Treatment of pulmonary arterial hypertension:  
The role of prostacyclin and prostaglandin analogs

Zeenat Safdar*

Baylor College of Medicine, 6620 Main Street, Suite 11B.09, Houston, TX 77030, USA

Received 18 August 2010; accepted 20 December 2010
Available online 26 January 2011

Summary
Pulmonary arterial hypertension is a progressive, fatal disease characterized by elevated pulmonary arterial pressure ≥25 mm Hg and normal pulmonary capillary wedge pressure ≤15 mm Hg. Physiological features of pulmonary arterial hypertension are characterized clinically by the presence of pre-capillary pulmonary hypertension not caused by other conditions such as lung diseases or chronic thromboembolic pulmonary hypertension. There are several therapies currently available that have been shown to improve hemodynamics and improve outcomes in patients with pulmonary arterial hypertension. These therapies include synthetic prostacyclin and prostaglandin analogs, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors. Multiple prostacyclin and prostaglandin analog formulations are currently in use (both branded and generic), available for parenteral, inhaled, or oral administration. This review discusses the pharmacology, clinical effects, and routes of administration of prostacyclin and prostaglandin analogs, emphasizing the advantages and disadvantages of each from the clinical perspective.

© 2010 Elsevier Ltd. All rights reserved.

Contents

Introduction .................................................................................................................. 819
Parenteral prostacyclin and prostaglandin analogs .................................................... 819
Epoprostenol ............................................................................................................ 819
Pharmacological properties ...................................................................................... 820
Clinical effects ........................................................................................................ 820
Administration ........................................................................................................... 820
Treprostinil ................................................................................................................ 822
Pharmacological properties ...................................................................................... 822

* Tel.: +713 798 2400; fax: +713 798 2688.
E-mail address: safdar@bcm.tmc.edu.

0954-6111/ $ - see front matter © 2010 Elsevier Ltd. All rights reserved.
Clinical effects .......................................................... 822
Administration ........................................................ 822

Inhaled prostaglandin analogs ......................................... 822
Inhaled iloprost .......................................................... 822
Pharmacological properties ........................................... 822
Clinical effects ........................................................... 822
Administration ........................................................ 823

Inhaled treprostinil ...................................................... 823
Pharmacological properties ........................................... 823
Clinical effects ........................................................... 823
Administration ........................................................ 824

Oral prostaglandin analogs ........................................... 824
Switching between PAH therapies ................................ 824
Conclusions .................................................................. 824
Competing interests ....................................................... 824
Author contributions ..................................................... 824
Acknowledgements ........................................................ 824
Conflict of interest statement .......................................... 824
References .................................................................. 825

Introduction

Pulmonary hypertension is characterized by hemodynamic criteria of elevated mean pulmonary arterial pressure (mPAP) ≥25 mm Hg. Pulmonary arterial hypertension (PAH) (Diagnostic Group I) is defined by an elevated mPAP ≥25 mm Hg and normal pulmonary capillary wedge pressure of ≤15 mm Hg.1 Other causes of pulmonary hypertension such as parenchymal lung diseases, sleep disorders, and chronic thromboembolic disease must be excluded before PAH diagnosis can be made.2 PAH is a progressive disorder that leads to right ventricular failure and death.4,5 The median survival in patients with untreated PAH in the 1990s was 2.8 years.6 However, recent data suggest that 1-year survival in patients with PAH (both treated and untreated) enrolled in prospective registries ranges from 88% to 91%.7,8 This increase in survival may be due, in part, to improved recognition of the presence of PAH or a greater availability of drugs to treat this condition.

The 4th World Symposium on pulmonary hypertension classified PAH as idiopathic, heritable (formerly familial) including germline mutations in a number of genes and familial cases with or without identified germline mutations, drug- and toxin-induced, persistent pulmonary hypertension of the newborn, and the subcategories classified under PAH associated with other conditions, ie, connective tissue diseases, human immunodeficiency virus infection, portopulmonary hypertension, congenital heart disease, schistosomiasis, or chronic hemolytic anemia as Group 1 pulmonary hypertension, and pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis as Group 1’ pulmonary hypertension.9 Criteria used to stratify patients with PAH include the 6-minute walk test distance (6MWD) and World Health Organization (WHO) functional class (I through IV). Patients with functional class I are essentially asymptomatic, and patients with functional class IV exhibit signs of right heart failure and experience shortness of breath, fatigue (even at rest), and syncope.10 Evidence suggests that endogenous prostacyclin, which is produced by endothelial cells of blood vessels, is decreased in patients with PAH.7,8 Four prostanoid receptors in the lung have been identified to be involved in regulating vascular tone, platelet activation, and immunological cell responses (for an in-depth review, please see KK Mubarak, 201011). Thus, synthetic prostaglandin I2 (PGI2), also referred to as prostacyclin, and prostaglandin analogs are a logical choice for the treatment of this disease, and current guidelines recommend their use in patients with functional class II–IV PAH.12 Endothelin receptor antagonists and phosphodies- terase type-5 inhibitors are also used as treatment for patients with PAH.12 In addition, sequential combination therapy with these agents should be considered if adequate response with monotherapy is not achieved or if patients deteriorate with monotherapy.12 However, data supporting the use of combination therapy are limited, and such therapies are the focus of current research.13

Prostacyclin and prostaglandin analogs have been used in routine clinical practice since the 1990s, although there are reports of the investigational use of prostacyclin in patients with PAH dating back to the 1980s.14,15 Currently, there are several different prostacyclin and prostaglandin analog formulations available (for intravenous [IV] use, as a subcutaneous [SC] injection, and for inhalation) in the United States.16 This review discusses the use of prostacyclin and prostaglandin analogs (both branded and generic) to treat patients with Group 1 PAH, with an emphasis on the advantages and disadvantages of the different routes of administration used for these agents.

Parenteral prostacyclin and prostaglandin analogs

Epoprostenol

Epoprostenol, also known as synthetic PGI2 or prostacyclin, was the first therapy approved by the United States Food
and Drug Administration (FDA) for the treatment of PAH in 1995. Derived from the metabolism of arachidonic acid, it is a potent pulmonary and systemic vasodilator, an inhibitor of platelet aggregation, and it may modulate pulmonary vascular remodeling.

Epoprostenol sodium, which is formulated for IV injection, is available as Flolan® (GlaxoSmithKline, Research Triangle Park, NC), Veleti® (Actelion Pharmaceuticals US, Inc., South San Francisco, CA), and a generic formulation (Teva Parenteral Medicines, Inc., Irvine, CA). The pharmacological and clinical properties of the active ingredient (epoprostenol sodium) are identical. Veleti® (epoprostenol sodium for injection) is formulated with extended stability; however, the clinical indication of this compound is identical to that of Flolan®. For the purposes of this article, the brand names Flolan®, Veleti®, and the generic formulation epoprostenol sodium for injection will be referred to as epoprostenol sodium for injection, epoprostenol with extended stability, and generic epoprostenol sodium for injection, respectively. The term epoprostenol will be used to indicate properties that refer to all 3 drugs.

**Pharmacological properties**

The systemic half-life ($t_{1/2}$) of epoprostenol is 2—3 min. Epoprostenol metabolism in humans results in 2 major and 14 minor metabolites, which are excreted primarily via the kidneys. Epoprostenol with extended stability is more stable upon reconstitution and administration than branded or generic epoprostenol sodium for injection due to the use of a buffer that lacks sodium chloride, substitutes arginine for glycine, and has a higher pH. In addition, epoprostenol with extended stability can be diluted for delivery with Sterile Water for Injection or Sodium Chloride 0.9% for Injection, whereas branded and generic epoprostenol sodium for injection require a special diluent. Additional pharmacological properties of epoprostenol are summarized in Table 1.

**Clinical effects**

Clinical studies in patients with PAH have shown that IV epoprostenol treatment improves hemodynamic parameters, significantly improves symptoms of dyspnea and fatigue, and increases exercise capacity (6MWD). Significant dose-dependent decreases in several hemodynamic parameters, including total pulmonary resistance, pulmonary vascular resistance (PVR), and mPAP, and increases in cardiac index and stroke volume were observed with IV epoprostenol therapy. The hemodynamic effects of epoprostenol are similar in acute and chronic settings. In addition, IV epoprostenol has been shown to improve survival and is the only PAH medication to have an indication for improved survival in its prescribing information. However, in patients with PAH due to the scleroderma spectrum of diseases, no significant improvement in survival was observed with epoprostenol therapy relative to conventional therapy.

Adverse events attributable to chronic epoprostenol administration include headache, flushing, jaw pain, anxiety/nervousness, diarrhea, flu-like symptoms, nausea, and vomiting. Patients who receive epoprostenol may also experience adverse events related to the route of administration. Finally, the short systemic $t_{1/2}$ of epoprostenol has considerable disadvantages due to the potential for rebound pulmonary hypertension, cardiovascular compromise, and death in the event of a brief interruption of IV administration.

**Administration**

Because of its short systemic $t_{1/2}$, epoprostenol must be administered by continuous IV infusion. The drug is administered through a central venous catheter and by the use of an ambulatory infusion pump. Branded and generic epoprostenol sodium for injection can be administered at room temperature for a maximum of 8 h, which can be accomplished by using smaller pump cassettes; however, if the drug is to be administered over 24 h, it must be kept cold via use of a cold pouch that should be replaced every 12 h depending on the ambient temperature. Epoprostenol with extended stability, when diluted completely and administered immediately, can be infused at room temperature for up to 24 h at concentrations ranging from ≥6000 ng/mL to <30,000 ng/mL without the use of a cold pouch or ice packs.

There are several important considerations in the administration of epoprostenol. Long-term administration requires a permanent indwelling catheter and a continuous infusion pump, which increases the risks for infection and thrombosis. Adverse events may be associated with infusion system malfunctions and subsequent over- or underdosing of the drug, and patients receiving the IV drug can experience bloodstream infections and sepsis. In addition, considerable patient education and instruction are required for the care and maintenance of the catheter and pump, both of which necessitate sterile techniques.

The 3 different epoprostenols each come in slightly different sizes and packaging, and each requires different storage conditions (Table 1). Branded epoprostenol sodium for injection is supplied in powder form in 17 mL glass vials. Two different quantities are available: 0.5 mg (blue cap) and 1.5 mg (red cap). The lyophilized powder can be stored at room temperature. The drug must be reconstituted using a specific sterile diluent (Flolan® Sterile Diluent for Injection), which is also stored at room temperature. The reconstituted solution can be stored at 2—8°C for a maximum of 48 h before use due to the unstable nature of the reconstituted soluble compound.

Generic epoprostenol sodium for injection is supplied in powder form in 10 mL glass vials. Two different quantities are available: 0.5 mg (blue cap) and 1.5 mg (red cap). The storage conditions of the lyophilized powder, the reconstituted solution, and the diluent (Flolan® Sterile Diluent for Injection) are identical to those indicated for branded epoprostenol sodium for injection.

Epoprostenol with extended stability is supplied in powder form in 10 mL glass vials of 1.5 mg quantity (red cap). Unlike branded and generic epoprostenol sodium for injection, epoprostenol with extended stability can be reconstituted using either Sterile Water for Injection or Sodium Chloride 0.9% for Injection. The lyophilized powder can be stored at room temperature. When diluted completely and administered immediately at concentrations ranging from ≥6000 ng/mL to <30,000 ng/mL, epoprostenol with extended stability can be infused for 24 h at room temperature without the use of ice packs.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Pharmacological properties</th>
<th>Vial size</th>
<th>Concentrations</th>
<th>Diluent</th>
<th>Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epoprostenol sodium for injection (Flolan)</strong>&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Clearance&lt;sup&gt;a&lt;/sup&gt;: 93 mL/kg/min&lt;br&gt;Volume of distribution&lt;sup&gt;a&lt;/sup&gt;: 357 mL/kg&lt;br&gt;( t_{1/2} &lt;sup&gt;a&lt;/sup&gt; ): 2.7 min</td>
<td>Drug: 17 mL&lt;br&gt;Diluent: 50 mL</td>
<td>0.5 mg, blue cap&lt;br&gt;1.5 mg, red cap</td>
<td>Flolan&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;Diluent: 94 mg glycine;&lt;br&gt;73.3 mg NaCl; NaOH (to adjust for pH); and Sterile Water for Injection</td>
<td>Protect from light&lt;br&gt;Reconstituted: up to 8 h at RT; &gt;8 h requires cold pack refrigeration</td>
</tr>
<tr>
<td><strong>Generic epoprostenol sodium for injection</strong>&lt;sup&gt;21&lt;/sup&gt;</td>
<td>As above</td>
<td>Drug: 10 mL&lt;br&gt;Diluent: 50 mL</td>
<td>0.5 mg, blue cap&lt;br&gt;1.5 mg, red cap</td>
<td>As above</td>
<td>Protect from light&lt;br&gt;Reconstituted: up to 8 h at RT; &gt;8 h requires cold pack refrigeration</td>
</tr>
<tr>
<td><strong>Epoprostenol with extended stability (Veletri)</strong>&lt;sup&gt;24&lt;/sup&gt;</td>
<td>As above</td>
<td>Drug: 10 mL&lt;br&gt;Diluent: 50 mL</td>
<td>1.5 mg, red cap</td>
<td>Sterile Water for Injection, or Sodium Chloride 0.9% for Injection</td>
<td>Protect from light&lt;br&gt;Reconstituted ≥6000 ng/mL and &lt;30,000 ng/mL: can be administered immediately over 24 h at RT&lt;br&gt;Reconstituted ≥30,000 ng/mL: can be stored for 7 days at 2–8 °C and then administered over 24 h at RT</td>
</tr>
<tr>
<td><strong>IV/SC treprostinil (Remodulin)</strong>&lt;sup&gt;37&lt;/sup&gt;</td>
<td>Clearance&lt;sup&gt;b&lt;/sup&gt;: ~429 mL/kg/h&lt;br&gt;Volume of distribution&lt;sup&gt;b&lt;/sup&gt;: ~1.4 L/kg&lt;br&gt;Terminal ( t_{1/2} &lt;sup&gt;b&lt;/sup&gt; ): ~4 h&lt;br&gt;Bioavailability: 100%</td>
<td>20 mL</td>
<td>1.0 mg/mL, yellow cap&lt;br&gt;2.5 mg/mL, blue cap&lt;br&gt;5.0 mg/mL, green cap&lt;br&gt;10 mg/mL, pink cap</td>
<td>5.3 mg NaCl;&lt;br&gt;3.0 mg metacresol;&lt;br&gt;6.3 mg Na citrate;&lt;br&gt;H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>IV: up to 48 h at 37 °C&lt;br&gt;SC: up to 72 h at 37 °C</td>
</tr>
</tbody>
</table>

H<sub>2</sub>O, water; IV, intravenous; Na, sodium; NaCl, sodium chloride; NaOH, sodium hydroxide; RT, room temperature; SC, subcutaneous; \( t_{1/2} \), half-life.

<sup>a</sup> In animals.

<sup>b</sup> For a person with an ideal body weight of 70 kg.
Treprostinil

Treprostinil is a prostaglandin analog that is stable at room temperature and has a neutral pH. Similar to epoprostenol, treprostinil is a potent pulmonary and systemic vasodilator and an inhibitor of platelet aggregation. Parenteral treprostinil is available as a branded product only (Remodulin; United Therapeutics Corp., Research Triangle Park, NC). The manufacturer recommends that treprostinil be administered via a continuous SC infusion, with IV infusion used only in the event of intolerance to SC administration (eg, severe injection site pain/reactions).

Pharmacological properties

The pharmacological properties of treprostinil are summarized in Table 1. It is metabolized by the liver into 5 metabolites, which are primarily excreted in the urine. Treprostinil has linear pharmacokinetics over the dose range of 1.25–125 ng/kg/min.

Clinical effects

Treatment of patients with PAH with IV or SC treprostinil improves hemodynamic parameters and exercise capacity. The effects of treprostinil on hemodynamics have been mixed: some studies show significant improvement in hemodynamics compared to baseline or placebo, whereas others do not. In a study comparing IV treprostinil with epoprostenol, the hemodynamic changes were similar for both of these agents. A study in healthy volunteers showed that IV and SC treprostinil were bioequivalent. In animal studies, the use of treprostinil reduced ventricular afterload (both right and left) and increased stroke volume and cardiac output.

The most frequent adverse events associated with chronic SC treprostinil administration are infusion site pain, infusion site reactions, and bleeding. Other prostacyclin-related adverse events include headache, diarrhea, nausea, jaw pain, and vasodilation. Adverse events associated with infusion system malfunctions include over- or underdosing of treprostinil, and patients receiving IV treprostinil can experience bloodstream infections and sepsis. The increased risk of infections associated with treprostinil may be due to its receptor affinity; unlike other prostaglandin analogs, in vitro studies and animals, treprostinil modulates T lymphocyte and dendritic cell functions in an IP receptor-independent fashion and may affect endogenous immune function. Recent preliminary results of an observational study suggest that adjusting the pH of the buffer from neutral to basic by using Flolan diluent may reduce the incidence of sepsis following treatment with IV treprostinil.

Administration

Patients receive SC treprostinil via a self-inserted SC catheter coupled to an infusion pump. Those receiving IV treprostinil require a central venous catheter and infusion pump. SC treprostinil requires no dilution before use; however, IV treprostinil must first be diluted using Sterile Water for Injection, Sodium Chloride 0.9% for Injection, or Flolan Sterile Diluent for Injection. Treprostinil is supplied as a solution in multi-use, 20 mL vials. Four different concentrations are available, ranging from 1 to 10 mg/mL (Table 1). Unopened vials of treprostinil can be stored at room temperature. When used subcutaneously, treprostinil can be administered for up to 72 h at 37 °C; however, the diluted solution for IV administration can only be used for up to 48 h at 37 °C.

The basic pH and short systemic t1/2 of epoprostenol necessitate IV infusion, whereas the neutral pH and longer systemic t1/2 of treprostinil enable either IV or SC administration. The longer t1/2 lowers the risk for rebound PAH with infusion cessation, and no cases of rebound PAH have been reported in the medical literature. In addition, because treprostinil does not require refrigeration, it has the potential to considerably improve quality of life for these patients.

Inhaled prostaglandin analogs

Inhaled prostaglandin analogs were developed, in part, due to the limitations of parenteral administration and are often used as a bridge to IV therapy or lung transplantation. The adverse event profile is similar to that seen following parenteral administration, whereas complications due to continuous parenteral administration are eliminated. It is thought that the incidence of adverse events associated with parenteral prostacyclin and prostaglandin analogs (ie, catheter-induced sepsis or thromboembolism and infusion site pain/reaction) is obviated with inhaled prostaglandin analogs due to the direct delivery of the drug to the lung.

Inhaled iloprost

Like epoprostenol and treprostinil, inhaled iloprost is a systemic and pulmonary vasodilator that also has antiplatelet properties. Inhaled iloprost is available as a mixture of the 4S and 4R stereoisomers; with respect to vasodilation, the 4S isomer is more potent than the 4R isomer. Iloprost is marketed under the brand name Ventavis (Actelion Pharmaceuticals US, Inc., South San Francisco, CA) in the United States. There are no generic versions of inhaled iloprost available. Despite lack of supportive clinical evidence, an IV formulation of iloprost is approved for the treatment of PAH in New Zealand and has been used off-label in a number of countries including Germany, Switzerland, and Australia.

Pharmacological properties

The systemic t1/2 of inhaled iloprost is 20–30 min; additional pharmacological properties are summarized in Table 2. Inhaled iloprost is metabolized via oxidation to produce one major metabolite, which is excreted primarily in the urine.

Clinical effects

Inhaled iloprost improves hemodynamic parameters, functional status, and exercise capacity in patients with PAH. Furthermore, the addition of inhaled iloprost to stable ongoing bosentan therapy significantly delayed the time to...
clinical worsening in a 12-week, randomized, double-blind trial of 67 patients with PAH. Hemodynamic effects of inhaled iloprost in humans include decreases in PVR and mPAP and increases in cardiac output and oxygen saturation after 12 weeks and 2 years of treatment. Unlike parenteral epoprostenol and treprostinil, the effect of inhaled iloprost on mean systemic arterial pressure has been variable; some studies show no effect, whereas others demonstrate a significant reduction. It has also been shown that patients receiving inhaled iloprost do not experience rebound symptoms during the night, which may occur with interruption of parenteral infusion of epoprostenol or treprostinil.

Adverse events associated with inhaled iloprost are similar to those seen with prostacyclin and prostaglandin analogs, ie, headache, flushing, flu-like symptoms, nausea, and vomiting. Patients receiving inhaled iloprost can also experience jaw muscle spasm. Additional adverse events include cough and tongue pain, and syncope. Notably, when iloprost was added to bosentan therapy, syncope was infrequent and less severe (1 patient) than in an iloprost monotherapy study in which there were 5 cases of serious syncope.

Administration

Inhaled iloprost should be administered 6–9 times a day as needed (no more frequently than once every 2 h) during waking hours using the I-neb/AAD System (Philips Respironics, Respiratory Drug Delivery Ltd., Chichester, UK), which may be a limitation for young patients with an active lifestyle. Iloprost for inhalation is supplied in 1 mL ampules in concentrations of 10 mg/mL (for patients receiving either 2.5 or 5 mg per dose) and 20 mg/mL (for patients experiencing extended treatment times when maintained on 5 mg iloprost/dose). The ampules should be stored at room temperature. Properties of the inhaled iloprost solution are included in Table 2.

Inhaled treprostinil

The inhaled formulation of treprostinil is the most recent prostaglandin analog to be approved by the US FDA (July 2009). It is marketed by United Therapeutics under the brand name Tyvaso.

Pharmacological properties

Data available for the inhaled form of treprostinil include the following. A systemic exposure of inhaled treprostinil was proportional to the administered dose in a single-dose study in healthy volunteers. In one study that included patients with PAH, 30 μg/dose (4 ×/day) and 45 μg/dose (4 ×/day) caused a maximum blood concentration of 0.33 ng/mL and 0.96 ng/mL, a time to maximum concentration of 15 min and 45 min, and a t1/2 of 44 min and 52 min, respectively. A similar dose proportionality in patients with PAH has been reported in a second study. The bioavailability of inhaled treprostinil was 64% after administration of 18 μg and 72% after 36 μg in healthy volunteers (Table 2).

Clinical effects

Clinical studies of inhaled treprostinil have been conducted in patients already receiving the endothelin receptor antagonist bosentan or the phosphodiesterase type-5 inhibitor sildenafil.
and have shown that inhaled treprostinil significantly improves hemodynamics, functional class, and exercise capacity when added to oral therapy.\textsuperscript{68–70} However, in one study (TRIUMPH-I), inhaled treprostinil significantly improved exercise capacity (6MWD), but not functional class, when added to oral therapy.\textsuperscript{69} Hemodynamic effects of inhaled treprostinil include decreases in mPAP and PVR.\textsuperscript{69,70}

Adverse events associated with inhaled treprostinil include cough, headache, pharyngolaryngeal pain and throat irritation, nausea, flushing, and syncope.\textsuperscript{68}

**Oral prostaglandin analogs**

Oral formulations of prostaglandin analogs are currently in development for use in the United States. An oral formulation of treprostinil has been developed by United Therapeutics; however, this formulation has not yet been approved in the United States and is currently undergoing assessment in clinical trials.\textsuperscript{16,71–73} Similarly, beraprost (Procyclin\textsuperscript{9}) has launched in Japan and Korea by Kaken Pharmaceuticals and is also undergoing assessment in the United States.\textsuperscript{74–85}

**Switching between PAH therapies**

The challenges of administration and adverse events associated with parenteral epoprostenol or treprostinil therapy (particularly the IV route) occasionally necessitate switching therapy, either from one analog to another or from prostaglandin analog therapy to another drug class, such as endothelin receptor antagonists or phosphodiesterase type-5 inhibitors.

The literature on switching between prostacyclin and prostaglandin analogs mainly documents switching from IV epoprostenol to IV or SC treprostinil,\textsuperscript{86–90} in all of these studies, switching from epoprostenol to treprostinil was successful in that it did not cause any clinical deterioration or change in functional status and generally resulted in an improvement in treatment-related adverse events. Evidence for transitioning patients from parenteral to inhaled therapies is primarily anecdotal with few controlled studies.\textsuperscript{88} Practice patterns for transitioning patients vary greatly from transitioning over a period of weeks, to over hours, and often with an overlap period.

Although functional tests (eg, 6MWD and Borg dyspnea index) generally remain the same after transitioning from epoprostenol to treprostinil,\textsuperscript{86–90} the effect upon hemodynamics is more variable; one study reported increases in mPAP and PVR and a decrease in cardiac index,\textsuperscript{86} but two others reported no change in hemodynamics.\textsuperscript{87,89} and hemodynamics were not reported in two additional studies.\textsuperscript{88,90} Despite the potential worsening hemodynamics, there is little evidence that clinical deterioration in patients on treprostinil differs from those receiving epoprostenol.\textsuperscript{87,88,90}

The results of studies investigating the transition of patients with PAH from prostacyclin or prostaglandin analogs to oral agents of a different class were mixed; while generally the transitions were successful, some patients did deteriorate when switched to oral therapy, and the conclusions generally called for care when selecting patients suitable for transition.\textsuperscript{91–94} Those patients most likely to successfully transition from parenteral epoprostenol or treprostinil therapy to bosentan or sildenafil had better hemodynamics at the time of the transition.\textsuperscript{92,94} Patients successfully transitioned may have to go back on parenteral prostacyclin or prostaglandin analog therapy as their disease progresses.\textsuperscript{93} However, it may be worth considering transitioning carefully selected patients to an oral therapy due to decreased adverse events reported on transitioned patients.\textsuperscript{91–94}

**Conclusions**

Administration of prostacyclin and prostaglandin analogs in patients with PAH requires attention to detail due to numerous differences among the drugs. These differences include package size, concentration or dose, route of administration, ease of use, cost, availability, and administration device. Thus, the clinician should not only weigh the pharmacological benefits of prostacyclin and prostaglandin analogs when deciding on treatment in patients with PAH but also whether the patient can comply with drug storage requirements, route of administration, and use of the administration device.

**Competing interests**

Dr Safdar is on advisory boards and consultant committees for Actelion Pharmaceuticals US, Inc, Gilead, and United Therapeutics.

**Author contributions**

Dr Safdar conceived the manuscript topic, helped to draft the manuscript, and approved the final manuscript.

**Acknowledgements**

The author thanks Jennifer M. Kulak, PhD, Sheridan Henness, PhD, and Sohita Dhillon, PhD, of InScience Communications, a Wolters Kluwer business, for medical writing and editorial support. Preparations of this manuscript was supported by Actelion Pharmaceuticals US, Inc.

**Conflict of interest statement**

Dr Safdar is on advisory boards and consultant committees for Actelion Pharmaceuticals US, Inc. Gilead, and United Therapeutics.
Therapeutics. Preparation of this manuscript was supported by Actelion Pharmaceuticals US, Inc.

References


Prostacyclin and prostaglandin analogs in the treatment of PAH


