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MINIREVIEW

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The prostacyclin analogue treprostinil in the treatment of pulmonary arterial hypertension

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Abstract

Pulmonary arterial hypertension (PAH) is a rare but life-threatening disease that progresses rapidly and is currently without a cure. Pharmacological treatments aim to slow down disease progression and to reduce symptoms by targeting the prostacyclin, the endothelin or the nitric oxide pathway. Drugs targeting the prostacyclin pathway have been shown to be favourable for PAH patients by causing vasodilatative, anti-proliferative as well as anti-inflammatory effects, but tend to be underused, partially due to adverse effects and difficulties associated with their intravenous administration. Treprostinil, a stable prostacyclin analogue, was FDA-approved in 2002 to improve exercise capacity in PAH patients and is available in intravenous, subcutaneous, inhaled and oral form. The four different possible ways of administration, a long half-life and its stability at room temperature give treprostinil an advantage over epoprostenol, iloprost and selexipag, the three other FDA-approved drugs targeting the prostacyclin pathway. In clinical trials, treprostinil improved exercise capacity, quality of life (QOL), functional class and clinical status. While the different forms of treprostinil lead to specific complications, its general adverse effects are dizziness, nausea, pain in the jaw and extremities, diarrhoea, flushing and headache. This MiniReview will assess the benefits and drawbacks of treprostinil in the treatment of PAH by examining its specific mechanism of action and pharmacological properties, such as pharmacokinetics, pharmacodynamics, adverse effects and interactions. In addition, we will analyse and discuss results from different clinical trials, comparing treprostinil's four different forms to each other as well as to other drugs targeting the prostacyclin pathway.

KEYWORDS

clinical trials, prostacyclin analogue, pulmonary arterial hypertension, treprostinil

1 | INTRODUCTION

Pulmonary hypertension (PH) is a condition of elevated blood pressure within the pulmonary arterial vessels. The subdivision into categories by the World Health Organization (WHO) is based on the underlying pathology, haemodynamic characteristics as well as the therapeutic approaches (Table 1).[1]

Pulmonary arterial hypertension (PAH) is a rare but serious form of PH, with an annual incidence of 2.4 cases/million in the United States.[2] The incidence is estimated to be similar

in Europe.[3] It comprises incidents of high blood pressure in the arteries leading blood from the heart to the lungs.[4] The increased pulmonary vascular resistance, possibly ending in right ventricular failure, makes it both a progressive and fatal disease.[2]

Pulmonary arterial hypertension is still not curable, but since the approval of the first specific PAH therapy in 1995, several new medicaments have become available, all of which primarily function as pulmonary vasodilators.[5]

A group of drugs that have proven to be very beneficial for PAH patients are synthetic prostacyclin (PGI_2) and PGI_2 analogues. However, due to difficulties associated with their administration among other issues, their use is not as widespread as it could be.[2]

Treprostinil, a synthetic PGI_2 analogue, has the advantage of being available in four different routes of administration, perhaps making it possible to avoid classical side effects caused by continuous intravenous (iv) administration.[6]

2 | METHODS

This MiniReview is based on the literature found using online databases, including PubMed (www.ncbi.nlm.nih.gov/pubmed) and to some extent SCOPUS (www-scopus-com.ez.statsbiblioteket.dk).

Keywords used included 'Pulmonary hypertension' (61 673 results) and 'Pulmonary arterial hypertension AND treatment' (12 620 results). The search 'Pulmonary arterial hypertension gave 20 239 results, and by adding 'treprostinil', the results were narrowed down to 347.

Information about relevant completed and recruiting clinical trials was found at clinicaltrials.gov (www.clinicaltrials.gov), last accessed on 19 June 2019.

3 | BACKGROUND

3.1 | Definition of PAH

Pulmonary arterial hypertension is characterized by a reduced production of the vasodilators nitric oxide (NO) and PGI_2, and by an elevated production of the vasoconstrictors endothelin (ET) and thromboxane. Such an imbalance causes vasoconstriction and an increase in the cell proliferation of the arterial walls, overall resulting in increased pulmonary vascular resistance (PVR) and thereby hypertension.[7] This persistent overload on the heart leads to right ventricular remodelling, maladaptation and in the worst-case failure.[8]

The diagnosis of PAH is defined as having a mean pulmonary arterial pressure (mPAP) of >25 mm Hg at rest, PVR >3 wood units and pulmonary capillary wedge pressure <15 mm Hg in the absence of a lung or thromboembolic disease.[9] The prevalence of PAH is around 15 cases/million and the incidence 2.4 cases/million per year, making it a relatively rare disease.[2]

To describe the severity of PAH in patients, the WHO distinguishes cases based on a class system (Table 2).[10]

TABLE 1 WHO classification of PH

World Health Organization Pulmonary Hypertension Groups	
Group 1	Pulmonary arterial hypertension
Group 2	Pulmonary hypertension due to left heart disease
Group 3	Pulmonary hypertension due to lung disease
Group 4	Pulmonary hypertension due to blood clots in the lungs
Group 5	Blood and other rare disorders that lead to pulmonary hypertension

Note: Based on information from http://pulmonaryhypertensionrn.com/.

3.2 | Treatment of PAH

The disease has no cure, and the long-term survival of PAH patients is not optimal, with a 5-year mortality rate of 57%.[2] Current treatments aim to slow down the disease progression and to reduce symptoms. Survival has been shown to be closely related to right ventricular function, since the failure of such is the leading cause of death in PAH patients, but so far there is no treatment specifically targeting this symptom.[8]

Therefore, the most common pharmacological treatment options are to improve right heart function and to manage PAH are pulmonary vasodilators, targeting one of the pathways as described in Figure 1.[5]

Besides these options, general measures such as physical activity, rehabilitation and prevention of infection are also included in the management of PAH patients.[11]

3.2.1 | Endothelin pathway

Endothelin stimulates the ET receptors (ET_A and ET_B) of the pulmonary arterial smooth muscle cells (PASMC) and acts as a strong vasoconstrictor in addition to causing PASMC proliferation.[12] By giving endothelin receptor antagonists (ERAs) to PAH patients, ET_A and ET_B are blocked, and the up-regulated ET pathway is inhibited. Their use has shown promising results on PAH symptoms, with the most prominent adverse effect being dose-dependent hepatotoxicity.[8]

Examples of ERAs are bosentan and the newer drug macitentan which are both non-selective ERAs, since they block ET_A and ET_B equally.[12]

3.2.2 | NO/sGC/cGMP pathway

Normally, nitric oxide (NO) is produced in the endothelium and functions as a strong vasodilator in the pulmonary

TABLE 2 WHO classification of PAH patients' functional symptoms

World Health Organization PAH Functional Class	
Class 1	No limitation of PA or dyspnoea, fatigue and chest pain
Class 2	Slight limitations of PA. Ordinary PA causes dyspnoea, fatigue and chest pain. Comfortable at rest
Class 3	Marked limitation of PA. Less than ordinary PA causes dyspnoea, fatigue and chest pain. Comfortable at rest
Class 4	Inability to perform any PA without symptoms. Perhaps dyspnoea and fatigue at rest. Signs of right heart failure

Note: Based on information from.[10]
Abbreviations: PA, physical activity; PAH: pulmonary arterial hypertension.

circulation by relaxing PASMC and hindering their proliferation. The effect of NO is a rise in the intracellular levels of cGMP—a second messenger degraded by the enzyme phosphodiesterase-5 (PDE-5).[12] Supplying PAH patients with PDE-5 inhibitors compensates for the reduced production of NO, by selectively optimizing its endogenous effect.[8]

Sildenafil is an example of a PDE-5 inhibitor and has shown good results with minor AEs.[5]

3.2.3 | Prostacyclin pathway

Prostacyclin is an active metabolite of arachidonic acid formed in vascular endothelial cells. It primarily works via the IP receptor, a G_s protein-coupled receptor that converts ATP to cAMP when activated, due to initiation of adenylyl cyclase. This conversion increases the activity of protein kinase A leading to downstream events including anti-proliferative and anti-inflammatory effects, inhibition of platelet aggregation and relaxation of PASMC causing vasodilation of the pulmonary arteries.[13]

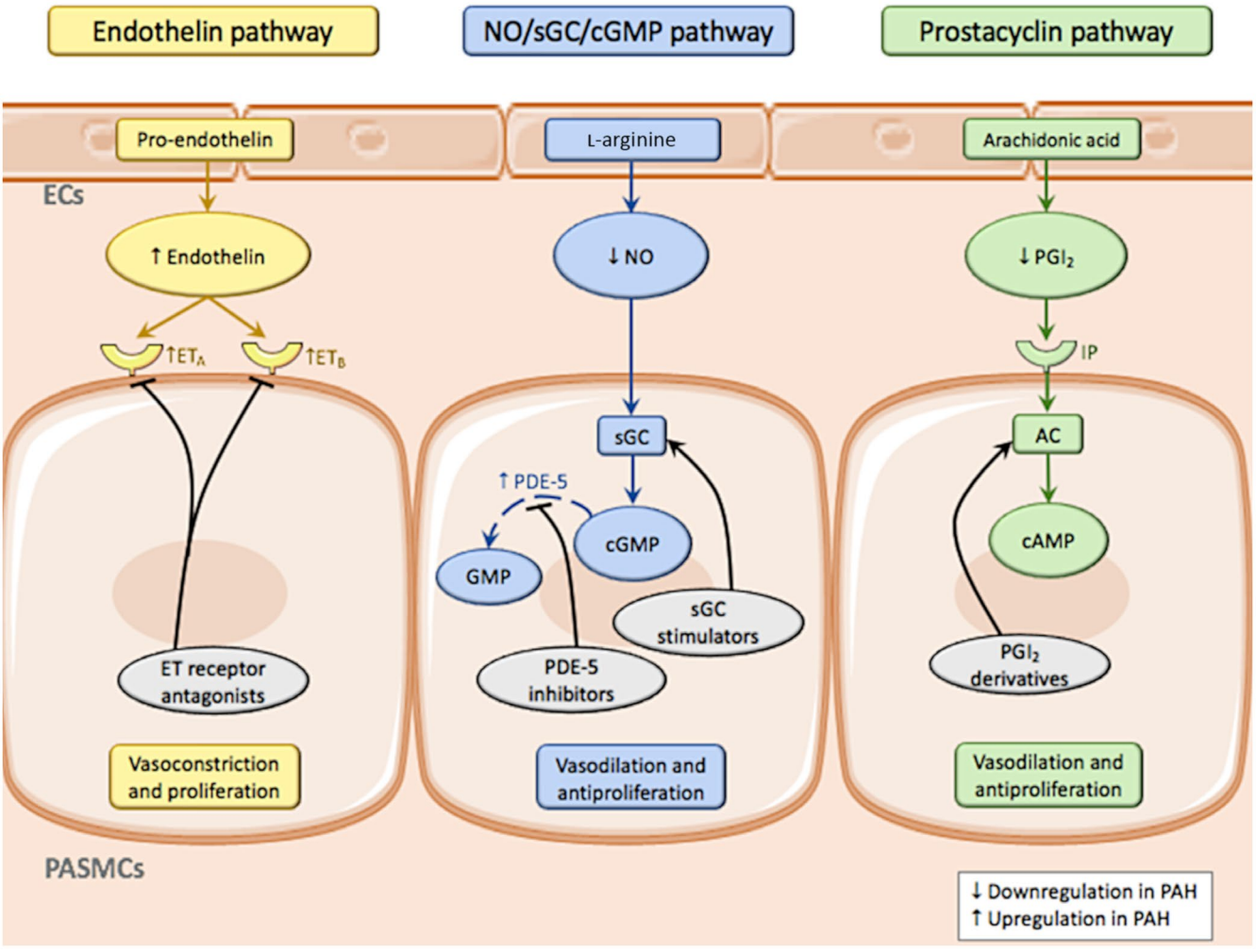

FIGURE 1 Overview of the three pathways targeted in PAH treatment regimes (adapted from[5]). AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; ECs, endothelial cells; ET, endothelin; ET_x, endothelin receptor; GMP, guanosine monophosphate; IP, prostacyclin receptor; NO, nitric oxide; PAH, pulmonary arterial hypertension; PASMCs, pulmonary arterial smooth muscle cells; PDE-5, phosphodiesterase-5; PGI_2, prostacyclin also called prostaglandin I_2; sGC, soluble guanylyl cyclase

Pulmonary arterial hypertension patients lack the enzyme PGI_2 synthase, resulting in a reduced production of PGI_2. Drugs targeting the PGI_2 pathway all stimulate the IP receptors in some way and have shown to be favourable for PAH patients, but tend to be generally underused, partially due to difficulties associated with their administration and AEs.[11] PGI_2 does not selectively affect the pulmonary circuit, and it therefore causes AEs of systemic vasodilation; however, since it is viewed as the most effective group of drugs in treating PAH, it is still a first-line drug in severe PAH.[7]

Epoprostenol, the first approved PAH therapeutic agent, is a synthetic PGI_2 and has shown improvements in both exercise capacity, quality of life (QOL) and mortality in PAH patients. However, there are several complications regarding administration since epoprostenol is unstable at room temperature and pH values below 10.5. In addition to this, its half-life in the circulation is only 3-5 minutes, making the continuous iv infusion by a pump the only possible way of administration, possibly causing AEs such as local pain, infection and thrombotic complications.[9]

Through the years, several PGI_2 analogues have been approved, including iloprost and treprostinil, which have advantages in the form of additional administration ways besides iv. Inhaled iloprost has shown inconsistent benefits and most commonly leads to AEs such as headache, jaw pain, flushing and chest pain.[11]

The newest FDA-approved drug is selexipag, an oral PGI_2 receptor agonist that selectively targets the IP receptor.[14] It has shown both a reduction in PVR and mortality. Similar AEs as for iloprost were reported with an addition of nausea, vomiting and diarrhoea.[11]

4 | TREPROSTINIL

Treprostinil ($C_{23}H_{34}O_5$; M = 390.53 g/mol) is a stable tricyclic PGI_2 analogue (Figure 2).[2] It was FDA-approved as a PAH therapy in 2002, and since the approval of oral treprostinil in 2013, there are now four possible routes of administration: intravenous (iv), subcutaneous (sc), inhaled and oral. Often, when treating with the parental routes, external delivery devices in the form of pumps are used to administer the dose.[6]

4.1 | Indication

Treprostinil via iv or sc is indicated for PAH patients with WHO functional class 2-4 symptoms to reduce symptoms associated with exercise, as well as for patients requiring transition from epoprostenol to reduce the rate of clinical deterioration.

However, the indication of iv treprostinil is often restricted to patients who do not tolerate sc treprostinil.[1] Today, the indication for inhaled and oral treprostinil is primarily for patients with WHO functional class 2-3 symptoms, to improve exercise capacity.[15]

4.2 | Pharmacokinetics

Treprostinil has the advantage of being stable at neutral pH and room temperature, making the administration process easier partially since it is not required to be kept on ice.[1]

Once treprostinil enters the bloodstream, approximately 91% is bound to plasma proteins and is eliminated biphasically with a terminal half-life of around 4 hours.[2] It is mainly metabolized oxidatively in the liver via CYP2C8 enzymes, after which the majority is excreted in the urine (79%).[2]

The more specific pharmacokinetic features of treprostinil vary among the different routes of administration and are summarized in Table 3.

4.3 | Pharmacodynamics

Treprostinil's primary mechanism of action is the direct vasodilation of the pulmonary and systemic arterial vascular beds,

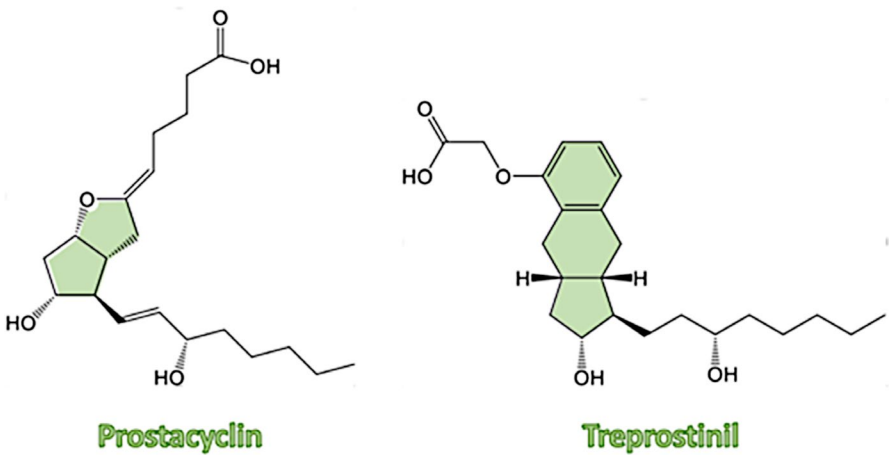

FIGURE 2 The chemical structure of PGI_2 and PGI_2 analogue treprostinil drawn in ChemSketch, modified from[2]

thereby reducing mPAP leading to an improved systemic oxygen transport and increased cardiac output with a minimal alteration of the heart rate.[6]

The smooth muscle cells of the pulmonary vascular system exhibit a number of prostanoid receptors playing a role in the regulation of vascular tone, platelet activation and immunological cell responses.[2] A number of these are G_s-coupled receptors and lead to vasodilation (IP, DP_1, EP_2 and EP_4), while others are G_q- or G_i-coupled and initiate vasoconstriction (EP_1, EP_3, FP and TP).[15]

Whereas endogenous and synthetic PGI_2 primarily bind IP, treprostinil has shown a high affinity for both IP, DP_1 and EP_2. By activating these receptors, the intracellular levels of cAMP rise, enabling the Ca^{2+}-activated K^+ channels to open, hyperpolarizing the cell and causing vasodilation (Figure 3).[15]

4.4 | Adverse effects

Although all four treprostinil formulations seem to improve the health of PAH patients, they also carry risks of AEs and complications, some of which they share and some which are exclusive to the specific route of administration. The general AEs are primarily due to the fact that treprostinil has a systemic effect on receptors throughout the body, and include dizziness, nausea, pain in the jaw and extremities, diarrhoea, flushing and headache.[17]

4.5 | Interactions

A study designed to investigate the interactions between treprostinil and drugs related to the CYP2C8 system showed that inhibitors of the system (eg gemfibrozil) increased the systemic concentration of treprostinil two times, while inducers (eg rifampin) reduced the concentrations by 30%.[6]

Using treprostinil in combination with antihypertensive agents, diuretics or vasodilators may increase the risk of symptomatic hypotension, and its antiplatelet effects could enhance the risk of bleeding when combined with anticoagulants.[6]

No interactions have been shown between treprostinil and other PAH treatments such as sildenafil or bosentan, making the combination of therapies a possibility.[2]

4.6 | Contraindications

The clearance of oral treprostinil is reduced by up to 80% in PAH patients with hepatic insufficiency due to liver disease, making it important to be cautious in regard to dosing.[2]

5 | CLINICAL TRIALS WITH TREPROSTINIL

Throughout the years, several studies investigating treprostinil's effects in general and in regard to the different routes of administrations have been conducted, some of which are shown in Tables 4 and 5. Since there are still many unknown factors and questions, new clinical trials are on their way and recruiting.

Exercise intolerance is the main characteristics of PAH, and the 6-min walk distance (6MWD) is a commonly used main end-point in studies, giving information about treatment efficacy with minimal expenses.[18] An overview of completed and currently ongoing studies is given in Tables 4 and 5.

6 | DISCUSSION

Today, three different prostanoids (epoprostenol, treprostinil and iloprost) and one non-prostanoid (selexipag) drug are approved for clinical use in the treatment of PAH symptoms.

This MiniReview primarily aims to assess the strengths and weaknesses of treprostinil and its four different forms of administration in the treatment of PAH.

TABLE 3 Comparison of different forms of administration of treprostinil[2,6]

Pharmacokinetic parameters and features	iv/sc	Inhaled	Oral
Daily dose	Start: 1.25 ng/kg/min Increase with 1.25 ng/kg/min per week for 4 wk, and then with 2.5 ng/kg/min per week for the remaining treatment	Start: 18 μg four times daily End-point: 54 μg four times daily	Start: 0.25 mg two times daily OR 0.125 mg three times daily End-point: Determined by tolerability
Bioavailability	100%	18 μg: 64% 36 μg: 72%	17% Affected by food intake
C_{max}	1.7 ng/mL	1 ng/mL	3-5.3 ng/mL

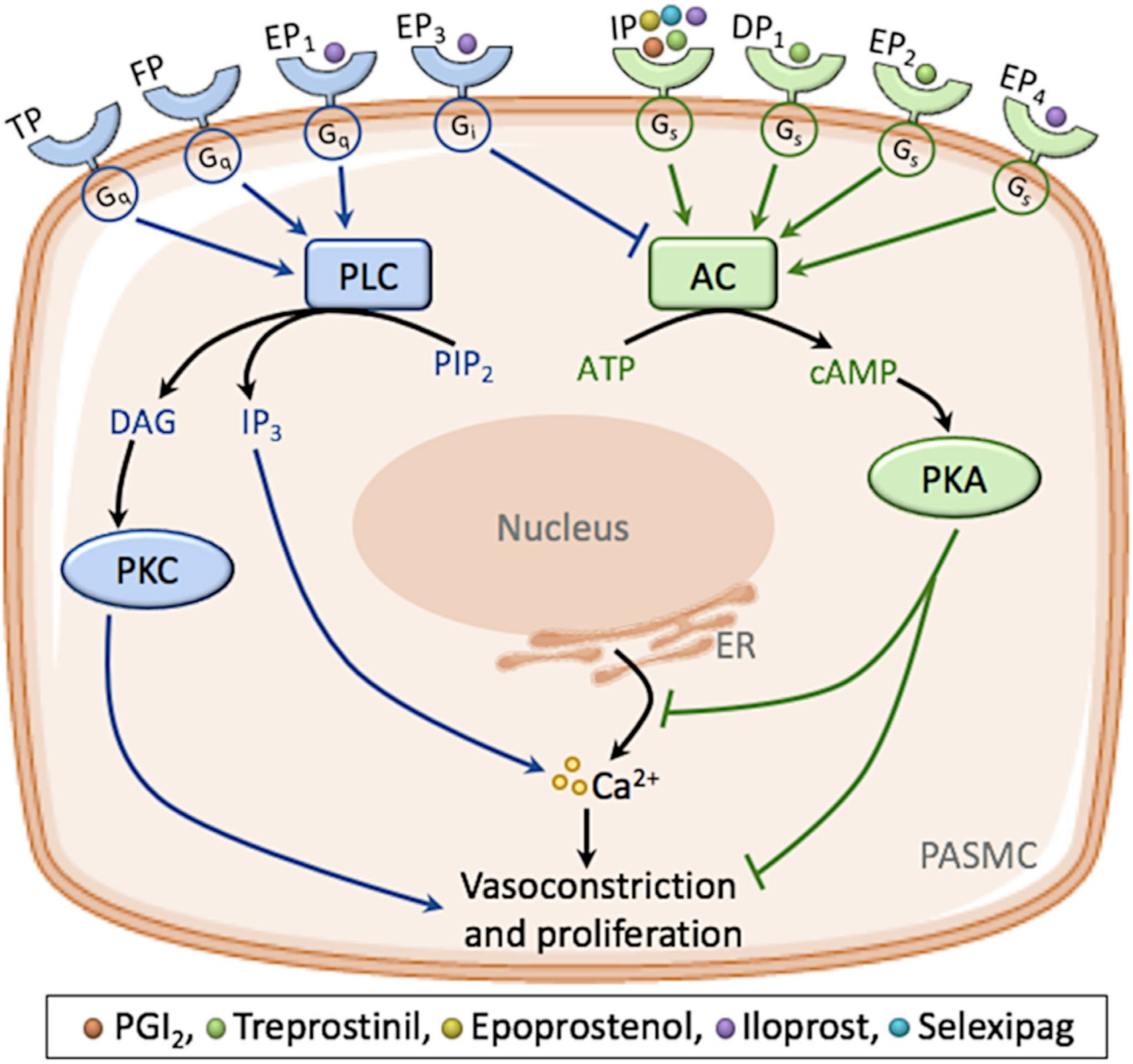

FIGURE 3 The pharmacodynamics of common drugs targeting the PGI_2 pathway, modified from.[14,16] Blue: contractile pathway; green: dilatory pathway. AC, adenylyl cyclase; AG, diacylglycerol; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; DP_x, prostaglandin D_2 receptor; EP_x, prostaglandin E_2 receptor; ER, endoplasmic reticulum; FP, prostaglandin F receptor; G_i, inhibitory G protein; G_q, PLC-activating G protein; G_s, stimulatory G protein; IP, prostacyclin receptor; IP_3, inositol trisphosphate; PASMC, pulmonary arterial smooth muscle cell; PIP_2, phosphatidylinositol bisphosphate; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; TP, thromboxane receptor

Therapies targeting the PGI_2 pathway are mainly used in severe cases[1]; in fact, there is a general agreement that parentally administered prostanoid is the most effective treatment for patients with severe PAH.[13]

Intravenous epoprostenol was the first approved prostanoid for PAH treatment, but it is hindered by its instability and short half-life (3-5 minutes).[9] Treprostinil has the longest half-life of all drugs targeting the PGI_2 pathway and is stable at room temperature, leading to a less frequent changing of the external infusion pump and catheters.[2] In addition to a longer half-life, iv treprostinil has shown bioequivalence and linear dosing compared to epoprostenol.[19] Benza et al[20] conducted a small 48-week study with iv treprostinil, showing a 125 m higher 6MWD in treatment-naïve patients and a stable 6MWD in patients transitioned from iv epoprostenol.

Intravenous administration in general has serious and potentially life-threatening AEs caused by the central venous catheters, risking bloodstream infections, sepsis and thrombosis.[2] A large placebo-controlled study of iv treprostinil was terminated early because of safety concerns, even though the collected data

TABLE 4 A list of completed clinical trials investigating the efficacy of treprostinil in the treatment of PAH

Title and trial identifier	Objective	Design	Status and results
TRIUMPH-I Clinical Investigation Into Inhaled Treprostinil Sodium in Patients With Severe Pulmonary Arterial Hypertension (PAH) NCT00147199	To evaluate the safety and efficacy of adding inhaled treprostinil to PAH patient already treated with bosentan or sildenafil	12-wk, double-blind, randomized placebo-controlled study Phase 3	Completed (2007) Patients who remain symptomatic on other treatments can benefit from adding inhaled treprostinil to their treatment
FREEDOM-M Oral Treprostinil as Monotherapy for the Treatment of Pulmonary Arterial Hypertension (PAH) NCT00325403	To evaluate the safety and efficacy of oral treprostinil as initial treatment for PAH patients	12-wk international, double-blind, randomized, placebo-controlled study Phase 3	Completed (2013) Treatment-naïve patients showed improved exercise capacity (6MWD), but experienced common AEs.
DelIVery for Pulmonary Arterial Hypertension (PAH) Clinical Study NCT01321073	To evaluate the use of a fully implantable iv delivery system in PAH patients, comparing it to external pumps.	Interventional, single-arm multi-centre study. Phase 4	Completed (2016) Patients received a stable iv treprostinil dose. No catheter-related infections or occlusions, and overall patient satisfaction.
RAPID Safety and Tolerability of Rapid Dose Titration of Subcutaneous Remodulin Therapy in PAH Subjects NCT02847260	To evaluate the safety, tolerability and clinical effect of a rapid dose uptitration of sc treprostinil in PAH patients when using proactive site pain management	16-wk, interventional multi-centre study. No masking/open-label. Phase 4	Completed (2017) Rapid uptitration was well tolerated, and a clinically effective dose was reached after 16 wk with a good safety profile and few withdrawals

indicated a significantly improved exercise capacity compared to placebo.[21] When analysing data from the PAH patient registry *REVEAL*, it showed a three-time increased risk of bloodstream infections associated with iv treprostinil compared to epoprostenol.[22] Hence, the indication of iv treprostinil is currently restricted to patients who do not tolerate sc treprostinil.[1]

Within the last couple of years, several studies investigating the possibility of an implantable pump to replace the high-risk external pump have been initiated, with an upcoming study evaluating the safety and QOL in PAH patients treated via a LenusPro pump which is implanted under the skin of the stomach, continuously administering treprostinil iv[23] among them. In 2016, Bourge et al[24] presented promising results with the implantable intravascular delivery system DelIVery, since it only caused catheter-related complications in 6 out of 60 PAH patients during a 48-week clinical trial accompanied by a high rate of patient satisfaction.

The preferred route of administering parental treprostinil is sc.[6] Transitioning from iv treprostinil to the sc form has shown to reduce the mentioned risks,[25] and in a clinical trial on healthy volunteers, it was concluded that iv and sc treprostinil are bioequivalent at steady-state.[26] Similar study results indicate a safe transition from iv epoprostenol to sc treprostinil in well-selected patients, even showing a delay in time to clinical worsening.[27]

Simonneau et al[25] published the study that led to the approval of sc treprostinil, based on a 12-week, double-blind, placebo-controlled trial with 470 PAH patients, in which the median change in 6MWD was 10 m for the treprostinil group and 0 m for the placebo group. These results were accompanied by improved haemodynamics, breathing and QOL. However, 85% of patients receiving sc treprostinil experienced severe infusion site pain, compared to 27% in the placebo group, a factor that could be treatment-limiting in practice.[25]

The long-term efficacy and safety of sc treprostinil have been evaluated in several studies covering exposures of up to 9 years.[2] Barst et al[28] followed 860 PAH patients treated with sc treprostinil for up to 4 years, focusing mainly on survival. For the overall population, Kaplan-Meier survival rates were 87%, 78%, 71% and 68%, respectively, compared to the predicted survival of 69%, 65%, 46% and 38% at 1, 2, 3 and 4 years, respectively. Subcutaneous treprostinil showed a safety profile consistent with the short-term trials and no unexpected AEs; however, in this study the majority (92%) suffered from infusion site pain as well. Patients with very severe pain might benefit from transitioning to iv treprostinil.[6]

With the approval of inhaled iloprost in 2004, the number of patients gaining access to prostanoid therapy expanded radically[29]; however, it requires administration every 2-4 hours and patients experience extensive AEs in form of coughing.[13] In 2007, the *TRIUMPH-I* study conducted by Mclaughlin et

TABLE 5 A list of upcoming clinical trials investigating the efficacy of treprostinil in the treatment of PAH

Title and trial identifier	Objective	Design	Status
An Open-Label, Long-Term Study of Oral Treprostinil in Subjects With Pulmonary Arterial Hypertension NCT01560637	To evaluate oral treprostinil's long-term safety and effect on exercise capacity in PAH patients	International, multi-centre study with no masking. 2.5-year follow-up. Phase 3	Recruiting
Assessment of Safety and Efficacy of Implantable Pump (LenusPro) in Patients With Pulmonary Arterial Hypertension Treated With Treprostinil. NCT02889315	To evaluate safety and QOL in patients treated with treprostinil via an implantable LenusPro pump (iv)	Prospective observational cohort study	Recruiting
Trial of the Early Combination of Oral Treprostinil With Background Oral Monotherapy in Subjects With Pulmonary Arterial Hypertension (FREEDOM-Ev) NCT01560624	To evaluate the effect of adding oral treprostinil to background oral monotherapy in PAH patients, focussing on 6MWD and time to first clinical worsening event.	Interventional, multi-centre, randomized, placebo-controlled study. Quadruple masking. 2.5-year follow-up. Phase 3	Active, not recruiting
A Patient Registry of the Real-world Use of Orenitram® (ADAPT) NCT03025029	To evaluate oral treprostinil's dosing regimens, titration schedules, AE's and clinical outcome	Prospective, multi-centre, observational patient registry.	Recruiting
Investigation of the Safety and Pharmacology of Dry Powder Inhalation of treprostinil (INSPIRE) NCT03399604	To evaluate the long-term tolerability and safety of inhaled treprostinil in PAH patients	Interventional, open-label, multi-centre study. Phase 3	Recruiting

al[30] revealed an improved exercise capacity and QOL after prescribing inhaled treprostinil to PAH patients who were treated with either bosentan or sildenafil at the time but were still symptomatic, leading to the approval of inhaled treprostinil for the treatment of PAH. After 12 weeks, the maximum dose of 54 μg four times daily was obtained in 72% of the 235 participants, leading to a 6MWD improvement of more than 20 m in 52% of these patients, and greater than 50 m in 31%.[30] The long-term effect in patients from the *TRIUMPH-I* study was later evaluated by Benza et al[31] showing a median change in 6MWD of 18 m ($P < .0001$) from baseline to 24 months, as well as a 91% survival rate. Similar promising results in regard to exercise capacity and QOL have been shown in other studies of varying size and duration; however, an improvement in time to clinical worsening and overall survival is yet to be shown.[32,33]

Inhaled treprostinil has shown a varying AE profile in different studies. Because of the local administration, a more selective effect is achieved minimalizing the systemic AEs. Generally, it is safe and well tolerated, but some studies have reported cough, bad taste and bronchoconstriction among the patients, depending on dose and composition of the solution; however, there have been reported fewer systemic AEs than with inhaled iloprost.[32,34]

When comparing the available inhaled prostanoid treatments, treprostinil has another advantage over iloprost due to fewer daily inhalation, making it more convenient for patients and thereby increasing their compliance.[1] The transition from inhaled iloprost to inhaled treprostinil has shown to be safe and without change of clinical status in PAH patients.[35]

The current need for more long-term data, required to expand to a more widespread use, will hopefully be met by the ongoing trial *INSPIRE*, evaluating long-term tolerability, effect and safety of inhaled treprostinil.[1]

For many years, extensive efforts have been put into the development of a tolerable and effective oral PGI_2, since it would increase the availability of treatment targeting the PGI_2 pathway and perhaps ultimately eliminate the need for iv and sc prostanoid therapy.[13]

Currently, treprostinil and IP receptor agonist selexipag are the only available orally administered PGI_2 treatments in most of the world, and both have some limitation in regard to efficacy.[11] Their use is complicated by complex dosing and AEs leading to low patient acceptance and tolerability.[9] Current guidelines recommend the use of oral treprostinil in severe PAH cases and selexipag in mild to moderate cases; however, recent studies have indicated selexipag to be advantageous over PGI_2 analogues, since it has shown a long-term reduction in morbidity.[11] In addition to this, the fact that selexipag selectively targets the IP receptor leads to less gastrointestinal AEs.[13]

Oral treprostinil is an extended-release tablet that uses osmotic release technology.[6] The tablet is covered by a semi-permeable membrane with a clinically made hole that creates a hydrostatic pressure gradient upon contact with water, enabling treprostinil to leave the tablet gradually and controlled.[29] It was approved in 2013 after initially being

declined twice, and so far, clinical trials have been disappointing.[1] Tapson et al conducted the first completed oral treprostinil study (*FREEDOM-C*) [36] as well as the follow-up (*FREEDOM-C2*),[37] both of which were 16-week placebo-controlled studies of PAH patients already treated with an oral background therapy in the form of either ERAs or PDE-5 inhibitors. None of the studies showed any statistically significant improvement in exercise capacity; however, they increased the understanding of oral treprostinil dosing, setting the stage for additional studies. Nearly, all patients in the *FREEDOM-C* and *FREEDOM-C2* studies experienced some form of AEs (99% and 100%, respectively), headache, diarrhoea and nausea being the most common, which lead to less than clinically effective doses, perhaps resulting in the negative results.[36,37]

The trial leading to the approval of oral treprostinil (*FREEDOM-M*) [38] recruited 349 treatment-naïve PAH patients randomly assigned to either oral treprostinil (n = 233) or placebo (n = 116) and followed them for 12 weeks. Results showed a 23 m ($P = .0125$) change in 6MWD in the treprostinil group compared to an either unaffected or negative change in the placebo group; however, no change was seen in PAH symptoms, clinical worsening or dyspnoea.[38]

The clinical relevance of a positive monotherapy study is questionable, since very few PAH patients will be treated with oral treprostinil alone.[29] Taking this into account, the upcoming 24-week placebo-controlled trial (*FREEDOM-Ev*) [39] aims to evaluate the long-term effect of adding three daily doses of oral treprostinil to a background therapy of ERAs or PDE-5 inhibitors.[13] All previous *FREEDOM* studies have used twice-daily dosing, but a recent study showed improved tolerability with three times daily dosing, because of reduced peak-to-trough serum levels.[40]

Whether oral treprostinil is an effective PAH treatment still remains uncertain, but there are high hopes for the *FREEDOM-Ev* to finally provide the needed information about the long-term impact on symptoms and survival benefit.[29]

Another possible approach to improve tolerability and patient acceptance of oral treatments is transitioning PAH patients who are stable on iv or sc treprostinil to oral treprostinil.[9] By doing so, a small study on well-selected patients managed to reach clinical effective oral doses and showed preserved 6MWD and PVR after 24 weeks.[41] This raises the possibility of initially stabilizing patients through parental treprostinil before transitioning them to oral tablets, avoiding severe pain in the infusion site or catheter AEs.[9]

7 | CONCLUSION AND OUTLOOK

Until today, PAH has no cure and progresses rapidly, making the goal of treatment to minimize symptoms and extend the time to clinical worsening extremely difficult. Since the FDA approval of epoprostenol, a lot of work was performed to develop other PAH treatments,[42-44] trying to minimize administration-related risks and AEs. Treprostinil and its four different formulations (iv, sc, inhaled and oral) have significantly increased the treatment options for patients with PAH, due to its pharmacological stability and long half-life. It has shown clinical improvements in exercise capacity, QOL, functional class and clinical status. However, there are still many unanswered questions, especially concerning dosing and timing, some of which are being addressed in upcoming clinical trials. These include an evaluation of the LenusPro pump for iv administration and long-term effects of inhaled treprostinil. Oral treprostinil could increase the number of PAH patients who could benefit from treatment while reducing AEs, but has shown limitations in regard to efficacy. The results of *FREEDOM-Ev* assessing the long-term effect of oral treprostinil are eagerly awaited.

Overall, treprostinil shows a valuable role in the PAH treatment strategies and offers flexibility in terms of available routes of administration.

CONFLICT OF INTEREST

On behalf of all authors, the corresponding author states that there is no conflict of interest.

REFERENCES

1. O'Connell C, Amar D, Boucly A, et al. Comparative safety and tolerability of prostacyclins in pulmonary hypertension. *Drug Saf*. 2016;39(4):287-294.
2. Torres F, Rubin LJ. Treprostinil for the treatment of pulmonary arterial hypertension. *Expert Rev Cardiovasc Ther*. 2013;11(1):13-25.
3. Rarediseases.org. https://rarediseases.org/rare-diseases/pulmonary-arterial-hypertension/. Accessed June 19, 2019.
4. Pulmonary arterial hypertension WebMD: Suzanne R. Steinbaum; 2017. https://www.webmd.com/lung/pulmonary-arterial-hypertension. Accessed June 19, 2019.
5. Tsai H, Sung YK, de Jesus Perez V. Recent advances in the management of pulmonary arterial hypertension. *F1000Res*. 2016;5:2755.
6. Kumar P, Thudium E, Laliberte K, Zaccardelli D, Nelsen A. A comprehensive review of treprostinil pharmacokinetics via four routes of administration. *Clin Pharmacokinet*. 2016;55(12):1495-1505.
7. Kim D, George MP. Pulmonary hypertension. *Med Clin North Am*. 2019;103(3):413-423.
8. Matsubara H, Ogawa A. Treatment of idiopathic/hereditary pulmonary arterial hypertension. *J Cardiol*. 2014;64(4):243-249.
9. El Yafawi R, Wirth JA. What is the role of oral prostacyclin pathway medications in pulmonary arterial hypertension management? *Curr Hypertens Rep*. 2017;19(12):97.
10. Taichman DB, Mandel J. Epidemiology of pulmonary arterial hypertension. *Clin Chest Med*. 2013;34(4):619-637.

11. Del Pozo R, Hernandez Gonzalez I, Escribano-Subias P. The prostacyclin pathway in pulmonary arterial hypertension: a clinical review. *Expert Rev Respir Med*. 2017;11(6):491-503.
12. Seferian A, Simonneau G. Therapies for pulmonary arterial hypertension: where are we today, where do we go tomorrow? *Eur Respir Rev*. 2013;22(129):217-226.
13. Pugliese SC, Bull TM. Clinical use of extended-release oral treprostinil in the treatment of pulmonary arterial hypertension. *Integr Blood Press Control*. 2016;9:1-7.
14. Sorensen LM, Wehland M, Kruger M, et al. A special focus on selexipag - treatment of pulmonary arterial hypertension. *Curr Pharm Des*. 2017;23(34):5191-5199.
15. Mubarak KK. A review of prostaglandin analogs in the management of patients with pulmonary arterial hypertension. *Respir Med*. 2010;104(1):9-21.
16. Clapp LH, Gurung R. The mechanistic basis of prostacyclin and its stable analogues in pulmonary arterial hypertension: role of membrane versus nuclear receptors. *Prostaglandins Other Lipid Mediat*. 2015;120:56-71.
17. Tapson VF, Gomberg-Maitland M, McLaughlin VV, et al. Safety and efficacy of iv treprostinil for pulmonary arterial hypertension: a prospective, multicenter, open-label, 12-week trial. *Chest*. 2006;129(3):683-688.
18. Demir R, Kucukoglu MS. Six-minute walk test in pulmonary arterial hypertension. *Anatol J Cardiol*. 2015;15(3):249-254.
19. McSwain CS, Benza R, Shapiro S, et al. Dose proportionality of treprostinil sodium administered by continuous subcutaneous and intravenous infusion. *J Clin Pharmacol*. 2008;48(1):19-25.
20. Benza RL, Tapson VF, Gomberg-Maitland M, Poms A, Barst RJ, McLaughlin VV. One-year experience with intravenous treprostinil for pulmonary arterial hypertension. *J Heart Lung Transplant*. 2013;32(9):889-896.
21. Hiremath J, Thanikachalam S, Parikh K, et al. Exercise improvement and plasma biomarker changes with intravenous treprostinil therapy for pulmonary arterial hypertension: a placebo-controlled trial. *J Heart Lung Transplant*. 2010;29(2):137-149.
22. Kitterman N, Poms A, Miller DP, Lombardi S, Farber HW, Barst RJ. Bloodstream infections in patients with pulmonary arterial hypertension treated with intravenous prostanoids: insights from the REVEAL REGISTRY®. *Mayo Clin Proc*. 2012;87(9):825-834.
23. LenusPro Pump in PAH Treated With Treprostinil clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT02889315. Accessed June 19, 2019.
24. Bourge RC, Waxman AB, Gomberg-Maitland M, et al. Treprostinil administered to treat pulmonary arterial hypertension using a fully implantable programmable intravascular delivery system: results of the DelIVery for PAH trial. *Chest*. 2016;150(1):27-34.
25. Simonneau G, Barst R, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med*. 2002;165(6):800-804.
26. Laliberte K, Arneson C, Jeffs R, Hunt T, Wade M. Pharmacokinetics and steady-state bioequivalence of treprostinil sodium (Remodulin) administered by the intravenous and subcutaneous route to normal volunteers. *J Cardiovasc Pharmacol*. 2004;44(2):209-214.
27. Rubenfire M, McLaughlin VV, Allen RP, et al. Transition from IV epoprostenol to subcutaneous treprostinil in pulmonary arterial hypertension: a controlled trial. *Chest*. 2007;132(3):757-763.
28. Barst RJ, Galie N, Naeije R, et al. Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil. *Eur Respir J*. 2006;28(6):1195-1203.
29. Feldman J, Habib N, Radosevich J, Dutt M. Oral treprostinil in the treatment of pulmonary arterial hypertension. *Expert Opin Pharmacother*. 2017;18(15):1661-1667.
30. McLaughlin VV, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J Am Coll Cardiol*. 2010;55(18):1915-1922.
31. Benza RL, Seeger W, McLaughlin VV, et al. Long-term effects of inhaled treprostinil in patients with pulmonary arterial hypertension: the Treprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension (TRIUMPH) study open-label extension. *J Heart Lung Transplant*. 2011;30(12):1327-1333.
32. Voswinckel R, Enke B, Reichenberger F, et al. Favorable effects of inhaled treprostinil in severe pulmonary hypertension: results from randomized controlled pilot studies. *J Am Coll Cardiol*. 2006;48(8):1672-1681.
33. Channick RN, Olschewski H, Seeger W, Staub T, Voswinckel R, Rubin LJ. Safety and efficacy of inhaled treprostinil as add-on therapy to bosentan in pulmonary arterial hypertension. *J Am Coll Cardiol*. 2006;48(7):1433-1437.
34. Chen H, Rosenzweig EB, Gotzkowsky SK, Arneson C, Nelsen AC, Bourge RC. Treatment satisfaction is associated with improved quality of life in patients treated with inhaled treprostinil for pulmonary arterial hypertension. *Health Qual Life Outcomes*. 2013;11:31.
35. Bourge RC, Tapson VF, Safdar Z, et al. Rapid transition from inhaled iloprost to inhaled treprostinil in patients with pulmonary arterial hypertension. *Cardiovasc Ther*. 2013;31(1):38-44.
36. Tapson VF, Torres F, Kermeen F, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C study): a randomized controlled trial. *Chest*. 2012;142(6):1383-1390.
37. Tapson VF, Jing Z-C, Xu K-F, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients receiving background endothelin receptor antagonist and phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C2 study): a randomized controlled trial. *Chest*. 2013;144(3):952-958.
38. Jing Z-C, Parikh K, Pulido T, et al. Efficacy and safety of oral treprostinil monotherapy for the treatment of pulmonary arterial hypertension: a randomized, controlled trial. *Circulation*. 2013;127(5):624-633.
39. Trial of the early combination of oral treprostinil with background oral monotherapy in subjects with pulmonary arterial hypertension (FREEDOM-Ev) Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT01560624. Accessed June 19, 2019.
40. White RJ, Frutiger K, Theuer A, Weaver C, Crawford K, Laliberte K. A pharmacokinetic and tolerability comparison in subjects transitioning from twice daily to three times daily dosing of oral treprostinil. *Chest*. 2014;146(4):865A.
41. Chakinala MM, Feldman JP, Rischard F, et al. Transition from parenteral to oral treprostinil in pulmonary arterial hypertension. *Heart Lung Transplant*. 2017;36(2):193-201.

42. Toxvig AK, Wehland M, Grimm D, Infanger M, Krüger M. A focus on riociguat in the treatment of pulmonary arterial hypertension. *Basic Clin Pharmacol Toxicol*. 2019;125(3):202-214.
43. Bedan M, Grimm D, Wehland M, Simonsen U, Infanger M, Krüger M. A focus on macitentan in the treatment of pulmonary arterial hypertension. *Basic Clin Pharmacol Toxicol*. 2018;123(2):103-113.
44. Pedersen J, Hedegaard ER, Simonsen U, Krüger M, Infanger M, Grimm D. Current and future treatments for persistent pulmonary hypertension in the newborn. *Basic Clin Pharmacol Toxicol*. 2018;123(4):392-406.

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