Prostacyclins

Horst Olschewski

Abstract Prostacyclins have a favourable pharmacological profile for treatment of pulmonary hypertension as they possess vasodilative, antiproliferative, anti-aggregatory, and anti-inflammatory properties that may compensate the main pathologic changes in the small pulmonary arteries. In severe pulmonary hypertension these vessels show a deficit in the endogenous prostacyclin secretion. The therapeutic potential of prostacyclin for pulmonary hypertension has been known since 30 years, and since nearly 20 years prostacyclin has been approved for idiopathic PAH. There are intravenous, subcutaneous, and inhaled approaches of different substances who share many but not all pharmacologic properties. However, none of these approaches are easy and free of adverse effects. Long-term experience and careful decision-making are instrumental to achieve favourable clinical long-term results.

Keywords Prostacyclin • Epoprostenol • Iloprost • Treprostinil • Beraprost • Selexipag

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1 Introduction

Prostacyclin and its stable analogues possess a chemical prostaglandin structure and preferentially bind to the prostaglandin I (IP) receptor. Prostacyclins are potent vasodilators and possess antithrombotic, antiproliferative, and anti-inflammatory properties. They also reduce matrix secretion in smooth muscle cells (SMC), endothelial cells, and fibroblasts (Fig. 1). The endothelial cells are the major source of endogenous prostacyclin. Due to the short half-life, the prostacyclin action will be directed both on the local vascular wall and on passing blood cells that get in contact with the endothelium. Pulmonary arterial hypertension (PAH) is associated with vasoconstriction, thrombosis, proliferation, inflammation, and a lack of endogenous prostacyclin secretion. This provides a strong rationale for prostacyclin use as therapy for PAH.

2 History of Prostacyclin and Analogues

Endogenous prostacyclin was discovered in 1976 (Moncada et al. 1976). In the same year, prostacyclin was chemically synthesised (epoprostenol) and investigated in animals and humans (Gryglewski 1980). Chemically stable analogues were synthesised in the 1980s. Clinical studies in PAH patients were performed with epoprostenol, iloprost, beraprost, and treprostinil while cicaprost, a highly specific IP-receptor agonist, was not clinically developed.

The first applications of prostacyclin in pulmonary hypertension were published in 1980 (O'Grady et al. 1980) and the first long-term therapy for severe idiopathic pulmonary arterial hypertension (PAH) was applied in 1984 (Higenbottam et al. 1984). Despite many new developments in PAH therapy, prostacyclins remain a mainstay in the treatment of PAH.

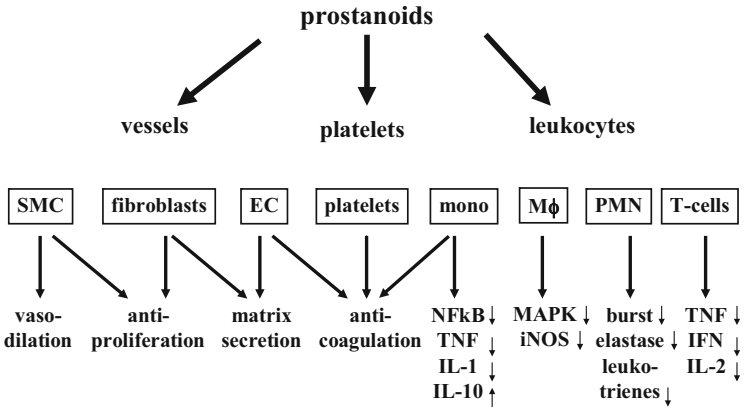

Fig. 1 Effects of prostacyclins on the vessel wall and adherent blood cells. *SMC* smooth muscle cells; *EC* endothelial cells; *mono* mononuclear cells; *MΦ* macrophages; *PMN* polymorphonuclear neutrophils; *T-cells* T-lymphocytes; *TNF* transforming nuclear factor α; *IL* interleukin; *MAPK* mitogen-activated protein kinase, burst, generation of reactive oxygen species, elastase, elastase secretion; *IFN* interferon γ. From Olschewski et al. (2001b)

3 Pharmacologic Properties

The main target of prostacyclin and its analogues is the human IP receptor which is abundantly expressed in blood vessels, leucocytes, and thrombocytes and is rapidly activated by binding of the ligand. The IP receptor in small animals is much less sensitive to prostacyclin as the human receptor. Therefore predictions about dose-response relationships based on such animal models may not be reliable. The IP receptor is coupled with Gs proteins and activates adenylate cyclase, leading to increased cAMP levels in the target cells which explain most of the biologic effects. Principally, it also couples with Gq proteins and might activate vasoconstrictive pathways under certain instances (Chow et al. 2003; Wise 2003). In addition, prostacyclin and analogues are not highly specific to the IP receptor but may also activate EP receptors (Abramovitz et al. 2000) which are located on the cell surface as well as in the nucleus (Bhattacharya et al. 1998, 1999). They may further activate the peroxisome proliferator-activated receptor delta (PPARδ) (Gupta et al. 2000). Both PPARα and PPARδ may also be activated via IP receptor-dependent PKA activation, but the intracellular prostacyclin produced by the endogenous PGI synthase seems to specifically activate the apoptosis pathway by activation of PPARδ (Hatae et al. 2001) (Fig. 2). There is evidence that PPARδ is also involved in the acute signalling in prostacyclin-induced vasodilatation (Li et al. 2012). Specifically, prostacyclins activate the most important potassium channels, the TWIK-related acid-sensitive potassium channel (TASK1) and the calcium-activated potassium channel (KCA) and thereby cause membrane hyperpolarization and inhibition of L-type calcium channels in SMCs. Figure 3 represents the current knowledge about the mechanisms underlying the powerful activation of potassium current

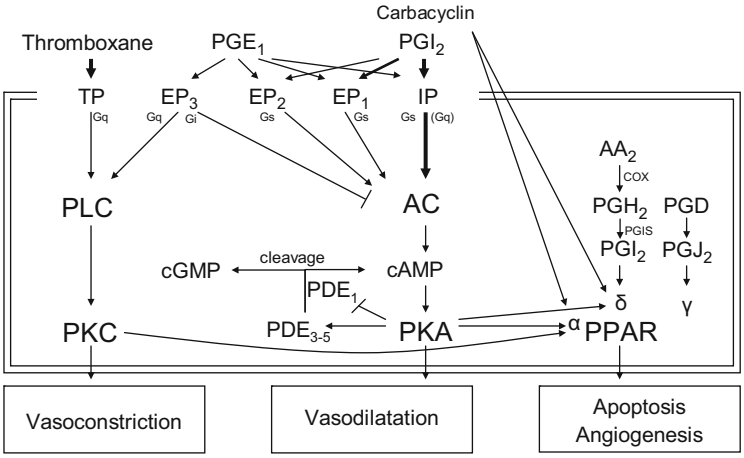

Fig. 2 Intracellular targets of prostacyclin. Extracellular PGI_2 mainly but not specifically acts on the IP receptor and the EP1 receptor while PGE1 is more specific to EP receptors. *Gs, Gq, and Gi* G-proteins, *PLC* phospholipase C, *PKC* proteinkinase C, *AC* adenylyl-cyclase, *PKA* protein kinase A, AA_2 arachidonic acid, *COX* cyclooxygenases 1 and 2, PGH_2 protaglandin H_2, *PGIS* prostacyclin synthase, *PPAR* peroxisome proliferator-activated receptors, *PGD* prostaglandin D, PGJ_2 prostaglandin J_2, *PDE* phosphodiesterases. From Gomberg-Maitland and Olschewski (2008)

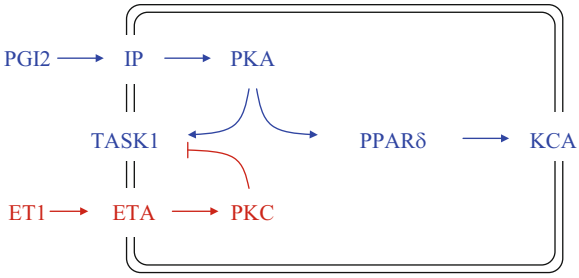

Fig. 3 Prostacyclin-induced activation of potassium channels prostacyclin (PGI2) activates proteinkinase A (PKA) via IP receptors of the cell membrane. PKA activates both the TWIK-related acid-sensitive K channel (TASK1) and the calcium-activated potassium channel (KCA). The activation of KCA is critically dependent on activation of PPARδ, while TASK1 activation is independent of PPARδ. Endothelin1 (ET1) counteracts the activation of TASK1 via proteinkinase C (PKC) activation. Data from Li et al. (2012) and Tang et al. (2009)

from TASK1 and KCA channels by prostacyclin and the opposite effects of endothelin-1 (Tang et al. 2009). In human pulmonary arterial smooth muscle cells, TASK1 is the only active potassium channel at physiologic membrane potential and is therefore mainly responsible for the negative membrane potential which provides a low vascular tone (Olschewski et al. 2006). It has recently been shown that TASK1 activity depends on both oxygen and src tyrosine kinase activity (Nagaraj et al. 2012).

3.1 Differences Between Prostacyclin Analogues

Epoprostenol is provided as a dry powder with a highly basic glycine buffer as a solvent drug. After mixing drug powder with the solvent, the solution has to be used within 12–24 h due to spontaneous degradation of the compound. A new formulation that was FDA approved in 2009 (Veletri®) allows for 48 h use at 25 °C and 5 days of storage at 2–8 °C. All other prostanoids are chemically stable in solution and their plasma half-life is much longer. It is about 30 min with iloprost and beraprost and up to 4.5 h with treprostinil. Vein irritation is common to all prostanoids. All stable prostanoids have been provided as oral preparations; however, only beraprost has received approval for PAH in Japan and some Eastern countries (see below). Iloprost has been approved as inhalative therapy and treprostinil as subcutaneous infusion or intravenous infusion or inhalation (see below). The doses that are needed for strong vasodilative effects differ considerably among prostanoids. A continuous intravenous dose of 50 ng/kg/min of epoprostenol is, on average, translated into 100 ng/kg/min of treprostinil but just 3 ng/kg/min of iloprost. The reasons for these huge differences are not known.

Apart from differences in pharmacokinetics and pharmacodynamics, there may be other specific differences between the prostacyclin analogues. The antiproliferative effects of treprostinil appeared more impressive than those of other compounds (Clapp et al. 2002), but due to differences in chemical stability such results must be interpreted with caution. Non-IP-receptor effects of prostacyclin analogues have attracted some interest in tumour biology (Keith and Geraci 2006) and might be interesting for pulmonary hypertension as well. Iloprost and cicaprost were found to have different effects in the murine corneal model of angiogenesis. While iloprost caused significant angiogenesis, comparable to VEGF, cicaprost had no such effects (Pola et al. 2004). The explanation may be that iloprost and carbacyclin but not cicaprost activate peroxisome proliferator-activated receptors (PPAR) (Reginato et al. 1998), which results in VEGF secretion (Forman et al. 1995; Barger 2002). VEGF increase may antagonise endothelial dysfunction and represents a potential beneficial factor (le Cras et al. 2002; Taraseviciene-Stewart et al. 2001).

Some effects have only been described in one of the compounds but may be common to all prostacyclin analogues. Treprostinil augments the positive inotropic effects of catecholamines in isolated ventricular myocytes (Fontana et al. 2007), although it has no positive inotropic effects of its own. This effect may have clinical relevance because during right heart failure there is an increased catecholamine drive. These effects may add on indirect effects that originate from systemic vasodilation and subsequent baroreflex activation (Fig. 4) and improved ventriculoarterial coupling (Kerbaul et al. 2007).

Iloprost suppresses neutrophil adhesion, respiratory burst, and elastase secretion (Rose et al. 2003). This may be important because inflammation appears to play a role among the pathologic mechanisms of pulmonary arterial hypertension (Stacher et al. 2012). In SMC, a number of beneficial changes in gene expression

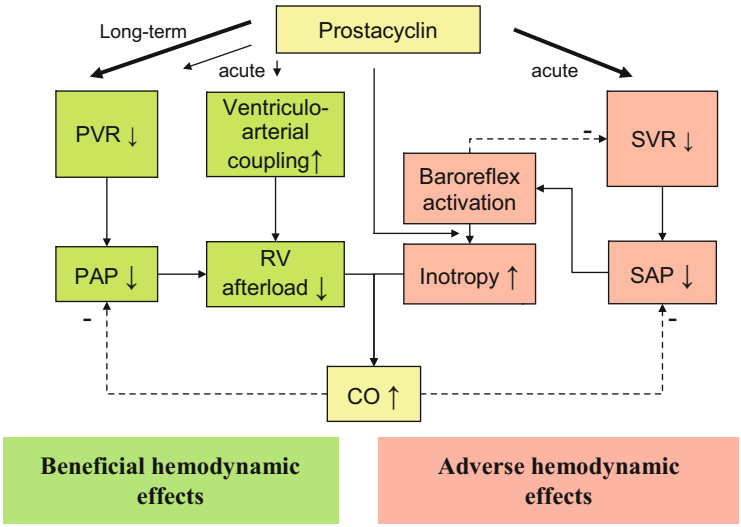

Fig. 4 Hemodynamic effects of systemically applied prostacyclins or its analogues. Within minutes, prostacyclins cause a strong vasodilatation which in most patients is more prominent on the systemic (SVR) compared to the pulmonary vascular resistance (PVR). The decrease in systemic pressure (SAP) activates the arterial baroreflex which increases SVR and has positive inotropic effects. The reduction in PVR would decrease pulmonary arterial pressure (PAP); however, in the acute phase, the increase in cardiac output counteracts this resulting in an unchanged PAP. Within weeks, PVR decreases more prominently and SVR does not further decrease which may result in a significant PAP decrease. For ventriculoarterial coupling and inotropic effects of prostacyclin, see text. Adapted from Olschewski and Olschewski (2011)

(hyaluronidonic acid, COX 2, and VEGF upregulation; monocyte chemotactic protein and plasminogen activator inhibitor-1 downregulation) were shown after incubation with iloprost (Meyer-Kirchrath et al. 2004; Sussmann et al. 2004). If we consider that endothelial dysfunction or damage may play a major role in the pathologic development of pulmonary artery remodelling, this translates into a number of beneficial effects of iloprost (Fig. 5).

3.2 Hemodynamic Effects

The hemodynamic effects and the associated side effects of all prostacyclin analogues are similar while the mode of application and the applied doses differ. In the case of continuous intravenous infusion there is a relatively fast dose increase with systemic prostacyclin analogues over the first weeks, followed by a gradual dose increase over many months. Interestingly, there is no loss of pharmacological effect if the infusion rate is adequately adapted. The doses for epoprostenol typically start at 4 ng/kg/min and increase to about 20–60 ng/kg/min after a year.

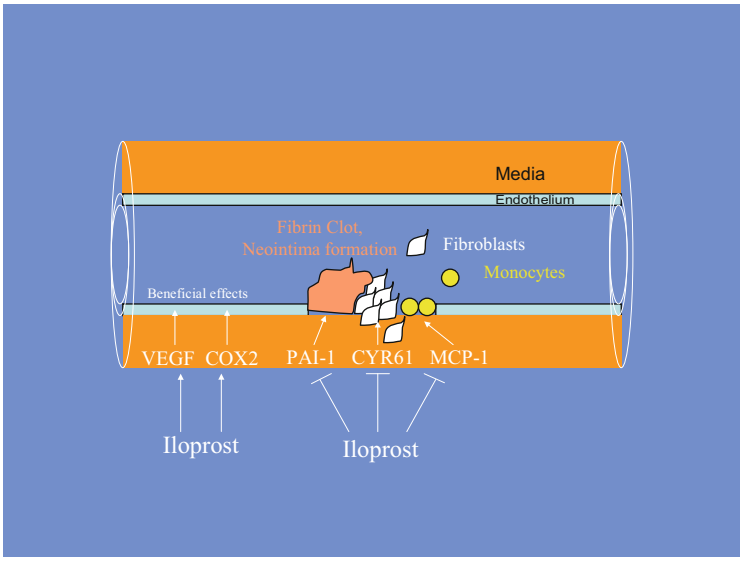

Fig. 5 Hypothesis for neointimal formation and possible role of prostacyclins. After endothelial damage, monocytes, fibroblasts, and the coagulation system will form a neointima, which leads to intima fibrosis. Iloprost has been shown to inhibit the mRNA expression of important mediators of these processes. *VEGF* vascular endothelial growth factor, *COX2* cyclooxygenase 2, *PAI-1* plasminogen activator inhibitor, *Cyr 61* cysteine-rich angiogenic protein, *MCP-1* monocyte chemotactic protein. From Gomberg-Maitland and Olschewski (2008)

In the majority of patients, the beneficial hemodynamic effects, characterized by a significant decrease in pulmonary vascular resistance, will occur after some days of therapy; however, they may be obscured by systemic side effects. It takes several weeks until the patient will fully anticipate the beneficial effect of the drug because the pulmonary effects become more and more prominent while the systemic side effects fade away.

If the prostacyclin analogues are applied by inhalation every 2–3 h, there is no need for dose increase in the majority of patients (Olschewski et al. 1996, 2000, 2003, 2010), suggesting that this mode of application may not cause receptor desensitisation.

4 Clinical Application

4.1 Epoprostenol: Intravenous

Continuous intravenous prostacyclin (epoprostenol) was the first therapy for idiopathic and heritable PAH. Case reports and small case series (Higenbottam

et al. 1984; Weir et al. 1989; Rubin et al. 1982) demonstrated improvement in symptoms and hemodynamics and were followed by a prospective, randomised open-label controlled trial (Barst et al. 1996) for 12 weeks. The 6 min walk distance (6MWD) improved by 32 m in the epoprostenol group compared with a decrease of 15 m in the control group. The mean pulmonary vascular resistance decreased by 21 % in the epoprostenol group vs. an increase of 9 % in the conventional group. This study also suggested a survival benefit as those eight patients who died during the 12-week trial were all in the conventional therapy group.

Long-term effects of epoprostenol have never been compared with placebo because this is considered unethical due to the substantial treatment benefit after 3 months of therapy. Observational cohort analyses comparing the survival of epoprostenol-treated IPAH and HPAH patients with historical controls suggested long-term benefits (McLaughlin et al. 2002; Sitbon et al. 2002).

In scleroderma-associated PAH, intravenous epoprostenol improved exercise capacity (Badesch et al. 2000). Similar improvements in functional capacity and functional class have been seen in subjects with congenital left-to-right cardiac shunts (Rosenzweig et al. 1999) and infection with the human immunodeficiency virus (HIV) (Nunes et al. 2003; Aguilar and Farber 2000) while results are ambiguous in portopulmonary hypertension (Krowka and Swanson 2006) and show unfavourable effects in pulmonary hypertension secondary to left heart failure (Califf et al. 1997).

Increasing use of epoprostenol was associated with a considerable decrease in the number of lung transplantations for pulmonary hypertension. A US survey indicated that treatment with epoprostenol allowed two-thirds of subjects to deactivate from the transplant list (Robbins et al. 1998). It is unclear how long the disease will remain stable and therefore frequent clinical follow-up with examination, exercise, and hemodynamics is recommended (Badesch et al. 2007; Galie et al. 2009).

4.1.1 Combination with Other PAH Medication

In the BREATHE 2 study, subjects with PAH were started on epoprostenol with uptitration for 16 weeks and randomised in a 2:1 ratio to bosentan or placebo (Humbert et al. 2004). Addition of bosentan caused a trend, but no significant benefit in clinical or hemodynamic measurements.

Simonneau et al. reported the results of a 16-week multinational, double-blind, placebo-controlled trial assessing the safety and efficacy of sildenafil in addition to epoprostenol (PACES) (Simonneau et al. 2008). Patients had improvements in exercise capacity (adjusted increase 26 m, $p < 0.001$), hemodynamics, and time to clinical worsening in favour of sildenafil. The long-term open-label extension at 1 year maintained this benefit.

4.1.2 Limitations of Intravenous Epoprostenol

Limitations are mainly based on the pharmacology of epoprostenol with its chemical instability and extremely short half-life after infusion. Long-term administration of epoprostenol requires a permanent central venous catheter and a portable infusion pump. Conventional medication needs to be prepared daily and to be kept cold, requiring ice packs to be worn with medication in 24 h cassettes. The new formulation provides more stability after dissolving the drug, but the plasma half-life remains unchanged.

Patients need education of sterile techniques, operation of the pump, taking care of the catheter, and a strong support system to help ensure a safe environment prior to initiation. A "caregiver," a family member, or a friend who lives in close proximity to the patient is strongly recommended to obviate problems if the subject is too ill or unable to prepare medication on a given day. Serious complications include infection and thrombosis of the catheter and temporary interruption of the infusion because of inadvertent disconnection or pump malfunction. The incidence of catheter-related sepsis ranges from 0.04 to 0.6 cases per patient-year in experienced centres (Sitbon et al. 2002; Humbert et al. 1999; Kitterman et al. 2012) but may be much higher in less experienced centres.

Side effects are usually well tolerated, provided the dose is uptitrated at an adequate rate. The most common side effects include flushing, headache, nausea, loose stool, jaw pain, and foot pain and ascites (Barst et al. 1996; McLaughlin et al. 2002; Sitbon et al. 2002). While jaw pain is mostly transient and well tolerated, foot pain and ascites may deteriorate physical activity and quality of life.

4.2 Iloprost: Intravenous

Intravenous iloprost has been approved for pulmonary hypertension in New Zealand, but it has also been used in other countries like Germany, Switzerland, England, Australia, Thailand, Israel, Argentina, and Brazil. Intravenous iloprost has similar acute hemodynamic effects as epoprostenol (Higenbottam et al. 1998). It comes as concentrated solution in glass ampoules and does not require cooling. Due to its longer half-life it is less risky in the case of accidental therapy disruption. In Europe, the typical starting dose is 0.5 ng/kg/min and the long-term dose of infused iloprost is mostly 3 ng/kg/min (Ewert et al. 2007). In a few cases doses up to 10 ng/kg/min were applied. It has not been formally tested if infused iloprost has the same clinical efficacy as infused epoprostenol or treprostinil.

4.3 Treprostinil: Intravenous

The FDA approved the use of intravenous treprostinil for patients who do not tolerate subcutaneous treprostinil therapy. The advantage over epoprostenol is the chemical stability and the longer half-life that may also decrease the risk of rebound pulmonary hypertension in case of inadvertent cessation of the infusion. When patients transitioned from IV epoprostenol to IV treprostinil they finished on more than twice the dose of treprostinil compared with epoprostenol (Gomberg-Maitland et al. 2005a; Sitbon et al. 2007). It is unclear why a higher treprostinil dose is required compared to epoprostenol as, theoretically, its longer half-life would suggest the opposite. There were significantly more septic events with treprostinil as compared to epoprostenol in the USA; particularly the number of gram-negative sepsis episodes was increased (Kitterman et al. 2012). This might be associated with the different pump system, the slower infusion rate, or pharmacologic effects of the drug. There was no indication that the drug itself was contaminated.

4.4 Treprostinil: Subcutaneous

Treprostinil was originally approved as subcutaneous (sc) infusion. Subcutaneous therapy avoids a permanent central venous catheter. Medication is infused via a small self-inserted sc needle with continuous injection by syringe by a battery-driven pump. The infusion site should be changed every 3–4 days according to the package insert. In clinical practice patients often leave sites for 2–4 weeks (Lang et al. 2006). The drug comes as a ready-to-use solution and there is no need for cooling. The most common side effect occurring in up to 85 % of the patients is local infusion site pain (Simonneau et al. 2002). Patients are treated with variable response with a combination of local anaesthetic solutions, nonsteroidal anti-inflammatory agents, gabapentin, pregabalin, or low-dose narcotics. The pain does not appear to be dose related and cannot be predicted before therapy starts.

Class IV patients and patients receiving higher doses of treprostinil had a more significant improvement. There was also an improvement in hemodynamic parameters, including right atrial pressure, mean pulmonary artery pressure, pulmonary vascular resistance, and cardiac output. The drug was FDA approved for the treatment of NYHA class II–IV PAH patients in 2002 and EMA approved for PAH NYHA III in 2005.

Recent retrospective and observational studies of sc treprostinil suggest long-term clinical improvement and survival benefits. Lang and colleagues evaluated clinical outcomes in 99 PAH patients and 23 patients with inoperable chronic thromboembolic pulmonary hypertension for a mean follow-up of 26 $\pm$ 17 months in the open-label phase of a randomised clinical trial (Lang et al. 2006). The mean dose was 40 $\pm$ 3 ng/kg/min (range 16–84 ng/kg/min). Patients maintained their improved exercise tolerance (6MWD) and FC at 3 years. Event-free survival was

83 % at 1 year and 69 % at 3 years and overall survival was 89 % at 1 year and 71 % at 3 years, similar rates to those observed on iv epoprostenol.

Evaluation of all patients who had been enrolled in randomised controlled trials with open-label extension and available long-term observations revealed 860 patients who were treated for up to 4 years (Barst et al. 2006). Survival in patients on monotherapy censoring patients with the addition of targeted PAH therapy (130 patients) or premature discontinuation due to adverse events (199 patients) was 88, 79, 73, and 70 % at 1, 2, 3, and 4 years, respectively; however, only few patients remained on therapy for more than 2 years. The most frequently reported side effect was site pain.

Addition of sildenafil to sc treprostinil improved exercise capacity (6MWD) and functional class (Gomberg-Maitland et al. 2005b) and the same was found for the addition of sildenafil to inhaled treprostinil (Voswinckel et al. 2008).

4.4.1 Treprostinil Oral

The oral form of treprostinil is an extended release formulation. This therapy had a significant benefit in treatment-naïve PAH patients (FREEDOM-M) but no significant effect in patients on other targeted PAH medications (FREEDOM-C). Recently, the FDA decided not to approve oral treprostinil based on the moderate effects on 6 min walk distance and no evidence for a delay in clinical worsening achieved in the FREEDOM trials.

4.5 Beraprost: Oral

Beraprost is absorbed rapidly after oral administration and has an elimination half-life of 20–40 min. In Europe, 130 FC II and III subjects were enrolled in a 12-week randomised double-blind placebo-controlled trial of beraprost (Galie et al. 2002). Subjects had pulmonary arterial hypertension caused by IPAH, connective tissue diseases, congenital left-to-right shunts, portal hypertension, and HIV. At a median dose of 80 μg, four times daily, the 6MWD improved by 25 m, compared to placebo ($p = 0.04$). Subjects with IPAH had a mean increase of 46 m whereas PAH from other causes had no significant improvement. In the USA, PAH patients in functional class II and III were included in a 12-month study. The 6 min walk distance improved at 3 and 6 months compared with placebo, but this benefit was not sustained at 9 and 12 months (Barst et al. 2003). Beraprost has not been approved in the USA and Europe but is approved in Japan and several other Far East countries.

4.6 Selexipag

Selexipag is a non-prostanoid substance that specifically activates the IP receptor (Morrison et al. 2012). It has been investigated in a phase II study and had significant hemodynamic effects and side effects as expected for a prostacyclin analogue (Simonneau et al. 2012). Currently, a phase III study is performed.

4.7 Iloprost: Inhaled

The lung anatomy allows direct access to the precapillary vessels of the lung via drug deposition in the alveolar space or the surface of the bronchiolus terminalis (Fig. 6). Inhalation of prostacyclin as compared to infusion was shown to provide intrapulmonary selectivity and pulmonary selectivity with less systemic side effects (Olschewski et al. 1996, 2003; Walmrath et al. 1993, 1996). The inhalative approach was used with epoprostenol from the early 1990s, with iloprost from 1994 and with treprostinil from 2003.

When iloprost is delivered by different appropriate nebulizers, the pharmacodynamic and pharmacokinetics applied by the same dose are very similar (Olschewski et al. 2003). To ensure alveolar deposition, the delivery system produces small aerosolized particles with a median diameter of 3.0–5.0 μm. Iloprost must be inhaled six to nine times a day to achieve good clinical results. The inhaled doses for significant clinical effects were much smaller with inhaled iloprost (about 0.31 ng/kg/min) (Olschewski et al. 2002), compared to the intravenous infusion of iloprost for PAH.

Inhaled iloprost was approved for PAH, NYHA III + IV in the USA; for PAH, NYHA III and IV as well as inoperable CTEPH in Australia; and for IPAH, NYHA III in Europe. In the European study patients with IPAH, HPAH, PAH associated with connective tissue diseases, or inoperable CTEPH in FC III or IV were enrolled in a 12-week multi-centre placebo-controlled trial (Olschewski et al. 2002). The primary endpoint was a combined clinical endpoint where four criteria had to be met to be counted as a responder: a 10 % increase in 6MWD, an improvement in NYHA functional class, no deterioration, and no death. Seventeen percent of patients on iloprost reached this endpoint compared with 4 % in the placebo group ($p = 0.007$). The mean increase in 6MWD was 37 m ($p = 0.004$) and 59 m amongst subjects with primary pulmonary hypertension. Subjects' well-being improved as evidenced by quality of life scores and the Mahler dyspnea index. Hemodynamic trough values (before inhalation) at 12 weeks improved slightly but significantly in the treatment group compared with placebo ($p < 0.001$). There was a major improvement when post-inhalation values were considered. Side effects consisted of symptoms related to systemic vasodilation. More syncopal episodes (8 vs. 5, NS) occurred in the iloprost group, although they were not associated with clinical deterioration.

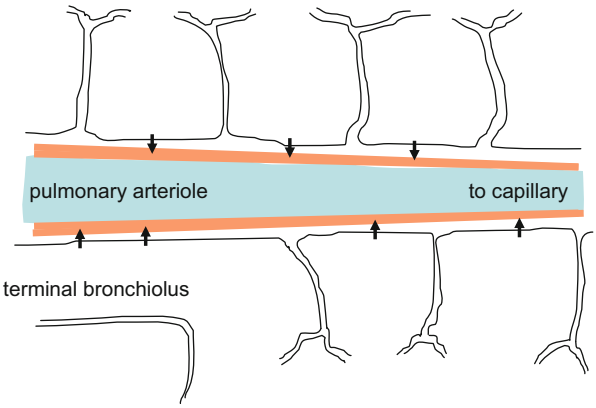

Fig. 6 The inhaled route of application for prostacyclin or its analogues. *Black arrows* mark areas where locally deposited drug penetrates the airway wall and diffuses into the pulmonary artery wall. From Gomberg-Maitland and Olschewski (2008)

Iloprost also improved hemodynamics and physical capacity in a small series of lung fibrosis patients (Olschewski et al. 1999), decompensated right heart failure (Olschewski et al. 2000), and HIV patients (Ghofrani et al. 2004). In a long-term observational study from Germany, the survival after 1 and 2 years was 92 % and 87 % and event-free survival was 84 % and 74 % in the IPAH patients (Olschewski et al. 2010). These results are comparable with the recent long-term data with endothelin receptor antagonists.

4.7.1 Combination Studies with Inhaled Iloprost

Hoeper et al. studied 20 patients with IPAH that were on either inhaled iloprost or oral beraprost. Three months of therapy with bosentan added to the prostacyclin resulted in improvement in exercise capacity (6MWD) and maximal oxygen consumption (Hoeper et al. 2003).

The reverse order, addition of inhaled prostacylin to oral endothelin antagonist, was used in the STEP trial (Iloprost inhalation solution safety and pilot efficacy trial in combination with bosentan for evaluation in pulmonary arterial hypertension), a double-blind placebo-controlled trial of 67 FC III and IV patients on a stable dose of bosentan for 3 months (McLaughlin et al. 2006). Subjects were randomised to either iloprost 5 μg six to nine times daily or placebo with 6MWD distance post-inhalation as the primary endpoint. The mean improvement of 26 m vs. placebo did not meet statistical significance ($p = 0.051$), but improvements in secondary endpoints including functional class and time to clinical worsening favoured inhaled iloprost.

Hoeper et al. in their 12-week study randomised stable IPAH patients FC III, currently on bosentan (125 mg twice daily) to either inhaled iloprost 5 μg six times daily or no additional therapy. According to slow recruitment and the results of the interim analysis (36 completed and 40 enrolled patients), this trial was early terminated (Hoeper et al. 2006).

Sildenafil may act synergistically with prostanoids due to its interaction with cAMP breakdown via inhibition of phosphodiesterase 3 via cGMP (Olschewski et al. 2001a). Ghofrani et al. (2002) demonstrated impressive additive effects of inhaled iloprost on sildenafil-induced pulmonary vasodilatation and beneficial clinical effects of adjunct therapy with sildenafil in patients on inhaled iloprost. Over 9–12 months of follow-up, exercise capacity and hemodynamics improved (Ghofrani et al. 2003).

4.8 Treprostinil: Inhaled

Inhaled treprostinil has effects similar to inhaled iloprost; however, there are significant differences in the pharmacodynamics (Voswinckel et al. 2006). This allows for a shorter inhalation time and less inhalations per day. It may be even possible to inhale the full dose with one single breath (Voswinckel et al. 2009). The maximally tolerated dose with a near maximal acute decrease in pulmonary vascular resistance occurred with the 30 μg dose.

In a small cohort, the addition of inhaled treprostinil to oral PAH therapy found significant improvements in 6MWD with nearly all patients improving physical capacity and functional class (Channick et al. 2006). The same was found in a large multinational study (TRIUMPH-1). Study drug or placebo was inhaled with a special ultrasonic nebulizer four times daily. Patients were on a stable treatment with bosentan or sildenafil before enrollment and this therapy was not changed during the study period. Patients on inhaled treprostinil improved significantly as compared to placebo ($p < 0.001$) both post-inhalation and pre-inhalation. Side effects were mostly mild and did not involve toxic effects (McLaughlin et al. 2010). Based on these results inhaled treprostinil was approved by the FDA, while the EMA declined approval based on formal issues.

Combination of sildenafil with inhaled treprostinil had synergistic hemodynamic effects (Voswinckel et al. 2008).

5 Management of Prostacyclin Therapy

5.1 Decision for a Prostacyclin or Its Analogues

The decision for a prostacyclin therapy is—in most of the cases—equivalent with a lifelong commitment for this kind of drug. Because all approved drugs employ demanding application modes and are prone to side effects, this decision must be based on solid ground.

5.2 Potential Treatment Hazards

Left ventricular dysfunction, either systolic or diastolic, represents a contraindication for prostacyclins due to the results of the FIRST study (Califf et al. 1997). In this study, 471 patients with left ventricular failure and mild pulmonary hypertension were randomised to continuous intravenous epoprostenol or placebo. After 6 months there was a significantly higher mortality in the epoprostenol group compared to control.

There was no study in patients with mild left ventricular failure and severe pulmonary hypertension and there is no consensus how to treat "out of proportion" pulmonary hypertension in left heart failure. However, there is consensus, although not formally studied, not to employ prostacyclin or its analogues in patients with a PAWP $>$ 15 mmHg. As a consequence, all candidates for this therapy should have undergone right heart catheterization and a number of further diagnostic tests before a prostacyclin therapy is started.

There are several diseases and conditions that may amplify adverse effects of prostacyclins even if they are not clinically manifest before application. This is the case in pulmonary veno-occlusive disease (PVOD) (Gunther et al. 2012; Rabiller et al. 2006), where prostacyclins can have beneficial effects but are prone to lung edema and hypoxemia (Montani et al. 2009), and in chronic thromboembolic pulmonary hypertension (CTEPH), where any vasodilators will primarily increase the blood flow of the hyper-perfused areas, resulting in worsening of hypoxemia. Patients with obstructive lung disease or lung fibrosis have both heterogeneous ventilation and heterogeneous perfusion and are prone to ventilation/perfusion mismatch and shunt blood flow with any kind of pulmonary vasodilator.

The inhalative application as compared to the systemic application of prostacyclins may be advantageous in patients who are prone to V/Q mismatch (Olschewski et al. 1999). This also applies for liver diseases (Krowka and Swanson 2006; Reichenberger et al. 2006). However, prostacyclin or its analogues have not been approved in any of these conditions.

5.3 Practical Issues of Prostacyclin Treatment

As prostacyclin patients represent a small population with a life-threatening disease and a risky medication, a strong partnership between the patient and the health professionals is very important. In most specialised centres there is a long-lasting personal relationship between individual patients and nurses and/or physicians.

Most patients experience some degree of side effects. They must learn to accept this for the sake of their physical capacity and survival. They often need to talk with an experienced professional about these issues. Both water retention and overnutrition can cause significant clinical deterioration. Patients must learn to control their water, salt, and calorie intake and to adapt the diuretic dose to their needs. Infection management is very important, particularly in patients on iv or sc medication. This may be very demanding for both the patient and the caregiver (Hall et al. 2012).

Patients profit from a written plan for the correct response to a given situation including antibiotic treatment and eventually removal of the intravenous line or change of the sc line.

It seems that an oral-first treatment strategy is not associated with a disadvantage in patients with pulmonary hypertension (Cornwell et al. 2011). Actually, most of the patients who start a prostacyclin treatment have been treated with non-prostanoid medication like endothelin receptor antagonists or phosphodiesterase-5 inhibitors. If they are in WHO class III or IV, they receive a prostacyclin or analogue on top of their oral therapy. A complete switch is mostly due to severe side effects from the oral drugs.

Patients who are primarily started on prostacyclin therapy are mostly in NYHA III or IV with signs of right heart decompensation and severely reduced cardiac index and central venous oxygen saturation. Sometimes these patients need to stay in an intensive care unit. It may be advantageous to start these patients on upfront combination therapy, but the evidence for such an approach is based on small uncontrolled case series (Kemp et al. 2012).

Before starting the therapy with prostacyclin or its analogues, water retention is treated with iv diuretics. If systemic pressure is too low, patients receive low-dose catecholamines in parallel. There is some experience with dobutamine, dopamine, adrenaline, and noradrenalin in such a setting. Noradrenalin should only be used in parallel with a continuous prostacyclin because it may further constrict the pulmonary vessels and promote right heart decompensation and death. The prostacyclin dose is then uptitrated while the resting medication is downtitrated as soon as possible.

If a patient is recompensated on prostacyclin treatment, it may be possible to switch to a less demanding therapy like an endothelin receptor antagonist, a phosphodiesterase inhibitor, or even a calcium channel blocker if the patient is a responder.

5.4 Switch from iv Prostacyclins to Other Forms of Application

If a patient is on intravenous medication, it may be considered to switch to a less demanding application form. Transition from iv epoprostenol to inhaled iloprost or from iv treprostinil to inhaled treprostinil is possible. The advantage is to have less systemic side effects. There are small series of patients where this transition worked in most of the cases (Ivy et al. 2008; Perez et al. 2012).

5.5 Switch from Inhaled Prostacyclins to Continuous Infusion

There are three major reasons to consider this switch: (1) the inhalations are too time-consuming and demanding, (2) there are specific side effects (mostly

coughing), and (3) the effect is not sufficient. The first reason normally becomes evident within the first days or weeks of therapy and the second normally goes away after the first days of therapy, but the third may become evident after months or years. Although the dose of inhaled prostacyclin analogues is quite stable over long periods of time, the needed dose may gradually increase.

6 Conclusion

In pulmonary hypertension, a lack of prostacyclin is an important feature of the pathologic changes. Therapy with prostacyclin or its analogues restores physiological pathways involving the pulmonary arterial vessel wall, the platelets, and inflammatory cells and exerts beneficial clinical effects antagonising vasoconstriction, inflammation, and aggregation of circulating cells in the pulmonary vessels. Prostacyclin therapy has been shown to be efficacious, particularly in advanced disease. Combination of other targeted therapies with prostacyclin or its analogues appears to be effective and safe. Despite demanding application methods, this class of drugs remains a mainstay in the treatment of PAH.

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