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REVIEW

Prostacyclins in Pulmonary Arterial Hypertension: the Need for Earlier Therapy

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ABSTRACT

Pulmonary arterial hypertension (PAH) is a rare but serious condition, which if untreated, is associated with a 2-3-year median survival time. A number of treatment options are available for PAH, leading to improvements in exercise capacity, symptoms, and hemodynamics. However, the disease remains incurable and most patients will ultimately progress to right heart failure and death. Three classes of drugs are currently available to improve PAH outcomes, although this review will focus solely on a class of potent vasodilators known as prostacyclins. Currently, four prostacyclin analogs are licensed for the treatment of PAH: epoprostenol, treprostinil, and iloprost in the USA and some European countries, and beraprost in Japan and Korea. Prostacyclins have become the treatment of choice in patients with severe PAH, but there is also evidence to suggest that their earlier use may also benefit patients with mild-to-moderate disease. This review discusses the advantages of prostacyclins in terms of their usefulness in patients whose condition has deteriorated following monotherapy with other agents, and their integral role in combination therapy. The latter appears to offer the potential for pulmonary vasculature remodeling and could be regarded as an emerging paradigm to treat and prevent the progression of PAH.

Keywords: beraprost; epoprostenol; iloprost; prostacyclin; pulmonary arterial hypertension; treprostinil

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INTRODUCTION

Pulmonary hypertension (PH) is defined as an increased mean pulmonary arterial pressure (PAP) of ≥25 mmHg at rest, assessed by right heart catheterization.[1] It is a hemodynamic and pathophysiological state that occurs in a variety of medical conditions. A clinical classification of PH (Dana Point 2008)[1,2] has been recently proposed, differentiating five clinical groups: pulmonary arterial hypertension (PAH), PH due to left heart disease, PH due to lung disease and/or hypoxia, chronic thromboembolic PH (CTEPH), and PH with unclear and/or multifactorial mechanisms.[1,2]

PAH is a rapidly progressive disease of small pulmonary vessels, ultimately leading to right heart failure and death. When untreated, median survival of the idiopathic form (IPAH) is less than 3 years after diagnosis.[3] Currently, eight drugs have been approved for PAH treatment in North America and in parts of the European Union (EU): three endothelin receptor antagonists (ambrisentan, bosentan, and sitaxentan), two phosphodiesterase type 5 inhibitors (PDE5) (sildenafil and tadalafil), and three prostacyclin analogs (epoprostenol, iloprost, and treprostinil). The route of administration and the approval status of prostanoids are subject to variations: intravenous (i.v.) epoprostenol is licensed in the USA and in most EU countries, inhaled iloprost in the USA and Europe. Treprostinil is licensed for subcutaneous (s.c.) administration in the USA and Europe, but only in the USA for the inhaled and the i.v. route. Although used in some centers, i.v. iloprost is neither licensed in Europe nor in the USA. All of these therapies have been shown to improve exercise capacity, hemodynamics, and decrease symptoms. However, clinical improvement remains insufficient throughout the middle- and long-term and the condition gradually deteriorates despite treatment escalation. During the late stage of disease, lung transplantation and atrial septostomy may be indicated, but only a limited number of patients have access to these interventions.[4,5] Therefore, PAH mortality remains high and there is no current convincing evidence of disease reversal despite the numerous available treatment options.

The objectives of this manuscript are to review current prostacyclin knowledge and discuss the use of prostacyclins in PAH treatment, in particular, their potential for earlier use in the course of disease, use in patients with more severe and/or deteriorating disease, and inclusion as an integral component of combination therapy.

OVERVIEW OF AVAILABLE PROSTACYCLINS

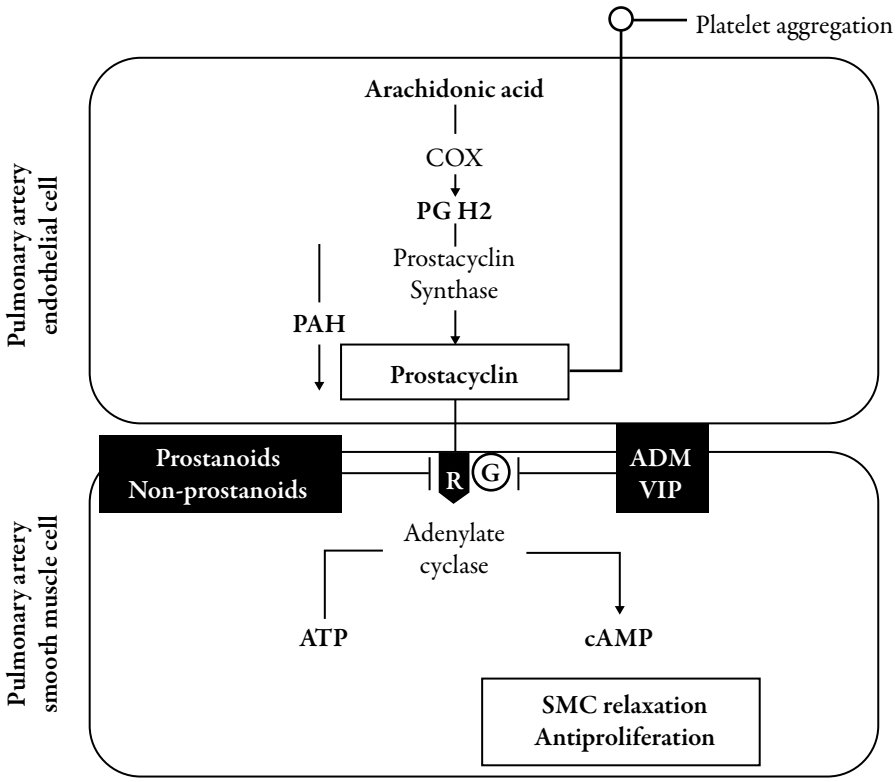
Prostacyclin is produced by endothelial cells from prostaglandin H_2 by the enzyme prostacyclin synthase (Figure 1[6,7]). Prostacyclin and prostacyclin analogs are potent vasodilators and have antithrombotic, antiproliferative, and anti-inflammatory effects.[6] As PAH is associated with vasoconstriction, thrombosis, and proliferation, there is a strong rationale for using prostacyclin treatment (Figure 1[6,7]).[6-9] Three prostacyclins are used for the treatment of PAH: i.v. epoprostenol; i.v., s.c., and inhaled treprostinil; and inhaled iloprost. These three drugs are approved in the USA and some European countries under various conditions that are beyond the scope of this paper. Another prostacyclin, oral beraprost, has been approved in Japan and Korea.[9] An overview of currently available prostacyclins is provided in Table 1.[2]

Although sharing qualitatively similar pharmacodynamic effects, the available prostacyclins differ in terms of their chemical structure and pharmacokinetic profile, thus explaining their different routes of administration, as shown in Table 2.[1,8,10-45]

Epoprostenol

Epoprostenol was the first synthetic prostacyclin analog approved for the treatment of PAH. It has a short half-life ($t_{½}$) of 3-5 minutes and requires continuous i.v. infusion. The highest concentrations of the drug are found in the liver, kidneys, and small intestine. Tissue levels decline rapidly and there is no evidence of accumulation of the drug. Plasma steady-state concentrations are reached within 15 minutes and concentrations are proportional to the infusion rate.

Figure 1. Prostacyclin pathway in pulmonary arterial hypertension. Arachidonic acid is transformed by cyclo-oxygenase (COX) into prostaglandin (PG) H2, a substrate of prostacyclin synthase, which produces prostacyclin in the endothelial cell. Prostacyclin binds to a membrane receptor on the smooth muscle cell (SMC) that stimulates adenylate cyclase through a family of prostacyclin receptors (R) to produce cyclic adenosine monophosphate (cAMP). The latter induces SMC relaxation and has anti-proliferative effects. Prostacyclin also inhibits platelet aggregation. Both prostacyclin synthase activity and prostacyclin levels are decreased in pulmonary arterial hypertension (PAH). This can be in part restored by prostanoids or non-prostanoids acting on prostacyclin receptors. Other substances, such as adrenomedullin (ADM) and vasoactive intestinal peptide (VIP), may also stimulate adenylate cyclase when binding to G proteins. Prostacyclin synthase is also stimulated by endothelin-1 type B receptors present on the endothelium (not shown). ATP=adenosine triphosphate.[6,7]



Epoprostenol has been shown to improve symptoms, exercise capacity, and hemodynamics, mostly in IPAH and PAH associated with connective tissue disease (CTD). Randomized clinical trials have reported decreases in total pulmonary resistance (TPR) and mean PAP, improvements in exercise capacity as measured by the 6-minute walk distance (6MWD), improved New York Heart Association Functional Class (NYHA FC) (Table 3[46]), and a longer time to clinical worsening (TtCW).[10-12]

Longer-term studies have evaluated the durability of response to epoprostenol. A retrospective, longitudinal cohort study investigated the effect of epoprostenol as a first-line treatment in 37 patients with PAH and NYHA FC III.[13] In addition to improvements in 6MWD, the 1-year survival was 94% of patients, while 75% survived for 3 years. Absence of disease progression was noted in 75% of patients after 1 year and in 44% of patients after 3 years. Similar findings were observed in another retrospective study in 91 patients, also confirming that patients with PAH associated with systemic sclerosis fare much less well compared with the other group.[14] Two long-term, single-center studies reported

Table 1. Clinical classification, pathology, and hemodynamic characteristics of pulmonary hypertension.[2]

Group/subgroup	Pathology	Pulmonary hemodynamic
1. Pulmonary arterial hypertension 1.1 Idiopathic 1.2 Heritable 1.2.2 BMPR2 1.2.2 ALK 1, endoglin (with/without hereditary hemorrhagic telangiectasia) 1.2.3 Unknown 1.3 Drug- and toxin-induced 1.4 Associated with (APAH) 1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart disease 1.4.5 Schistosomiasis 1.4.6 Chronic hemolytic anemia 1.5 Persistent pulmonary hypertension of the newborn	Particularly pathological lesions affecting the pulmonary arteries (<500 μm diameter). Pulmonary veins classically unaffected	Precapillary pulmonary hypertension • Mean PAP >25 mmHg • PCWP <15 mmHg
1. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis	Mainly PVOD involving septal veins and pre-septal venules. May be medial hypertrophy or fibrotic areas in distal pulmonary arteries	Precapillary pulmonary hypertension • Mean PAP >25 mmHg • PCWP <15 mmHg
2. Pulmonary hypertension (PH) owing to left heart disease 2.1 Systolic dysfunction 2.2 Diastolic dysfunction 2.3 Valvular disease	Enlarged and thickened pulmonary veins, pulmonary capillary dilatation, interstitial edema, alveolar hemorrhage, lymphatic vessel, and lymph node enlargement. Medial hypertrophy and intimal fibrosis may affect distal pulmonary arteries.	Postcapillary pulmonary hypertension • Mean PAP >25 mmHg • PCWP >15 mmHg • Passive: TPG ≤12 mmHg • Reactive (disproportionate): TPG >12

(continued on next page)

Table 1. Clinical classification, pathology, and hemodynamic characteristics of pulmonary hypertension (*Continued*).[2]

Group/subgroup	Pathology	Pulmonary hemodynamic
3. PH owing to lung diseases and/or hypoxia 3.1 Chronic obstructive pulmonary disease 3.2 Interstitial lung disease 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern 3.4 Sleep-disordered breathing 3.5 Alveolar hypoventilation disorders 3.6 Chronic exposure to high altitude 3.7 Developmental abnormalities	Pathological changes include medial hypertrophy and intimal obstructive proliferation of distal pulmonary. arteries May be variable vascular bed destruction in emphysematous or fibrotic areas.	Precapillary pulmonary hypertension • Mean PAP >25 mmHg • PCWP <15 mmHg
4. Chronic thromboembolic PH (CTEPH)	Pathological lesion characteristics: organized thrombi attached to the pulmonary arterial medial layer in elastic pulmonary arteries, replacing normal intima. Collateral vessels from systemic circulation may grow to at least partially reperfuse areas distal to complete obstructions.	
5. PH with unclear and/or multifactorial mechanisms 5.1 Hematological disorders: myeloproliferative disorders, splenectomy 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, , lymphangioleiomyomatosis neurofibromatosis, vasculitis 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders 5.4 Others: tumoral obstruction, fibrosing, mediastinitis chronic renal failure on dialysis	Heterogeneous conditions with different pathological features with unclear or multifactorial etiology.	

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ALK1=activin receptor-like kinase; APAH=associated pulmonary arterial hypertension with other diseases; BMPR2=bone morphogenetic protein receptor type II; HIV=human immunodeficiency virus; PAP=pulmonary arterial pressure; PCWP=pulmonary capillary wedge pressure; TPG=transpulmonary gradient.

Table 2. Currently available prostacyclin analogs for the treatment of pulmonary arterial hypertension (PAH). Brief summary of some of the characteristics of prostacyclin analogs for the treatment of PAH. Based on Summary of Product Characteristics (SPC) for epoprostenol (Flolan; GlaxoSmithKline), iloprost (Ventavis; Bayer Plc), (http://www.medicines.org.uk/emc), the Internet Drug Index for treprostinil (Remodulin; United Therapeutics Corp.) (www.rxlist.com/script/main/hp.asp) and published data on prostacyclins.[1,8,10-45]

	Epoprostenol	**Iloprost**	**Treprostinil**	**Beraprost**
Indication	Treatment of PAH in NYHA FC III/IV patients who did not have adequate response to conventional therapy	Treatment of patients with PAH (NYHA FC III) to improve exercise capacity and symptoms	Treatment of PAH (NYHA FC II/IV) to diminish symptoms associated with exercise	Primary PAH
Initial dose	Short-term: 2 ng/kg per minute	2.5 μg	1.25 ng/kg per minute Incremental increases of 1.5 ng/kg per minute per week for the first 4 weeks and then 2.5 ng/kg per minute per week for the remaining duration of treatment.	60 μg/day t.i.d.
Maximum recommended dose	None stated	5.0 μg	None stated	180 μg/day t.i.d./q.i.d.
Route of administration	Continuous infusion via a central venous line (a peripheral line can be used in emergency situations)	Inhalation	Subcutaneous or intravenous infusion, and inhalation (United States only)	Oral
$t_{½}$	max 6 min (possibly 2-3 min)	5-25 min	4 h	0.5 (0.21) to 0.91 (0.27) h
Contraindications	Hypersensitivity, congestive heart failure due to severe left ventricular dysfunction. Should not be used chronically in patients who develop pulmonary edema during dose-ranging.	Hypersensitivity, increased risk of hemorrhage, severe coronary heart disease or unstable angina, myocardial infarction (last 6 months), decompensated cardiac failure (if not closely supervised by physician), severe arrhythmias, cerebrovascular events, PH due to venous occlusive disease, pregnancy and lactation.	Hypersensitivity, PH due to venous occlusive disease, pregnancy and lactation.	
Most common adverse events	Facial flushing, headache, jaw pain, nausea, sepsis, line infection, septicemia, vomiting, thrombocytopenia.	Cough increased, hypotension, vasodilatation.	Diarrhea, headache, infusion-site pain and reaction, jaw pain, nausea, rash, vasodilatation.	Diarrhea, headache, hot flushes, nausea.

NYHA FC=New York Heart Association Functional Class; $t_{½}$=half-life; t.i.d.=twice daily; q.i.d.=four times daily; PH=pulmonary hypertension.

Table 3. Functional classification (FC) of pulmonary arterial hypertension (PAH) (adapted from Barst et al. 2004).[46] The original World Health Organization (WHO) FC of PAH has been modified by the New York Heart Association Functional Class (NYHA FC). NYHA FC has proved to be a powerful predictor of survival.

NYHA FC	Description
I	PAH but no limitation of physical activity. Ordinary physical activity: no unwarranted dyspnea or fatigue, chest pain, or near syncope.
II	PAH resulting in slightly limited physical activity, but comfortable at rest. Ordinary physical activity: unwarranted dyspnea or fatigue, chest pain, or near syncope.
III	PAH resulting in markedly limited physical activity, but comfortable at rest. Less than ordinary activity: unwarranted dyspnea or fatigue, chest pain, or near syncope.
IV	PAH and unable to perform any physical activity without symptoms. Manifest signs of right heart failure, and dyspnea and/or fatigue may be present at rest. Increased discomfort with physical activity.

Adapted from "Updated evidence-based treatment algorithm in pulmonary arterial hypertension." J Am Coll Cardiol. 2009;54;S78-S84. With permission from Elsevier.

that i.v. epoprostenol improves survival in IPAH compared with historical controls[15] or the prediction from the National Institutes of Health (NIH) equation.[16] In the first of these studies, 162 patients receiving i.v. epoprostenol at a mean (standard deviation) dose of 48.6 (24.9) ng/kg were followed for a mean of 36.3 months.[15] The observed survival in patients treated with epoprostenol was significantly longer than the expected survival based on historical data at 1 year (87.8% vs. 58.9%), 2 years (76.3% vs. 46.3%), and 3 years (62.8% vs. 35.4%). In the second study, epoprostenol also evoked an improvement in exercise capacity in patients with severe PAH, with a mean event-free follow-up of 23 months.[16]

The starting dose of epoprostenol is usually 2-4 ng/kg per minute, which can be increased according to dose-limiting side effects: flushing, headache, jaw pain, diarrhea, and leg pain.[1,10-16] Patients may also experience erythroderma, anxiety, and thrombocytopenia.[1,17] The optimum dose for most patients is 20-40 ng/kg per minute. In clinical practice, changes in long-term infusion rate (by increments of 1-2 ng/kg per minute) depend on the persistence, worsening, or recurrence of PAH symptoms, or the incidence of adverse events such as those reported above.[11-16,18,19]

Although infrequent, there are possible serious side effects associated with the delivery system for epoprostenol, and these include: pump malfunction, local infections, obstruction of the catheter, and sepsis.[1,10-16] Four nonfatal sepsis were reported in the seminal clinical trial.[11] In long-term experience, the annual rate of line infection has been reported to be about 0.24 episodes/patient[16], while sepsis ranged from 0.14[16] to 0.19[15] episodes/patient. The short $t_{½}$ and instability of the drug at room temperature requires continuous infusion. In addition, the drug has to be reconstituted at least on a daily basis. Finally, cases of high output failure due to systemic vasodilation have been reported in patients receiving high doses of epoprostenol.[18] A thermostable formulation of epoprostenol is currently under investigation.

The use of epoprostenol is not recommended in patients with pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis, because of the risk of pulmonary edema, although careful administration in expert centers may be considered as a bridge to transplantation.[1]

Epoprostenol in Combination Treatment

Studies evaluating various therapies used in combination have been conducted over the past years. Interestingly enough, two-thirds of the currently published phase 3 studies included a prostanoid in the treatment regimen.[19-21] In a 16-week, double-blind, placebo-controlled trial, 267 patients with PAH already receiving long-term epoprostenol were randomized to sildenafil 20 mg t.i.d. or placebo.[19] The combination led to improvement in the 6MWD (the primary endpoint) and was most marked in patients with a baseline 6MWD of ≤325 meters. Combination therapy also resulted in a significantly longer TtCW (P=0.002): 6.2% of the combination group versus 19.5% of the epoprostenol monotherapy group experienced a worsening event. Interestingly enough, this was not necessarily seen in the sickest patients. The explanation for this observation is, however, unclear. An improvement in health-related quality of life was also noted with the combination compared with monotherapy.

The concept of upfront combination therapy has been tested in the Bosentan Randomized Trial of Endothelin Antagonist Therapy for PAH (BREATHE-2) study. In this trial, bosentan or placebo was added within a few days after initiation of epoprostenol therapy in 33 patients with PAH.[22] Patients were randomized in a 2:1 ratio to bosentan (62.5 mg twice a day [b.i.d.]) for 4 weeks and then bosentan (125 mg b.i.d.) or placebo. A nonsignificant trend to decrease TPR, the primary endpoint, was observed in the active treatment group (P=0.08 vs. placebo). Similar observations were made for 6MWD and NYHA FC.

Treprostinil

Treprostinil is a longer-acting and stable prostacyclin analog, which can be delivered by various routes (s.c., i.v., and inhalation).[23] The pharmacokinetics of treprostinil is linear over the dose range 1.25-125 ng/kg per minute, which corresponds to plasma concentrations of 0.015-18.25 ng/mL. In addition, it has been shown in healthy volunteers that s.c. and i.v. steady-state administrations of treprostinil at 10 ng/kg per minute are bioequivalent.[47] Rapid and complete absorption of treprostinil occurs after s.c. administration with approximately 100% bioavailability, and steady-state concentrations are reached in about 10 hours. Elimination of treprostinil from the plasma is biphasic, with a terminal $t_{½}$ of approximately 4 hours.

Improvements have been reported in clinical state, FC, exercise capacity, and quality of life when treprostinil has been given subcutaneously in a wide range of PAH etiologies. A randomized, double-blind, placebo-controlled trial of 470 patients with PAH reported improved exercise capacity with 12 weeks treprostinil s.c. treatment, as well as improvement in PAH symptoms.[24] In addition, sustained long-term improvement resulting from treprostinil s.c. treatment was shown in a retrospective, open-label study involving 38 patients with moderate-to-severe PAH.[25] Significant and sustained improvements in 6MWD and mean PAP were reported, with a mean final dose of treprostinil of 37.8 ng/kg per minute. Long-term (up to 4 years) treprostinil s.c. treatment in 860 patients with PAH resulted in a survival advantage of 88%-70% over 1-4 years compared with a predicted survival of 69%-38%.[26] However, 23% of the patients discontinued treprostinil due to adverse events and 11% were switched to other therapies.[26] A retrospective study conducted in three European university hospitals noted significant improvements in 6MWD and NYHA FC after 3 years of treatment with treprostinil s.c. in 99 patients with PAH.[27] Event-free survival was 83.2% after 1 year and 69% after 3 years, with corresponding overall survival of 88.6% and 70.6%, respectively.

Treprostinil can be administered by continuous s.c. infusion using a portable mini-delivery system. This route presents a significant advantage over epoprostenol, as it does not require an i.v. line, thus avoiding adverse events associated with a permanent catheter.[28] Similar to other prostacyclins, treprostinil is contraindicated in patients with PAH due to veno-occlusive disease and in previous hypersensitivity to the compound. In addition, the effects of treprostinil during pregnancy and lactation are unknown.

Pain at infusion site is a major side effect of s.c. delivery, affecting more than 80% of patients[24-27] and leading to a high dropout rate and an obvious underdosing in the seminal randomized trial.[24] Compared with placebo, patients in the active group experienced more pain (87% vs. 27%) and site reaction (83% vs. 27%).[24] However, this issue can be managed appropriately by providing proactive nursing support, less frequent catheter changes (up to 2 weeks) and pre-emptive pain control. In addition, the dose can be increased despite the presence of pain in order to overcome side effects via clinical improvement.[27] Such strategies have led to a much lower rate of dropouts due to pain (6%-14%), and better dose titrations.[27-29]

Subcutaneous infusion of treprostinil commences at a dose of 1.25 ng/kg per minute; in rare cases, this can be reduced to 0.625 ng/kg per minute if the initial dose cannot be tolerated. In order to reach a dose at which PAH symptoms are improved, clinical practice reveals that daily incremental dose increases of 1-2 ng/kg per minute can safely be performed during the first week of treatment, to reach a dose of 10 ng/kg per minute after a week. This is followed by weekly increases of 2.5 ng/kg per minute for the remainder of treatment, according to symptom improvement. Treprostinil concentrations should be titrated slowly in patients with hepatic or renal insufficiency due to the likely greater systemic exposure in such patients. Although better tolerated than with epoprostenol therapy, abruptly withdrawing treprostinil or large dose reductions may lead to worsening of PAH symptoms within hours and should be avoided.

Although available data are less compelling, treprostinil has been studied using the i.v. route. In a 12-week open and uncontrolled trial, treprostinil i.v. has been reported to improve exercise capacity (6MWD) and hemodynamic parameters (mean PAP, cardiac index, and pulmonary resistance).[30] A placebo-controlled trial has been conducted in naive patients with PAH.[31] However, a significant rate of delivery system-related side effects led to trial interruption for safety reasons: of the 45 included patients, three died due to central catheter implantation (n=2, including one before randomization) or sepsis (n=1).[31] This clearly underscores the concerns raised by the implantation of a permanent i.v. line for prostacyclin infusion and the importance of a strict protocol for patient follow-up when treated with i.v. prostacyclins. As a result, 44 patients were randomized and a post-hoc analysis has nevertheless been performed in the 31 patients completing the study. Improvements in the 6MWD and NYHA FC were observed in the treated group and there was a trend towards increased survival.[31] However, these results have to be interpreted with great caution given the early interruption of the trial due to safety issues.

Inhaled treprostinil has also been administered using an ultrasonic nebulizer. Using this device, marked pulmonary vasodilatation was observed,[32] with a near maximal acute decrease in pulmonary vascular resistance at a 30 µg dose and has received approval by the US Food and Drug Administration (FDA). A metered-dose inhaler delivery system has now been developed for treprostinil. Inhaled treprostinil

evoked improvements in hemodynamics and a sustained improvement in pulmonary selective vasodilatation at doses of 30, 45, and 60 µg.[33] The effects of treprostinil were comparable with those obtained using an ultrasonic nebulizer.

Treprostinil in Combination Treatment

Inhaled treprostinil has been studied in combination with other PAH therapies, although few prospective data are available. However, a randomized-controlled study by McLaughlin et al.,[21] involving 235 patients with NYHA FC III or IV PAH found that for patients with PAH who remained symptomatic on bosentan or sildenafil, inhaled treprostinil (four times daily [q.i.d.]) improved exercise capacity and quality of life, and was safe and well-tolerated.[21] However, this trial failed to demonstrate a benefit in terms of prevention of clinical worsening and most other secondary endpoints studied. This may be due to the stability of a prevalent PAH population less likely to display clinical events in a short observation time.

There are no prospective data available on the combination of s.c. or i.v. treprostinil with other PAH therapies.

Iloprost

Iloprost is a chemically stable prostacyclin analog that can be administered by aerosol.[1,20,34-38] The theoretical advantage of this mode of delivery is based on the belief that the treatment could be selective for the pulmonary circulation. At a mouthpiece dose of 5.0 µg, maximum plasma concentrations of 100-200 pg are reached at the end of an inhalation session and decline with a $t_{½}$ between 5 and 25 minutes. Iloprost is undetectable 0.5-1.0 hour after inhalation. Acute and short-term inhalation of iloprost has been shown to produce pulmonary vasodilatation[13,34] and to improve exercise capacity.[35] A large, placebo-controlled, randomized study compared iloprost (2.5 or 5.0 µg) inhaled six to nine times daily with placebo in 203 patients with severe PAH and distal CTEPH.[36] A combined endpoint of 6MWD increase by 10% and improvement by one NYHA FC was met by 16.8% of patients treated with iloprost compared with 4.9% given placebo (P=0.007). In addition, significant improvements in hemodynamic parameters were noted in iloprost-treated patients after 12 weeks.

The long-term efficacy of inhaled iloprost has been reported recently where first-line treatment for IPAH was studied in 76 patients who were followed for approximately 5 years.[37] Event-free survival was 81% (3 months), 53% (1 year), 29% (2 years), 20% (3 years), 17% (4 years), and 13% (5 years). Inhaled iloprost was investigated in a prospective, open-label study lasting for 2 years,[38] and was administered to 63 patients either at baseline or after 3 months. Inhalation was performed six to nine times daily using a jet nebulizer delivering a single 4 µg dose. The 2-year survival, correcting for differential dropouts, was 87% in patients who received inhaled iloprost compared with a predicted survival of 63%. Iloprost was well tolerated, and no significant increase in dose was necessary.

Adverse events, very commonly observed following iloprost inhalation, are increased cough, hypotension, and flushing. Compared with placebo, patients randomized to receive iloprost presented more cough (38.6% vs. 25.5%) and vasodilation (26.7% vs. 8.8%).[36] Dizziness, headache, jaw pain, and syncope are also observed, although not different from placebo in the Aerosolized Randomized Iloprost Study (AIR)[36] and reported less frequently compared with other prostacyclins. The use of iloprost is contraindicated in: patients with hypersensitivity to the drug or excipients, patients with an increased risk of hemorrhage,

severe coronary heart disease or unstable angina, myocardial infarction within the last 6 months, cerebrovascular events (eg, transient ischemic attacks or stroke) in the previous 3 months, PAH due to venous occlusive disease, and in pregnancy or lactation.

The recommended dose of inhaled iloprost is 2.5 or 5.0 µg, with the former as the first inhalation and the latter as the second inhalation. The dose can be reduced from 5.0 to 2.5 µg if tolerability is poor. Inhalations are performed six to nine times daily according to the patient's needs and tolerability. The elimination of iloprost is reduced in patients with hepatic impairment; in these cases, a dose of 2.5 µg should be administered at intervals of at least 3 hours (maximum of six administrations per day). Dosage intervals may then be shortened cautiously according to tolerability. If the 5.0 µg is deemed necessary, then dosing intervals of at least 3 hours should again be used.

Iloprost in Combination Treatment

Inhaled iloprost (5 µg) was added to stable bosentan therapy for 12 weeks in 34 patients with PAH and compared with 33 patients who received an additional placebo to bosentan therapy.[20] In the combination group, a nonsignificant improvement in the placebo-adjusted difference in 6MWD, the primary endpoint, of +26 meters (P=0.051) was achieved, although a treatment effect of +30 meters (P=0.001) was observed. The NYHA FC improved by one class in 34% of iloprost-bosentan patients compared with 6% of placebo-bosentan patients (P=0.002). The TtCW was also significantly delayed in iloprost-bosentan patients (P=0.022).

Beraprost

Beraprost is the first orally active and chemically stable prostacyclin analog evaluated in randomized clinical trials in PAH. The effective and best-tolerated dose of beraprost has been found to be in the range of 120-180 µg b.i.d.[39] After single doses of beraprost (20, 40, and 60 µg) and repeated doses (t.i.d. for 3 days), the terminal dose-independent $t_{½}$ of beraprost was 0.51 (0.21) to 0.91 (0.27) hours.[48]

Beraprost was shown to improve exercise capacity and symptoms in patients with NYHA FC II and III PAH (n=130) in a randomized, double-blind study using the maximum dose of beraprost (80 µg q.i.d.) or placebo for 12 weeks.[40] However, no improvement in pulmonary hemodynamics was reported and the benefit on exercise capacity was limited to patients with IPAH. The effects of beraprost were also studied in a long-term randomized controlled trial.[41] A total of 116 patients with distal CTEPH and PAH were randomized to the maximum tolerated dose of beraprost (120 µg q.i.d.) or placebo for 12 months. Patients treated with beraprost showed improvements in 6MWD and less evidence of disease progression at 6 months (P=0.002) compared with placebo. However, the beneficial effects of beraprost were no longer present at 9 or 12 months. This may be explained, at least in part, by a lack of durability of response, or by the unique design of the trial, as no other drug for PAH has been studied for more than 3-6 months.

Data on the long-term effects of oral beraprost are scarce and have been reported in a few retrospective analyses performed on a limited number of patients with PAH[44] or distal CTEPH.[43,44] It is therefore unclear whether oral beraprost has a sustained effect over time. For this reason, the approval status of the drug is limited to Japan and Korea.

The adverse events noted in studies on beraprost were as expected for a prostacyclin analog. Drug-related adverse events were common in the dose titration phase but appear

to decrease in the maintenance period. The main adverse events noted were headache, hot flushes, diarrhea, and nausea.[45] These side effects can be poorly tolerated and have been limiting dose adaptation in clinical trials.[40-42,45] Compared with placebo, patients receiving beraprost for 3 months experienced more symptoms during the titration phase, including headache (67.7 vs. 16.9%), flushes (53.8% vs. 12.3%), jaw pain (27.7% vs. 1.5%), and diarrhea (26.2% vs. 6.2%). These adverse events were less frequent during the maintenance phase of the trial[42] and appear to decrease over time.[45]

THE PLACE OF PROSTACYCLIN ANALOGS IN CURRENT TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

The recent European Guidelines for the diagnosis and treatment of PH,[1] recommend the use of prostacyclins according to disease severity as determined by NYHA/WHO FC. For patients in NYHA FC IV, epoprostenol has the most robust evidence and the highest grade of recommendation. A snapshot of the published literature shows that a greater proportion of studies of FC IV patients involve i.v. epoprostenol (about 27%) than either treprostinil (7%) or oral therapies (0%-5%).[49] Indeed, although the evidence remains sparse, some experts recommend the use of upfront combination therapy with epoprostenol and oral therapies in the most severe patients.[1,49]

Similar recommendations regarding the use of epoprostenol as first-line treatment in "high-risk" patients were made by the American College of Cardiology Foundation (ACCF) Task Force on Expert Consensus Documents and the American Heart Association (AHA).[50] It was recommended that the administration method and side effects of prostacyclins should be carefully assessed when considering patients with PAH for prostacyclin treatment. However, the guidance also recommends that, given the complexities of drug administration, epoprostenol use should be limited to centers with experience in administering this drug and that perform systematic patient follow-up.[50] In the interests of balance, the complexities of both i.v. and s.c. administration of treprostinil were also noted, with the suggestion again being that treprostinil administration should be limited to centers with experience of this drug.[50]

For patients in NYHA FC III, the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines recommend inhaled iloprost and s.c. treprostinil as first-line therapies (with a lower grade of evidence and recommendation for treprostinil), although in NYHA FC III patients with severely impaired hemodynamics, epoprostenol can also be offered.[1]

The ESC/ERS guidelines also advocate that for all patients, disease status should be evaluated 3-4 months after initiation of first-line therapy, with such assessment (based on clinical, functional, and hemodynamic variables) allowing for the classification of patients in three categories: improving, stable but not satisfactory, or unstable/deteriorating.[1] In the latter two categories, although evidence is still limited, the guidelines include the option of sequential combination therapy, but only for patients treated in expert centers.

FUTURE DIRECTIONS OF PROSTACYCLIN ANALOGS IN THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

Earlier Use of Prostacyclins

The treatment algorithm devised by the ESC/ERS is based on a graded intensification of treatment,

comprising general measures, supportive therapy, and referral to an expert center.[1] In the current guidelines, prostacyclin (epoprostenol) is strongly recommended for the most severe cases (NYHA FC IV) as first-line therapy. In mild-to-moderate PAH, therapy typically starts with oral drugs, although some experts are still using prostacyclins in this situation. Interestingly enough, two combination strategies are also recommended: (1) sequential combination for patients who fail to respond to first-line therapy; (2) upfront combination therapy in severe (NYHA FC IV) cases. However, the clinical evidence supporting both strategies is rather limited to date. In addition, it is very likely that prostacyclins are used too late in the course of the disease. Indeed, recent data coming from the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) show that 40% and 26% of all patients receive combination and parenteral prostacyclins, respectively.[51] In addition, historical data from two expert centers suggest that the use of i.v. epoprostenol may also benefit patients in less advanced stages of disease (NYHA FC III).[15,16] Of course, this has not yet been demonstrated in any clinical trial available and it is unknown whether or not the survival benefit observed in one trial with i.v. epoprostenol[11] could be reproduced today in the era of oral therapy. Therefore, further research needs to be undertaken to determine the most appropriate timing of prostacyclin administration during the PAH course, ie, upfront or in combination with an aggressive treat-to-goal strategy.

This has been underscored by studies that have investigated prostacyclin analogs as add-ons to endothelin receptor antagonists and/or PDE5 inhibitors in patients who remained symptomatic or whose condition had deteriorated.[19-22] Only one study, involving the addition of sildenafil in patients already receiving epoprostenol,[19] reached both the primary endpoint 6MWD and the important secondary endpoint, TtCW. The efficacy and safety of inhaled treprostinil (up to 54 µg) was assessed in 235 patients with PAH who remained symptomatic while receiving bosentan or sildenafil treatment.[21] An improvement in 6MWD (11 meters, P=0.0066) was noted after addition of treprostinil and the patients' quality of life also improved. However, no improvement was observed in TtCW. This may be explained, at least in part, by the stability of the studied population and the selection of "survivors" unlikely to present clinical events. This has recently been supported by the outcome of patients in the French PAH registry, where prevalent patients (ie, the study population in most combination trials) are more likely to have a prolonged survival when compared with incident cases.[52] These observations clearly pave the way for future developments in PAH, in terms of compound and strategy choice, especially with prostacyclins.

New Formulations and Modes of Delivery

Currently used prostacyclin analogs have drawbacks, such as their pharmacokinetic properties or the need for i.v. and continuous administration. There is also a lack of pulmonary and intrapulmonary selectivity with these routes of administration, which may lead to life-threatening pulmonary and systemic side effects.[53] Inhaled iloprost, has evoked improvements in exercise capacity and hemodynamics and has an excellent tolerability and safety profile. As such, it has been approved in many countries for the treatment of severe PH. However, it has a short $t_{½}$ and short duration of hemodynamic effects, necessitating six to nine administrations per day.

An inhaled formulation of epoprostenol effectively reduced PAP in groups of critically ill patients with minimal side effects,[54] although

further studies are needed to determine clinical outcomes. Treprostinil has a longer $t_{½}$ than iloprost, and the longer duration of its hemodynamic effects would require fewer administrations per day. Delivery of treprostinil via a metered dose inhaler produced a sustained vasodilatation that was selective for the lungs in 39 patients with precapillary PH.[33]

Other possible approaches are combinations of an inhaled prostacyclin with oral drugs such as endothelin receptor antagonists or PDE5 inhibitors.[53] Development of controlled-release aerosol formulations using liposomes or nanoparticles may also lead to more sustained and durable effects of the prostacyclins.[53]

Development of prostacyclin analogs that can be administered orally without any loss of efficacy would be an important improvement in the treatment options for PAH.[55] Beraprost was the first oral prostacyclin developed, but its clinical effects were relatively modest and transient and its use was also associated with a high percentage of patients experiencing intolerable side effects.[56] Trials involving an oral formulation of treprostinil,[57] and the nonprostanoid-prostacyclin receptor agonist, selexipag, are currently ongoing, the latter being studied in an event-driven trial.

Peroxisome Proliferator-Activated Receptor Gamma

Peroxisome proliferator-activated receptor gamma (PPARγ) is expressed in lung tissue and pulmonary vasculature, but its expression is reduced in vascular lesions of patients with PH.[58] PPARγ also has an inhibitory effect on pulmonary vascular remodeling, which is a major factor involved in elevated pulmonary vascular resistance in PAH.[58] The thiazolidinedione, rosiglitazone, which has been used in the treatment of type 2 diabetes, activated PPARγ and reduced hypoxia-induced PH in a murine model.[59,60] Prostacyclin analogs have been shown to activate PPARγ in the presence of the cell surface prostacyclin receptor (IP), which couples with G protein and increases cyclic adenosine monophosphate (cAMP) levels by activation of adenylate cyclase.[61] Moreover, the PPARγ antagonist GW9662 partially inhibited the antiproliferative effects of treprostinil in IP-expressing cells.[61] Therefore, PPARγ may be a novel therapeutic target in PH and the development of prostacyclins that more specifically and potently activate this target may provide a new approach to treatment. However, great caution should be used with rosiglitazone, as it appears to increase cardiovascular mortality in patients treated for diabetes.[62]

New Combinations

A multitude of intracellular mediators are implicated in the pathophysiology of PAH, including those that produce abnormal cellular growth, vasoconstriction, and deleterious effects on hemodynamics.[63] Many overlapping secondary messenger systems are involved in the disease process and the inherent redundancy explains why currently available treatments fail to reverse or prevent progression of PAH. These factors emphasize the need for combinations of treatments, which act by different means. Combination therapy is an accepted standard of care in other diseases, such as cancer, human immunodeficiency virus infections, and left ventricular dysfunction. In terms of PAH, combination treatment would seem to offer the greatest potential for remodeling the pulmonary vasculature, by inhibiting as many pathways as possible that are implicated in PAH. Although current data remain insufficient, combination treatment for PAH can be viewed as an emerging paradigm, and may involve existing agents as

well as new agents that become available for patients with suboptimal responses to current treatment.

Current trials involving a prostacyclin combined with an endothelin receptor antagonist or a PDE5 inhibitor have shown beneficial effects of combination treatment, but there is still much scope for improving the treatment and prognosis of PAH. Although the translation from animal models to PAH has been proven difficult, experimental models of PH have been used to investigate a variety of pharmacological agents with different modes of action. These include agents that are antimitogenic, proendothelial, proangiogenic, anti-inflammatory, and antioxidative.[5] In rodent models of PH, tyrosine kinase inhibitors, multikinase inhibitors, elastase inhibitors, metabolic modulators, survivin inhibitors, and hydroxy-methyl coenzyme A reductase inhibitors have reversed PH.[64] Clinical investigations are also underway on other potential new agents for treating PAH, including serotonin antagonists, vasoactive intestinal peptide, soluble guanylate cyclase stimulators, and tyrosine kinase inhibitors.[65] Future treatment of PAH may involve combinations of established treatments and newer agents.

Strategy

The field of PAH is currently facing several challenges that may endanger further progresses. With eight drugs available on the European market, it is becoming increasingly difficult to finish clinical trials in due time. Most trials recently closed or those still underway are facing slow recruitment rates and delays in delivering results. In addition, most trials reported so far have presented clinical benefits that remain far from being convincing. This may be due to the use of PAH drugs in less expert centers, maybe less familiar with or not involved in clinical research. As a result, the recruitment rate per center has been poor. Another factor impacting the success of clinical trials is associated with the type of trial performed: most if not all are aimed at bringing a new compound on the market, even when done in combination, with a primary endpoint being exercise capacity assessed by the 6MWD and over a rather short observation time (12-18 weeks). In addition, most combination trials (BREATHE 2 excepted[22]) have been performed in a prevalent patient population, less likely to present clinical events, with a sequential approach. A paradigm shift is currently evolving towards strategy trials, for example testing the benefit of an upfront combination, and using a more robust endpoint such as prevention of clinical worsening.

CONCLUSION

PAH is often diagnosed late, resulting in progressive deterioration and premature death. With eight to nine drugs available worldwide and improved management, patients outcome is without a doubt better than previously reported. However, the disease remains incurable: survival in the idiopathic form at 1, 2, and 3 years has recently been reported to reach 85.7%, 69.6%, and 54.9% respectively for newly diagnosed cases.[66] This contrasts significantly with more optimistic survival rates reported in the open-label phase of clinical trials. There is no drug that can cure PAH today, or even modify the disease process.

More than 20 years ago, prostacyclin and its analogs had been a critical breakthrough in the treatment of PAH. These compounds are at the forefront of our current management. They should also be part of future direction that includes an improvement in their mode of delivery and the development of new drugs acting on different targets. This should not obviate the need to improve in our strategy,

including the earlier use of prostacyclins in an upfront combination trial. There is a unique opportunity to perform such a trial in selected centers. As there is a responsibility to find the best for patients, it is now time to make it happen.

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