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Treprostinil for the treatment of pulmonary hypertension

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Background: Pulmonary hypertension (PH) is a severely disabling disorder characterized by sustained elevations of pulmonary arterial pressure, ultimately leading to right-heart failure and death. Pulmonary arterial hypertension (PAH) usually occurs in the absence of an evident cause (idiopathic PAH) or may be associated with connective tissue disease, HIV infection, congenital heart disease, chronic liver disease or result from the use of toxic agents and anorexigens. *Objective/method*: Intravenous epoprostenol has been widely used in patients with PAH, leading to long-term clinical benefits and improved survival. Epoprostenol has to be delivered through a permanently implanted intravenous catheter. This may expose patients to potentially life-threatening complications. Thus, more stable compounds and alternative modes of prostacyclin delivery have been sought. *Conclusion*: Treprostinil sodium is a stable prostacyclin analogue, sharing pharmacologic actions similar to epoprostenol with comparable haemodynamic effects. Treprostinil is chemically stable at room temperature and has a long half-life (2 – 4 h), making this drug suitable for subcutaneous administration, with practical benefits in avoiding the risk of line infection and thrombosis, and cardiovascular reactions due to abrupt drug discontinuation.

Keywords: prostacyclin analogue, pulmonary arterial hypertension, treprostinil

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1. Introduction

Pulmonary hypertension (PH) covers a heterogeneous group of disorders. PH may complicate a variety of cardiopulmonary diseases, including severe chronic obstructive pulmonary disease, left ventricular failure and chronic thromboembolic obstruction of the pulmonary arteries. Severe pulmonary arterial hypertension (PAH) is characterised by a progressive obliteration of the pulmonary vascular bed and increased pulmonary arterial pressure, leading to right heart failure and death. PAH is a rare disease with a prevalence of 15/million, and can be idiopathic (iPAH) or associated with connective tissue disease, congenital heart disease, HIV infection, appetite suppressant use and liver disease [1]. All these conditions share a similar histological picture. Endothelial dysfunction, resulting in exaggerated vasoconstriction and impaired vasodilatation, appears to play a key role in the early pathogenesis of PAH [2]. It is speculated that remodelling of the pulmonary vessels and *in situ* thrombosis might determine the disease course. Endothelial cells are the major source of mediators of pulmonary vascular tone, platelet aggregation and muscular cell growth. Several abnormalities in endothelial function have been noted, including decrease of prostacyclin synthesis and secretion [3], nitric oxide synthase [4] and endothelin expression [5]. These well-defined abnormalities provide rational therapeutic targets. This article focuses on prostacyclin analogue treprostinil, its characteristics, clinical efficacy, safety and tolerability.

Table 1. Characteristics of epoprostenol, treprostinil and iloprost.

	Epoprostenol	Treprostinil	Iloprost
Half-life	< 6 min	2 – 4 h	20 – 25 min
Stability at room temperature and at pH 7.4	No	Yes	Yes
Administration route	i.v	s.c., i.v., inhaled, oral	i.v., inhaled

2. Overview of the market

The introduction of prostacyclin and endothelin receptor antagonist (ERA) therapy represents a major step forward for PH, however PAH remains incurable, and is associated with high mortality. Only 63% of epoprostenol-treated iPAH patients remain alive after 3 years [6,7]. All available effective treatments involve significant side effects. These include nonspecific side effects of prostacyclins, such as jaw pain, flushing, headache and abdominal cramping, pain at the subcutaneous infusion site (treprostinil), frequent inhalations (iloprost) and liver intolerance in < 2 – 8% of patients (ERAs). Transition from one of these therapies to another may be required in certain patients. Multi-drug regimens are used frequently in patients who fail to show adequate responses to single agents. However, there is presently a paucity of data supporting this practice [8].

3. Prostacyclins and prostanoids

Prostaglandins are a family of lipid compounds derived from arachidonic acid. These substances, mediators of many biologic functions, were discovered in seminal fluid [9], but it was not until the early 1960s that some representative compounds of the prostaglandin family were isolated, characterised and synthesised. Synthetic derivatives of prostaglandins have been called prostanoids. To date, more than 100 prostaglandins with different structures and functions have been detected in almost every tissue and body fluid. In 1976, while investigating how blood vessel walls make unstable prostanoids [10], a group of investigators led by Nobel prize winner John Vane discovered prostaglandin I_2 (PGI_2) and named it prostacyclin. The ability of the normal vessel wall to synthesise PGI_2 is greatest at the endothelial surface and progressively decreases toward the adventitia. PGI_2 causes relaxation of vascular smooth muscle through binding to its membrane-associated G protein-coupled receptor [11], with subsequent activation of adenylyl cyclase and increased production of cAMP.

PGI_2 is the most potent endogenous inhibitor of platelet aggregation, involved in the complex interactions between vessel wall, blood and platelet function. It seems to be protective against excessive vasoconstriction, platelet deposition and cellular proliferation in the vessel wall [12]. A dysregulation of the PGI_2 metabolic pathway has been shown in patients with PAH and in animal models of hypoxic pulmonary hypertension.

Christman *et al.* [13] reported a deficiency of prostacyclin and an excess of thromboxane-A_2 urinary metabolites in patients with iPAH. Tuder *et al.* [13] showed decreased expression of prostacyclin synthase in the lungs of patients with PAH. Although it has not been clarified whether the dysregulation of the PGI_2 metabolic pathway has a causative role or is a consequence of pulmonary hypertension, it represents a convincing rationale for the therapeutic use of PGI_2. Clinical studies have explored the possibility that chronic therapy with exogenous prostacyclin analogues might have long-term benefits in patients with moderately severe to severe PAH.

The breakthrough came in the early 1980s when it was shown that patients could safely be maintained on continuous intravenous epoprostenol [14], which improves both exercise capacity and haemodynamics [15]. Subsequently it was also shown that long-term treatment with intravenous epoprostenol improved survival [7]. Although epoprostenol is an effective therapy for PAH, the nature of the delivery system has a number of potential complications, which range in severity from local exit site infections easily treated with oral antibiotics to life-threatening sepsis. Due to its short half-life, epoprostenol must be given continuously through a permanent catheter into a large central vein, with the attendant risks of air embolism and sepsis. Any interruptions in therapy related to catheter displacement or pump malfunctions may be life-threatening, associated with syncope and death from an acute rebound pulmonary hypertensive crisis. Rare adverse events associated with the delivery system include pneumothorax, thrombosis and paradoxical embolus. The efficacy of epoprostenol, coupled with the limitations of the delivery system, has led to the development of prostacyclin analogues with alternative routes of delivery (**Table 1**).

4. Characteristics of treprostinil sodium

Treprostinil (Remodulin®, United Therapeutics, Research Triangle Park, NC, USA) is a tricyclic benzindine prostacyclin analogue with similar anti-platelet and vasodilatory actions to epoprostenol [16]. It has no apparent direct cardiac effects as assessed by indices of contractility and by electrocardiogram, no intrinsic effect on the autonomous nervous system and no significant effect on respiratory mechanics.

Treprostinil tends to inhibit gastrointestinal motility and decrease pentagastrin-stimulated gastric acid secretion, and therefore has gastric anti-ulcer and mucosal protective actions [17]. The safety profile is favourable, with, in particular, no reproductive toxicity and no mutagenetic effects [17]. Treprostinil is rapidly and completely absorbed after subcutaneous administration and has an absolute bioavailability of 100% [18]. Treprostinil is chemically stable in either sterile water or 0.9% sodium chloride at room temperature. These characteristics and a relatively long half-life (2 – 4 h) make this drug suitable for subcutaneous administration. Continuous subcutaneous infusion of treprostinil results in steady-state plasma concentrations after about 10 h [18]. Administration rates of subcutaneous and intravenous treprostinil between 12.1 to 125 ng/kg/min correspond to plasma levels of 14.9 – 18.25 pg/ml [19]. The metabolism of treprostinil is hepatic. Treprostinil is 91% bound to human plasma proteins. Treprostinil is eliminated in a biphasic distribution, approximately 79% of the administered dose is excreted in the urine either as unchanged drug (4%) or an identifiable metabolite (64%) [17]. The clearance of treprostinil is decreased by up to 80% in patients with hepatic insufficiency, therefore cautious dosing is required in patients with liver disease. Although only 4% of treprostinil is excreted unchanged in the urine, five metabolites are excreted in the urine and cautious dosing is therefore recommended in patients with PAH and impaired renal function [17]. Treprostinil does not interfere with the metabolism of paracetamol, warfarin or digoxin [17,18]. In contrast to epoprostenol, which requires sterile daily or twice-daily reconstitution and cooling, treprostinil is supplied in 20 ml vials containing either 1, 2.5, 5 or 10 mg/ml of the drug, that may be stored at room temperature and is stable in the syringe during subcutaneous infusion for up to 3 days.

5. Clinical efficacy of injectable (subcutaneous/intravenous) treprostinil

5.1 Subcutaneous treprostinil

The effects of treprostinil and epoprostenol were compared in three pilot trials of iPAH patients. In the first trial both drugs were given intravenously. In the second trial, intravenous treprostinil was compared with subcutaneous treprostinil. Intravenous epoprostenol and treprostinil at comparable doses resulted in similar short-term decrements in pulmonary vascular resistance (PVR), in the range of 22 – 28% [20]. The third trial was a Phase II, 8-week, multi-centre, double-blind, randomised, parallel comparison of treprostinil plus conventional therapy versus conventional therapy alone in 26 World Health Organisation (WHO) functional classes (as modified for PAH from the New York Heart Association classification [21]) III/IV patients with iPAH. Treprostinil dose ranged between 1.25 and 5 ng/kg/min during the first week and was then increased in steps ranging from 2.5 to 5 ng/kg/min. Treprostinil improved the 6-min walk distance by 24 m in 17 patients, with no change in Borg Dyspnoea score. PVRI decreased by 4.8 Wood units m^2 under treprostinil therapy.

The effects of subcutaneous treprostinil were studied in two identical international pivotal trials enrolling a total of 470 PAH patients [17]. In this 12-week study, treprostinil compared with placebo improved exercise capacity (assessed by 6-min walking distance), Borg Dyspnoea Score, WHO functional class and haemodynamics [22]. The difference in median distance walked between the two groups at week 12 was 16 m ($p = 0.006$). Improvement was greater in the severely ill patients and in those who could tolerate the highest doses. The improvement was independent of disease aetiology. An analysis by quartile revealed that an improvement of +37 m was present in patients receiving doses above 14 ng/kg/min. Dose escalation was limited by protocol to avoid pain at the infusion site and consequently many patients did not receive therapeutic doses.

In a retrospective multi-centre study, 122 patients with PH were treated with subcutaneous treprostinil and followed for a mean of 26 months [23]. Six-minute walking distance improved by +100 m and WHO functional class improved from 3.2 to 2.1 on average. Survival was 88.6 and 70.6% at 1 and 3 years compared with historical controls, respectively. Patients with iPAH whose chronic treatment included subcutaneous treprostinil had a similar survival to patients treated with intravenous epoprostenol [7]. The recently published US–European study [24] involving a large group of patients with PAH has summarised significant benefits of treprostinil treatment with regard to exercise capacity and survival. Survival was 87 – 68% over 1 – 4 years for all 860 patients and 88 – 70% over 1 – 4 years with subcutaneous treprostinil monotherapy. In this study, 78 patients in WHO functional class IV were included. Their long-term survival appears to be similar to idiopathic WHO functional class IV patients treated with first/line intravenous epoprostenol.

In a recently published prospective single-centre study [25], we followed 25 consecutive class III and IV patients with chronic thromboembolic pulmonary hypertension (CTEPH) over 12 to 33 months of continuous subcutaneous treprostinil, that was initiated after at least one hospitalisation for right heart decompensation. A historical group of 31 untreated patients with inoperable CTEPH matched for disease severity was studied for comparative survival analyses. Treprostinil-treated patients demonstrated significant improvements in 6-min walking distance, functional class, B-type natriuretic peptide (BNP) serum levels, cardiac output and PVR. Treprostinil plasma concentrations correlated with subcutaneous dose of the drug, indicating consistent absorption despite local site reactions in 86% of cases. Treated patients within this study experienced significantly improved long-term survival, compared with controls, at doses between 12.5 and 42 ng/kg/min.

Recently, a study of 22 PAH patients treated with intravenous epoprostenol who were randomised for 8 weeks to subcutaneous treprostinil versus a placebo has been

reported [26]. This represents the only withdrawal trial reported in PAH. Seven of the eight patients withdrawn to placebo had the expected clinical deterioration, while this was observed in only one of the 14 patients withdrawn to subcutaneous treprostinil. The authors concluded that subcutaneous treprostinil is effective in PAH and maintains functional status in patients transitioned from intravenous epoprostenol [26].

Since the lack of a pharmacokinetic drug interaction was demonstrated between treprostinil and bosentan [27] and between treprostinil and sildenafil [28] in healthy volunteers, combination therapy has been implemented in clinical settings. Treprostinil in combination with oral PAH therapies seems to be safe and appears to contribute to improvement in 6-minute walk distance, Borg dyspnoea scores and PAH symptoms in patients who remain symptomatic on phosphodiesterase type 5 inhibitor (PDE5I) and/or ERA therapies [29-31].

Taken together, these results on the long-term survival of PAH and CTEPH patients treated with first-line subcutaneous treprostinil are encouraging. Subcutaneous treprostinil is a valuable treatment option for CTEPH and PAH patients in WHO functional classes III and IV [23,25,32].

6. Safety and tolerability of subcutaneous treprostinil

Pain at the infusion site has been a major drawback of subcutaneous treprostinil, hampering dose titration and leading to a 10% discontinuation rate. Long-term practice reveals that a more aggressive titration regimen is feasible, does not lead to premature discontinuation and the site pain is not dose-reliant [33]. Moreover, most patients are able to reach a minimal effective dose of approximately 15 mg/kg/min within 1 month. Pain appears to decrease over time when patients maintain the infusion site for more than a week [23]. Topical ointments or cold packs also appear to help. In our recently performed study, we confirmed that the site pain was not dose-reliant [33].

Adverse consequences of the long-term use (high doses) of treprostinil include headaches, diarrhoea, flushing, jaw pain and foot pain, which also occur commonly with chronic intravenous epoprostenol therapy. Despite an elimination half-life of treprostinil of 4.5 h, the distribution half-life is about 40 min, therefore patients off subcutaneous treprostinil may become symptomatic in under an hour. Nevertheless, even longer periods of interruption of the subcutaneous therapy have not resulted in adverse events.

7. Intravenous treprostinil

The additional clinical interest in treprostinil as an alternative intravenous prostacyclin for the treatment of pulmonary hypertension has developed due to its chemical stability at room temperature, up to 48 h stability in the delivery system, a longer half-life and easy drug preparation. When treprostinil was delivered in 51 normal volunteers for 72 h, intravenously and subcutaneously administered treprostinil were bioequivalent at steady-state [34]. An open-label study demonstrated that intravenous treprostinil therapy improved exercise capacity, Borg dyspnoea score, WHO functional class and haemodynamics at week 12 compared with baseline [35]. A study recently conducted in India, a multi-centre, placebo-controlled 12-week study in WHO Class III and IV patients with iPAH or collagen vascular disease- or HIV-associated PAH patients confirmed the efficacy of intravenous treprostinil in improving 6-min walking distance, Borg score and WHO class [36].

Transitioning from intravenous epoprostenol to intravenous treprostinil was safe and effective in 31 patients with PAH in a 12-week open-label study [37]. The intravenous infusion of treprostinil was increased while intravenous epoprostenol was reduced. Treprostinil was dosed on the basis of dyspnoea on exertion as a clinical end point, similar to current intravenous epoprostenol dosing recommendations. The 12-week dose of intravenous treprostinil was greater than twice the dose of intravenous epoprostenol before transition. Whether the haemodynamic differences seen after 12 weeks of intravenous treprostinil will persist requires further follow-up. The safe transitioning from intravenous epoprostenol to intravenous treprostinil by a direct switch of the medication reservoir (1:1 ng/kg/min) from epoprostenol to treprostinil was reported [38]. Subsequently, the initial dose of treprostinil was adjusted to twice the baseline epoprostenol dose. Most patients reported prostacyclin-related side effects of intravenous treprostinil as less severe than epoprostenol side effects. Administration of both intravenous prostacyclin analogues (epoprostenol and treprostinil) are associated with the risk of line infection. A recently published study revealed an increased number of Gram-negative bloodstream infections among PAH patients treated with intravenous treprostinil [39]. The difference in rates might have been caused by differences in preparation and storage, repeated puncture of treprostinil vials, differences in catheter care practices, or differences in the anti-inflammatory activity of the agents.

8. Inhaled treprostinil

The rationale for the use of inhaled treprostinil was the longer plasma half-life compared with iloprost and alternative tissue binding characteristics that could result in favourable pharmacodynamic features when delivered via the inhaled route. In a study including 123 patients with different forms of precapillary pulmonary hypertension [40], treprostinil showed a more sustained effect on PVR and fewer systemic side effects compared to iloprost, at relatively low doses. Furthermore, the addition of inhaled treprostinil in symptomatic PAH patients added to bosentan therapy [41] led to significant improvements in clinically important end points and was well tolerated. No safety concerns or delivery

device problems emerged during the 12-week trial. These findings suggest that inhalation of treprostinil may offer a new strategy for first-line treatment as well as an add-on combination therapy in PAH patients. Recently, the 12-week double-blind TRIUMPH-1 trial yielded significant primary outcome results regarding improvement of the 6-min walk distance by 20 m ($p < 0.0006$; United Therapeutics press release). However, the clinical significance remains to be determined.

In conclusion, current data suggest that continuous subcutaneous and intravenous are effective treatment options for patients with PAH. Currently an international, multi-centre, randomised, double-blind, placebo-controlled study in patients with PAH given oral treprostinil alone (FREEDOM-M) or in combination with an ERA and/or a PDE5I (FREEDOM-C) is being evaluated. Thus, treprostinil is the only prostacyclin with versatile administration modes including intravenous and subcutaneous dosing.

9. Regulatory affairs

Treprostinil subcutaneous has received approval for the treatment of PAH in the USA, Israel, Australia and Canada (WHO functional classes II – V) and by the European Medicines Evaluation Agency (EMEA) for idiopathic PAH (WHO functional class III).

10. Expert opinion

Treprostinil is a useful treatment option in patients with PAH. However, the evaluation of prostacyclins appears to require 6 – 12 months of observation. Therefore, it is difficult to interpret 12-week randomized controlled trials.

Our experience suggests that treprostinil is improving the exercise capacity and quality of life in patients with other subsets of pulmonary hypertension; this is primarily based on prospective databases and personal experience.

Currently, it is most common for goal-oriented treatment regimens to be practised [8]. Although at the time of the first clinical presentation more than 75% of patients are in an advanced stage of their disease process [42], no data exist comparing this concept with a 'hit hard and early' regimen. In the absence of such data, we are performing frequent reassessments of patients by invasive measurements every 3 – 6 months in the early phase of treatment, before stabilization is reached. However, this is not a general recommendation.

While oral therapies have obviously become the first-line management of WHO functional class III patients with PAH, parenteral prostacyclin therapy remains the reference treatment for WHO functional class IV patients and for WHO functional class III patients after other approaches have failed. In conclusion, the availability of continuous subcutaneous treprostinil allows an important treatment alternative in patients with.

Declaration of interest

The authors have no conflict of interest to declare and no fee has been received for the preparation of this manuscript.

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