REVIEW ARTICLE

Recent advances in the pharmacotherapy of pulmonary hypertension: practical considerations

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ABSTRACT
Pulmonary arterial hypertension (PAH) is a rare disease characterized by pulmonary vascular remodeling leading to increased vascular resistance. The increased afterload contributes to the development of right ventricular dysfunction and heart failure, which is the leading cause of death among patients with PAH. The development of specific treatments has markedly improved the prognosis of this population. However, PAH continues to be an incurable, life-limiting condition, which creates a major burden for healthcare systems. This review describes the currently used treatments for PAH and provides insight into novel therapeutic targets that aim to reduce vascular remodeling, which ultimately leads to right ventricular failure.

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Introduction Pulmonary hypertension (PH) is characterized by increased pulmonary artery (PA) pressure with a mean pulmonary artery pressure (mPAP) of 25 mm Hg or higher at rest. Pulmonary arterial hypertension (PAH) is defined by the presence of increased mPAP with a pulmonary capillary wedge pressure of 15 mm Hg or lower and increased pulmonary vascular resistance (PVR) exceeding 3 Wood units.[1,2]

Pulmonary arterial hypertension is a complex physiopathological mechanism that affects small pulmonary vessels and leads to increased PVR. These changes are mediated by a severe endothelial dysfunction, leading to vasoconstriction and thrombosis.[3] Following endothelial damage, an additional complex response with perivascular inflammation, cell proliferation, and vascular remodeling occurs.[3] These vascular changes cause an increased right ventricular (RV) afterload resulting in RV remodeling and subsequent heart failure, which is the most common cause of death among patients with PAH.[4]

The currently used therapeutic options for patients with PAH are limited to vasodilation aimed at reducing the RV afterload. Despite the continuous improvement in PAH survival, patients remain the chronically ill population at a higher risk of fatal outcomes.[5] There is a need for new alternative therapies away from treating imbalance of vasoactive mediators, focused on structural remodeling of the pulmonary vasculature.[6,7] The aim of this review is to summarize all novelties regarding PAH treatment and to identify future therapeutic targets.

Recent therapeutic weapons for pulmonary arterial hypertension Pharmacologic therapies for PAH are divided into 4 groups according to their mechanism of action[1,8] (TABLE 1):

1 Calcium channel blockers are effective in patients with idiopathic and hereditary PAH who present a positive response to acute vasodilator testing. Calcium channel blockers (amlodipine, diltiazem, or nifedipine) act directly over pulmonary artery smooth muscle cells (PASMCs), avoiding the intracellular increase of Ca^{2+}, which mainly causes vascular contraction and is also related to cell proliferation.[9] Patients with PAH should be treated with high doses of calcium channel blockers and require close monitoring to confirm a sustained response.[10]

2 Drugs targeting the nitric oxide pathway act by inhibiting phosphodiesterase 5 (PDE5), which is mainly responsible for cyclic guanosine

TABLE 1 Available treatments for pulmonary arterial hypertension

Drugs		Dosage	Adverse effects	Recommendations
Calcium channel blockers				
Diltiazem		240–720 mg/24 h	Hypotension, edema	IPAH, HPAH, and DPAH responding to vasoreactivity testing
Nifedipine		120–240 mg/24 h		
Amlodipine		10–20 mg/24 h		
Nitric oxide pathway				
PDE5 inhibitors	Sildenafil	20–80 mg/8 h	Headache, flushing, epistaxis, priapism	Contraindicated in recent AMI, in combination with nitrates, and in ischemic optic neuropathy
	Tadalafil	40 mg/24 h		
Soluble guanylate cyclase agonist	Riociguat	1–2.5 mg/8 h	Syncope, hypotension, diarrhea	Contraindicated in a combination therapy with PDE5 inhibitors
Endothelin receptor antagonists				
Bosentan		125 mg/12 h	Hepatotoxicity, diarrhea, edema, teratogenic effects	Recommended in WHO-FC class III patients with Eisenmenger syndrome. Periodic liver function testing should be performed.
Ambrisentan		10 mg/24 h	Abnormal liver function, diarrhea, edema, teratogenic effects	–
Macitentan		10 mg/24 h	Anemia, edema, teratogenic effects	Tested in PAH associated with portal hypertension. Periodic hemoglobin testing should be performed.
Inhaled prostanoids				
Iloprost		2.5–5 mg inhalation 6–9 times	Headache, jaw pain, flushing, hypotension, nausea, vomiting, diarrhea	–
Parenteral prostanoids				
Epoprostenol		20–40 ng/kg/min i.v.	Thrombocytopenia, headache, jaw pain, flushing, hypotension, nausea, vomiting, diarrhea, increased risk of bleeding	Complications secondary to central catheter placement or local pain. The initial dose of 1–2 ng/kg/min should be titrated considering adverse effects and treatment goals.
Treprostinil		20–80 ng/kg/min i.v. or s.c.		
Oral prostanoids				
Selexipag		200–1600 μg/12 h	Headache, diarrhea, nausea, jaw pain	Stable condition

Abbreviations: AMI, acute myocardial infarction; DPAH, drug-induced pulmonary arterial hypertension; HPAH, hereditary pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; i.v., intravenously; PAH, pulmonary arterial hypertension; s.c., subcutaneously; PDE5, phosphodiesterase 5; WHO-FC, World Health Organization functional class

monophosphate (cGMP) hydrolysis in the lungs (sildenafil, tadalafil),[11,12] or by directly stimulating soluble guanylate cyclase to generate cGMP (riociguat).[13] Cyclic guanosine monophosphate causes smooth muscle cell relaxation, decreases proliferation of PASMCs, and increases apoptosis of PASMCs. Both PDE5 inhibitors and cGMP stimulators have been shown to have favorable effects on patients with PAH, improving exercise capacity, World Health Organization functional class (WHO-FC) and hemodynamics.[14]

3 Endothelial receptor antagonists (ERAs)—bosentan, ambrisentan, and macitentan—block the effect of endothelin overexpression in PAH, which leads to a potent vasoconstrictor, prothrombotic, and inflammatory response, increases exercise capacity, as well as improves hemodynamic parameters.[15,16] The main limitation of this therapy is hepatic injury. Macitentan has been proven to have a better safety profile and was tested in patients with portopulmonary PAH with good effectiveness and safety outcomes.

4 Prostanoid analogues are arachidonic acid–derived eicosanoids that act as vasoactive mediators. These molecules, produced by the endothelium in healthy conditions, interact with their respective receptors in the PASMC membrane and provoke vascular relaxation through cyclic adenosine monophosphate production. Prostanoid analogues can be classified as follows:

a. Inhaled prostanoids: Iloprost is a stable analogue of prostacyclin that causes selective pulmonary vasodilation. Added to other vasodilators, it is an effective and safe drug for patients in WHO-FC III to IV. It improves hemodynamics and exercise capacity with a lower rate of adverse effects than systemic prostanoids.[17,18] Treprostinil, a prostacyclin analogue that has pulmonary vasodilator

activity, improves WHO-FC, hemodynamics, and RV function when added to background PAH therapies. It is well tolerated and do not cause significant adverse effects.[19]

b. Parenteral prostacyclin analogues (intravenous epoprostenol or, generally subcutaneous, treprostinil) are the most potent and effective pulmonary vasodilators, which improve exercise capacity, hemodynamics, and symptoms. Despite their great effectiveness, the drugs have several adverse effects including those related to intravenous or subcutaneous infusion catheter use.[20-22]

Novelties of the classic

New proposal for the diagnosis of pulmonary hypertension Pulmonary hypertension has been classically defined as an mPAP of 25 mm Hg or more measured by right heart catheterization, leaving aside a subset of patients with an mPAP between 19 and 24 mm Hg (known as borderline PH). Recently, a new threshold has been proposed (mPAP >20 mm Hg), based on normal hemodynamic values of healthy individuals (14 ± 3.3 mm Hg). This change has been prompted by the risk of disease progression and poorer prognosis observed in patients with systemic sclerosis–associated PAH with an mPAP of 21 to 24 mm Hg.[23] However, most clinical trials evaluating PAH treatments only enrolled patients with an mPAP exceeding 25 mm Hg. There was a randomized, double-blind, placebo-controlled study of patients with systemic sclerosis and mPAP at rest ranging between 21 and 24 mm Hg and/or exceeding 30 mm Hg during exercise, which showed a possible benefit of ambrisentan (5–10 mg/d) noted with regard to hemodynamic parameter values in these patients.[24] Thus, the benefits of treating patients with an mPAP below 25 mm Hg are still to be explored.

Justification for using a more aggressive approach The latest therapeutic recommendations advocated a more aggressive treatment from early stages with an upfront dual oral combination therapy in patients at low or intermediate risk. Furthermore, combination therapy including intravenous prostacyclin is the first-line treatment in high-risk patients.[25]

The AMBITION (Initial Use of Ambrisentan Plus Tadalafil in Pulmonary Arterial Hypertension) study demonstrated that combination treatment with ambrisentan and tadalafil in treatment-naïve patients reduced the risk of a composite of death, hospitalization, disease progression, or unsatisfactory long-term clinical response by 50%.[26] A more aggressive approach in the TRITON (Efficacy and Safety of Initial Triple Oral Versus Initial Double Oral Combination Therapy in Patients with Newly Diagnosed Pulmonary Arterial Hypertension) trial, which compared initial dual therapy with macitentan combined with tadalafil with triple oral therapy with selexipag added, showed an improvement in PVR in both strategies and a reduction in the risk of disease progression in patients on triple therapy.[27] Based on those results, currently, there is no evidence for initial triple oral therapy versus dual therapy.

Finally, the REPLACE (A Prospective, Randomized Trial of Riociguat Replacing Phosphodiesterase 5 Inhibitor Therapy in Patients with Pulmonary Arterial Hypertension Who Are Not at Treatment Goal) study tested the benefit in switching from PDE5 inhibitors to riociguat in patients at intermediate risk who did not reach treatment goals. That randomized controlled trial demonstrated that switching from PDE5 inhibitors (with or without ERAs) to riociguat resulted in a higher likelihood of clinical improvement and a reduced rate of clinical worsening and can be a strategic option for treatment escalation.[28]

This aggressive therapeutic algorithm is proposed for patients with classic PAH who usually have no cardiopulmonary comorbidities. Conversely, in patients with atypical PAH, usually elderly patients with features of left heart disease or lung disease, a more conservative approach with a single drug is proposed, regardless of their risk status, in order to avoid possible adverse effects of the combined therapy.[25]

Oral formulations of prostanoids The main disadvantage of intravenous prostanoids is catheter-related complications such as infections or displacements.[22] There are also difficulties in obtaining an adequate venous access in some patients or poor tolerance to subcutaneous infusion due to pain at the infusion site.[20] On the other hand, less invasive alternatives, such as inhaled iloprost, are not associated with good therapeutic adherence owing to the frequency of drug administration needed to make it effective.[29] In this regard, oral systemic drugs have been developed in recent years and presented promising results in randomized clinical trials.

Selexipag is an oral selective prostacyclin receptor agonist, which can be used alone or in a combination with with ERAs or PDE5 inhibitors. It has been shown to reduce morbidity and disease progression, regardless of background treatment with ERAs, PDE5 inhibitors, or both.[30,31] It is well tolerated, and its common adverse effects include headache, diarrhea, nausea, and jaw pain. After being tested in more than 500 patients with PAH, selexipag has been deemed an appropriate treatment for patients at intermediate risk.

Ralinepag, a highly selective oral prostacyclin receptor agonist with a longer half-life, has been tested in a phase 2 placebo-controlled study of patients on mono- or dual background therapy. It has demonstrated a significant improvement in PVR,[32] but phase 3 clinical trials continue to

recruit participants owing to delay related to the COVID-19 pandemic.

Emerging therapies in pulmonary arterial hypertension Despite a major improvement in quality of life and survival, specific treatments that aim to reduce pulmonary vascular remodeling in PAH are lacking.[6] Identifying the pathobiological mechanisms underlying PAH may help to develop new drugs targeting alternative pathways that can reverse pulmonary vascular remodeling, inhibit disease progression, and improve survival.[7]

The direct consequence of pulmonary vascular remodeling is obliteration of small pulmonary arterioles and vascular dysfunction. It is preceded by pulmonary endothelial dysfunction involving both the impairment of endothelium-dependent vasodilation causing vasoconstriction and reduced anticoagulant properties with increased expression of adhesion molecules and perivascular inflammation.[3] The subsequent remodeling and obliteration implies intimal thickening, medial and adventitial hypertrophy due to increased proliferation and resistance to apoptosis of PASMCs, and formation of angioproliferative plexiform lesions in the last instance.[33,34] Additionally, histological evidence suggests that plexiform lesions are derived from the vasa vasorum and bronchial arteries within the adventitia of pulmonary arteries and connect the systemic vasculature to pulmonary arteries and veins.[35]

Up to date, various drugs are being tested to specifically limit pulmonary vascular remodeling by reducing endothelial dysfunction (vasoconstriction), inflammation, thrombosis, and cell proliferation.

Drugs reducing the proliferative response Endothelial dysfunction produces an abnormal response to various growth factors such as platelet-derived growth factor (PDGF). The overexpression or activation of PDGF and PDGF receptors in the lung tissue in patients with PAH activates transduction pathways associated with smooth muscle hyperplasia. This mechanism mimics a neoplastic disorder with increased proliferative response and reduced apoptosis, establishing potential drug targets for PAH.[36,37] Imatinib, an antagonist to the PDGF receptor, was tested for the treatment of PAH in numerous studies. Although it improved exercise capacity and hemodynamics in patients with PAH, treatment was frequently discontinued because of serious adverse events and significant adverse effects such as central nervous system hemorrhage; therefore, its use is not recommended in patients with PAH.[38-40]

Bone morphogenetic protein receptor 2 (BMPR2), a member of the transforming growth factor β receptor superfamily, and protein expression are mainly observed in the endothelium in the normal pulmonary circulation. It is the main genetic factor in hereditary types of PAH, but reduced BMPR2 protein expression is also found in patients with PAH devoid of *BMPR2* mutations.[41] BMPR2 protein expression is reduced in the lungs of patients with severe PAH. Abnormal BMPR2 signaling can adversely impact the endothelial barrier function, driving the transition of PA endothelial cells to smooth muscle–like mesenchymal cells, involved in vascular remodeling.[42] Thus, targeting the BMPR2 pathway has emerged as a novel treatment strategy. Lungs collected from transplanted patients with idiopathic PAH and PAH associated with collagen vascular disease also showed features of marked perivascular inflammation.[33,34] BMPR2 deficiency is also related to inflammatory response that prolongs PH, suggesting the potential link between the BMPR2 pathway and inflammation.[43]

Sotatercept is the main novelty in PAH treatment. It blocks the tumor growth factor β superfamily signaling pathway and could promote rebalancing of BMPR2 signaling and reverse vascular remodeling. The PULSAR (Sotatercept for the Treatment of Pulmonary Arterial Hypertension) trial is a phase 2 randomized, double-blind, placebo-controlled study assessing the efficacy and safety of subcutaneous sotatercept each 21 days (doses of 0.3 mg/kg and 0.7 mg/kg) in adults with PAH receiving background therapy for PAH (including mono-, dual, and triple therapies). It demonstrated a reduction of PVR and improvement in a 6-minute walk test at both doses. Sotatercept was well tolerated and did not cause any significant adverse effects, basically erythrocytosis and thrombocytopenia.[44] Multiple phase 3 trials are planned to support the use of sotatercept as a therapy in patients with PAH.

Tacrolimus binds FK-binding protein 12, a repressor of BMP signaling, and removes it from all 3 BMPR type 1 receptors (ALK1, ALK2, and ALK3), including those preferred by BMPR2 (ALK1 and ALK3). In PA endothelial cells from patients with idiopathic PAH, low-dose FK506 reversed dysfunctional BMPR2 signaling, so it could be useful to reverse medial hypertrophy.[45] A phase 2 clinical trial concluded that low-dose FK506 is safe and increases BMPR2 expression in subgroups of patients with PAH; it also could be beneficial in treating PAH.[46]

Another promising drug is elafin, the endogenous human protein that plays a direct role in tumor suppression. Elafin has been reported to induce PASMC apoptosis by promoting the interaction with BMPR2 caveolin 1, which reversed vascular remodeling in experimental models of PAH.[47,48] Those findings have encouraged the initiation of clinical trials to evaluate the efficacy of elafin in PAH (ClinicalTrials.gov identifier, NCT03522935).

Drugs targeting metabolism and oxidative stress Oxidative stress is another mechanism involved in the pathogenesis and vascular remodeling in

PAH. In this regard, bardoxolone is an emerging promising drug. Bardoxolone methyl activates nuclear factor erythroid 2–related factor 2, a protein that controls the expression of genes involved in protection against free radicals. Additionally, bardoxolone is an NF-κB suppressor, a proinflammatory factor related to immune response regulation. A phase 2 study on the efficacy and safety of bardoxolone in PAH has demonstrated a significant improvement in the results of the 6-minute walk test in patients with PAH on background oral vasodilator therapies as well as good drug tolerance.[49]

Metabolic dysfunction is a hallmark present in PAH-affected vessels and RV where a shift from oxidative phosphorylation to glycolysis and lactate production occurs. In this case, dichloroacetate is another promising molecule.[50] Dichloroacetate was deemed useful in reversing the metabolic switch, thus re-establishing glucose oxidation, when administered in patients with idiopathic PAH.[51] Nevertheless, more clinical trials are needed to further demonstrate the usefulness of this therapeutic strategy.

Drugs decreasing the inflammatory response As mentioned before, an association between PAH with dysregulated immunity and inflammation has been established. Pulmonary vascular lesions include accumulation of inflammatory cells, mainly both macrophages and lymphocytes, but neutrophils and dendritic cells have also been described. Altered T regulatory cell function and changes in B-cell gene expression with an increase in interleukin 6 levels were also observed. Here, tocilizumab is a monoclonal antibody that antagonizes the interleukin 6 receptor and is under evaluation for its use in PAH.[52]

Accumulation of macrophages in lung arterioles is an abnormal feature of PH. Macrophages express high levels of leukotriene B4, which induces proliferation and hypertrophy of PASMCs. In relation to this, Ubenimex (bestatin) has proven to inhibit formation of the proinflammatory mediator leukotriene B4, which plays a role in inflammation in rat models of PAH. Nevertheless, the LIBERTY (A Study of Ubenimex in Patients with Pulmonary Arterial Hypertension) phase 2 study (ClinicalTrials.gov identifier, NCT02664558) failed to improve PVR or exercise capacity in patients with PAH.

Rituximab, an anti-CD20 monoclonal antibody that selectively targets B cells, inducing their lysis, has also been tested after good results were obtained in preclinical models. However, despite the good results of rituximab in decreasing PASMC proliferation, lowering mPAP, and decreasing RV remodeling,[53] few studies support its efficacy in humans. A phase 2 trial on systemic sclerosis–associated PAH will bring new evidence (ClinicalTrials.gov identifier, NCT01086540).

Interleukin 1 (IL-1) is the key player in innate immune response in PAH and contributes to inflammation and vascular remodeling. Interestingly, the recombinant IL-1 receptor anakinra, which inhibits both IL-1α and IL-1β, has been shown to be beneficial in patients with PAH in a pilot study.[54] However, a larger, randomized, placebo-controlled trial is needed to further expand on these findings and explore the potential role of IL-1 blockade in PAH.

Drugs improving vascular function Vasoactive intestinal polypeptide (VIP) leads to relaxation of smooth muscles causing vasodilation and is deficient in patients with PAH. There is a small study with the Aviptadil (VIP) aerosol, in which it was well tolerated after a single application, but its effects on pulmonary hemodynamics and gas exchange were modest.[55] Based on the results of that study, a systemic administration of VIP should be considered to obtain a greater therapeutic effect, and its subcutaneous administration is under investigation in a phase 2 study (ClinicalTrials.gov identifier, NCT03 556 020).

Other vasoactive strategies, such as the use of aldosterone antagonists or angiotensin II receptor antagonists, have also been studied. However, although they are generally well tolerated, the appearance of some severe systemic adverse effects, such as hypotension, bradycardia or hypoxemia, could compromise RV function and everyday life of patients with PAH.[8]

Drugs improving right ventricular function Animal models of RV hypertrophy and failure in PAH have demonstrated downregulation of mitochondrial oxidative metabolism causing glycolysis. Ranolazine is an approved medication for the treatment of chronic stable angina, which inhibits the activation of late sodium ion channels, thus preventing calcium overload. It activates pyruvate dehydrogenase and inhibits fatty acid oxidation. In a rodent model, it successfully reversed metabolic dysfunction and improved cardiac output and exercise capacity.[56] A randomized, placebo-controlled, phase Ib study showed that ranolazine is safe in patients with PAH who receive background PAH therapies, but in that study, it did not reach therapeutic levels and no effects on pulmonary hemodynamics were noted. A phase 2, randomized, double-blind, placebo-controlled multicenter study is currently testing this drug in patients with PAH and RV dysfunction.[57] Similarly, trimetazidine has also been presented as promising therapy for PAH, since it has the potential to activate the RV by increasing glucose oxidation,[58] as evidenced by the results of the TRIMETA-PH (The Role of Trimetazidine on Right Ventricle Function in Pulmonary Arterial Hypertension) clinical trial.[59]

As there has been supportive evidence that β-blockers exert a favorable effect on RV

function, it has been suggested that these drugs may be effective in PAH. Among them, carvedilol, a β1/β2-blocker with vasodilator properties due to its ability to block the α1-adrenergic receptor and release nitric oxide,[60] was not associated with any serious adverse events in a recent trial.[61] However, larger long-term studies are required to examine the safety and efficacy of β-blockers for improving RV function in PAH.

Conclusions Despite currently used therapeutic options and novel drugs being tested in clinical trials, PAH continues to be a disease with a poor prognosis. Due to its low prevalence, it is difficult to perform large clinical trials in order to develop new drugs that would improve prognosis. The development of new potential therapeutic options has provided some alternatives for these patients, but the mechanisms of action and optimal dosage of these drugs remain unclear. Large, randomized trials are necessary to implement these novelty therapies in our clinical practice, and treatment strategies for patients with atypical PAH and cardiopulmonary comorbidities need to be further investigated.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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