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What Is the Role of Oral Prostacyclin Pathway Medications in Pulmonary Arterial Hypertension Management?

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Abstract
Purpose of Review Prostacyclin pathway medications have been shown to be highly efficacious in the treatment of pulmonary arterial hypertension (PAH) through multiple prospective clinical trials and more than two decades of clinical experience. The strongest support for prostacyclin use in PAH management is with parenteral administration. Numerous risks and limitations of parenteral delivery systems as well as significant patient burdens restrict widespread parenteral use. Highly effective and tolerable oral prostacyclin preparations to manage PAH have long been sought. We review the development of the oral prostacyclin agents beraprost, treprostinil, and selexipag and including current indications and limitations. Research into new approaches to the management of PAH, expanding indications for existing agents, and development of novel agents are also discussed.
Recent Findings Two oral prostacyclin pathway medications, oral treprostinil and selexipag, were FDA approved in December 2013 and 2015, respectively. Current guidelines recommend use of selexipag in WHO-FC II and III (class 1, level B recommendation) and oral treprostinil in WHO-FC III (class 2b, level B recommendation). The use of these medications is challenging due to complexity in dosing and their side effect profiles which limit patient tolerability and acceptance.
Summary There is a promising role for oral prostacyclin pathway medications in patients with PAH. Future investigations are underway of alternative dose regimens and transitioning from parenteral therapies in order to improve efficacy and tolerability.

Keywords Prostacyclin · Beraprost · Treprostinil · Selexipag · Oral prostacyclin

Introduction

Pulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure (mPAP) > 25 mmHg at rest, measured during right heart catheterization [1]. The 5th World Pulmonary Hypertension Symposium guidelines identify five groups of pulmonary hypertension. Group 1 Pulmonary Hypertension (Pulmonary Arterial Hypertension or PAH) is defined by a mPAP > 25 mmHg at rest, with a pulmonary capillary wedge pressure (PWCP) < 15 mmHg and pulmonary vascular resistance (PVR) > 3 wood units, in the absence of significant lung disease or chronic thromboembolic disease [2•]. The most common forms of PAH include idiopathic PAH, PAH-related to connective tissue disease (PAH-CTD), and PAH-related to congenital heart disease. Other subcategorizes include heritable PAH, drug- or toxin-induced PAH, PAH associated with HIV infection, and portopulmonary hypertension (POPH) [3]. The clinical course and life expectancy for affected individuals varies based on the underlying etiology and severity of PAH. PAH-CTD (specifically PAH-related to scleroderma) and POPH carry a worse prognosis compared with idiopathic PAH [4, 5].

The pathobiology of PAH involves abnormalities in multiple biochemical pathways. Vasoconstriction is observed due to decreased prostacyclin and nitric oxide production was well as endothelin overproduction. Abnormal cellular changes include pulmonary vascular endothelial proliferation and dysfunction, smooth muscle hypertrophy, pulmonary

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microvascular remodeling, and in situ thrombosis in the pulmonary vascular microcirculation [6•, 7]. The treatment of PAH includes nonspecific interventions as well as specific drug therapy targeting these pathways; endothelin receptor antagonists target the endothelin pathway, phosphodiesterase inhibitors and soluble guanylate cyclase stimulators target the nitric oxide pathway, and prostacyclins and prostacyclin receptor agonist medications target the prostacyclin (prostaglandin I2, PGI2) pathway [2, 8•, 9].

Prostacyclin (also known as prostaglandin I2 or PGI2) is a potent vasodilator which also inhibits platelet adhesion and cell growth. Studies have shown that patients with PAH have a decrease in expression of the critical enzyme PGI2 synthase (PGI2-S) and reduced production of prostacyclin [10, 11]. Epoprostenol, a synthetic prostacyclin, has been shown to improve hemodynamics, exercise capacity, and quality of life in patients with advanced PAH (NYHA functional class III or IV) [12•]. However, multiple limitations to epoprostenol delivery exist including instability at pH values below 10.5 and room temperature, as well as its short half-life (3–5 min) in the circulation. As a result, it can only be administered as a continuous intravenous infusion with a cumbersome outpatient delivery system [13]. The risks associated with intravenous therapy include those associated with the need for chronic vascular access (both thrombotic and infectious complications), continuous infusion pumps, and possible life-threatening interruptions of infusions. Treprostinil is a modified prostacyclin analogue, which unlike epoprostenol, is stable at room temperature and has a longer half-life (~ 3–4 h). It can be administered by continuous intravenous or subcutaneous infusion, as well as oral and inhalational routes [2•]. Subcutaneous treprostinil infusion is an alternative mode of parenteral prostacyclin therapy that avoids many of the risks and inconvenience of intravenous infusion but is associated with local irritation at the infusion site. Iloprost is a chemically stable prostacyclin analogue which is available for intravenous and inhaled administration but is approved in the USA only for inhaled delivery. The inhaled formulations of both treprostinil and iloprost can be cumbersome to administer and have dose-limiting side effects, including cough and headache that prevent dose escalation. Their rapid metabolism following inhalation results in long periods between treatments in which no drug can be detected. As a result of the many limitations to parenteral and inhaled prostacyclin therapy, there has been a longstanding interest in developing oral prostacyclin agents. The focus of this review will be on the oral agents beraprost, treprostinil, and selexipag and their role in the management of PAH.

Beraprost

Beraprost was the first oral prostacyclin to be developed for clinical use in pulmonary hypertension. Initial small retrospective studies of beraprost given to treat PAH were promising with respect to hemodynamics and prognosis [14, 15]. This was further supported by a double-blind, placebo-controlled study with 130 PAH patients, showing beraprost improved exercise capacity and symptoms in patients with NYHA functional class II and III PAH at 12 weeks [16•] . In a longer-term study, which randomized 116 PAH patients to receive beraprost (n = 60) or placebo (n = 56) for 12 months, the primary endpoint was disease progression (defined as death, transplantation, need for epoprostenol rescue, or 25% decrease in peak oxygen consumption by cardiopulmonary exercise testing). The secondary endpoints included exercise capacity assessed by 6-min walking distance and peak oxygen consumption on cardiopulmonary exercise testing, Borg dyspnea score, pulmonary hemodynamics, symptoms of PAH, and quality of life drug-related adverse events were common and were related to the disease and/or expected prostacyclin adverse events [17•]. Patients treated with beroprost exhibited less evidence of disease progression at 6 months (1 vs 11 patients, p = 0.002) and improved 6-min walking distance test results at 3 and 6 months (p = 0.01 and 0.016, respectively); however, these effects were not sustained at longer follow-up intervals (9 and 12 months) [17•]. Currently, oral beraprost is approved for use to treat PAH in Japan and South Korea [18] and is undergoing clinical trials in the USA (reference BEAT study).

Treprostinil

Treprostinil is a prostaglandin analog that is chemically stable at room temperature and neutral pH [19]. Oral treprostinil was studied in a series of randomized, prospective, placebo-controlled clinical trials (the "FREEDOM" trials) beginning in 2013.

In the FREEDOM-M (for "monotherapy") trial, 349 PAH patients, not receiving other PAH-specific therapies were randomized to treprostinil (n = 233) or placebo (n = 116). The treprostinil dose was started at 0.25 mg orally twice daily and escalated by an additional 0.25–0.5 mg orally twice daily every 3 days to a maximum possible dose of 12 mg twice daily. The primary endpoint was change from baseline in 6MWD at week 12. Secondary endpoints included Borg dyspnea index, clinical worsening, and symptoms of PAH. Patients receiving oral treprostinil demonstrated an improved 6-min walking distance test (p = 0.0125) and combined 6-min walking distance test/Borg dyspnea score (p = 0.0497) compared to placebo at 12 weeks; however, there was no observed difference in clinical worsening due to PAH [20•]. The average dosing achieved in this study was 3.4 ± 1.9 mg twice daily which was calculated to be equivalent to approximately 10–30 ng/kg/min of the intravenous treprostinil formulation.

In the FREEDOM-C (for "combination therapy") trial, 350 PAH patients on background oral PAH therapy with an ERA

and/or a PDE-5 inhibitor were randomized to the addition of oral treprostinil or placebo for 16 weeks. Primary endpoint was Hodges-Lehmann placebo-corrected median difference in change from baseline 6-min walking distance at 16 weeks. Secondary endpoints included time to clinical worsening, change in World Health Organization functional class, Borg dyspnea score, and dyspnea fatigue index score. The treprostinil dosing was initially started at 0.5 mg orally twice daily and, if clinically tolerated, increased by 0.5-mg increments every 3 days. Each patient's dose was gradually increased up to a maximum of 16 mg orally twice daily over 16 weeks as tolerated, depending upon individual adverse events as well as signs and symptoms of PAH [21•, 22•]. The study found no difference in the group median 6-min walking distance test results at week 16 ($p = 0.07$) or in the predetermined secondary outcomes. However, it should be noted that many patients could not reach a dose greater than 1 mg twice daily due to side effects of the medication, which included headache, nausea, diarrhea, jaw pain, and vomiting [21•, 22•]. It was observed that patients who achieved doses of 1.25 to 3.25 mg and 3.5 to 16 mg twice daily at 16 weeks experienced a greater increase in 6-min walking distance (18 and 34 m, respectively) than patients only achieving a twice daily dose below 1 mg.

Because of drug tolerability issues and the likelihood of sub-therapeutic treprostinil dosing in FREEDOM-C, the FREEDOM-C2 trial was subsequently conducted. This prospective study sought to examine the safety and efficacy of oral treprostinil in a similar patient population to the FREEDOM-C population (i.e., PAH patients on background therapy) with the same primary and secondary endpoints but with a larger study population and smaller treprostinil dose formulations. This study began with a lower treprostinil dose (0.25 mg twice daily) and more gradual dose escalation (additional 0.25 mg twice daily every 3 days) as clinically indicated. In this study, a mean dose of 3.1 ± 1.9 mg twice daily was achieved at 16 weeks for the treated population as a whole. Despite the higher mean dose achieved in this study compared to FREEDOM M and FREEDOM C, no statistically significant differences were observed in the study endpoints between the active medication and placebo arms.

In longer-term follow-up of 37 patients from the FREEDOM studies up to 7 years (most of whom were on background therapy) demonstrated longer-term tolerability of the medication but did not demonstrate a significant improvement in 6-min walking distance, functional class assessment, or hemodynamics compared with pretreatment values [22•].

Based primarily on the results of the FREEDOM M studies, oral treprostinil was FDA approved in the USA for use as twice daily oral monotherapy to treat PAH. The negative results observed in the FREEDOM-C trials may have been due to side effects of the oral formulation when administered in a twice daily dosing regimen that prevented most patients from achieving adequate treprostinil doses within the short time frame of the trial [23]. Studies of three times daily dosing have demonstrated reduced serum peak-to-trough treprostinil serum level variability and improved patient tolerance [24]. The FREEDOM-Ev (Early Combination of Oral Treprostinil With Background Oral Monotherapy in Subjects With Pulmonary Arterial Hypertension, NCT01560624), studying three times daily dosing, is currently underway to formally investigate the tolerability of this dosing regimen and the effectiveness of oral treprostinil in less severely affected patients. In summary, treprostinil is an orally active pulmonary vasodilator with significant delivery challenges identified in multiple clinical trials. Presently, the US FDA has approved oral treprostinil for monotherapy in pulmonary arterial hypertension with a beginning dose of 0.25 mg orally twice daily. It may be uptitrated every 3 to 4 days (as clinically tolerated) by 0.25–0.5 mg twice daily or 0.125 mg three times daily.

Selexipag

Selexipag is an oral, selective non-prostanoid prostacyclin receptor agonist, which is a potent and selective agonist of the prostaglandin I2 (PGI2) receptor [25]. In 2012, a randomized, placebo-controlled, proof-of-concept study showed that the use of selexipag in 43 PAH patients on stable doses of ERA and/or PDE-5 inhibitor was associated with a 30.3% reduction in PVR compared to placebo after 17 weeks of treatment. A significant increase in the 6-min walking distance was also seen in the selexipag versus placebo study populations. Selexipag patients were also found to have significant improvements in cardiac index, right atrial pressure, and pulmonary vascular resistance compared to placebo. As with oral treprostinil, the majority of the patients were unable to tolerate the maximum target dose due to side effects (principally headache, jaw pain, or GI symptoms). Only 42.4% (14/33) of the selexipag patients reached the maximum allowable dose of 600 μg twice daily. About 18% (7/33) reached a dose of 400 μg twice daily while 12% (4/33) could only tolerate a dose of 200 μg twice daily [26•].

In 2015, the GRIPHON (Prostacyclin [PGI2] Receptor Agonist in Pulmonary Arterial Hypertension) trial was performed [27•]. This was a multi-center, double-blinded, randomized, parallel-group, and placebo-controlled phase 3 trial. A total of 1156 PAH patients who had not previously taken PAH oral medications or who were taking stable doses of ERA or PDE-5 inhibitors medications (single or dual oral background therapy) were enrolled. Patients with PAH who had received prostacyclin pathway drugs were excluded. Patients were randomized to selexipag in escalating doses twice daily or placebo. The primary end point was a composite of death from any cause or a complication related to pulmonary arterial hypertension up to the end of the treatment

period (defined for each patient as 7 days after the date of the last intake of selexipag or placebo). Secondary end points included the change in the 6-min walk distance from baseline to week 26, the absence of worsening of WHO functional class from baseline to 26 weeks, and death or hospitalization due to PAH. Selexipag was started at dose of 200 μg twice daily and increase in 200 μg increments over 12 weeks until intolerable side effects (e.g., headache or jaw pain) were experienced. The highest dose allowed was 1600 μg twice daily. Patients on selexipag had a 40% risk reduction in PAH-related complications which included time to progression of PAH, initiation of parenteral prostacyclin agent for treatment of PAH, initiation of long-term oxygen therapy, or lung transplantation. Overall, 23.2% of patients received a maintenance dose in the low-dose stratum (200–400 μg twice daily), 31.2% in the medium-dose stratum (600–1000 μg twice daily), and 42.9% in the high-dose stratum (1200–1600 μg twice daily). In addition, 82 patients (14.3%) discontinued selexipag at 200 μg twice daily dose due to side effects. Dose-limiting adverse events commonly included headache, diarrhea, nausea, and jaw pain [27•]. A composite endpoint of death from PAH or hospitalization for worsening PAH was significantly reduced with selexipag against placebo (17.8 vs 23.5%, $p = 0.003$); however, mortality was not different between the groups. The 6-min walk distance decreased 9 m from baseline in the placebo group and increased 4 m in the selexipag group (placebo-adjusted difference = 12 m favoring selexipag). There was no difference in the number of patients who had no change in WHO functional class between placebo and selexipag treated groups.

Selexipag is approved in the USA to treat PAH patients with NYHA FC II or III with or without background oral PAH therapy [2•]. The FDA has approved selexipag for group 1 PAH, with starting dose 200 mcg twice daily and increasing the dose by 200 mcg twice daily at weekly intervals to the highest tolerated dose up to 1600 mcg twice daily. No dose adjustments are required in patients with renal insufficiency, although data in those receiving dialysis is not available. No dose adjustments are needed for patients with mild hepatic impairment (Child-Pugh class A); whereas, a once-daily regimen of selexipag is suggested in patients with moderate hepatic impairment (Child-Pugh class B) [28].

Future Directions

Currently, the role of oral prostacyclin therapy in the management of PAH is unclear. Data from clinical trials do not support the addition of oral treprostinil to background therapy to improve 6-min walk distance in PAH patients who are being treated with other PAH specific medications, but may be an effective therapy for patients who are treatment naïve. Conversely, the use of selexipag has been shown to delay disease progression in patients on background therapy, but with no effect on functional class and a modest effect on 6-min walk distance. Overall, oral prostacyclin therapy does not appear to be as effective as prostacyclin therapies administered by continuous intravenous or subcutaneous infusion. However, these drugs may be beneficial for patients who are unable to manage or tolerate parenteral prostacyclin therapy. They also offer an addition oral option for patients who are unable to tolerate PDE5 inhibitors or endothelin receptor antagonists. Whether or not their use as part of an upfront triple combination therapy offers advantages over initial dual drug therapy is currently being investigated in the TRITON trial (The Efficacy and Safety of Initial Triple Dual Oral Combination Therapy in Patients with Newly Diagnosed Pulmonary Arterial Hypertension) (NCT02558231). This study will examine the role of upfront triple therapy with an ERA medication, a PDE-5 inhibitor along with selexipag compared to dual an ERA medication, a PDE-5 inhibitor along with placebo.

Transitioning from subcutaneous/parenteral prostacyclin to oral prostacyclin is another possible approach to improving the tolerability and patient acceptance of oral agents. Recently, Chakinala and colleagues enrolled 33 PAH subjects on stable subcutaneous or intravenous treprostinil (85 and 15%, respectively) with a favorable PAH risk profiles into a study evaluating the transition from parenteral to oral treprostinil. The protocol outlined a 5-day in-hospital titration from the parenteral therapy to a targeted oral treprostinil regimen taken three times daily. A favorable risk profile was defined as having WHO Functional Class I or II symptoms, a baseline cardiac index > 2.2 l/min/m^2, a right atrial pressure < 11 mmHg, and a 6-min walk distance ≥ 250 m prior to transitioning. In addition to being on parenteral treprostinil, endothelin receptor antagonist (ERA) or phosphodiesterase-5 inhibitor (PDE-I) treatments were mandated as background therapy. The primary endpoint was successful transition to oral therapy at 24 weeks. Baseline and end-of-study assessments included 6-min walk distance, echocardiography, hemodynamics by right heart catheterization, pharmacokinetics, treatment satisfaction, and quality of life. All 33 subjects transitioned to oral treprostinil therapy within 4 weeks, but 2 transitioned back to parenteral drug prior to the end-of-study at 24 weeks. The results showed that 6-min walk distance was preserved. Hemodynamic variables, including pulmonary vascular resistance, were similar at 24-week post-transition except for the median mixed venous saturation, which fell from 71 to 68% ($p < 0.001$). The overall quality of life and treatment satisfaction measures did not change; however, mood-related symptom and treatment convenience subscores improved. Adverse effects included headache, nausea, flushing, and diarrhea [29•]. By 24-week subjects were taking a median total daily dose of 44 mg (range 15 to 75 mg), with 25/31 (80%) following a three times daily oral dosing regimen. Notably, these significantly higher doses were much better tolerated than seen in the FREEDOM trials.

Table 1 FDA-approved oral prostacyclin medications

Medication (trade name)	US FDA indication		ESC/ERS Guidelines			Doses supplied	Titration dosage (do not split, crush, or chew tablets)
	PH diagnostic group	NYHA class	Recommended use in PAH	Class	Level of evidence		
Treprostinil (Orenitram®)	Group 1 PAH	II-III	Monotherapy: WHO-FC III	IIb	B	Extended-release tablets: 0.125 mg, 0.25 mg, 1 mg, 2.5 mg, and 5 mg	Begin 0.25 mg twice daily, titrate by 0.25 mg or 0.5 mg twice daily or 0.125 mg three times daily, not more frequently than every 3 to 4 days as tolerated Maximum dose is determined by tolerability Mild hepatic impairment (Child-Pugh Class A): initiate at 0.125 mg twice daily. Increment at 0.125 mg twice daily every 3 to 4 days as tolerated
			Sequential polytherapy: WHO-FC II, III	IIb	C		Avoid use in patients with moderate hepatic impairment
Selexipag (Uptravi®)	Group 1 PAH	II-III	Monotherapy: WHO-FC II, III	I	B	Tablets: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg, and 1600 mcg	Begin 200 mcg twice daily, increase the dose by 200 mcg twice daily at weekly intervals to the highest tolerated dose up to 1600 mcg twice daily Maintenance dose is 1600 mcg twice daily or lower as determined by tolerability
			Sequential polytherapy: WHO-FC II, III	I	B		Moderate hepatic impairment: Starting dose 200 mcg once daily, increase the dose by 200 mcg once daily at weekly intervals to the highest tolerated dose up to 1600 mcg

This study raises the possibility of PAH patients being initially stabilized and desensitized to prostacyclin therapy through parenteral therapy use and subsequently transitioned to an oral regimen at higher (therapeutic) doses. It should be noted that this was a highly selected cohort of stable PAH patients who had an excellent response to parenteral treprostinil therapy on initial management and were on parenteral therapy for a significant time prior to the transition attempt. Clinicians need to closely monitor these patients following oral transition as late deterioration was observed in a several participants despite careful patient selection. Further studies are needed to report on longer-term results of transitioning to oral therapies.

Research is currently underway to evaluate the effect of continued long-term oral treprostinil therapy for the treatment of pulmonary hypertension (PH) associated with heart failure with preserved ejection fraction (HFpEF) in the SOUTHPAW study (NCT03043651).

Finally, in development is ralinepag, a novel oral selective prostacyclin receptor agonist with a significantly longer half-life of 20–26 h. This prolonged half-life may allow for once daily dosing and reduce side effects associated with use of oral prostanoids [30]. A phase 2 randomized, double-blind, parallel-group, placebo-controlled trial of ralinepag in patients with PAH (NCT02279160) has completed enrollment of 60 patients worldwide. This study aims to examine the change from baseline in pulmonary vascular resistance and 6-min walk distance in patients receiving daily ralinepag compared to placebo.

Conclusions

Multiple studies have confirmed strong efficacy for the of intravenous prostacyclins in PAH, and the 5th World Pulmonary Hypertension Symposium guidelines recommend

intravenous prostacyclin for patients with WHO FC IV disease and those with evidence of rapid progression. The burden and risks associated with the parenteral therapy are numerous and include the need for continuous infusion pumps, thrombotic and infectious complications, and the possibility of life-threatening interruption of infusions [24]. The availability of highly efficacious and tolerable oral prostacyclin preparations has been a longstanding goal of the PAH community. Selexipag and treprostinil are the only available prostacyclin pathway medications in the USA given by the oral route (Table 1). The use of these medications is currently limited by both complexity in dosing as well as their side effect profiles which limit patient acceptance. Joint European Society for Cardiology/European Respiratory Society Guidelines recommend use of selexipag in WHO-FC II and III (class 1, level B recommendation) and oral treprostinil in WHO-FC III (class 2b, level B recommendation) [2•].

Compliance with Ethical Standards

Conflict of Interest Dr. Wirth reports grants from United Therapeutics and Arena Pharmaceuticals, during the conduct of the study. Dr. El Yafawi declares no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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