



Therapies for pulmonary arterial hypertension: where are we today, where do we go tomorrow?

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ABSTRACT Pulmonary arterial hypertension (PAH) is a progressive disease characterised by remodelling of small pulmonary arteries leading to an increased pulmonary vascular resistance, right ventricular failure and death. Available treatments try to re-establish the equilibrium on three signalling pathways: the prostacyclin, the endothelin (ET)-1 and the nitric oxide. Prostanoids, such as epoprostenol or treprostinil have a vasodilator, antiproliferative and immunomodulatory effect and, despite the administration inconveniences, represent established therapies for severe cases of PAH. Recently oral prostacyclin receptor agonists have shown encouraging results. Many clinical studies targeting the vasoconstrictor ET-1 pathway with receptor antagonists like bosentan and ambrisentan have shown strong results, even more optimism coming from macitentan, the newest drug. Sildenafil and tadalafil, two phosphodiesterase type-5 inhibitors, have shown improved exercise capacity by increasing the nitric oxide level. Riociguat, acting on the same nitric oxide pathway, as a guanylatecyclase activator, has shown promising results in clinical trials and will be available soon. Long-awaited results for tyrosin-kinase inhibitor, imatinib, as an antiproliferative therapy in PAH have been disappointing, due to severe adverse events. In conclusion, although it remains a disease with severe prognosis, the past 20 years have represented a huge progress in terms of treatments for PAH with interesting opportunities for the future.



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A step forward in PAH therapy; same signalling pathway but a new generation of drugs
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Introduction

Pulmonary arterial hypertension (PAH) is a rare and progressive disease characterised by remodelling of the small, pulmonary arteries, which leads to an increase in pulmonary vascular resistance (PVR), right ventricular failure and subsequently death [1]. According to the latest classification of pulmonary hypertension, PAH is included in group 1 and can be idiopathic, heritable or associated with: connective tissue disease, congenital heart disease, HIV infection, portal hypertension, and exposure to toxins/drugs [2]. All these forms of PAH have in common an altered production of various endothelial vasoactive mediators, such as nitric oxide, prostacyclin or endothelin (ET)-1. Current therapies help re-establish the right balance between vasoconstriction and vasodilatation, while some of them have in addition an antiproliferative effect that tackles the abnormal proliferation of endothelial and pulmonary arteries smooth muscle cells (PASMC) [3–6]. Although the disease remains incurable, with the development of these new

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therapies the survival rates are increased to 83% and 58% at 1 and 3 years, respectively [7, 8]. Treatment is initiated according to the clinical and functional impairment of each patient and, as the disease progresses, combination therapy is needed according to guidelines table 1 [9]. The only therapeutic option for patients with uncontrolled disease, despite maximal therapy, is heart–lung transplantation, which is unfortunately only available in selected surgical centres worldwide and with a survival rate of ~50% at 5 years [10].

In the present review we try to bring you the latest data available on the management of PAH and the latest therapy available or under investigation up to January 2013.

The prostacyclin pathway

Prostaglandin I₂ (or prostacyclin) signalling is a major pathway in the pathophysiology of PAH [11]. The prostacyclin synthase and its metabolites are reduced in PAH patients [12, 13]. Prostacyclin is mostly produced by endothelial cells and acts in a paracrine manner with a very short half-life as a potent pulmonary vasodilator; at the same time, prostacyclin is a potent antithrombotic, antiproliferative, antimitogenic and an immunomodulatory factor [14–17]. Nowadays different stable prostacyclin analogues are available for the treatment of PAH.

Prostanoids

Epoprostenol

With a <5 min half-life, epoprostenol is administered continuously *via* an indwelling central venous catheter connected to an infusion pump and requires careful preparation and strict hygiene standards. The most recent guidelines recommend intravenous epoprostenol for PAH patients with New York Heart Association functional classes (NYHA FC) III and IV [9, 18]. These recommendations come from the early studies performed at the beginning of the 1990s, where epoprostenol was used to demonstrate an improvement in haemodynamics, exercise capacity and survival when compared with conventional therapy [19–21]. Symptoms of systemic vasodilatation, such as a headache, flushing, jaw pain or diarrhoea, are the main side-effects of the treatment, which is generally well tolerated. To reduce some of the inconveniences of the other formulation, Veletri (Actelion, Allschwil, Switzerland), a novel formulation of epoprostenol, which is stable for up to 24 h, has recently become available.

TABLE 1 Recommendations for efficacy of specific drug therapy for pulmonary arterial hypertension (group 1) according to New York Heart Association functional class (NYHA FC)

Treatment	NYHA FC		
	II	III	IV
Prostanoids			
Epoprostenol <i>i.v.</i>		I-A	I-A
Iloprost inhaled		I-A	IIa-C
Iloprost <i>i.v.</i>		IIa-C	IIa-C
Treprostinil subcutaneous		I-B	IIa-C
Treprostinil <i>i.v.</i>		IIa-C	IIa-C
Treprostinil inhaled		I-B	IIa-C
Endothelin receptor antagonists			
Bosentan	I-A	I-A	IIa-C
Ambrisentan	I-A	I-A	IIa-C
Phosphodiesterase type 5 inhibitors			
Sildenafil		I-A	I-A
Tadalafil		I-B	I-B
Calcium channel blockers			
		I-C [#]	I-C [#]
Initial drugs combination therapy			
Sequential drugs combination therapy			
		IIa-C	IIa-B

Data are presented as conflicting evidence [levels of evidence A–C] and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure (termed class I–III). Class I: evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective; class II and IIa: weight of evidence/opinion is in favour of usefulness/efficacy; class IIb: usefulness/efficacy is less well established by evidence/opinion; class III: evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful; level A: data derived from multiple, randomised clinical trials or meta-analyses; level B: data derived from a single, randomised clinical trial or large nonrandomised studies; level C: consensus of opinion of the experts and/or small studies, retrospective studies, registries. #: only for responders to acute vasoreactivity tests.

Treprostinil

Treprostinil is a prostacyclin analogue with a greater stability and a longer half-life than epoprostenol (up to 4 h). It can be administered subcutaneously, intravenously, orally and also by inhalation. The most widely available form of treprostinil (Remodulin; United Therapeutics, Research Triangle Park, NC, USA) is administered subcutaneously *via* a microinfusion pump and unfortunately causes infusion-site pain in many patients. Subcutaneous treprostinil improved in a dose-dependent manner, exercise capacity and haemodynamics, the improvement being greater in more severe patients, independent of disease aetiology [22]. The *i.v.* and inhaled forms of treprostinil, available in the USA showed some clinical and haemodynamic improvements with greater tolerability [23–25]. Recently oral treprostinil added to stable PAH patients on oral therapy, failed to show improvement in the 6-min walking distance (6MWD), the primary end-point in the FREEDOM-C study with a 22% discontinuance rate in the treatment arm [26]. The preliminary results of the FREEDOM-M study, which evaluated the use of oral treprostinil as monotherapy in PAH patients, showed a 23 m improvement in the 6MWD, while preliminary analysis of other secondary efficacy measures, time to clinical worsening (TTCW), NYHA FC and PAH signs and symptoms, did not differ significantly between oral treprostinil and placebo [27].

Iloprost

Iloprost (Ventavis; Bayer Schering Pharma, Leverkusen, Germany) is a chemically stable derivative of prostacyclin with a longer half-life. In the Aerosolized Iloprost Randomized (AIR) study, the use of inhaled iloprost in patients with PAH or chronic thromboembolic pulmonary hypertension (CTEPH) on NYHA FC III or IV improved symptoms, exercise capacity and haemodynamics after 12 weeks [28]. Unfortunately, a further study showed that only a minority of patients could be stabilised with inhaled iloprost monotherapy during a follow-up period of up to 5 years [29]. In addition, iloprost requires multiple daily nebulisations, up to 15 min each, and may be responsible for cough, flushing, jaw pain and headache [28]. In a retrospective German study, *i.v.* iloprost failed to show clinical improvement and was associated with poor survival [30].

Beraprost

Beraprost, an orally active prostanoid, licensed only in Japan and South Korea, showed initial effectiveness in improving functional capacity and symptoms in PAH patients [31]; unfortunately these improvements were not sustained at 12 months [32].

Prostacyclin receptor agonists

Recently selexipag, an oral nonprostanoid agonist of the prostacyclin IP receptor, is being tested as treatment of PAH. After hydrolysis, selexipag and its active metabolite, MRE-269, have a 130-fold higher affinity for the IP receptor than for the prostaglandin receptors and although they have modes of action similar to endogenous prostacyclin, they are chemically distinct and have a different pharmacology [33]. A phase II proof-of-concept study evaluated the impact of the use of selexipag on 43 stable PAH patients. Dosage was up-titrated in 200 µg increments from 200 µg, twice a day on day 1, to a maximum tolerated dose by day 35 (maximum allowed dose of 800 µg twice a day). At 17 weeks the results show that treatment with selexipag was associated with a 30.3% reduction in PVR *versus* placebo [34]. Selexipag was well tolerated and was associated with only mild side-effects that included: headache, pain in jaw, nausea or nasopharyngitis. Results from a phase III event-driven trial, GRIPHON, involving 1150 patients are expected early on 2014.

The endothelin pathway

ET-1 is a very potent vasoconstrictor with a proliferative effect on vascular, smooth muscle cells as it interacts with two types of ET receptors: ET receptor isoform A (ETA), localised mainly on PSMCs; and ET receptor isoform B (ETB) localised mainly on the vascular endothelium and less on PSMC (fig. 1) [35, 36]. Activation of the ETA isoform (and the ET_B isoform on smooth muscle cells) induces vasoconstriction and proliferation of vascular smooth muscle cells [37]. The ET_B receptors are principally involved in the clearance of ET-1, particularly in the vascular beds of the lungs and kidney, and may induce vasodilation *via* release of nitric oxide and prostacyclin from the endothelial cells [38, 39].

Currently, both selective and nonselective ET receptor antagonists (ERA) are approved and available for treating PAH. Theoretically, selective ETA-ERAs should be more effective than non-selective ERA, given the role played by ET_B in both vasodilation and ET-1 clearance, but up-to-date clinical trials failed to demonstrate such a difference. Therefore, other features are likely to be of greater relevance when considering treatment, such as the potential for serious drug–drug interactions, convenience of dosing schedules, or rates of limiting side-effects. These characteristics bear more relation to the chemical or pharmacological properties of the drug than to receptor selectivity itself [40].

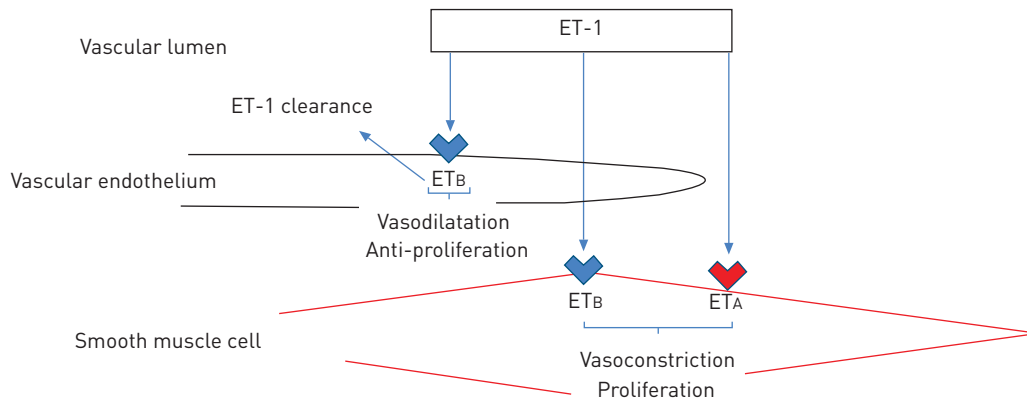


FIGURE 1 Schematic representation of the endothelin system in vascular tissue. ET-1: endothelin type 1; ETA: endothelin receptor isoform A; ETB: endothelin receptor isoform B.

Bosentan

Bosentan (Tracleer; Actelion) is an oral nonselective ERA used for the treatment of PAH since the beginning of the last decade. The first study, BREATHE-1, which included 213 PAH patients, showed an improved 6MWD and NYHA FC with both 125 mg and 250 mg daily doses of bosentan [41]. It was observed that ~13% of patients, in both groups, experienced increased levels of liver transaminases >3 times the upper limit. Therefore, therapy with the drug was started for 4 weeks at the lower dose (62.5 mg twice a day), which was increased to 125 mg twice a day, if the liver transaminases remained at normal levels. A later study, EARLY, showed improved PVR levels and significantly delayed TTCW as compared with placebo for patients with mildly symptomatic PAH [42]. Bosentan was also proven to improve haemodynamics for patients with Eisenmenger syndrome [43], HIV-related PAH [44] or portopulmonary hypertension [45], and the latest guidelines recommend it for patients in NYHA FC II and III [9].

Ambrisentan

Compared to bosentan, ambrisentan (Volibris; GlaxoSmithKline, Brentford, UK) is an oral selective ETA receptor antagonist with a lower rate of hepatic injury [46]. In two large, multicentre, clinical trials ARIES-1 and -2, ambrisentan showed improved 6MWD, longer TTCW (ARIES-2 only) and improved NYHA FC (ARIES-1 only) [47]. The 2-year extension study confirmed the persistent improvements in the 6MWD and good tolerability profile [48]. Positive results were obtained in the ARIES-3 study [49], which tested ambrisentan in patients with various PH aetiologies and background therapies. The drug has been approved worldwide for patients with NYHA FC II and III and for NYHA FC IV in the USA.

Macitentan

Macitentan is a new oral dual (ETA and ET_B) ERA with increased *in vivo* preclinical efficacy *versus* existing ERAs resulting from sustained receptor binding and tissue penetration properties [50, 51]. Promising results in animal models were confirmed in Phase I and II clinical trials [52]. The phase III SERAPHIN trial enrolled a total of 742 patients, being the largest prospective PAH study to date. Initial analysis indicated that treatment with macitentan for up to 3.5 years, at both the 3 mg and 10 mg dose, decreased the risk of a morbidity/mortality event *versus* placebo. This risk was reduced by 45% in the 10 mg dose group, while at 3 mg the observed risk reduction was 30%. Secondary efficacy end-points, including change from baseline in 6MWD, NYHA FC and TTCW, also showed a dose-dependent effect with a trend in favour of 10 mg macitentan being observed on all-cause mortality [53]. Only ~3.5% of patients experienced elevations of liver transaminases >3 times the upper limit. A decrease in haemoglobin was observed more frequently on macitentan than placebo, with no difference in treatment discontinuation between groups [54].

Sitaxentan

Sitaxentan, a selective ETA receptor antagonist with a moderate clinical efficacy [55] was withdrawn from the market worldwide in 2010, due to an increasing number of deaths attributed to acute liver failure [56].

The guanosine monophosphate and the nitric oxide pathways

At the endothelial level the nitric oxide synthase is responsible for the production of nitric oxide. Afterwards, at the PSMC level, nitric oxide binds to the soluble guanylatecyclase (sGC) and, *via* the production of cyclic guanosine monophosphate (cGMP), acts as a vasodilator and an inhibitor of cell

proliferation (fig 2) [57]. Phosphodiesterase type 5 (PDE-5) degrades cGMP, and inhibition of this process with sildenafil and tadalafil has shown both acute and long-term beneficial effects in patients with PAH [58, 59]. Since the therapeutic effect of PDE-5 inhibitors is dependent on baseline nitric oxide expression (levels of which are typically reduced in PAH), treatments that act directly on sGC could, potentially, have a greater efficacy than PDE-5 inhibitors [60]. Riociguat, which acts on the sGC nitric oxide receptor, is being tested in patients with PAH and CTEPH [61].

Phosphodiesterase type 5 inhibitors

Sildenafil

Used initially for the treatment of the erectile dysfunction, sildenafil (Revatio; Pfizer, New York, NY, USA) showed, independently of the tested dose, improvements in the 6MWD, NYHA FC and pulmonary haemodynamics in the SUPER-1 study [58]. The improvements were sustained at 1 year. Adverse events were observed more frequently with sildenafil than with the placebo and included headache, flushing, and dyspepsia. The 3-year extension, the SUPER-2 study, showed sustained improvements in 6MWD and NYHA FC with an estimated 3-year survival rate of 79% [62]. With all the favourable results, the currently approved dosage is 20 mg three times a day, for patients in NYHA FC II, III and NYHA FC IV in the USA and Canada).

Tadalafil

Tadalafil (Adcirca; Lilly, Indianapolis, IN, USA) is another PDE-5 inhibitor used in PAH patients. In the PHIRST-1 trial, 405 patients either treatment-naïve or already receiving bosentan were assigned to placebo or one of several doses of tadalafil (2.5 mg, 10 mg, 20 mg, or 40 mg) [59]. After 16 weeks, significantly improved 6MWD, haemodynamics and longer TTCW were only obtained with the 40 mg dose. Improvements were less marked in patients already on bosentan therapy. Treatment was generally well tolerated and most common adverse events reported with tadalafil were headache, myalgia, and flushing. Early results of the continuation study, PHIRST-2, show that the 6MWD improvements were maintained at 1 year with a good tolerability.

Guanylatecyclase activators

In a phase II clinical trial on patients with PAH and CTEPH riociguat improved NYHA FC, 6MWD and pulmonary haemodynamics after 12 weeks. Doses of 1–2.5 mg three times a day, titrated according to systemic blood pressure were well tolerated (only 4% withdrawals). In late 2012 the preliminary results of the phase III PATENT-1 trial, which evaluated riociguat in 445 PAH patients, showed statistically significant improvements on the primary end-point, the 6MWD, and also across secondary end-points including PVR, NYHA FC and TTCW [63]. Results from the extension trial, PATENT-2, are expected in 2014. To date, the improvements in the 6MWD in all the trials might be partially due to vasodilatation and better blood perfusion at the muscular level [64, 65].

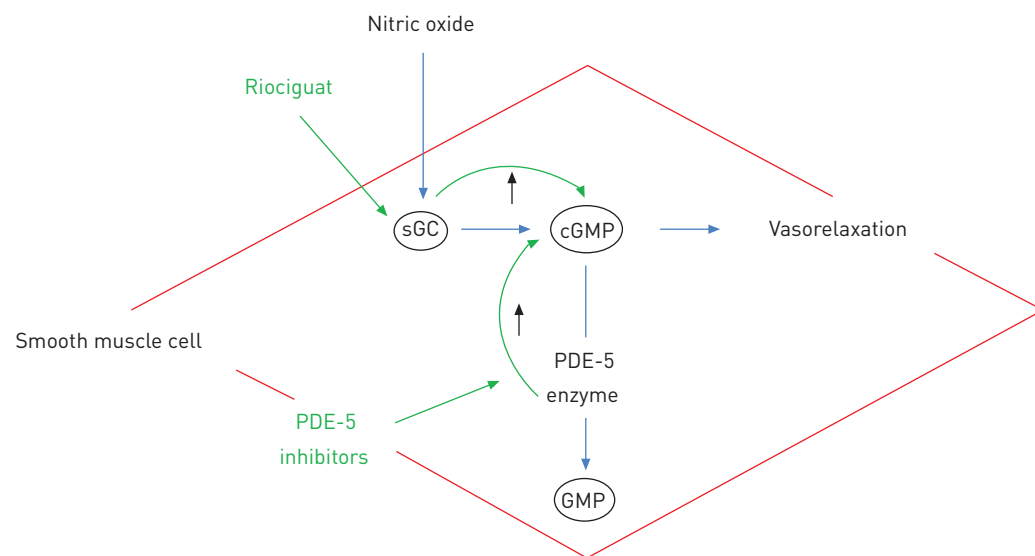


FIGURE 2 Schematic representation of the guanosine monophosphate (GMP) and nitric oxide pathways. sGC: soluble guanylate cyclase; cGMP: cyclic GMP; PDE-5: phosphodiesterase type 5.

Calcium channel blockers

Initial response to acute pulmonary vasodilator testing, during right-heart catheterisation, is found in <10% of all PAH patients. In this setting, calcium channel blockers are being initiated and these patients experienced improved functional class and haemodynamics as well as an improved survival compared with non-responders [66, 67]. The agents commonly recommended are long-acting nifedipine, diltiazem or amlodipine [68] at high dosages with a progressive up-titration over a few weeks [69]. If clinical improvement is not obtained additional therapies are added, using the same pattern as for the non-responders PAH patients [9].

New therapies under development

Tyrosin kinase inhibitors

Based on an increased expression of platelet-derived growth factor (PDGF) receptors in PAH patients, research, taken from the last 15 years, has shown the role of the PDGF signalling in PAH as a smooth muscle mitogen, responsible for pulmonary arterial remodelling [70, 71]. Imatinib (Gleevec, Novartis, Basel, Switzerland) is a tyrosin kinase inhibitor (TKI) drug used for the treatment of chronic myelogenous leukaemia (CML), it is also an inhibitor of PDGF. A phase II clinical study, involving 59 PAH patients, tested imatinib as an add-on therapy [72]. Although imatinib reduced PVR and improved cardiac output, the primary efficacy outcome, the 6MWD, was negative and in addition results must be interpreted with caution due to a 30% drop-out rate in the treatment group. *Post hoc* analyses showed that patients with a severe haemodynamic profile ($PVR > 1000 \text{ dyn}\cdot\text{s}^{-1}\cdot\text{cm}^{-5}$) responded better to imatinib. IMPRES, a phase III clinical trial, evaluated imatinib in patients with $PVR \geq 800 \text{ dyn}\cdot\text{s}^{-1}\cdot\text{cm}^{-5}$. A total of 202 patients were enrolled and results showed a significantly difference in 6MWD and improved haemodynamic parameters in the imatinib group *versus* placebo [73]; however, due to the serious adverse events, like subdural haematomas, in early 2013 Novartis decided to withdraw its marketing authorisation application for imatinib as treatment for PAH from the European Medicines Agency.

A clinical trial involving nilotinib, another TKI in use for CML with *in vitro* vasodilative properties was stopped due to a high rate in prolonged QT interval and a few cases of sudden death [74]. In addition, there is already a case report of a patient developing reversible pulmonary hypertension on echocardiography after being treated with nilotinib [75].

The rationale behind the use of TKIs in PAH is very strong, but it is very difficult to design an effective and safe molecule, with all the reports showing a cardiac toxicity, probably as a direct effect on cardiomyocytes [76, 77], and with the recent report cases of dasatinib induced PAH [78].

Serotonin receptor blockers

Plasma levels of serotonin are increased in PAH [79], and it is believed that serotonin is responsible for promoting both vasoconstriction and remodelling of the pulmonary vasculature, inducing proliferation of pulmonary arterial fibroblasts and PASMCs [80]. Terguride is capable of modulating a range of neurotransmitter receptors including the 5-hydroxytryptamine type 2 serotonin receptors and is also partially active on the dopamine receptors. *In vitro* it blocked proliferation and migration of cultured primary human PASMCs in a dose-dependent manner. Chronic terguride treatment prevented dose-dependently the development and progression of monocrotaline-induced PAH in rats [81]. Unfortunately the results of a phase II clinical trial in PAH patients were negative [82].

Other therapies

The vasoactive intestinal peptide

Decreased concentrations of the vasoactive intestinal peptide (VIP) have been found in the serum and lung tissue of patients with PAH [83]. Since VIP is an inhibitor of proliferation of vascular smooth muscle cells and of platelet aggregation [84, 85], it has been hypothesised that a replacement therapy with exogenous VIP could be useful in PAH. In a small study, aviptadil, a synthetically inhaled form of VIP, showed favourable haemodynamic effects [86]. However, the results from an unpublished, phase II study, showed no significant effects on exercise capacity or pulmonary haemodynamics after the addition of inhaled aviptadil [87].

The Rho signalling pathway

In vivo studies showed that the Rho GTPase/RhoA pathway and its downstream effectors, the Rho-kinases (ROCK-1 and ROCK-2), had an important role in PAH, due to its lasting effects on vasoconstriction and pulmonary cell proliferation, leading to vascular remodelling [88, 89]. Inhaled and *i.v.* formulations of fasudil, a potent ROCK inhibitor, showed favourable acute haemodynamic effects in patients with PAH [90, 91], while statins, which represent other inhibitors of the Rho signalling pathway, had no effect [92, 93].

Adrenomedullin

Circulating levels of adrenomedullin, a vasodilator peptide are increased in patients with PAH and correlate with the haemodynamic severity [94]. After promising results on experimental models, adrenomedullin (single inhaled dose) showed improved haemodynamics with no significant effects on systemic vascular resistance [95]. A multicentre, randomised, controlled trial with well-defined end-points is needed to verify the long-term safety and efficacy of adrenomedullin.

Epigenetics and PAH

Existing research does not adequately explain susceptibility to PAH, and recent evidence reveals that epigenetic alterations may be involved [96]. Epigenetics refers to all heritable changes in phenotype or in gene expression states, including chromatin remodelling, DNA methylation, histone modification and RNA interference, which are not involved in the DNA sequence itself [97]. As a response to increased reactive oxygen species found in PAH, the inhibition of the superoxide-generating enzyme induces apoptosis in PASMC, reduces inflammation, improves endothelial function and may represent potential strategies for the future [98–100].

For a long time we have known that mutations in the gene for bone morphogenetic protein receptor type II (*BMPR2*) are causally linked to PAH, with low levels of *BMPR2* being found even in the pulmonary vasculature of patients with secondary PAH [101, 102]. In the same line of new generation treatments in 2012, REYNOLDS *et al.* [103] showed that employing an adenoviral *BMPR2* gene delivery vector that was targeted to the pulmonary endothelium, significantly improved haemodynamics and reduced pulmonary arterial muscularisation in two animal models of pulmonary hypertension. For broad clinical utility, the technology the authors employed in this work needs to be suitably advanced to the level required for translation to be achieved.

General considerations

In addition to specific PAH therapies, oral anticoagulants are used to tackle the pulmonary *in situ* microthrombosis in most of the patients with idiopathic, heritable and anorexigen-associated PAH, although there is no clear data to support their beneficial effect [104]. Diuretics reduce fluid retention and show clear symptomatic benefits for all PAH patients. Long-term oxygen administration is limited to patients having arterial hypoxaemia. Appropriate contraception, cardiopulmonary rehabilitation programmes as well as psychological support are also required for all PAH patients [105, 106].

Conclusions

Although it remains an incurable disease with a severe prognosis, the past 20 years have represented a huge progress in terms of treatments for PAH. For the same well-studied signalling pathways, the upcoming availability of the new generation of drugs, such as selexipag, macitentan or riociguat, will represent a step forward in PAH therapy. Not only do they have a safer profile but the big challenge will be to replace the predecessors also in terms of efficacy.

Being a borderline disease, between pulmonology and cardiology, PAH has attracted the interest of the scientific community on both fields and the years to come represent a huge challenge to all of us.

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