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Targeted therapies in pulmonary arterial hypertension

David Montani [a,b,c], Marie-Camille Chaumais [c,d,e], Christophe Guignabert [a,b,c], Sven Günther [a,b,c], Barbara Girerd [a,b,c], Xavier Jaïs [a,b,c], Vincent Algalarrondo [a,f], Laura C. Price [g], Laurent Savale [a,b,c], Olivier Sitbon [a,b,c], Gérald Simonneau [a,b,c], Marc Humbert [a,b,c,*]

[a] Univ. Paris-Sud, Le Kremlin-Bicêtre, France
[b] AP-HP, Service de Pneumologie, DHU Thorax Innovation, Hôpital Bicêtre, Le Kremlin-Bicêtre, France
[c] INSERM U999, LabEx LERMIT, Centre Chirurgical Marie Lannelongue, Le Plessis Robinson, France
[d] Univ. Paris-Sud, Châtenay Malabry, France
[e] AP-HP, Pharmacie, DHU Thorax Innovation, Hôpital Antoine Béclère, Clamart, France
[f] AP-HP, Service de Cardiologie, DHU Thorax Innovation, Hôpital Antoine Béclère, Clamart, France
[g] National Heart and Lung Institute, Imperial College London, Royal Brompton Hospital, Dovehouse Street, London SW3 6LY, UK

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ABSTRACT

Pulmonary arterial hypertension (PAH) is a rare disorder characterized by progressive obliteration of small pulmonary arteries that leads to elevated pulmonary arterial pressure and right heart failure. During the last decades, an improved understanding of the pathophysiology of the disease has resulted in the development of effective therapies targeting endothelial dysfunction (epoprostenol and derivatives, endothelin receptor antagonists and phosphodiesterase type 5 inhibitors). These drugs allow clinical, functional and hemodynamic improvement. Even though, no cure exists for PAH and prognosis remains poor. Recently, several additional pathways have been suggested to be involved in the pathogenesis of PAH, and may represent innovative therapies. In this summary, we review conventional therapy, pharmacological agents currently available for the treatment of PAH and the benefit/risk ratio of potential future therapies.

Contents

Abbreviations: ACVRL1, activin A receptor type II-like kinase-1; BMPR2, bone morphogenetic protein receptor type 2; cAMP, cyclic adenosine monophosphate; CCB, calcium channel blockers; cGMP, cyclic guanosine monophosphate; CO, cardiac output; CYP, cytochrome P450; EC, endothelial cell; EGF, epidermal growth factor; ENG, endoglin; ET, endothelin; ERA, endothelin receptor antagonist; FGF2, fibroblast growth factor 2; iPAH, idiopathic PAH; IPr, PGI2 receptor; Kv, voltage-gated potassium channels; LVEF, left ventricular ejection fraction; MCT, monocrotaline; mPAP, mean pulmonary arterial pressure; NYHA, New York Heart Association; OS, oxidative stress; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; PASMC, pulmonary artery smooth muscle cells; PDE-5, phosphodiesterase type 5; PDGF, platelet-derived growth factor; PGI2, prostacyclin; PVR, pulmonary vascular resistance; RTK, receptor tyrosine kinase; ROCK, RhoA/Rho kinase; ROS, reactive oxygen species; sGc, soluble guanylate cyclase; SOD, superoxide dismutase; SMC, smooth muscle cell; TGF, transforming growth factor; TKI, tyrosine kinase inhibitor; TXA2, thromboxane; VIP, vasoactive intestinal polypeptide; VPAC, vasoactive intestinal polypeptide receptor.

* Corresponding author at: Service de Pneumologie, Hôpital Bicêtre, 78, rue du Général Leclerc, 94270 Le Kremlin-Bicêtre, France. Tel.: +33 1 45 21 79 72; fax: +33 1 45 21 79 71.
E-mail address: marc.humbert@bct.aphp.fr (M. Humbert).

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1. Introduction

Pulmonary hypertension (PH) is defined as an increase in mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg at rest as assessed by right heart catheterization (Galie et al., 2009a, 2009b). According to pulmonary capillary wedge pressure, pulmonary vascular resistance (PVR) and cardiac output (CO), different hemodynamic definitions of PH exist as follows. Pre-capillary PH includes the clinical groups 1, 3, and 4 while post-capillary PH includes the clinical group 2 (Table 1) (Oudiz, 2007; Simonneau et al., 2009). Group 5 corresponds to PH with unclear or multifactorial etiologies. PAH or 'group 1 PH' comprises PAH due to many different etiologies, despite which patients with PAH share clinical and pathological features. These pathological characteristics include pulmonary arterial endothelial cell (EC) dysfunction, pulmonary artery EC and smooth muscle cell (SMC) proliferation, vasoconstriction and in situ thrombosis. In addition, because sub-groups of PAH have common clinical characteristics, they share similarities in term of management (Simonneau et al., 2009). However, despite many new available therapies over the last two decades, PAH remains an incurable disease process, which if not interrupted, subsequently leads to right heart failure and death (Chin & Rubin, 2008; Humbert et al., 2010a,b).

2. Molecular basis of pulmonary arterial hypertension (PAH) and molecular targets

The imbalance in the production of endothelium-derived vasodilator and constrictor factors is a pivotal element in the development and progression of the disease (Fig. 1). Over the past two decades, this observation has led to the development of all current approved specific therapies for PAH.

Table 1
Classification of pulmonary hypertension (Galie et al., 2009a, 2009b).

1. Pulmonary arterial hypertension
   1.1 Idiopathic PAH
   1.2 Heritable
      1.2.1. BMPR2
      1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
      1.2.3 Unknown
   1.3 Drug- and toxin-induced
   1.4 Associated with
      1.4.1. Connective tissue diseases
      1.4.2 HIV infection
      1.4.3 Portal hypertension
      1.4.4 Congenital heart diseases
      1.4.5 Schistosomiasis
      1.4.6 Chronic hemolytic anemia
   1.5 Persistent pulmonary hypertension of the newborn
1′. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
2. Pulmonary hypertension due to left heart disease
   2.1 Systolic dysfunction
   2.2 Diastolic dysfunction
   2.3 Valvular disease
3. Pulmonary hypertension due 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
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. PH with unclear multifactorial mechanisms
   5.1 Hematologic disorders: myeloproliferative disorders, splenectomy
   5.2 Systemic disorders, sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   5.3 Metabolic disorders: glycogen storage disease, Gaucher's disease, thyroid disorders
   5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

2.1. Nitric oxide (NO) signaling pathway and phosphodiesterases (PDEs)

NO is a gaseous lipophilic free radical generated by three distinct isoforms of nitric oxide synthases (NOS): neuronal (nNOS), inducible (iNOS) and endothelial NOS (eNOS). NO dilates blood vessels, inhibits leukocyte adhesion, platelet aggregation, thrombus formation, and vascular proliferation and modulates many other physiological processes including cell metabolism and intracellular signaling pathways (Mayer & Hemmens, 1997; Lincoln et al., 1998). Reduced NO bioavailability has been reported to be associated with the development of many different vascular diseases including PAH. There are different molecular mechanisms explaining the decreased NO bioavailability in PAH including increased levels of endogenous competitive inhibitor of eNOS (such as asymmetric dimethylarginine or ADMA), eNOS "uncoupling", decreased L-arginine levels, increased NO scavenging by hemoglobin and reactive oxygen species (ROS) (Steinhorn, 2008; Zuckerbraun et al., 2011). It has been well documented that exogenous and endogenous NO inhibit vascular SMC proliferation and migration (Sarkar et al., 1996; Zuckerbraun et al., 2007; Tsihlis et al., 2011). Most of the effects of NO, on SMCs, platelets and cardiac myocytes, are mediated through its activation of soluble guanylate cyclase and amplification of the production of cyclic guanosine monophosphate (cGMP) (Rybalkin et al., 2003) (Fig. 1).

Phosphodiesterases (PDEs) are a superfamily of enzymes that inactivate cAMP and cGMP and have different tissue distributions. Among all PDEs, PDE-5 is abundantly expressed in lung tissue and is upregulated in PAH, contributing to endothelial dysfunction by inactivating cGMP. In addition, a PDE-1C upregulation in hyperproliferative pulmonary artery SMC (PASMCs) has been noted in patients with PAH (Schermuly et al., 2007). PDE-5 inhibitors facilitate the antiproliferative and vasodilating effects of endogenous NO and represent the rationale for the use of PDE inhibitors in PAH (Moncada & Higgs, 1993; Rabe et al., 1994; Giordano et al., 2001; Michelakis et al., 2002b; Corbin et al., 2005; Tantini et al., 2005; Wharton et al., 2005).

2.2. Prostacyclin (PGI2) signaling pathway

With its very short half-life (t1/2), the major active metabolite of arachidonic acid (AA) PGI2 is a critical endogenous regulator of vascular homeostasis. PGI2 is produced in vascular ECs and acts on neighboring vascular SMCs as well as circulating platelets and cells (Vane & Corin, 2003). PGI2 is a potent vasodilator with antithrombotic properties (Gryglewski et al., 1976; Vane & Corin, 2003). An imbalance in AA metabolism with decreased PGI2 and increased thromboxane (TXA2) urinary metabolites has been demonstrated in idiopathic PAH (iPAH) patients (Christman et al., 1992). In addition, expression of the key enzyme for PGI2 synthesis, PGI2 synthase (PGIS), is reduced in pulmonary arteries of PAH patients (Tuder et al., 1999) (Fig. 1).

The actions of PGI2 are mediated by binding to cell surface PGI2 receptors (IPr) or by binding to nuclear peroxisome proliferator-activated receptors (PPARs) (Lim & Dey, 2002; Vane & Corin, 2003; Wise, 2003; Falcetti et al., 2007; Midgett et al., 2011; Stitham et al., 2011). Binding of PGI2 to IPr induces cell-specific signaling that leads to elevation of intracellular cAMP through Gs-protein coupling to adenylate cyclase (Hashimoto et al., 1990; Coleman et al., 1994; Chaumais et al., 2010). Administration of PGI2 or its analogs in experimental PH leads to a decrease in PAP and PVR (Leffler & Hessler, 1979; Archer et al., 1986; Yuki et al., 1994; Miyata et al., 1996; Max et al., 1999).

2.3. Endothelin (ET-1) signaling pathway

ET-1 is a 21 amino acid peptide that is produced by the vascular endothelium from a 39 amino acid precursor, big ET-1, through the actions of an ET-1 converting enzyme (ECE) found on the EC membrane.