Epoprostenol and pulmonary arterial hypertension: 20 years of clinical experience

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The evolution of the place of epoprostenol in the management of pulmonary arterial hypertension
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ABSTRACT Epoprostenol was the first therapy to be approved for the treatment of pulmonary arterial hypertension (PAH). In the 20 years since the introduction of this prostacyclin analogue, the outlook for patients with PAH has improved, with survival rates now double those from the era before the development of disease-specific treatments. Today, there are a large amount of data on the clinical role of prostacyclin treatments and a body of evidence attesting the efficacy of epoprostenol in improving exercise capacity, key haemodynamic parameters and PAH symptoms, as well as in reducing mortality. The place of epoprostenol in the therapeutic management of PAH continues to evolve, with the development of new formulations and use in combination with other drug classes. In this review, we provide a historical perspective on the first 20 years of epoprostenol, a therapy that led to evidence-based study of PAH-specific treatments and the subsequent expansion of treatment options for PAH.

Introduction

Pulmonary arterial hypertension (PAH) is a rare, progressive disease associated with significant morbidity [1–4]. The disease is characterised by elevated pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR). Left untreated, PAH leads to right-sided heart failure and premature death [1–4]. In the 1980s, median survival was 2.8 years from diagnosis; the 5-year survival rate was 34% [5]. Although PAH remains incurable, insights into the underlying mechanisms have led to the development of disease-specific treatments that have approximately doubled survival rates [6–8]. Today there are 10 approved PAH-specific therapies [9]. The first of these was the prostacyclin analogue epoprostenol, which was approved in 1995 in the USA before being licensed, a year later, in Europe. This treatment is still regarded as the gold standard to which other therapies should be compared [10–12].

In this review, we take a historical perspective on epoprostenol and its place in PAH management over the past 20 years. We also consider the role of epoprostenol at a time when new formulations that are stable at room temperature are becoming more widely available. This review is based on our knowledge of the field,

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supplemented by a methodical literature search designed to provide a comprehensive historical overview of milestones since the approval of epoprostenol. The literature review comprised searches of a database of PAH pdf files, PubMed, Scopus and the abstract database Searchlight for relevant publications on epoprostenol in PAH using "epoprostenol" and "pulmonary arterial hypertension" as keywords. The period for the PubMed, Scopus and Searchlight searches was 1994 to December 2014 and all English language citations were captured. Titles and abstracts of original articles were manually searched and potentially relevant articles selected; the authors reviewed the resulting publication list and agreed papers of interest. Review articles that capture the historical narrative of the development and study of epoprostenol have been included.

Background

Impact of epoprostenol on PAH treatment

Before the approval of epoprostenol, PAH was treated using a combination of non-specific treatments including warfarin, calcium-channel blockers, digoxin, diuretics and supplemental oxygen. These therapies targeted specific aspects of the disease, but demonstrated little short-term or long-term benefit on major haemodynamic parameters or clinical outcomes (reviewed in [3, 13]), with the exception of long-term calcium channel blockers that improved outcomes in a majority of patients classed using strong criteria such as acute pulmonary vasodilator responders [14]. The introduction of epoprostenol transformed the care of patients with PAH [15]: epoprostenol improved exercise capacity, key haemodynamic parameters and PAH symptoms [16, 17] and, importantly, was the first pharmacological therapy to reduce mortality [18]. Twenty years later, epoprostenol remains the only treatment to have reduced mortality in patients with idiopathic PAH (IPAH) in a randomised study [17].

Early studies of epoprostenol improved our understanding of pulmonary hypertension from associated causes, and led to evidence-based studies of PAH-specific treatments and the subsequent expansion of treatment options for PAH [19, 20]. Lessons learned from studying epoprostenol have informed the development of other inhaled, oral and subcutaneously administered prostanoid therapies. More recently, epoprostenol and some other prostacylins have been shown to be effective and well tolerated when used in combination with other PAH drug classes [21–25]. Therapies previously reserved for patients with severe disease are now being considered for use in those with earlier stage disease, in an attempt to further prolong life and improve patient outcomes [11, 12, 26, 27].

Current recommendations and evolving terminology

The 2015 European Society of Cardiology and European Respiratory Society guidelines for the diagnosis and treatment of pulmonary hypertension outline the continued place of epoprostenol within treatment options for patients with PAH (World Health Organization (WHO) group 1 pulmonary hypertension) [11, 12]. Based on level A evidence of efficacy (data derived from multiple randomised clinical trials or meta-analyses), intravenous epoprostenol is recommended as a class I monotherapy in patients with PAH (WHO group 1) with WHO functional class (FC) III or IV. It should also be considered (class IIa) for use in upfront combination therapy in patients with WHO FC III or IV alongside bosentan, and alongside bosentan and sildenafil, based on level C efficacy evidence (consensus of opinion of experts and/or small studies, retrospective studies and registries) [11, 12]. Today, epoprostenol is approved in many countries including the USA where it is indicated to improve exercise capacity in patients with WHO group 1 pulmonary hypertension (specifically, patients with IPAH, heritable PAH and PAH associated with coexisting conditions such as connective tissue disease (PAH–CTD)) based on studies including predominantly patients with New York Heart Association (NYHA) FC III–IV symptoms [28]. The term IPAH had not been developed at the time of initial approval of epoprostenol; thus, early studies describe patients with primary pulmonary hypertension (PPH) which was the preferred term at this time. Current terminology will be used within this review wherever appropriate. WHO FC and NYHA FC are used interchangeably when characterising patients with PAH.

Early research and discovery

The development of epoprostenol stemmed from the discovery of endogenous prostacyclins in the vasculature by Moncada *et al.* [29] in the 1970s. Soon after this, epoprostenol was synthesised and shown to have anti-platelet activity and vasodilatory effects in humans [30–32]. One of the first patients given epoprostenol was a young, cyanotic, hospitalised and bed-bound woman with IPAH. Intravenous epoprostenol improved haemodynamic parameters and clinical symptoms and the patient was discharged to continue long-term treatment [33]. Another early proof-of-concept study involving seven patients with IPAH showed that epoprostenol increased cardiac output and reduced PAP and PVR [34]. These and other early explorations preceded the innovative clinical studies that led to the first approval of epoprostenol for the treatment of patients with IPAH in 1995 [16, 17].

Epoprostenol in profile

Pharmacology

Epoprostenol is a synthetic analogue of the naturally occurring eicosanoid prostacyclin (prostaglandin I_2 or PGI2), which is the main metabolite of arachidonic acid [30, 35]. Endogenous prostacyclin is produced predominantly by endothelial cells and acts both on local vasculature and on blood cells that adhere to the endothelium [26]. In PAH, the normal release of endogenous prostacyclin is depressed and release of the vasoconstrictor thromboxane A_2 is increased [36]. In addition, pulmonary endothelin-1 homeostasis is abnormal, and this may contribute to the progressive rise in PVR that typifies PAH [37].

Prostacyclins (and related prostanoids) have direct and potent vasodilatory effects resulting from their action on vascular smooth muscle cells; they inhibit platelet aggregation and thrombus formation, and have antiproliferative and anti-inflammatory actions (figure 1) [26, 38]. These effects are mediated *via* G-protein-coupled prostanoid IP receptors in blood vessels, leukocytes and thrombocytes [26]. Epoprostenol may also have indirect vasodilatory effects owing to inhibition of production of the potent vasoconstrictor endothelin-1 [39]. In patients with PAH, therapeutic use of prostanoids is associated with immediate vasodilatory action in the pulmonary and systemic circulation and resultant, longer-term haemodynamic changes that contribute to additional decreases in PVR [26]. It has been suggested that indirect positive inotropic effects of therapy may also ameliorate systemic hypotension [26]; however, such effects have not been established in any model of chronic pulmonary hypertension, and the effect of epoprostenol in chronic pressure overload on the right ventricle remains unknown.

The pharmacokinetic properties of the original formulation of epoprostenol are dominated by the lability of the molecule in aqueous fluids at physiological temperature and pH. Epoprostenol has a short elimination half-life of approximately 3–6 min in human blood, which necessitates administration *via* continuous intravenous infusion [15]. Treatment has to be initiated by an experienced physician, and long-term use requires a permanent central venous catheter and portable infusion pump [11, 12].

Clinical studies with epoprostenol in the treatment of PAH

Today there is substantial evidence from randomised controlled trials (RCTs) supporting the use of prostacyclin treatments in PAH, while data from observational studies and registries provide real-world evidence and experiences of patient management (for reviews see [6, 40]). Table 1 provides an overview of key studies that have contributed to our understanding of the clinical profile of epoprostenol.

RCTs with epoprostenol in PAH

Epoprostenol was initially approved for use in patients with "PPH and moderate-to-severe functional status", based on data from two RCTs [16, 17]. The first studied 24 patients with IPAH (NYHA FC II–IV), randomised to receive either intravenous epoprostenol or the conventional treatment of the time for 8 weeks [16]. Epoprostenol was associated with a significant and sustained decrease in total pulmonary resistance (–7.9 units; p=0.022) but there was no change for patients on conventional treatment (–0.2 units), and six out of 10 patients in the epoprostenol group compared with only one out of nine patients in the conventional treatment group had reductions in mean PAP (mPAP) of greater than 10 mmHg. This study also reported that continued epoprostenol treatment for up to 18 months was associated with

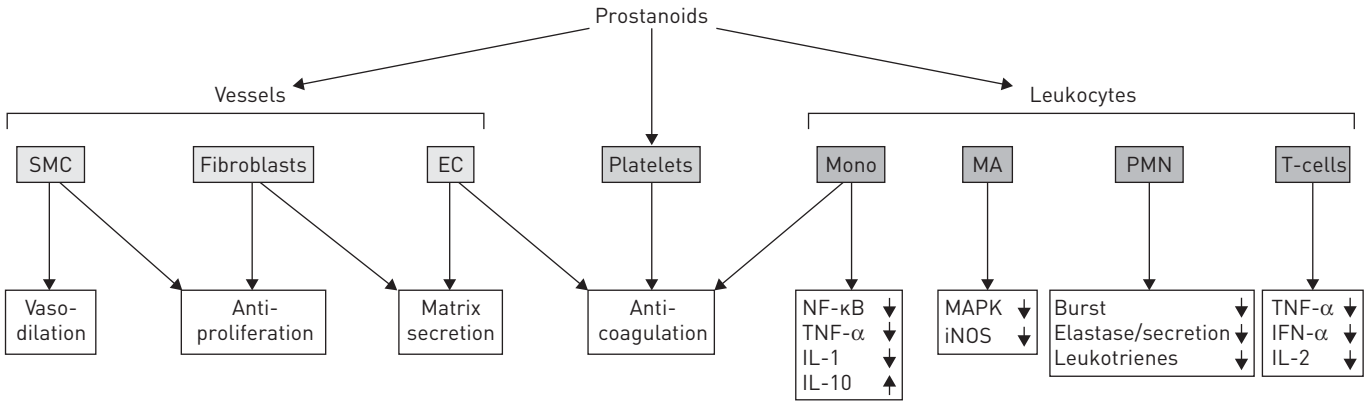

FIGURE 1 The effects of prostanoids on vasculature and blood cells; a variety of vascular cells, platelets and leukocytes have been identified as targets for the antiproliferative, anti-inflammatory and anti-aggregatory actions of prostaglandins. SMC: smooth muscle cells; EC: endothelial cells; Mono: mononuclear cells; NF: nuclear factor; TNF: transforming nuclear factor; IL: interleukin; MA: macrophages; MAPK: mitogen-activated protein kinase; iNOS: inducible nitric oxide synthase; PMN: polymorphonuclear neutrophils; Burst: generation of reactive oxygen species. Reproduced from [38] with permission from the publisher.

TABLE 1 Overview of key studies that have contributed to our understanding of the clinical profile of epoprostenol

Study, first author year [ref.]	Aetiology of PAH	Study design	Treatments/intervention	Patient characteristics	Efficacy assessments/ primary endpoint and key outcomes	PVR changes	Safety data
Early studies in patients with PAH							
Rubin 1982 [34]	IPAH	Exploratory study	Dose-ranging protocol (starting dose 2 ng·kg^{-1}·min^{-1} to maximum 12 ng·kg^{-1}·min^{-1}) and continuous *i.v.* epoprostenol in three patients for up to 48 h	Seven patients	mPAP decreased in six out of seven patients and total pulmonary resistance decreased by >20% in all patients; cardiac output and stroke volume increased by >40%	Total pulmonary resistance 17.1±8.7 units at baseline *versus* 9.7±5.9 units following epoprostenol infusion (mean±SD)	Headache (n=6); nausea (n=4); vomiting (n=2); cutaneous flushing (n=5); diplopia (n=1, resolved on discontinuation); systemic hypertension during dose-ranging (n=2; resolved on discontinuation); temporary significant reduction in systemic blood pressure during continuous infusion (n=1)
Higenbottam 1983 [33]	IPAH	Case: first report of long-term *i.v.* epoprostenol therapy	Continuous *i.v.* epoprostenol 4–20 ng·kg^{-1}·min^{-1}	Woman with uncontrolled post-partum PH	Decreased PVR, improved oxygenation and exercise tolerance allowed patient to live independently at home	PVR fell from baseline 25–30 units to 15 units; values maintained over 10 months	Sterile pleural effusion ascites (treated with diuretics); cannula-associated *Staphylococcal* bacteraemia (resolved by cannula change)
Key RCTs in patients with PAH							
Rubin 1990 [16]	IPAH	8-week RCT with an 18-month non-RCT extension	Continuous *i.v.* epoprostenol (starting dose 1–2 ng·kg^{-1}·min^{-1}) *versus* conventional treatment (optimum doses of oral vasodilators, anticoagulants, supplemental oxygen, cardiac glycosides and diuretics)	24 patients (NYHA FC II–IV)	Epoprostenol significantly decreased total pulmonary resistance after 8 weeks (decrease of 7.9 units from baseline of 21.6 units) (p=0.022) *versus* conventional therapy (decrease of 0.2 units from baseline of 20.6) (non-significant). Six out of 10 patients receiving epoprostenol showed >10 mmHg reductions in mPAP *versus* one out of nine patients on conventional treatment (p=0.057). Haemodynamic improvements were maintained over 18 months in nine patients	Total pulmonary resistance significantly decreased on epoprostenol	Loose stools (100%), jaw pain (57%) and photosensitivity (36%) were common with epoprostenol. One patient discontinued owing to pulmonary oedema; most complications were linked with the drug-delivery system

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TABLE 1 Continued

Study, first author year [ref.]	Aetiology of PAH	Study design	Treatments/intervention	Patient characteristics	Efficacy assessments/ primary endpoint and key outcomes	PVR changes	Safety data
Barst 1996 [17]	IPAH	12-week, prospective, multicentre, open-label RCT	Continuous *i.v.* epoprostenol (starting dose 2 ng·kg^{-1}·min^{-1} to maximum tolerated dose of 9.2±0.5 ng·kg^{-1}·min^{-1}) plus conventional treatment (anticoagulants, oral vasodilators, diuretic agents, cardiac glycosides and supplemental oxygen) *versus* conventional treatment alone	81 patients with severe disease (NYHA FC III–IV)	Exercise capacity by 6MWD (primary endpoint): patients on epoprostenol (n=41) showed improvements in median change in distance walked from baseline to week 12 (median increase, 31 m; median distance of 315 m at baseline, 362 m at 12 weeks) *versus* conventional therapy (median decrease, 29 m; median distance of 270 m at baseline, 204 m at 12 weeks) (p<0.002, nonparametric analysis). Mean distance walked increased by 32 m in the epoprostenol group (316 m at baseline; 348 m at week 12) and decreased by 15 m in the conventional therapy group (272 m at baseline; 257 m at week 12) (p<0.003, parametric analysis). mPAP changes: −8% for epoprostenol *versus* +3% for conventional therapy (difference in mean change, −6.7 mmHg; 95% CI, −10.7 to −2.6 mmHg; p<0.002). Indices of HRQoL improved in the epoprostenol group (p<0.01). Eight deaths in conventional therapy group *versus* no mortality in epoprostenol group (p=0.003)	mPVR changes of −21% for epoprostenol *versus* +9% for conventional therapy (difference in mean change: −4.9 mmHg·L^{-1}·min^{-1}; 95% CI: −7.6 to −2.3; p<0.001)	Jaw pain, diarrhoea, flushing, headaches, nausea and vomiting were frequent. Four episodes of catheter-related sepsis; one thrombotic event. Delivery system-related issues included device malfunction (n=26) and irritation/ infection (n=7), bleeding (n=4) and pain (n=4) at catheter site
Badesch 2000 [18]	PAH secondary to scleroderma	12-week, prospective, multicentre, open-label RCT	Continuous *i.v.* epoprostenol (starting dose ⩽2 ng·kg^{-1}·min^{-1} to mean dose 11.2 ng·kg^{-1}·min^{-1} at week 12) plus conventional treatment *versus* conventional treatment alone	111 patients with moderate-to-severe disease	Exercise capacity by 6MWD (primary endpoint): patients on epoprostenol (n=56) showed improvements from baseline (median, 270 m) to week 12 (316 m) *versus* conventional therapy (240 m at baseline; 192 m at week 12) (difference in median distance walked, 108 m, 95% CI, 55.2–180.0 m, p<0.001). Change from baseline in mPAP: epoprostenol, −5.03±1.09 mmHg *versus* conventional therapy, +0.94±1.10 mmHg (difference between groups, −5.97 mmHg; 95% CI, −8.98 to −2.96). 21 patients on epoprostenol *versus* zero patients on conventional therapy showed improvements in NYHA FC	PVR change from baseline: epoprostenol −4.58 ±0.76 mmHg·L^{-1}·min^{-1} *versus* conventional therapy 0.92±0.56 mmHg·L^{-1}·min^{-1} (mean±SE) (difference, −5.50 mmHg·L^{-1}·min^{-1}; 95% CI, −7.33 to −3.67)	Jaw pain (75% *versus* 0%), anorexia (66% *versus* 47%), nausea (41% *versus* 16%), diarrhoea (50% *versus* 5%) and depression (13% *versus* 4%) more common in epoprostenol *versus* conventional therapy group, respectively. Drug-delivery system associated with eight catheter-related AEs, including sepsis, cellulitis, haemorrhage and pneumothorax (4% each)

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