Recent advances in targeting the prostacyclin pathway in pulmonary arterial hypertension

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ABSTRACT Pulmonary arterial hypertension (PAH) is a severe disease characterised by increased pulmonary vascular resistance, which leads to restricted pulmonary arterial blood flow and elevated pulmonary arterial pressure. In patients with PAH, pulmonary concentrations of prostacyclin, a prostanoid that targets several receptors including the IP prostacyclin receptor, are reduced. To redress this balance, epoprostenol, a synthetic prostacyclin, or analogues of prostacyclin have been given therapeutically. These therapies improve exercise capacity, functional class and haemodynamic parameters. In addition, epoprostenol improves survival among patients with PAH. Despite their therapeutic benefits, treatments that target the prostacyclin pathway are underused. One key factor is their requirement for parenteral administration: continuous intravenous administration can lead to embolism and thrombosis; subcutaneous administration is associated with infusion-site pain; and inhalation is time consuming, requiring multiple daily administrations. Nevertheless, targeting the prostacyclin pathway is an important strategy for the management of PAH. The development of oral therapies for this pathway, as well as more user-friendly delivery devices, may alleviate some of the inconveniences. Continued improvements in therapeutic options will enable more patients with PAH to receive medication targeting the prostacyclin pathway.

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Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature characterised by vasoconstriction, vascular remodelling, smooth muscle cell and endothelial cell proliferation, and *in situ* thrombosis [1]. The three therapeutically exploited signalling pathways involved in the pathology of this disease are the prostacyclin (also called prostaglandin I_2 (PGI_2)), endothelin and nitric oxide pathways (fig. 1) [1–14]. Treatments that target these pathways have been approved for PAH [15, 16], and other agents are under investigation. Prostacyclin, its analogues and the IP receptor agonist selexipag (fig. 2) target the prostacyclin pathway; endothelin receptor antagonists (ERAs) target the endothelin pathway; and phosphodiesterase type 5 inhibitors (PDE-5i) and soluble guanylate cyclase stimulators target the nitric oxide pathway. Due to the involvement of all three pathways in disease progression, effective targeting of more than one pathway by combining drugs may improve treatment success in PAH.

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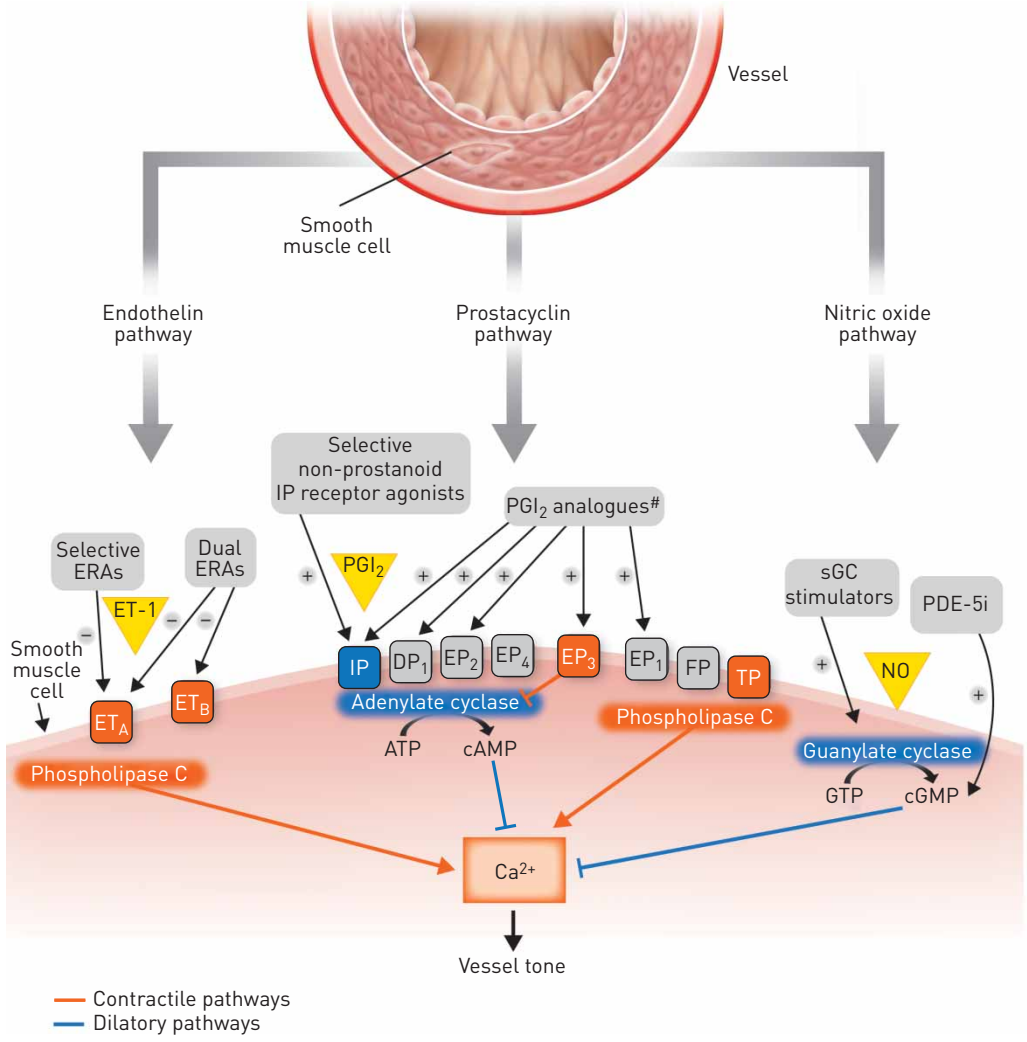

FIGURE 1 Involvement of the endothelin, nitric oxide and prostacyclin (PGI_2) pathways in the pathogenesis of pulmonary arterial hypertension [1–14]. DP_1, EP_2, EP_4, EP_1 and FP are not functionally expressed in the pulmonary artery and do not contribute to vessel tone in the pulmonary artery. In the endothelin pathway the effects of endothelin (ET)-1 are mediated *via* the ET_A and ET_B receptors. Receptor binding leads to activation of phospholipase-C and mobilisation of calcium, resulting in vasoconstriction. Selective and dual endothelin receptor antagonists (ERAs) inhibit this pathway. In the pulmonary artery the prostanoid receptors IP, EP_3 and TP regulate vessel tone. The prostacyclin pathway involves prostacyclin binding to the IP receptor, which belongs to a family of prostanoid target receptors. Prostanoid binding to the IP receptor induces adenylate cyclase activity, cAMP production and ultimately reduction of Ca^{2+} concentrations, and leads to vasodilation. TP binding activates phospholipase C, mediating mobilisation of calcium and vasoconstriction. EP_3 receptor binding leads to a decrease in cAMP, which blocks vasodilation. Prostacyclin analogues activate this pathway (EP_3 pathway). The nitric oxide (NO) pathway involves the production of cGMP, which leads to inhibition of calcium entry, resulting in vasodilation. Phosphodiesterase type 5 inhibitors (PDE-5i) and soluble guanylate cyclase (sGC) stimulators activate this pathway [2–5, 7–14]. #: prostacyclin analogues activate at least one prostanoid receptor in addition to IP. Reproduced and modified from [1], with permission from the publisher.

Epoprostenol, a synthetic prostacyclin, was the first drug to be approved for PAH [2] and is recommended for patients with severe disease [15, 16]. However, despite the availability and proven efficacy of prostacyclin or its analogues, many patients die without ever receiving a drug targeting the prostacyclin pathway [17]. Reluctance to use these treatments in clinical practice may be due to a number of limitations, including adverse effects, but are mainly due to shortfalls in the method of drug delivery.

New treatment strategies aim to optimise disease management with more emphasis on the prostacyclin pathway, by treating patients with combination therapy that targets two or even all three main pathways, and by reducing the burden of currently available delivery systems. In this review, we will outline the promise and the shortcomings of current therapies for PAH that target the prostacyclin pathway. Improvements in the administration of parenteral and inhaled therapies will be described, and recent developments with oral therapies that target the prostacyclin pathway will be discussed.

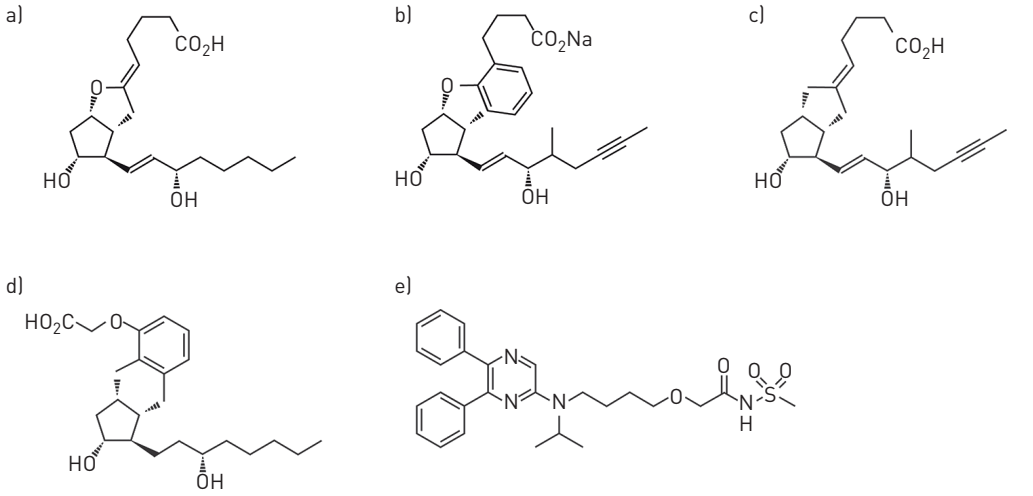

FIGURE 2 Chemical structures of drugs that bind to the prostacyclin pathway. a) Prostacyclin; b) beraprost sodium; c) iloprost; d) treprostinil; and e) selexipag.

The prostacyclin pathway in PAH

Prostacyclin is synthesised primarily by vascular endothelial cells and is a natural ligand for the prostacyclin IP receptor, which is expressed in multiple organs including the heart and lungs, pulmonary arteries, peripheral arteries, nerves and the gastrointestinal system (fig. 3) [3, 18–20]. Prostacyclin is a member of the prostanoid family of signalling molecules, which comprise two groups: prostaglandins (PGD_2, PGE_2, PGI_2 (prostacyclin) and PGF_{2a}) and thromboxane ($TX_{\alpha 2}$). These endogenous prostanoids elicit biological effects by activating corresponding cell surface G-protein-coupled prostanoid receptors located on various tissue types throughout the body (fig. 3) [4, 19, 21–29].

In PAH, the primary effects of IP receptor activation (*e.g.* by prostacyclin or its analogues) are the induction of pulmonary artery dilation and the inhibition of vascular smooth muscle cell proliferation [1]. Activation of the IP receptor can also lead to inhibition of platelet aggregation [2]. $TX_{\alpha 2}$ elicits contrary effects and is a potent pulmonary vasoconstrictor and activator of platelet aggregation [30]. In pulmonary hypertension, there is an imbalance in the production of the vasoactive mediators, prostacyclin and nitric oxide, on the one side and the vasoconstrictors, endothelin-1 and $TX_{\alpha 2}$, on the other side [30–32]. Similarly, in patients with idiopathic PAH, there is reduced expression of prostacyclin synthase in the pulmonary arteries [33], with an apparent reduction in prostacyclin release and a marked increase in $TX_{\alpha 2}$ [30]. The observation of reduced levels of prostacyclin in PAH provides a rationale for therapies that target the prostacyclin pathway [30, 34, 35].

With respect to vascular physiology, prostanoid target receptors can be grouped into two categories: relaxant receptors (IP, DP_1, EP_2 and EP_4) and contractile receptors (EP_1, EP_3, FP and TP), depending on the type of G-protein to which they bind [21] and their effects on vessel tone (fig. 1). In pulmonary arterial vessels, the IP receptor is the only functionally active relaxant receptor [3], whose activation induces adenylate cyclase activity and cyclic AMP synthesis. In peripheral vessel types, all four relaxant receptors can contribute to varying extents to vessel relaxation by inducing adenylate cyclase activity. In pulmonary arterial vessels, the contractile receptors TP and EP_3 mediate vasoconstriction. TP does so by activating phospholipase C, thus leading to calcium mobilisation. The EP_3 receptor induces contraction by inhibiting adenylate cyclase activity and, thus, reducing the concentration of cyclic AMP. In peripheral vessel types, all four contractile receptors contribute to vasoconstriction to varying extents by either activating phospholipase C and calcium mobilisation (TP, EP_1, FP), or by inhibiting adenylate cyclase (EP_3) [21, 26]. Some prostanoids bind to multiple receptors, thereby activating diverse signal transduction pathways and resulting in a range of biological responses [21].

Prostacyclin therapy for PAH

The currently available drugs that target the prostacyclin pathway are epoprostenol, iloprost, treprostinil and beraprost. These drugs are recommended for the treatment of patients with advanced PAH (World Health Organization (WHO) functional class (FC) III–IV) (table 1) [15, 16]. Selexipag, which is undergoing regulatory approval for use at the time of writing, is the only drug targeting the prostacyclin pathway that is recommended as an option for first-line therapy in patients in WHO FC II, in addition to those in WHO FC III. An overview of the key randomised clinical trials of these drugs is shown in table 2.

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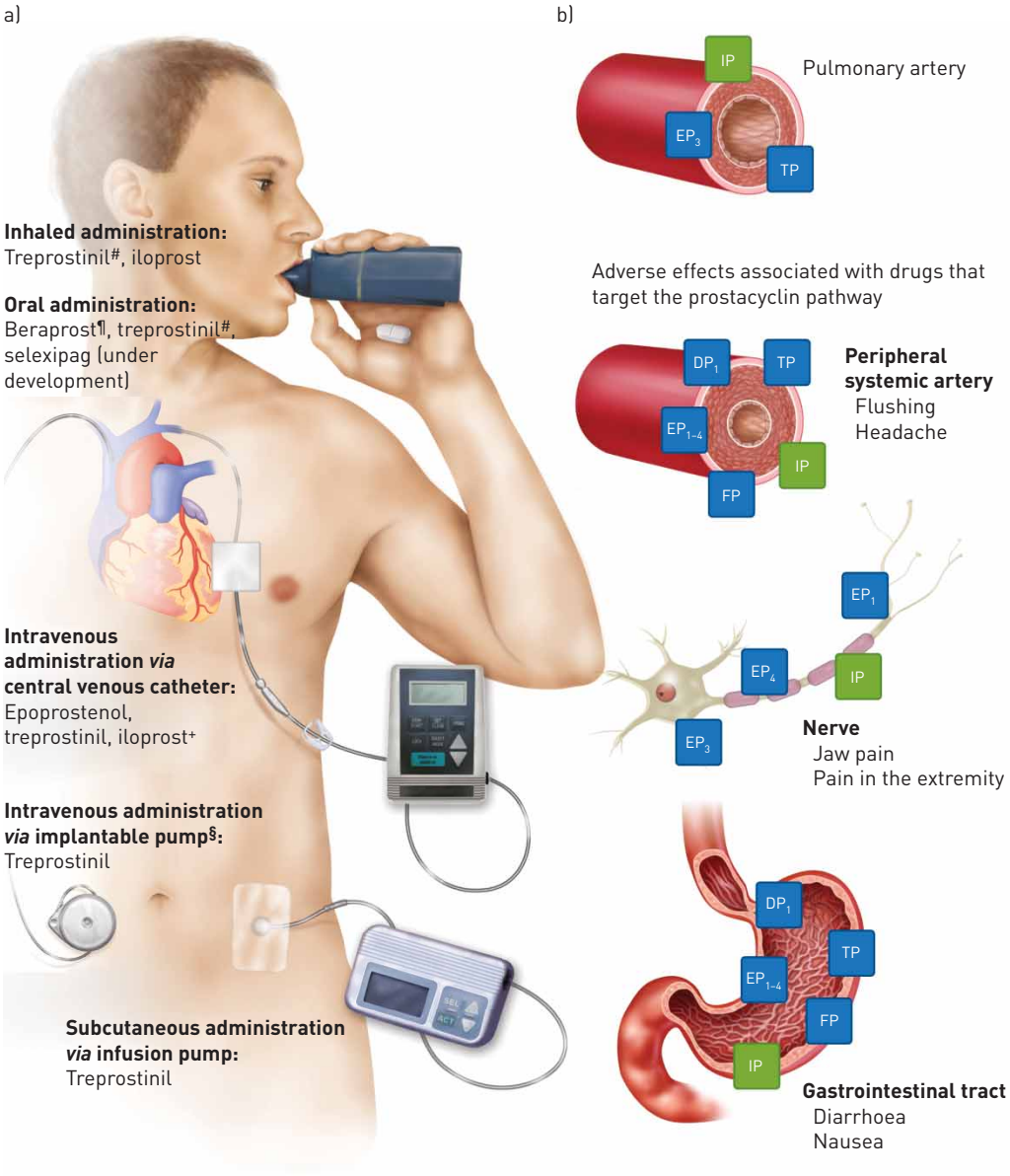

FIGURE 3 Drugs that target the prostacyclin pathway. a) Routes of administration, and b) target receptors and adverse events [3, 16, 19, 20]. Key tissues associated with known adverse effects are listed. #: approved only by the US Food and Drug Administration; ¶: approved only in Japan and South Korea; +: approved only in New Zealand; §: this pump is an innovation that is not yet widely available.

Epoprostenol

Epoprostenol, the sodium salt of prostacyclin, was the first exogenous prostanoid used for the treatment of PAH [2] and can be used as monotherapy or in combination with an ERA or a PDE-5i [37–42, 54, 55]. It is recommended as an initial treatment for patients in WHO FC III and IV and is currently recommended as an initial treatment for patients in WHO FC IV (table 1) [15, 16]. Epoprostenol is usually initiated at 2–4 $ng \cdot kg^{-1} \cdot min^{-1}$ and titrated in a stepwise manner to doses typically ranging from 20 to 40 $ng \cdot kg^{-1} \cdot min^{-1}$ [15]. However, extensive dose-ranging studies are not available. Clinically effective doses may take up to 6 months to be achieved and, in some patients, can exceed >100 $ng \cdot kg^{-1} \cdot min^{-1}$. However, in certain clinical cases such as pregnancy or urgent surgery, up-titration may be faster, allowing effective doses to be reached more rapidly. Epoprostenol is a chemically unstable compound, and its short half-life (~6 min) [56] necessitates continuous intravenous administration *via* a permanent indwelling central venous catheter (fig. 3) [56].

The formulation of epoprostenol has been adapted to enable more convenient delivery. The earliest formulation of epoprostenol had limited thermal stability, necessitating inconvenient administration using

TABLE 1 Evidence-based monotherapy treatment algorithm for drugs that target the prostacyclin pathway

Recommendation	Evidence	PAH severity		
		WHO FC II	WHO FC III	WHO FC IV
Recommended (class I)	Data derived from multiple randomised clinical trials or meta-analyses, or from a single randomised clinical trial or large nonrandomised studies	Selexipag oral[#]	Epoprostenol *i.v.*[¶]; iloprost inhaled[+]; treprostinil *s.c.* and inhaled[§]; selexipag oral[#]	Epoprostenol *i.v.*
Should be considered (class IIa)	Consensus of opinion of the experts and/or small studies, retrospective studies and registries		Iloprost *i.v.*[+]; treprostinil *i.v.*[§]	
May be considered (class IIb)	Data derived from a single randomised clinical trial or large nonrandomised studies		Beraprost oral[*f*]; treprostinil oral	Iloprost inhaled and *i.v.*; treprostinil *s.c.*, *i.v.* and inhaled

Recommendation IA for prostanoid use in sequential combination therapy for inadequate clinical response at maximal therapy [3]. WHO: World Health Organization; FC: functional class. [#]: not approved at the time of publication; [¶]: approved for continuous *i.v.* administration for pulmonary arterial hypertension (PAH) WHO FC III–IV by the US Food and Drug Administration (FDA) in 1995; [+]: approved for aerosol administration for PAH WHO FC III in the European Union and Australia in 2003, and PAH WHO FC III–IV by the FDA in 2004; [§]: approved for *s.c.* administration for PAH WHO FC II–IV by the FDA and Health Canada in 2002; [*f*]: approved for oral administration for idiopathic PAH in Japan in 1995 [36]. Information from [15, 16].

a frozen gel or ice pack [56, 57]. A more thermostable formulation has subsequently been developed, which overcomes the need for keeping the infusion solution cool or being replaced within every 24 h period [57, 58]. The Epoprostenol for Injection in Pulmonary Arterial Hypertension (EPITOME-2 and EPITOME-4) trials showed that this improved formulation of epoprostenol led to a significant increase in patients' perception of treatment convenience [59, 60].

The availability of epoprostenol has improved the prognosis for patients with PAH, and has been shown to improve haemodynamic measures [37, 55] and exercise capacity [38, 39, 55]. It is the only drug that has been shown to improve survival in a clinical trial with statistical significance [55]. In addition to monotherapy, short-term studies have shown the efficacy of combining epoprostenol with PDE-5i and/or ERAs (table 2). In a randomised, controlled trial (Bosentan Randomized trial of Endothelin Antagonist Therapy for PAH (BREATHE-2)), bosentan (an ERA) in combination with epoprostenol demonstrated a trend towards improvements in haemodynamics, exercise capacity and WHO FC. However, changes in these variables, including the primary efficacy parameter of total pulmonary resistance, were not statistically significant [41]. In another randomised, controlled trial (Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil (PACES)), oral sildenafil (a PDE-5i) or placebo was added to long-term treatment with *i.v.* epoprostenol [42]. Significant increases in 6-min walking distance (6MWD) at week 16 in the epoprostenol–sildenafil *versus* the epoprostenol–placebo group were observed [42]. In a retrospective, open-label study of initial triple therapy with epoprostenol, bosentan and sildenafil, statistically significant improvements in exercise capacity and cardiopulmonary haemodynamics ($p<0.01$) and improvements in FC were shown. Moreover, all patients were alive after a mean±SD follow-up of 41.2 ±13.4 months. Most adverse events were typical of epoprostenol (jaw pain, headache, diarrhoea or flushing) or ERA therapy (liver enzyme elevation) [54]. The results of this analysis suggest that further studies evaluating combinations of drugs that target the three major PAH signalling pathways are warranted.

Despite a body of evidence that supports the use of epoprostenol in PAH (table 2) [37–42, 54, 55], this treatment is underused. Epoprostenol has a short half-life and an inconvenient route of administration that is burdensome to patients [61]. Parenteral administration can be associated with catheter-related embolism and thrombosis, as well as mechanical complications such as catheter occlusion or dislodgement [62]. Bloodstream infections, including sepsis, have been reported in ~10% of patients who receive *i.v.* prostanoid therapy, resulting in an overall rate of 0.20 bloodstream infections per 1000 treatment days

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TABLE 2 Key randomised controlled clinical trials of drugs that target the prostacyclin pathway

First author [ref.]	Year (trial acronym)	Background therapy	Drug	Patients n	Duration	Primary end-point	Primary end-point met?
Epoprostenol[#]							
Rubin [37]	1990	None	*i.v.* epoprostenol	24	8 weeks	Change in total pulmonary resistance	Yes
Barst [38]	1996	None	*i.v.* epoprostenol	81	12 weeks	Change in 6MWD	Yes
Badesch [39]	2000	None	*i.v.* epoprostenol	111	12 weeks	Change in 6MWD	Yes
Badesch [40]	2009	None	*i.v.* epoprostenol	102	3 years	Survival	No
Humbert [41]	2004 (BREATHE-2)	None	*i.v.* epoprostenol with bosentan or placebo	33	16 weeks	Change in total pulmonary resistance	No
Simonneau [42]	2008 (PACES)	*i.v.* epoprostenol	Sildenafil or placebo	267	16 weeks	Change in 6MWD	Yes
Iloprost[¶]							
Olschewski [43]	2002	None	Inhaled iloprost or placebo	203	12 weeks	Composite ⩾10% increase in 6MWD and improvement in WHO FC	Yes
Hoeper [44]	2006 (COMBI)	Bosentan	Inhaled iloprost	40	12 weeks	Change in 6MWD	No
McLaughlin [45]	2006	Bosentan	Inhaled iloprost	67	12 weeks	Change in 6MWD and WHO FC	Yes
Treprostinil[+]							
Simonneau [46]	2002	None	*s.c.* treprostinil or placebo	470	12 weeks	Change in 6MWD	Yes
Jing [47]	2013 (FREEDOM-M)	None	Oral treprostinil or placebo	349	12 weeks	Change in 6MWD	Yes
Tapson [48]	2012 (FREEDOM-C)	ERA, PDE-5i or both	Oral treprostinil or placebo	350	16 weeks	Change in 6MWD	No
Tapson [49]	2013 (FREEDOM-C2)	ERA, PDE-5i or both	Oral treprostinil or placebo	310	16 weeks	Change in 6MWD	No
McLaughlin [50]	2010 (TRIUMPH-I)	Bosentan or sildenafil	Inhaled treprostinil or placebo	235	12 weeks	Change in 6MWD 10–60 min after inhalation	Yes
Beraprost[§]							
Galiè [51]	2002 (ALPHABET)	None	Oral beraprost or placebo	130	12 weeks	Change in 6MWD	Yes
Barst [52]	2003	None	Oral beraprost or placebo	116	12 months	Difference in disease progression	Yes
Selexipag							
McLaughlin [53]	2015 (GRIPHON)	None, ERA, PDE-5i or both	Oral selexipag[f]	1156	3 years	Time to first morbidity or mortality event	Yes

6MWD: 6-min walking distance; WHO: World Health Organization; FC: functional class; ERA: endothelin receptor antagonist; PDE-5i: phosphodiesterase type 5 inhibitor. [#]: approved for continuous *i.v.* administration for pulmonary arterial hypertension (PAH) WHO FC III–IV by the US Food and Drug Administration (FDA) in 1995; [¶]: approved for aerosol administration for PAH WHO FC III in the European Union and Australia in 2003, and PAH WHO FC III–IV by the FDA in 2004; [+]: approved for *s.c.* administration for PAH WHO FC II–IV by the FDA and Health Canada in 2002; [§]: approved for oral administration for idiopathic PAH in Japan in 1995 [36]; [f]: not approved at time of publication.

[63]. The majority of bloodstream infections associated with both *i.v.* epoprostenol and *i.v.* treprostinil are due to the Gram-positive organism, *Staphylococcus aureus*; the most common Gram-negative organism is *Pseudomonas aeruginosa* [63]. The rates of infection are significantly higher among patients who receive *i.v.* treprostinil rather than *i.v.* epoprostenol (0.36 *versus* 0.12 per 1000 patient days; p<0.001), which could be due to various factors, including the type of diluent [63]. One explanation could be that epoprostenol is traditionally mixed with a diluent with a basic pH, whereas the diluent for treprostinil is neutral, with the more alkaline preparation allowing for less bacterial growth [64]. Indeed, a lower rate of Gram-negative bloodstream infections has been demonstrated in patients who receive treprostinil that has been mixed with epoprostenol diluent *versus* the traditional pH-neutral preparation [65]. For patients who receive treprostinil *via* the subcutaneous route, two studies of large patient cohorts have reported no septic complications associated with this treatment [66, 67].

A variety of prostacyclin analogues are now available that can help improve how PAH is treated, along with the development of a thermostable formulation of epoprostenol.

Established prostacyclin analogues

Iloprost and treprostinil are prostacyclin analogues that are more chemically stable than epoprostenol, and are available in different formulations for the treatment of patients with PAH [24].

Iloprost

Iloprost is widely approved for administration by inhalation, yet is only available for *i.v.* administration in New Zealand [16]. The inhaled formulation is one of the drugs recommended for initial therapy in patients in WHO FC III, and the *i.v.* formulation should be considered for patients in WHO FC III. Both formulations may be considered for use in patients in WHO FC IV (table 1) [15]. When administered *via* inhalation, the starting dose is often 2.5 μg per inhalation, which, if well tolerated, can be up-titrated to 5 μg [68]. The *i.v.* starting dose should be in the range of 0.5–2.0 $ng{\cdot}kg^{-1}{\cdot}min^{-1}$, and may be up-titrated to a maximum of 1–8 $ng{\cdot}kg^{-1}{\cdot}min^{-1}$ [69]. When delivered by the *i.v.* route, iloprost has a half-life of 20–30 min, and, when inhaled, is undetectable in plasma 30–60 min post-inhalation [68]. Inhaled administration circumvents the complications and inconvenience associated with parenteral administration [24], and there is some suggestion that directly targeting the pulmonary circulation may confer additional benefits [15]. Nevertheless, administration *via* the inhalation route is cumbersome. Frequent inhalations are required (6–12 per day) [1], which places a burden on the patient and could also compromise treatment adherence.

Improvements in clinical parameters, including 6MWD and WHO FC have been observed when iloprost monotherapy was compared with placebo over a period of 12 weeks [43]. However, longer-term studies have shown inconsistent results; in one study, significant disease progression was observed in >50% of patients after 12 months of monotherapy with inhaled iloprost, and only a minority of patients were still receiving this regimen after 5 years [70]. The 2-year event-free survival rate in this study was 29% [70]. Another long-term study demonstrated a 2-year survival rate of 87% among patients who received inhaled iloprost monotherapy [71]. When iloprost was used in addition to baseline bosentan, a 12-week study demonstrated improvements in exercise capacity [45]. However, a second study provided conflicting results, with no improvement seen in 6MWD or any other secondary end-point (table 2) [44]. In current therapy for PAH, patients are not treated with inhaled iloprost monotherapy.

Treprostinil

Treprostinil can be administered *via* the *i.v.*, *s.c.*, inhaled and oral routes (fig. 3). However, it is important to note that inhaled and oral formulations have only been approved for use in the USA [72, 73]. The *s.c.* and inhaled formulations are recommended as an option for initial treatment of patients in WHO FC III, and the *i.v.* formulation should be considered in these patients. All formulations may be considered in patients in WHO FC IV (table 1) [15]. Treprostinil is chemically stable at room temperature and has a half-life of ~4 h [74]. The initial dose when administered *via* the *s.c.* and *i.v.* routes is 1.25 $ng{\cdot}kg^{-1}{\cdot}min^{-1}$ [74], which may be increased to 20–80 $ng{\cdot}kg^{-1}{\cdot}min^{-1}$ [15]. It can take, on average, 6 months to achieve an effective and stable dose of treprostinil, as measured by balancing clinical symptoms with adverse effects [66]. For inhalation, treprostinil is administered in four separate treatment sessions per day, at an initial dose of three breaths (18 μg) per treatment session, which can be increased by an additional three breaths at 1–2-week intervals, if tolerated [73]. Oral administration of treprostinil will be discussed later in this review.

In a randomised, double-blind, placebo-controlled study, 12 weeks of treatment with *s.c.* treprostinil monotherapy showed a small but significant improvement in 6MWD *versus* placebo [46]. This improvement was dose related, and more pronounced in patients who showed greater functional impairment at baseline. The study was limited by an unexpectedly high rate of infusion-site pain that was experienced by 85% of the *s.c.* treprostinil group (*versus* 27% for the *s.c.* placebo group) [46]. Improvements in 6MWD have also been demonstrated for *i.v.* treprostinil monotherapy [75] and inhaled treprostinil in combination with bosentan or sildenafil [50]. Furthermore, oral treprostinil tablets have shown utility in improving exercise capacity (table 2) [76].

Unmet needs and future strategies

There is an unquestionable need to develop new, more convenient therapies for patients with PAH that can offer sustained long-term benefits and improved safety and tolerability profiles. Current therapies that target the prostacyclin pathway are associated with numerous adverse effects, including those that affect the gastrointestinal (*e.g.* diarrhoea and nausea), nervous (*e.g.* jaw pain, pain in the extremities and headache) and vascular (*e.g.* flushing and headache) systems (fig. 3). Many of these adverse effects are common, and can occur during dose initiation, titration and chronic administration [24]. Prostacyclin analogues are not exclusively selective for the IP receptor and may also bind to other prostanoid receptors,

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such as DP_1, EP_1, EP_2 and EP_3 (fig. 1), potentially leading to more, or more intense, off-target effects (fig. 3) [5, 6, 77, 78].

More serious complications associated with current prostacyclin treatments are related to parenteral delivery of these agents [1], for which patients must learn how to administer their medication effectively and safely. Furthermore, the costs of treatments for PAH can be high [79], and the overall healthcare burden could be further impacted by the need for training and infrastructure to deliver parenteral therapies. Many of these aspects are likely to contribute to the discrepancies between published recommendations to treat PAH with drugs that target the prostacyclin pathway [15, 16] and actual clinical practice, which shows that these therapies are underused [17].

Administration devices for drugs that target the prostacyclin pathway

Despite the availability of different routes of administration for prostacyclin and its analogues (fig. 3), *i.v.* delivery of epoprostenol continues to be the gold standard therapy for patients with severe PAH [15]. Battery-driven ambulatory pump systems are available for infusion of prostanoids into the body *via* a surgically positioned permanent central venous catheter. For *i.v.* epoprostenol, the CADD-1 HFX 5100 (SIMS Deltec, Inc., St Paul, MN, USA) has been the pump of choice in recent clinical trials [58] and for *i.v.* treprostinil, the CADD-Legacy (SIMS Deltec, Inc.) has been used [75].

A recent development in the management of PAH is the availability of implantable pump systems for continuous *i.v.* delivery of treprostinil, which avoid many of the previously mentioned complications that are associated with continuous *i.v.* administration *via* an indwelling line [46]. Implantation of the device requires a surgical procedure that connects a catheter, placed in the superior vena cava, to a pump that is positioned in the subcutaneous tissue of the abdominal wall [80]. Benefits of these systems include a reduced risk of line infections and battery-associated malfunctions as well as improved patient comfort [80]. However, there is a lack of systemic data on the use of implantable pump systems.

There are several delivery devices available for inhaled prostacyclin therapy, such as the I-neb Adaptive Aerosol Delivery System (Philips Healthcare, Andover, MA, USA) for iloprost and the Tyvaso Inhalation Systems (TD-100 or Optineb; United Therapeutics, Research Triangle Park, NC, USA) for treprostinil [81]. Possible adverse effects associated with the inhalation route of delivery include cough, chest pain, pharyngolaryngeal pain and a dry mouth, as demonstrated by clinical trials [45, 50]. Cough is a highly relevant side-effect of PAH drugs, because of the excessive pulmonary pressure rise during coughing. Improved carrier systems for aerosolised prostacyclin analogues, for example *via* nanoparticles (*e.g.* liposomes), could provide more controlled release of the active substance [82]. The potential benefits of liposomal encapsulation of drugs include: 1) more stabilised and longer duration of therapeutic effect *in vitro*; 2) reduced drug-related side-effects; and 3) reduced local irritation [83]. Furthermore, a liposomal nanoparticle carrier system for delivery of iloprost has been evaluated [83]. When tested for pharmacological efficacy *in vivo* and *ex vivo*, this formulation led to enhanced vasodilation of mouse pulmonary arteries compared with free iloprost.

Development of new oral therapies to target the prostacyclin pathway

To overcome some of the limitations associated with parenteral and inhaled formulations of prostacyclin and its analogues, there has been much interest in the clinical development of oral therapies that target the prostacyclin pathway [84].

Beraprost

Beraprost was the first orally available prostacyclin [51]. It was approved for the treatment of idiopathic PAH in Japan in 1995 [36], and is currently also approved in South Korea for use in patients with PAH [16]. The availability of oral beraprost for the treatment of PAH is restricted to these two countries. Beraprost may be considered for use in patients in WHO FC III (table 2) [15]. A clinical study demonstrated significant positive effects of oral beraprost on disease progression, as measured by 6MWD and dyspnoea [51]. Improvements in exercise capacity have also been demonstrated with oral beraprost after 3 and 6 months of treatment; however, the treatment effect was not significantly different to placebo at later time points, suggesting that the effect is not sustained (table 2) [52]. A longer-acting modified-release formulation of beraprost has been developed, which, compared with the conventional preparation, enables optimal plasma concentrations to be sustained over longer periods [85]. In an open-label, short-term 12-week trial, patients treated with 120 µg per day (divided into two separate doses) of this formulation experienced improvements in exercise capacity and haemodynamic variables compared with baseline assessments [85]. A phase 3 trial, Beraprost 314d Add-on to Tyvaso (BEAT) (clinicaltrials.gov identifier: NCT01908699), that is evaluating the longer-term efficacy and safety of modified-release beraprost tablets when added to inhaled treprostinil is ongoing. The primary outcome measure is the time from randomisation to clinical worsening (death,

hospitalisation due to PAH, initiation of *i.v.* or *s.c.* prostacyclin due to PAH worsening, disease progression and unsatisfactory long-term clinical response). It is expected that this study will be completed in late 2016.

Treprostinil

Oral treprostinil tablets were approved in the USA in 2013 as monotherapy for the treatment of PAH to improve exercise capacity [76]. Oral treprostinil may be considered for use in patients in WHO FC III (table 1) [15]. The recommended starting dose is 0.25 mg twice daily or 0.125 mg three times daily, with upward titration by 0.25 mg or 0.5 mg twice daily, or 0.125 mg three times daily every 3–4 days based on tolerability [72]. Clinical studies have evaluated the effect of oral treprostinil on exercise capacity (table 2) [47–49]. While one clinical study demonstrated a modestly significant effect on 6MWD and dypsnoea of oral treprostinil as monotherapy when compared with placebo [47], other studies failed to show an effect with adding oral treprostinil in patients receiving stable background therapy with an ERA and/or a PDE-5i [48, 49]. Currently, a phase 3 trial is in progress that is investigating oral treprostinil in patients with PAH who are receiving therapy at baseline with an ERA or PDE-5i (Early Combination of Oral Treprostinil With Background Oral Monotherapy in Subjects With Pulmonary Arterial Hypertension (FREEDOM-Ev)) (clinicaltrials.gov identifier: NCT01560624). The co-primary outcome measures are change in 6MWD at week 24 and time to first clinical worsening event from the date of randomisation.

Selexipag

Selexipag is not currently approved for use, yet is recommended for initial therapy in patients in WHO FC II and III [15]. It is the only drug directed towards the prostacyclin pathway that is recommended for sequential double and triple combination therapy in patients in WHO FC II and III (*i.e.* selexipag in addition to an ERA and/or PDE-5i) [15].

Selexipag is a novel, orally available, long-acting (half-life of 6.2–13.5 h), highly selective IP receptor agonist that targets the prostacyclin pathway (fig. 1) [34, 77, 86, 87]. Selexipag is a diphenylpyrazine derivative with a chemical structure unrelated to prostacyclin and its analogues (*e.g.* it lacks the typical cyclopentane ring of prostacyclin analogues). As a consequence, its pharmacokinetics and molecular pharmacology are favourably differentiated from those of prostacyclin and its analogues, thus allowing for twice-daily oral dosing and highly selective activation of the target IP receptor without the potential for tachyphylaxis (fig. 2) [2, 7, 77, 78, 88].

In a placebo-controlled phase 2 trial among patients already receiving treatment for PAH (ERAs and/or PDE-5i), selexipag significantly reduced pulmonary vascular resistance by 30.3% (primary end-point) and increased cardiac index (+0.5 $L \cdot min^{-1} \cdot m^{-2}$). There was also a trend in favour of selexipag for change in 6MWD at 17 weeks in patients who received selexipag (+24.7 *versus* +0.4 m for placebo) [89].

The phase 3, double-blind, placebo-controlled PGI_2 Receptor agonist In Pulmonary arterial HypertensiON (GRIPHON) study (clinicaltrials.gov identifier: NCT01106014) is the first long-term, event-driven study with an agent that targets the prostacyclin pathway. This study investigated the effect of oral selexipag (up to 1600 µg twice daily) on the composite primary end-point of time to first morbidity or mortality event in patients with PAH. Morbidity events were defined as: disease progression or PAH worsening resulting in hospitalisation; initiation of parenteral prostanoid therapy or chronic oxygen therapy; or need for lung transplantation or balloon atrial septostomy. Selexipag demonstrated a significant reduction in the risk of an event as defined in the composite primary morbidity/mortality end-point, compared with placebo in patients with PAH. The treatment effect was consistent across predefined subgroups including age, PAH aetiology, baseline FC and background PAH therapy [53].

Conclusion

Treatments that target the prostacyclin pathway are crucial for the effective management of patients with PAH. Despite clinical evidence for these drugs, their use is frequently delayed and, in many cases, they are not used at all. The problematic delivery of parenteral and inhaled therapies is likely to contribute to this lack of use. Advances in delivery devices and alternative delivery routes, including oral delivery, promise to ensure that treatment adherence is improved and that drugs targeting the prostacyclin pathway are used more often.

Combination therapy that targets two or all three of the main pathways involved in the pathology of PAH is an important treatment strategy [41, 42, 44, 45, 54], and is supported by the recent European Society of Cardiology/European Respiratory Society guidelines [15]. However, further studies of different combinations are needed, as is validation of the treatment strategy of initial triple combination therapy [54, 90]. The investigation of oral prostacyclin analogues that target the prostacyclin pathway is an encouraging development in the management of PAH. Furthermore, the long-term data from the

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GRIPHON trial should provide a strong rationale for targeting the prostacyclin pathway as part of a combination strategy for managing patients with PAH.

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