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DRUG PROFILE

Treprostinil for the treatment of chronic thromboembolic pulmonary hypertension

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ABSTRACT

Introduction: Parenteral treprostinil for patients with pulmonary arterial hypertension has resulted in improvement of exercise capacity, functional class, hemodynamics, and survival. Recently, a first randomized trial performed in patients with chronic thromboembolic pulmonary hypertension confirmed the efficacy of subcutaneous treprostinil in this subset of pulmonary hypertension.

Areas covered: Treprostinil sodium is a prostacyclin analog produced synthetically. Drug characteristics include potent systemic and pulmonary vasodilatory effects. Local side-effects of subcutaneous treprostinil have been an obstacle for its use. However, in contrast to other prostacyclins, treprostinil has favorable features. We performed a literature survey by searching PubMed for clinical trials published in any language, investigating medicinal treatments for CTEPH. We used the search terms 'inoperable', and 'chronic thromboembolic pulmonary hypertension' with 'randomized clinical trial', and have put treprostinil for CTEPH in the contest of published literature.

Expert opinion: Drugs approved for PAH have recently shown excellent efficacy in patients with non-operable CTEPH. Rather than head-to-head comparisons of drugs, combination treatments are to be expected in the near future. Furthermore, drugs will have to be tested alongside with pulmonary endarterectomy (PEA), and alongside balloon pulmonary angioplasty, a promising percutaneous mechanical treatment for CTEPH that is not suited for PEA.

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Chronic thromboembolic pulmonary hypertension; subcutaneous treprostinil; balloon pulmonary angioplasty

1. Introduction

Venous thromboembolism is globally the third most frequent acute cardiovascular syndrome, behind myocardial infarction and stroke. Annual incidence for acute pulmonary embolism (PE) ranges from 39 to 115 per 100,000. Abnormal persistence of thrombi as fibrous residua combined with a poorly understood and variable microscopic pulmonary vasculopathy constitutes chronic thromboembolic pulmonary hypertension (CTEPH), a rare sequelae of PE [1] that is driven by inflammation, infection, malignancy, abnormal fibrinogens and resistance to thrombolysis. CTEPH is characterized by an obstruction of major pulmonary arteries with organized thrombi resulting in increased pulmonary vascular resistance (PVR), right heart failure and premature death in more than 50% of untreated patients within 5 years of diagnosis [2]. CTEPH is a long-term complication of PE with a cumulative incidence of 0.1–9.1% after symptomatic PE [3,4]. Besides lifelong anticoagulation, pulmonary endarterectomy (PEA) is the treatment of choice with a remarkable functional recovery of patients and low 30-day mortality [5]. However, more than half of CTEPH patients are not operated because of distal lesions inaccessible to surgery or because of comorbidities [4]. In addition, 16.7% of European patients are diagnosed with persistent/recurrent pulmonary hypertension (PH) after PEA [4], thus illustrating an unmet need for alternative treatments. The pathogenesis of PH is generally poorly understood, but excess vasoconstriction, an imbalance between vascular cell proliferation and apoptosis, an influx of cellular inflammation, and *in situ thrombosis* may contribute to the narrowing of the pulmonary arteriolar lumena and increased pulmonary vascular afterload in CTEPH [6]. This progressive vasculopathy contributes to right ventricular afterload increase. Excess of vasoconstrictor endothelin-1 and a deficiency of vasodilators including nitric oxide and prostacyclin (prostaglandin I_2) appear to play a role. Therefore, endothelin-receptor antagonists (ERA), phosphodiesterase-5 inhibitors (PDE-5, which promote downstream nitric oxide signaling), and prostacyclins are expected to be efficacious in CTEPH.

Medical therapy approved for pulmonary arterial hypertension (PAH) is established in patients with non-operable CTEPH or with persistent/recurrent PH after PEA [7]. Currently, based on the CHEST trials [8,9] only riociguat is approved as medical treatment for non-operable CTEPH in many countries worldwide. The recently proposed CTEPH treatment algorithm stipulates targeted medical therapy with or without interventional procedure [10], which may be PEA or balloon pulmonary angioplasty (BPA) for cases who are not operated. BPA was originally initiated in Europe in 1988 [11], and after a rough learning curve [12] Japanese interventionists have improved and refined the procedure to make it effective and safe over the following 15 years [13]. Currently, this interventional procedure is being adapted and established in expert European and US PH centers, with great success filling a large gap of unmet need. However, the role of medical treatments in the context of BPA is as poorly established as in the context of PEA.

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Article highlights

- Chronic thromboembolic pulmonary hypertension is a pulmonary vascular disease condition that relies on precise imaging of pulmonary arterial segmentation, identification of typical CTEPH lesions and functional characterization of dependent vascular beds.
- Pulmonary thromboendarterectomy should be considered as first line in appropriate patients with CTEPH center evaluation or review.
- The remaining at least 50% of non-operable CTEPH patients should be treated with medical therapy as proven effective in randomized controlled trials, while BPA should be considered, with and without medical treatment.
- Subcutaneous treprostinil sodium has shown excellent efficacy and safety in a recently published randomized trial.
- Randomized data are currently lacking on combination of medical therapies with BPA.
- Preliminary data suggest that upfront combination treatments are more effective than monotherapy.
- Preliminary data suggest that addition of subcutaneous treprostinil in CTEPH patients undergoing BPA improves hemodynamics.
- Preliminary data suggest that medical treatments mainly increase cardiac output, while BPA is also able to lower mean pulmonary arterial pressure.

2. Overview of the market

Currently, only a single drug, riociguat, is market-approved for CTEPH. Riociguat is targeting the nitric oxide (NO) pathway. Macitentan, which is targeting the endothelin-1 pathway has been submitted to health authorities for market authorization in the US and in Europe, all based on the concept that distal vasculopathy of CTEPH serves as an additional treatment target.

CHEST was a 16-week, randomized, double-blinded Phase III trial, investigating the efficacy and safety of riociguat in patients with non-operable and persistent/recurrent CTEPH [8]. Riociguat has a dual mode of action, sensitizing sGC to endogenous nitric oxide (NO) by stabilizing NO-sGC binding, and directly stimulating sGC via a different binding site, independent of NO. This restores the NO-sGC- cyclic guanosine monophosphate (cGMP) pathway and increases the generation of cGMP [14]. The improvement of clinical endpoints in the CHEST-1 trial and sustained improvements of clinical results in CHEST-2, the open-label extension trial, substantiated the approval of riociguat for the treatment of non-operable and persistent/recurrent CTEPH [8].

While the biological rationale to block the endothelin pathway in CTEPH was very strong [15], the first randomized controlled trial to test ERAs in CTEPH, the BENEFIT trial (Bosentan for Treatment of Inoperable Chronic Thromboembolic Pulmonary Hypertension – a Randomized, Placebo-Controlled Trial) [16], did not reach its primary endpoint.

Recently MERIT-1, a 16-week phase 2 trial with macitentan, a dual-endothelin receptor antagonist reported statistically significant improvement of PVR [17]. MERIT-1 included only patients diagnosed as non-operable, and the use of background PAH therapy was permitted. Approximately two-thirds of patients were on PDE-5 inhibitors or oral/inhaled prostacyclin at the study start.

Ambrisentan was also tested in CTEPH, but the study (AMBER-1) was stopped prematurely after 33 of the 160 planned patients had been enrolled. AMBER I was terminated due to futility of enrollment [18]. Several factors played a role on the early termination of the study: low screening rate (about 20% of expected) and high screening failure (about 60% mostly due to concerns regarding non-operability raised by the central adjudication committee). The low screening rate may have been due to the market release of riociguat [8] and new interventional therapy (BPA) for CTEPH after the study had started recruiting [2]. The available data from this study have been published on the *ClinicalTrials.gov* website and in *Pulmonary Circulation*. The improvement of six-minute walking distance (6MWD, primary end point) was 25 m at 16 weeks in the ambrisentan arm compared with a decrease of 10 m in the placebo arm. Median change from baseline in PVR was −130 dynes·s·cm^{-5} with ambrisentan and −103 dynes·s·cm^{-5} with placebo.

The majority of patients enrolled in all these trials was classified in functional class (FC) II/III, while randomized long-term data investigating PAH-targeted treatments in patients with severe non-operable CTEPH were lacking. This gap of evidence was closed with CTREPH (Subcutaneous Treprostinil for the treatment of severe non-operable Chronic Thromboembolic Pulmonary Hypertension), a double-blind, phase 3, randomized, controlled trial [19]. CTREPH is the first trial of subcutaneous treprostinil over a treatment period of 24 weeks investigating the effects and safety of this drug in patients with severe non-operable and persistent/recurrent CTEPH. The biggest challenge in this trial was the inevitable side-effects caused by subcutaneous administration of treprostinil. To resolve this problem, Sadushi-Kolici et al. employed a low-dose comparator reaching a maximal dose of about 5 ng/kg/min while the high-dose treatment group reached 30 ng/kg/min. Thus, unblinding in the active treatment arm was avoided. Approximately 30% of patients were on riociguat, ERAs, PDE-5 inhibitors, alone or in combination. Despite a severely diseased study population N-terminal pro-brain natriuretic peptide (NT-proBNP above 2000 pg/mL), despite the well-known side effect profile of subcutaneous treprostinil and despite the low-dose comparator, significant changes in 6MWD, hemodynamics and WHO FC were observed. At 24 weeks, 6MWD had improved by 45.4 m in the high-dose intention-to-treat population, and by 60.3 m in the high-dose per-protocol population. Thus, this drug serves severe CTEPH or patients who do not tolerate riociguat or need combination therapy. Meanwhile, a vast majority of patients originally randomized in the CTREPH trial have been subjected to BPA, and mean pulmonary artery pressures (mPAP) have been significantly lowered by roughly 20 mmHg as described in the Japanese registry [20], compared with only 3.4 mmHg in the 30 ng/kg/min arm of CTREPH (Table 1).

3. Introduction to the drug

3.1. General introduction

Treprostinil sodium is an analog of prostacyclin approved for the treatment of PAH, available in a parenteral (Remodulin®), inhaled (Tyvaso®) and oral formulation (Orenitram®). Only Remodulin® is approved in Europe. The major pharmacological actions of treprostinil mimic the effects of endogenous prostacyclin and include direct vasodilatation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. Previous pharmacokinetic studies with treprostinil

Table 1. Randomized controlled trials of drugs approved for PAH in chronic thromboembolic pulmonary hypertension.

Trial	Study drug	Duration Weeks	N	WHO FC	Δ6MWD m	ΔPVR %	ΔmPAP mmHg
BENEFIT [16]	Bosentan	16	157	II-IV	+2	−24	−2.5
CHEST-1 [8]	Riociguat	16	261	II-IV	+46	−31	−4.0
MERIT-1 [17]	Macitentan	16	80	II-IV	+34	−16	−3.5
CTREPH [19]	Treprostinil	24	105	III-IV	+45	−34	−3.4

WHO FC World Health Organization, Δ6MWD change in six-minute walking distance, m meters, ΔPVR change in pulmonary vascular resistance, ΔmPAP change in mean pulmonary arterial pressure.

sodium indicate that pharmacokinetics is proportional over a wide range of doses from 1.25 to 125 ng/kg/min with continuous subcutaneous or intravenous infusions [21]. Recently, treprostinil diolamine salt has been developed to deliver treprostinil via the oral route. Experience with treprostinil in CTEPH is sparse.

3.2. Chemistry

Treprostinil sodium, [[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro -2-hydroxy-1 [(3S)-3-hydroxyoctyl]-1H-benz [f]inden-5-yl]oxy] acetic acid, is a chemically stable, tricyclic prostacyclin analogue (Figure 1). Treprostinil possesses potent systemic and pulmonary vasodilatory effects as well as platelet anti-aggregatory properties [22].

3.3. Pharmacodynamics

Treprostinil produces vasodilation and tachycardia. In animals, the vasodilatory effects reduce right and left ventricular afterload and increase cardiac output (CO) and stroke volume. Other studies have shown that treprostinil causes a dose-related negative inotropic and lusitropic effect (Remodulin Summary of Products Characteristics, 2005). The administration by subcutaneous or intravenous routes has the potential to generate concentrations many-fold greater than those generated via the inhaled route (Remodulin Summary of Products Characteristics, 2005).

3.4. Pharmacokinetics and metabolism

Steady-state plasma concentrations of treprostinil are usually achieved between 15 and 18 h after initiation of subcutaneous infusion [23]. The pharmacokinetics of continuous subcutaneous treprostinil are linear over the dose range of 2.5 to 125 ng/kg/min (corresponding to plasma concentrations of about 260–18,250 pg/mL); however, it is not known whether the correlation between dose and steady-state plasma levels is maintained at infusion rates greater than 125 ng/kg/min.

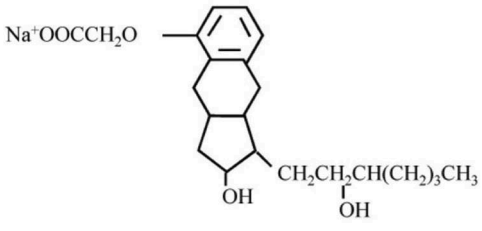

Figure 1. Chemical structure of treprostinil sodium.

The mean apparent elimination half-life following subcutaneous injection ranged from 1.32 to 1.42 h after infusions over 6 h, 4.61 h after infusions over 72 h, and 2.93 h after infusions lasting at least 3 weeks [24]

The mean volume of distribution for treprostinil ranged from 1.11 to 1.22 L/kg, and plasma clearance ranged from 586.2 to 646.9 ml/kg/h. Clearance is lower in obese subjects (BMI > 30 kg/m^2). Treprostinil is relatively rapidly and completely absorbed after subcutaneous infusion, with an absolute bioavailability approximating 100% [25]

Treprostinil is primarily metabolized by the liver, mainly by CYP2C8. In a study conducted on healthy volunteers using [^{14}C] radioactive treprostinil, 79% and 13% of subcutaneous radioactive doses were recovered in the urine and feces respectively over a period of 10 days [24] Five metabolites were detected in the urine, ranging from 10.2% to 15.5% of the dose administered. Three were products of oxidation of the 3-hydroxyloctyl side chain, one was a glucuro-conjugated derivative (treprostinil glucuronide) and one remained unidentified. Only 4% of the dose was recovered in the urine as unchanged parent drug.

An *in vitro* study demonstrated no inhibitory potential of treprostinil against major human hepatic microsomal cytochrome P450 isoenzymes. Moreover, administration of treprostinil had no inducing effect on hepatic microsomal protein, total cytochrome (CYP) P 450 content or on isoenzyme activities.

Diurnal variations were observed in a seven-day chronic pharmacokinetic study in 14 healthy volunteers with treprostinil doses ranging from 2.5 to 15 ng/kg/min administered by subcutaneous infusion. Treprostinil concentrations reached two daily peaks (at 1 am and 10 am, respectively) and two daily trough levels (at 7 am and 4 pm, respectively). The peak concentrations were approximately 20% to 30% higher than the trough concentrations.

Caution should be used in patients with hepatic impairment following subcutaneous application. In patients with hepatic insufficiency, treprostinil at a subcutaneous dose of 10 ng/kg/min for 150 min led to a dose area under the curve that was increased up to 510%, compared to healthy subjects. Clearance in patients with hepatic insufficiency was reduced by up to 80% compared to healthy adults.

Drug interaction studies have been carried out by coadministration with acetaminophen (4 g/day), esomeprazole (40 mg/day), bosentan (250 mg/day), sildenafil (60 mg/day), warfarin (25 mg/day), paracetamol (4 g/day) and fluconazole (200 mg/day), respectively, in healthy volunteers. These studies did not show a clinically

significant effect on the pharmacokinetics of treprostinil. Treprostinil does not affect the pharmacokinetics or pharmacodynamics of warfarin [23].

4. Clinical efficacy

4.1. Data on efficacy and safety in patients with PAH

4.1.1. Short-term studies

The efficacy and safety of subcutaneous treprostinil have been reported in two short-term (12 and 8 weeks, respectively) studies [26,27].

In the pivotal 12-week, double-blind, placebo-controlled, multicenter trial subcutaneous treprostinil was investigated in 470 patients with idiopathic PAH (iPAH), PAH associated with connective tissue disease (CTD-PAH) or congenital heart disease. The mean dose at week 12 was only 9.3 ng/kg/min in the active treatment group. Treprostinil improved exercise capacity (median 6MWD by 16 m, P =0.006), Borg Dyspnea Score (BDS), WHO FC and hemodynamics. Infusion site erythema and pain related to the subcutaneous route of infusion were the most common adverse events (AEs).

In a single – center, double-blind, placebo-controlled, randomized, 8-week trial reported by McLaughlin and al. the efficacy and safety of subcutaneous treprostinil compared with placebo were evaluated in 26 patients with iPAH [27]. At week 8 the mean dose was 13 ng/kg/min. Patients in the subcutaneous treprostinil arm improved exercise capacity by 37 m showing a trend toward improvement in the primary endpoint of 6MWD and also in hemodynamic variables. The majority of patients in this pilot trial developed the most common AEs (88% infusion site pain and 94% infusion site erythema) [27].

4.1.2. Long-term studies

Short-term efficacy of subcutaneous treprostinil has been confirmed in long-term studies, registries, and outcomes [28–30].

The US-European study included 860 patients with PAH treated with subcutaneous treprostinil for more than 1 year who were enrolled in three placebo-controlled trials or were included as de novo patients and investigated in a long-term outcome study [30]. The entire study period was up to 4.5 years, and the primary endpoint was survival. Survival rates were 87–68% over 1–4 years for all 860 patients and 88–70% over 1–4 years with subcutaneous treprostinil monotherapy.

A long-term, open-label, multicenter, retrospective study investigated 122 patients with PH treated with subcutaneous treprostinil from three European PAH centers [28]. They were followed for a mean of 26 months. The treatment with treprostinil provided sustained improvements in exercise capacity and survival benefits. The mean subcutaneous treprostinil dose was about 26 ng/kg/min after 1 year, 32 ng/kg/min after 2 years and about 40 ng/kg/min after 3 years. Survival rates were 88.6%, 70.6% and 65.6% at 1, 3 and 5 years, respectively. Improvement in 6MWD by more than 100 m and a significant decrease in WHO FC were observed.

4.1.3. Registry data

The longest observational prospective registry so far of patients treated with subcutaneous treprostinil was published by the Viennese center [29]. The objective of this registry was the evaluation of effects on exercise capacity, WHO FC, hemodynamics, survival and tolerability throughout a period of 10 years. One hundred and eleven Patients with severe pre-capillary PH were treated since 1999 first-line with subcutaneous treprostinil. Severity of clinical status was defined as WHO FC III/IV PH (Dana Point groups 1 and 4) and severe hemodynamic dysfunction (mean right arterial pressure >10 mmHg and/or cardiac index <2.2 l/min/m^2). This prospective registry differed from previous published studies and registries because of the inclusion of patients suffering from CTEPH and because of a high percentage of patients in WHO FC IV (49%). Of 111 patients, 12% stopped treatment prematurely because of drug side effects, about 10% underwent double lung transplantation and 44% died of any cause (36% on treatment, 7% after early drug discontinuation). Treprostinil-treated patients demonstrated significant improvements in 6MWD, WHO FC, BNP plasma levels, CO and PVR [29].

Overall survival rates at 1, 5 and 9 years were 84%, 53%, and 33%, respectively. Those who tolerated the subcutaneous treatment for more than 6 months survived longer with survival rates of 96%, 78% and 57% at 1, 5 and 9 years, respectively. The treated patients within this study experienced significantly improved long-term survival compared with the historical control group at doses between 12.5 and 42 ng/kg/min [29]. The authors concluded that the first-line treatment of severe pre-capillary PH with subcutaneous treprostinil is safe and efficacious over many years. If up-titration beyond 6 months is tolerated, effective doses are reached and outcomes are good.

4.2. Data on efficacy and safety in patients with CTEPH

A single-center prospective-uncontrolled observational cohort study investigated 28 patients treated between 1999 and 2005 with subcutaneous treprostinil [31]. Criteria for inclusion were severe non-operable CTEPH (WHO FC III and IV), 6MWD ≤ 380 m and at least one hospitalization for right heart decompensation within 6 months prior to the inclusion (not within 1 month before treatment start), mPAP > 25 mmHg, and a pulmonary vascular resistance (PVR) > 500 dynes.s.cm^{-5}. After a mean treatment period of 24 months, treprostinil-treated patients significantly improved exercise capacity, WHO FC, B-type brain natriuretic peptide plasma levels, and hemodynamics. Mean treprostinil dose was 21 ± 5 ng/kg/min. WHO FC improved in 50% of patients. At week 24, the mean 6MWD increased by 59 m. The improvement in exercise capacity (mean increase in 6MWD by 105 m) was sustained at 12 months follow up. Significant improvements were also observed for CO (increase by 0.7 L/min), cardiac index (increase by 0.3 L/min/m^2) and PVR (decrease by 116 dynes.s.cm^{-5}). Despite the open-label-uncontrolled design of this study treatment with subcutaneous treprostinil was superior over conventional treatment with diuretics and anticoagulation alone in patients with severe non-operable CTEPH. This study was the first to urge the need for randomized, placebo-controlled trials with drugs approved for PAH.

CTREPH (Subcutaneous Treprostinil for the treatment of severe non-operable Chronic Thromboembolic Pulmonary Hypertension), a double-blind, phase 3, randomized, controlled trial is the first trial of subcutaneous treprostinil over a treatment period of 24 weeks investigating the effects and safety of this drug in patients with severe non-operable and persistent/recurrent CTEPH [19]. Authors used a low-dose comparator with about 5 ng/kg/min while the high-dose treatment group reached 30 ng/kg/min. Thus, potential unblinding in the active treatment arm was avoided. Approximately 30% of patients were on riociguat, ERAs, PDE-5 inhibitors, alone or in combination. Despite a severely diseased study population (NT-proBNP above 2000 pg/mL), despite the well-known side effect profile of subcutaneous treprostinil and despite the low-dose comparator, significant changes in 6MWD, hemodynamics and WHO FC were observed. At 24 weeks, 6MWD had improved by 45.4 m in the high-dose intention-to-treat population, and by 60.3 m in the high-dose per-protocol population [29]. Thus, this drug serves severe CTEPH patients who need combination therapy.

5. Regulatory affairs

Treprostinil has been approved in North America, some South American countries, and in most countries of Europe for continuous subcutaneous infusion treatment of idiopathic or heritable PAH to improve exercise tolerance and symptoms of the disease in patients classified as WHO FC III. Since 2011 the approval of intravenous administration has been announced for 22 European member nations, each of which had previously approved subcutaneous treprostinil.

6. Conclusion

According to the PAH guidelines, subcutaneous treprostinil is currently recommended (level of evidence I and class of recommendation B) for patients suffering from PAH and classified in WHO FC III and for patients in WHO FC IV requiring transition from epoprostenol [32]. Intravenous treprostinil has only a recommendation of 2a-C for patients with PAH in WHO FC III and IV.

The routine use of treprostinil is more liberal in countries where the medication is approved. According to the PAH treatment algorithm newly diagnosed patients in WHO FC III first are treated with initial oral combination therapy [7]. Those PAH patients deteriorating or in WHO FC IV are treated with combination therapy including at least one intravenous prostacyclin analog. A handful of countries including Austria still practice initiation of subcutaneous treprostinil as first-line treatment in patients with a WHO FC III/IV, mRAP > 10 mmHg and a CI < 2.2 L/min. Despite one approved drug (riociguat) for treatment of non-operable CTEPH, there is still an unmet need for those patients diagnosed with severe CTEPH and not improving or deteriorating under riociguat treatment. The CTREPH trial established a new treatment option for patients with severe non-operable CTEPH. The future will be seeing trials of medical treatments combining with PEA or BPA.

7. Expert opinion

The management of CTEPH has been significantly improved over the past 5 years. This change has been triggered by a paradigm shift in treatments. Instead of PEA as a stand-alone treatment option for CTEPH patients, efficacious medical treatments and BPA have become available for CTEPH care, particularly for all CTEPH patients who are not suited for PEA.

PAH-targeted treatments have shown efficacy in patients with non-operable CTEPH [8,19], and in those with persistent or recurrent PH after PEA. Vasodilators predominantly increase CO and decrease PVR in the range of 16 [17] to 34% [19] of baseline PVR, while effects on mPAP are modest (Table 1). If one looks at the four RCTs of drugs approved for PAH in the indication of CTEPH, one observes that the lowest baseline 6-min walking distance (Table 1) and the oldest patients were treated in the CTREPH trial. Patients enrolled in CTREPH were almost 10 years older than in CHEST. Still, the net hemodynamic effect was similar to that of the CHEST trial; therefore, SC treprostinil may play a role in the treatment of CTEPH patients at highest risk. Those high-risk patients are defined by a low 6-min walking distance [33] and by hemodynamic criteria, such as a PVR >800 dynes.s.cm^{-5} and mPAP ≥40 mmHg.

A remaining question will be whether combination oral drug treatment will obviate the need for parenteral treprostinil in the future. While some patients experience significant improvement in the initial phase of medical therapies, treatment effects tend to decline over time if BPA is not performed. The RACE trial (NCT02634203) will soon shed light on the effect of medical treatments (riociguat) alone compared with BPA by assessing 26-weeks PVR, and secondary endpoints [34]. However, the future of CTEPH treatments will be defined by answer to the question of how treatments for CTEPH should be combined. No head – to – head comparisons of drugs, but trials of combination treatments of PEA, BPA and medical are to be expected in the near future [17,35]. Randomized data will have to be collected on medical therapies as a bridge to PEA and as a bridge to BPA with monotherapy or combinations, and on the use of medical treatments/combinations with BPA for operable patients with unacceptable surgical risk-benefit ratios or for operable patients who refuse surgery. BPA is in the course of gaining a more robust evidence base [36]. Initial data suggest that improvement in PVR and CO is enhanced by combining SC treprostinil with BPA [36].

Declaration of interest

R Sadushi-Kolici has relationships with drug companies including Actelion, AOP Orphan Pharmaceuticals Bayer-Schering, GlaxoSmithKline, and SciPharm Sàrl. In addition, R Sadushi-Kolici is an investigator in trials involving these companies, relationships include consultancy service, and research grants, outside the submitted work. I Lang has relationships with drug companies including Actelion, AOP Orphan Pharmaceuticals, Astra-Zeneca, Bayer-Schering, Cordis, Daiichi-Sankyo, Ferrer, GSK, Medtronic SciPharm Sàrl, and Servier. In addition, I Lang is investigator in trials involving these companies, relationships including consultancy service, research grants, and membership of scientific advisory boards. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer dislcosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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