling,[32–34] secretion of extracellular matrix,[35] platelet aggregation and thrombosis,[36,37] and enhance endothelial cell function.[36] 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.[38]

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.[39] 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.[40]

Pharmacokinetics

Absorption of subcutaneous treprostinil is rapid, complete, and 100% bioavailable.[41] 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.[42] Steady state pharmacokinetics of SC treprostinil in patients with PAH is dose proportional from 10 to 125 ng/kg/min.[43] 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.[39] 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.[44] Early comparisons of intravenous epoprostenol and intravenous treprostinil

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

Medication (n patients)	Mean dose (Standard deviation) *ng/kg/min*	Median dose [Interquartile range] *ng/kg/min*
IV epoprostenol (38)	42.5 (22.2)	38 [31–51]
IV treprostinil (26)	82.4 (49.4)	70.5 [58–102]
SC treprostinil (25)	74.4 (33.1)	76 [43–93.5]

revealed a similar reduction in pulmonary vascular resistance acutely (22% and 20% respectively) at short term maximal tolerated doses.[45] 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.[41]

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.[46] 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)[14] and SSc related PAH improved 94 meters (placebo-corrected),[15] 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.[47]

An observational study of 860 patients with PAH treated with subcutaneous treprostinil was reported by Barst et al in 2006.[48] 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 hemodyamics, 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 prostanoids 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.[46]

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[49] 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,[46,47,50] while most clinical trials used relatively low doses.[45,49–51] We and many other centers have emphasized the importance of rapid dose escalation for improved therapeutic effects, which may help patients tolerate painful sites and improve compliance. Soto et al reported beginning with SC treprostinil at 2 ng/kg/min with increases by 2 ng/kg/min every 8 to 12 hours during a 3–5 day hospitalization with discharge doses up to 40 ng/kg/min.[52] In our Pulmonary Hypertension Center we usually initiate therapy at 2–3 ng/kg/min with increases by 2–3 ng/kg/min twice weekly for the first 6 to 8 weeks as tolerated, and additional weekly increases of 2.5 ng/kg/min thereafter until reaching clinical targets or intolerable side effects. In our center, the average long-term dose of SC treprostinil is approximately 75 ng/kg/min (see Table 2). A more rapid titration is used in select patients, particularly those transitioning from inhaled treprostinil. Our 6 month target is improvement to WHO FC I or II, 6-minute hall walk at least 450 meters, and resolution of evidence for right heart failure. We often repeat the right heart catheterization at 1 year to assess the appropriateness of dosing, whether additional drugs are necessary, whether transplant listing should be considered, and other PAH specific treatment options.

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 prostanoids, 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.[53] 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.[55] They can act both centrally and peripherally to increase pain sensation,[56] 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

Table 4. Cost comparison of pulmonary arterial hypertension therapies.

Drug	Labeled indication	Dose	Drug cost/year/pt
IV epoprostenol (Flolan)	WHO FC III and IV	30–40 ng/kg/min	$48,027 to $63,620[a 75]
SC/IV treprostinil (Remodulin)	WHO FC II-IV	60–70 ng/kg/min	$142,350[a 75] $176,880 (40 ng/kg/min)[74]
Inhaled treprostinil (Tyvaso)	WHO FC III	18–54 mcg INH 4x daily	$104,755[b 78] $162,670[74]
Inhaled iloprost (Ventavis)	WHO FC III and IV	2.5–5 mcg INH 6–9x daily (10 mcg/mL)	$58,736–$88,104[c 78]
		2.5–5 mcg INH 6–9x daily (20 mcg/mL)	$103,718–$155,578[78] $162,936–$244,404[74]

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.

experienced in treprostinil treatment. Regular use of narcotics should be discouraged.

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 for a men 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 angiopoietin-2 levels in patients treated with treprostinil.[58] 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.[59] 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 suppport. 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.[60] An increase in bacteremia, particularly gram negative, was reported in association with treprostinil.[61] 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.[62]

Transition from Epoprostenol to Treprostinil

In 2007 a study showed that patients receiving intravenous epoprostenol could be safely transitioned to subcutaneous treprostinil.[30] 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.[63] Vachiery and colleagues reported that transition between epoprostenol and treprostinil can be done

in the hospital over a short period of time by physicians experienced in the use of these medications.[64] 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.[65] 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.[66,67] 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.[66] 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 hall walk by week 12 with a trend toward improvement in Borg dyspnea score.[67] 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 (Tyvaso®, 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 prostanoids to IV epoprostenol or IV or SC treprostinil. Because of the limited ability to achieve very high blood levels with inhaled prostanoids, 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 prostanoids has not been established.

Pharmacokinetics

The half-life of inhaled treprostinil is 44–52 minutes[68] as compared to inhaled iloprost which is 20–30 minutes.[69] 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.[68] 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.[70] It can be safely and effectively administered with a metered dose inhaler.[71]

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.[68] 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 al[76] 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 al[77] 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,[80] 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 prostanoids, 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 prostanoids alone or in combination with other PH specific drugs should be limited to clinicians with extensive experience, preferably in PH centers of excellence.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

References

1. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. Jun 30 2009;54(1 Suppl):S43–54.
2. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med*. Sep 1 1991;115(5):343–9.
3. Sitbon O, Humbert M, Jais X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation*. Jun 14 2005;111(23):3105–11.
4. McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. *Circulation*. Sep 26 2006;114(13):1417–31.
5. Tuder RM, Cool CD, Geraci MW, et al. Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. *Am J Respir Crit Care Med*. Jun 1999;159(6):1925–32.
6. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med*. Mar 21 2002;346(12):896–903.
7. Galie N, Olschewski H, Oudiz RJ, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation*. Jun 10 2008;117(23):3010–9.
8. Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med*. Nov 17 2005;353(20):2148–57.
9. Galie N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. *Circulation*. Jun 9 2009;119(22):2894–903.
10. Rubin LJ, Groves BM, Reeves JT, Frosolono M, Handel F, Cato AE. Prostacyclin-induced acute pulmonary vasodilation in primary pulmonary hypertension. *Circulation*. Aug 1982;66(2):334–8.
11. Higenbottam T, Wheeldon D, Wells F, Wallwork J. Long-term treatment of primary pulmonary hypertension with continuous intravenous epoprostenol (prostacyclin). *Lancet*. May 12 1984;1(8385):1046–7.
12. McLaughlin VV, Genthner DE, Panella MM, Rich S. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. *N Engl J Med*. Jan 29 1998;338(5):273–7.
13. Rubin LJ, Mendoza J, Hood M, et al. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. *Ann Intern Med*. Apr 1 1990;112(7):485–91.
14. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med*. Feb 1 1996;334(5):296–302.
15. Badesch DB, Tapson VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med*. Mar 21 2000;132(6):425–34.
16. Rosenzweig EB, Kerstein D, Barst RJ. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. *Circulation*. Apr 13 1999;99(14):1858–65.
17. McLaughlin VV, Genthner DE, Panella MM, Hess DM, Rich S. Compassionate use of continuous prostacyclin in the management of secondary pulmonary hypertension: a case series. *Ann Intern Med*. May 4 1999;130(9):740–3.
18. Petitpretz P, Brenot F, Azarian R, et al. Pulmonary hypertension in patients with human immunodeficiency virus infection. Comparison with primary pulmonary hypertension. *Circulation*. Jun 1994;89(6):2722–7.
19. Aguilar RV, Farber HW. Epoprostenol (prostacyclin) therapy in HIV-associated pulmonary hypertension. *Am J Respir Crit Care Med*. Nov 2000;162(5):1846–50.
20. Kuo PC, Johnson LB, Plotkin JS, Howell CD, Bartlett ST, Rubin LJ. Continuous intravenous infusion of epoprostenol for the treatment of portopulmonary hypertension. *Transplantation*. Feb 27 1997;63(4):604–6.
21. Robbins IM, Gaine SP, Schilz R, Tapson VF, Rubin LJ, Loyd JE. Epoprostenol for treatment of pulmonary hypertension in patients with systemic lupus erythematosus. *Chest*. Jan 2000;117(1):14–8.
22. Fisher KA, Serlin DM, Wilson KC, Walter RE, Berman JS, Farber HW. Sarcoidosis-associated pulmonary hypertension: outcome with long-term epoprostenol treatment. *Chest*. Nov 2006;130(5):1481–8.
23. Kerr KM, Rubin LJ. Epoprostenol therapy as a bridge to pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension. *Chest*. Feb 2003;123(2):319–20.
24. Bresser P, Fedullo PF, Auger WR, et al. Continuous intravenous epoprostenol for chronic thromboembolic pulmonary hypertension. *Eur Respir J*. Apr 2004;23(4):595–600.
25. Cabrol S, Souza R, Jais X, et al. Intravenous epoprostenol in inoperable chronic thromboembolic pulmonary hypertension. *J Heart Lung Transplant*. Apr 2007;26(4):357–62.
26. Shapiro SM, Oudiz RJ, Cao T, et al. Primary pulmonary hypertension: improved long-term effects and survival with continuous intravenous epoprostenol infusion. *J Am Coll Cardiol*. Aug 1997;30(2):343–9.
27. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation*. Sep 17 2002;106(12):1477–82.
28. Steffen RP, de la Mata M. The effects of I5AU8I, a chemically stable prostacyclin analog, on the cardiovascular and renin-angiotensin systems of anesthetized dogs [corrected]. *Prostaglandins Leukot Essent Fatty Acids*. Aug 1991;43(4):277–86.
29. McNulty MJ, Sailstad JM, Steffen RP. The pharmacokinetics and pharmacodynamics of the prostacyclin analog 15AU81 in the anesthetized beagle dog. *Prostaglandins Leukot Essent Fatty Acids*. Feb 1993;48(2):159–66.

30. Rubenfire M, McLaughlin VV, Allen RP, et al. Transition from IV epoprostenol to subcutaneous treprostinil in pulmonary arterial hypertension: a controlled trial. *Chest*. Sep 2007;132(3):757–63.
31. Best LC, Martin TJ, Russell RG, Preston FE. Prostacyclin increases cyclic AMP levels and adenylate cyclase activity in platelets. *Nature*. Jun 30 1977;267(5614):850–2.
32. Clapp LH, Finney P, Turcato S, Tran S, Rubin LJ, Tinker A. Differential effects of stable prostacyclin analogs on smooth muscle proliferation and cyclic AMP generation in human pulmonary artery. *Am J Respir Cell Mol Biol*. Feb 2002;26(2):194–201.
33. Jeffery TK, Morrell NW. Molecular and cellular basis of pulmonary vascular remodeling in pulmonary hypertension. *Prog Cardiovasc Dis*. Nov–Dec 2002;45(3):173–202.
34. Fetalvero KM, Martin KA, Hwa J. Cardioprotective prostacyclin signaling in vascular smooth muscle. *Prostaglandins Other Lipid Mediat*. Jan 2007;82(1–4):109–18.
35. Olschewski H, Rose F, Schermuly R, et al. Prostacyclin and its analogues in the treatment of pulmonary hypertension. *Pharmacol Ther*. May 2004;102(2):139–53.
36. Friedman R, Mears JG, Barst RJ. Continuous infusion of prostacyclin normalizes plasma markers of endothelial cell injury and platelet aggregation in primary pulmonary hypertension. *Circulation*. Nov 4 1997;96(9):2782–4.
37. Boyer-Neumann C, Brenot F, Wolf M, et al. Continuous infusion of prostacyclin decreases plasma levels of t-PA and PAI-1 in primary pulmonary hypertension. *Thromb Haemost*. Apr 1995;73(4):735–6.
38. Fontana M, Olschewski H, Olschewski A, Schluter KD. Treprostinil potentiates the positive inotropic effect of catecholamines in adult rat ventricular cardiomyocytes. *Br J Pharmacol*. Jul 2007;151(6):779–86.
39. Laliberte K, Arneson C, Jeffs R, Hunt T, Wade M. Pharmacokinetics and steady-state bioequivalence of treprostinil sodium (Remodulin) administered by the intravenous and subcutaneous route to normal volunteers. *J Cardiovasc Pharmacol*. Aug 2004;44(2):209–14.
40. Wade M, Hunt TL, Lai AA. Effect of continuous subcutaneous treprostinil therapy on the pharmacodynamics and pharmacokinetics of warfarin. *J Cardiovasc Pharmacol*. Jun 2003;41(6):908–15.
41. Wade M, Baker FJ, Roscigno R, DellaMaestra W, Hunt TL, Lai AA. Absolute bioavailability and pharmacokinetics of treprostinil sodium administered by acute subcutaneous infusion. *J Clin Pharmacol*. Jan 2004;44(1):83–8.
42. Wade M, Baker FJ, Roscigno R, et al. Pharmacokinetics of treprostinil sodium administered by 28-day chronic continuous subcutaneous infusion. *J Clin Pharmacol*. May 2004;44(5):503–9.
43. McSwain CS, Benza R, Shapiro S, et al. Dose proportionality of treprostinil sodium administered by continuous subcutaneous and intravenous infusion. *J Clin Pharmacol*. Jan 2008;48(1):19–25.
44. Phares KR, Weiser WE, Miller SP, Myers MA, Wade M. Stability and preservative effectiveness of treprostinil sodium after dilution in common intravenous diluents. *Am J Health Syst Pharm*. May 1 2003;60(9):916–22.
45. McLaughlin VV, Gaine SP, Barst RJ, et al. Efficacy and safety of treprostinil: an epoprostenol analog for primary pulmonary hypertension. *J Cardiovasc Pharmacol*. Feb 2003;41(2):293–9.
46. Simonneau G, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med*. Mar 15 2002;165(6):800–4.
47. Oudiz RJ, Schilz RJ, Barst RJ, et al. Treprostinil, a prostacyclin analogue, in pulmonary arterial hypertension associated with connective tissue disease. *Chest*. Aug 2004;126(2):420–7.
48. Barst RJ, Galie N, Naeije R, et al. Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil. *Eur Respir J*. Dec 2006;28(6):1195–203.
49. Skoro-Sajer N, Lang IM, Harja E, Kneussl MP, Sing WG, Gibbs SJ. A clinical comparison of slow- and rapid-escalation treprostinil dosing regimens in patients with pulmonary hypertension. *Clin Pharmacokinet*. 2008;47(9):611–8.
50. Skoro-Sajer N, Bonderman D, Wiesbauer F, et al. Treprostinil for severe inoperable chronic thromboembolic pulmonary hypertension. *J Thromb Haemost*. Mar 2007;5(3):483–9.
51. Lang I, Gomez-Sanchez M, Kneussl M, et al. Efficacy of long-term subcutaneous treprostinil sodium therapy in pulmonary hypertension. *Chest*. Jun 2006;129(6):1636–43.
52. Soto FJ. Safety and tolerance of a rapid 3–5 day in-hospital up-titration protocol of subcutaneous (SQ) treprostinil in patients with severe pulmonary arterial hypertension (PAH). *Chest*. 2007;132:634a.
53. Kingman MS, Tankersley MA, Lombardi S, Spence S, Torres F, Chin KS. Prostacyclin administration errors in pulmonary arterial hypertension patients admitted to hospitals in the United States: a national survey. *J Heart Lung Transplant*. Aug 2010;29(8):841–6.
54. Levin Y, Frutiger K, Heininger A, Wessman K, White RJ. SQ Works: Assessing the Efficacy of an Established Method for Managing Subcutaneous Treprostinil Infusion Sites. *Presented at Pulmonary Hypertension Association's International PH Conference and Scientific Sessions • June* 24–27, 2010; *Garden Grove, CA*. 2010.
55. Samad TA, Sapirstein A, Woolf CJ. Prostanoids and pain: unraveling mechanisms and revealing therapeutic targets. *Trends Mol Med*. Aug 2002;8(8):390–6.
56. Zhou W, Hashimoto K, Goleniewska K, et al. Prostaglandin I2 analogs inhibit proinflammatory cytokine production and T cell stimulatory function of dendritic cells. *J Immunol*. Jan 15 2007;178(2):702–10.
57. Ashby L HK, Latham L. Protocol for reduction of site pain in the administration of treprostinil. *Chest*. 2004;126(4 Suppl):882S.
58. Hiremath J, Thanikachalam S, Parikh K, et al. Exercise improvement and plasma biomarker changes with intravenous treprostinil therapy for pulmonary arterial hypertension: a placebo-controlled trial. *J Heart Lung Transplant*. Feb 2010;29(2):137–49.
59. Tapson VF, Gomberg-Maitland M, McLaughlin VV, et al. Safety and efficacy of IV treprostinil for pulmonary arterial hypertension: a prospective, multicenter, open-label, 12-week trial. *Chest*. Mar 2006;129(3):683–8.
60. Oudiz RJ, Widlitz A, Beckmann XJ, et al. Micrococcus-associated central venous catheter infection in patients with pulmonary arterial hypertension. *Chest*. Jul 2004;126(1):90–4.
61. Kallen AJ, Lederman E, Balaji A, et al. Bloodstream infections in patients given treatment with intravenous prostanoids. *Infect Control Hosp Epidemiol*. Apr 2008;29(4):342–9.
62. Zaccardelli D, Phares K, Jeffs R, Doran A, Wade M. Stability and antimicrobial effectiveness of treprostinil sodium in Sterile Diluent for Flolan. *Int J Clin Pract*. Jun 2010;64(7):885–91.
63. Gomberg-Maitland M, Tapson VF, Benza RL, et al. Transition from intravenous epoprostenol to intravenous treprostinil in pulmonary hypertension. *Am J Respir Crit Care Med*. Dec 15 2005;172(12):1586–9.
64. Vachiery JL, Hill N, Zwicke D, Barst R, Blackburn S, Naeije R. Transitioning from i.v. epoprostenol to subcutaneous treprostinil in pulmonary arterial hypertension. *Chest*. May 2002;121(5):1561–5.
65. Sitbon O, Manes A, Jais X, et al. Rapid switch from intravenous epoprostenol to intravenous treprostinil in patients with pulmonary arterial hypertension. *J Cardiovasc Pharmacol*. Jan 2007;49(1):1–5.
66. Benza RL, Rayburn BK, Tallaj JA, Pamboukian SV, Bourge RC. Treprostinil-based therapy in the treatment of moderate-to-severe pulmonary arterial hypertension: long-term efficacy and combination with bosentan. *Chest*. Jul 2008;134(1):139–45.
67. Feldman JPCM, Torres F, et al. Treprostinil sodium improves exercise capacity when added to existing oral pulmonary arterial hypertension therapy. *Chest*. 2007;132:474S–5.
68. Channick RN, Olschewski H, Seeger W, Staub T, Voswinckel R, Rubin LJ. Safety and efficacy of inhaled treprostinil as add-on therapy to bosentan in pulmonary arterial hypertension. *J Am Coll Cardiol*. Oct 3 2006;48(7):1433–7.
69. Olschewski H, Walmrath D, Schermuly R, Ghofrani A, Grimminger F, Seeger W. Aerosolized prostacyclin and iloprost in severe pulmonary hypertension. *Ann Intern Med*. May 1 1996;124(9):820–4.
70. Voswinckel R, Enke B, Reichenberger F, et al. Favorable effects of inhaled treprostinil in severe pulmonary hypertension: results from randomized controlled pilot studies. *J Am Coll Cardiol*. Oct 17 2006;48(8):1672–81.
71. Voswinckel R, Reichenberger F, Gall H, et al. Metered dose inhaler delivery of treprostinil for the treatment of pulmonary hypertension. *Pulm Pharmacol Ther*. Feb 2009;22(1):50–6.

72. Voswinckel R, Reichenberger F, Enke B, et al. Acute effects of the combination of sildenafil and inhaled treprostinil on haemodynamics and gas exchange in pulmonary hypertension. *Pulm Pharmacol Ther*. Oct 2008; 21(5):824–32.
73. McLaughlin VV, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J Am Coll Cardiol*. May 4 2010;55(18):1915–22.
74. Gandhi R, Baker N, Shex A, Yon J, Bishop D. Pulmonary arterial hypertension: Bridging the gap between efficacy, quality of life, and cost-effectiveness. *Formulary*. June 1, 2010
75. Oudiz RJ, Farber HW. Dosing considerations in the use of intravenous prostanoids in pulmonary arterial hypertension: an experience-based review. *Am Heart J*. Apr 2009;157(4):625–35.
76. Narine L, Hague LK, Walker JH, et al. Cost-minimization analysis of treprostinil vs. epoprostenol as an alternate to oral therapy non-responders for the treatment of pulmonary arterial hypertension. *Curr Med Res Opin*. Dec 2005;21(12):2007–16.
77. Highland KB, Strange C, Mazur J, Simpson KN. Treatment of pulmonary arterial hypertension: a preliminary decision analysis. *Chest*. Dec 2003; 124(6):2087–92.
78. Ditrick, D. National Drug Monograph. Treprostinil Inhalation. *VA Pharmacy Benefits Management Services*. June 2010.
79. Umar S, Steendijk P, Ypey DL, et al. Novel approaches to treat experimental pulmonary arterial hypertension: a review. *J Biomed Biotechnol*. 2010;2010:702836.
80. Wang XX, Zhang FR, Shang YP, et al. Transplantation of autologous endothelial progenitor cells may be beneficial in patients with idiopathic pulmonary arterial hypertension: a pilot randomized controlled trial. *J Am Coll Cardiol*. Apr 10 2007;49(14):1566–71.