Update on Medical Management of Pulmonary Arterial Hypertension

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KEYWORDS

• Pulmonary arterial hypertension • Pulmonary hypertension • Medical management • Therapy • Treatment

KEY POINTS

- Translational research over the past 25 years has led to targeted therapies for pulmonary arterial hypertension
- Upfront combination therapy targeting the endothelin, nitric oxide, and prostacyclin pathways have demonstrated significant clinical benefit
- Aggressive, goal-directed therapy improves patient outcomes and medical therapy has changed pulmonary arterial hypertension from an untreatable fatal disease to a highly manageable condition.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is characterized by pulmonary microvascular remodeling, leading to a progressive increase in pulmonary vascular resistance (PVR); untreated, it results in right ventricular failure and death. In 2019, the World Symposium on Pulmonary Hypertension updated the hemodynamic definitions and clinical classifications of pulmonary hypertension to include a mean pulmonary arterial pressure of 20 mm Hg or greater with pulmonary artery occlusion pressure of 15 mm Hg or less and PVR of more than 3 Wood units.[1] Risk stratification using clinical and hemodynamic parameters drives management decisions, and the progressive nature of PAH has led to recommendations involving aggressive combination therapy earlier in the disease course.

The pathogenesis of PAH (group 1 of the clinical classification of pulmonary hypertension) is complex and the implicated pathways remain central to modern medical therapy. Vasculature remodeling causes smooth muscle cell proliferation, intimal hyperplasia, and inflammation. Currently approved medical therapies target 3 mechanistic pathways: excess endothelin (ET) activity, abnormal nitric oxide (NO) activity, and prostacyclin (PGI_2) deficiency.

DISCUSSION

Endothelin Receptor Antagonists

ETs are an important class of regulatory molecules involved in vascular smooth muscle tone. Since the discovery of ET-1 in 1988,[2,3] 2 additional peptides, ET-2 and ET-3, have been identified.[4] The 2 receptors for these molecules are ET receptor A (ET_A) and ET receptor B, which are both expressed on pulmonary vascular smooth muscle and endothelial cells. Targeting these receptors with ET

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receptor antagonists (ERAs) remains a fundamental component of PAH treatment.[5]

ET-1 production is regulated by vascular endothelial cells to control vascular tone, and its interaction with ET_A in pulmonary vascular smooth muscle cells results in the release of intracellular calcium and vasoconstriction that persists beyond the ET-1–ET_A receptor interaction.[6] Under normal physiologic circumstances, ET-1 activates ET receptor B receptors on endothelial cells resulting in vasodilation mediated by PGI_2 and NO pathways, negative feedback and downregulation of ET-1 production, and ET-1 clearance. In pulmonary hypertension, ET-1 serum concentrations are elevated and ET-1 is found in higher amounts in pulmonary arterial smooth muscle cells.[7–9]

All 3 currently approved ERAs carry a risk of embryo–fetal toxicity and are likely to cause major birth defects based on animal studies. Pregnancy must be excluded before the initiation of treatment in women and prevented with 2 reliable forms of birth control during and up to at least 1 month after stopping therapy. A decrease in sperm counts have been observed in patients on ERA therapy. Peripheral edema is common in the progression of pulmonary hypertension, has been observed after initiation of ERA therapy, and may necessitate drug discontinuation if refractory to medical management.

Bosentan (Tracleer) is an ERA with slight affinity for ET_A over ET receptor B and was the first oral medication approved for the management of PAH. In BREATHE-1, bosentan demonstrated improved PVR, patient exercise capacity by the 6-minute walk test (6MWT), and time to clinical worsening.[10,11] Unlike other currently approved ERAs, bosentan is available for twice daily dosing in both tablet form (62.5 mg and 125.0 mg) and oral suspension (32 mg), allowing for nasogastric administration; however, it carries a risk of hepatotoxicity[12] and requires monthly monitoring of liver function tests. Owing to its significant induction of CYP3A and CYP2C9, bosentan is contraindicated with cyclosporin A and glyburide.

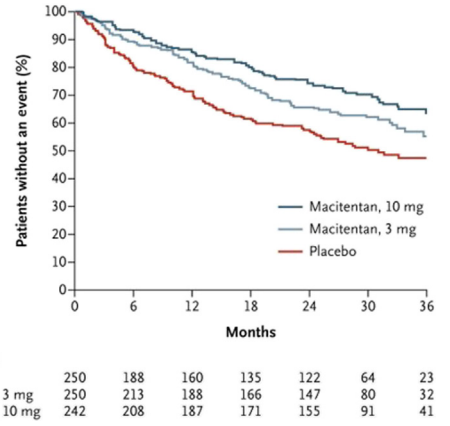
Ambrisentan (Letairis) predominantly affects ET_A and was approved in 2007 at 5 or 10 mg once daily dosing after the ARIES-1 and ARIES-2 randomized placebo-controlled trials demonstrated improvement in 6MWT and time to clinical worsening.[13] Ambrisentan is contraindicated in patients with idiopathic pulmonary fibrosis after it demonstrated an increased risk of disease progression or death in patients with idiopathic pulmonary fibrosis, regardless of pulmonary hypertension in the ARTEMIS-IPF study.[14]

Macitentan (Opsumit) is a dual ERA approved at 10 mg once daily dosing in 2013 after the SERAPHIN trial demonstrated a decrease in morbidity and mortality in patients with PAH.[15] The composite primary outcomes of events related to PAH or any-cause death was reduced by 45% in patients on 10 mg macitentan compared with placebo (**Fig. 1**). A PAH-related event was worsening PAH, need for intravenous or subcutaneous PGI_2 medication, lung transplantation, or atrial septostomy. Worsening PAH was defined as a decrease of 15% in the 6MWT from baseline, worsening symptoms of PAH, and the need for additional PAH treatment. Secondary end points included demonstrated improvement in World Health Organization (WHO) functional class and 6MWT.

Nitric Oxide Pathway Agents

NO production is chronically impaired in PAH. NO, produced in endothelial cells, is a vasoactive mediator that increases cyclic guanosine monophosphate (cGMP) production by activating soluble guanylate cyclase. Release of cGMP results in vasodilation and inhibits smooth muscle cell proliferation.[16,17] An increase in cGMP is accomplished either by the phosphodiesterase type-5 inhibitors (PDE5i) sildenafil and tadalafil, which block cGMP breakdown, or directly by the soluble guanylate cyclase stimulator, riociguat.

Sildenafil (Revatio) is a PDE5i approved for PAH at 20 mg based on improvement of exercise capacity by 6MWT in the SUPER trial.[18] The 20-mg 3 times daily regimen improved 6MWT equivalently to higher doses, despite a dose-dependent improvement in the mean pulmonary artery pressure, cardiac index, and PVR up to 80 mg 3 times



No. at risk

Placebo	250	188	160	135	122	64	23
Macitentan, 3 mg	250	213	188	166	147	80	32
Macitentan, 10 mg	242	208	187	171	155	91	41

Fig. 1. Effect of macitentan on the composite primary end point of a first event related to PAH or death from any cause. (*From* Pulido T, Adzerikho I, Channick RN, et al. Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension. N Engl J Med. 2013;369(9):809-818; with permission.)

daily. Some clinicians do use higher doses in practice. Sildenafil is available as a tablet, oral suspension, or for intravenous use.

Tadalafil (Adcirca, Alyq) is a longer acting PDE5i approved for PAH in 2009. The PHIRST trial demonstrated that 40 mg once daily of tadalafil increased 6MWT after 16 weeks of therapy, even in patients already on background therapy with bosentan.[13] Time to clinical worsening (defined as death, lung or heart–lung transplantation, atrial septostomy, hospitalization owing to worsening PAH, initiation of new PAH therapy, or worsening WHO functional class) was improved in the tadalafil 40 mg group compared with placebo, with incidence of clinical worsening demonstrating a relative risk reduction of 68% ($P = .038$). Similar to sildenafil, tadalafil is contraindicated with the use of nitrates, and both medications carry similar adverse effect profiles. These include headache, flushing, myalgia, and dyspepsia, which typically improve or resolve over time and rarely result in the need for drug discontinuation. Transitions between sildenafil and tadalafil are generally well-tolerated.[19]

Riociguat (Adempas) is an soluble guanylate cyclase stimulator and directly increases cGMP, acting downstream of endogenous NO.[20] To date, it is the only agent approved for inoperable or postoperative chronic thromboembolic pulmonary hypertension. The PATENT-1[21] and CHEST-1[22] trials showed improvement in 6MWT in patients with PAH and patients with chronic thromboembolic pulmonary hypertension with 2.5 mg 3 times daily therapy, respectively. This effect was shown in both treatment-naïve patients and those on background ERA or PGI_2 analogue therapy in PATENT-1. A decrease in PVR and *N*-terminal pro brain natriuretic peptide and improvement in WHO functional class were also observed in both trials. The adverse effects of riociguat include headache, dyspepsia, dizziness, and hypotension. The average decrease in mean arterial pressure in both trials was 9 mm Hg, thus requiring a slow uptitration to the target dose of 2.5 mg 3 times daily. Riociguat is typically started at 1 mg 3 times daily and increased every 2 weeks by 0.5 mg 3 times daily if systolic blood pressure remains greater than 95 mm Hg. When studied in combination with sildenafil, there was no evidence of a positive benefit–risk ratio and more pronounced hypotension.[23] As such, riociguat is contraindicated with nitrates and PDE5i. Unlike PDE5i medications, riociguat is contraindicated in pregnancy.

Given its known deficiency in PAH and the role of drugs indirectly increasing NO, inhaled NO (iNO) is a logical therapeutic agent; iNO was approved in 1999 for the treatment of neonates with pulmonary hypertension.[24,25] Despite a lack of clinical trial data, iNO is recommended for use in acute vasoreactivity testing to identify patients with PAH who may have a long-term clinical and hemodynamic effect from calcium channel blockers[26] and is also used postoperatively after cardiothoracic surgery and for acute right ventricular failure.[27,28] The inhaled route offers theoretic advantages over systemic administration of medication. By directly delivering medication to the target organ, a greater local concentration may be attained with lower systemic levels, decreasing systemic toxicity. Portable iNO has demonstrated hemodynamic effects,[29] and strategies to leverage this factor for long-term ambulatory use are still under investigation.[30]

Prostacyclin Pathway Agents

PGI_2 is a potent vasodilator and inhibitor of platelet aggregation, with an important role in maintaining vascular homeostasis. Its actions are mediated by the IP receptor, causing cyclic adenosine monophosphate production, leading to marked vasodilation and inhibition of smooth muscle cell proliferation.[31,32] There are currently 3 FDA-approved PGI_2 analogues: epoprostenol, iloprost, and treprostinil, as well as an IP receptor agonist, selexipag.

Epoprostenol (Veletri, Flolan), a synthetic form of PGI_2, was the first approved PAH-specific drug in 1996. It requires a pH of 10 for stability in solution and its half-life is 3 to 6 minutes at physiologic conditions, requiring a continuous infusion by intravenous pump.[33] Epoprostenol is a highly effective therapy and is the only PAH therapy shown to improve survival in a randomized controlled trial. The primary end point of this 12-week prospective trial in 81 patients with severe PAH was the 6MWT, where it showed a 31-m improvement compared with placebo, and no patients on epoprostenol died compared with 8 patients in the conventional therapy group.[34] Given its proven efficacy in severe PAH, epoprostenol is recommended as the first-line therapy for patients with WHO functional class IV symptoms and a high risk profile with evidence of right heart failure.[35] PGI_2 side effects are common, may be dose limiting, and include headache, jaw pain, flushing, diarrhea, nausea, and vomiting.[36] Infusions are typically initiated at 1 to 2 ng/kg/min and may be increased in small increments until dose-limiting effects are elicited. Pretreatment or aggressive treatment of transient side effects may improve tolerability during dose escalation. This treatment efficacy must be balanced against significant challenges associated with treatment, including the need for a chronic indwelling venous catheter, daily

preparation of the medication, and experience operating a pump with fleeting windows for troubleshooting owing to the short medication half-life.

Treprostinil (Remodulin [IV/SQ], Tyvaso [IH], Orenitram [PO]) is a more stable PGI_2 analogue with a half-life of 4 to 6 hours. It is approved as a continuous intravenous or subcutaneous infusion and also as an intermittent inhaled or oral formulation. Subcutaneous delivery was shown to improve 6MWT by 16 m versus placebo and avoids the need for an indwelling intravenous catheter, but may cause significant infusion site reactions and pain in some patients.[37] As with epoprostenol, a gradual dose escalation to ensure tolerance is required to achieve maximal efficacy. Transitions between epoprostenol and treprostinil infusions have been shown to be safe and effective.[38,39]

Inhaled treprostinil is administered 4 times daily with a goal dose of 9 inhalations (54 μg) at each dose by handheld nebulizer. Primarily studied as an add-on therapy to oral agents, inhaled treprostinil gained FDA approval in 2011 after showing an improved 6MWT in patients with PAH.[40] More recent data in patients with pulmonary hypertension owing to interstitial lung disease not on background therapy found the 6MWT to be increased at 12 weeks compared with placebo.[41] Inhaled treprostinil is dosed in 4 equally spaced treatment sessions during waking hours, with initial therapy typically starting with 3 breaths per treatment session. If tolerated, regular dose increases until the target dose of 9 breaths per treatment is recommended. If adverse events prevent reaching 9 breaths 4 times per day, the maximum tolerated dose should be continued.

Iloprost (Ventavis) is a shorter acting inhaled PGI_2 that requires 6 to 9 inhalations of 2.5 to 5.0 μg each day, which may limit its widespread use despite also being shown to improve exercise capacity.[42] Inhaled therapy has theoretic advantages, including direct delivery to the site of action, ideally with fewer systemic side effects, although transient cough and throat irritation have been noted.

There are currently 2 FDA-approved oral agents acting on the PGI_2 pathway that are particularly appealing given the challenges associated with parenteral and inhaled therapy. Initially approved by the FDA in 2002, oral treprostinil (Orenitram) monotherapy demonstrated improved 6MWT in treatment-naïve patients with PAH with WHO functional class II or III symptoms in the FREEDOM-M trial.[43] The FREEDOM-C trial examined oral treprostinil as add-on therapy to background ERA and/or PDE5i therapy, but failed to meet its primary exercise tolerance end point. Although this outcome was attributed to the dosing strategy and high rates of adverse events limiting tolerability, the follow-up FREEDOM C2 trial also did not show significant improvement in 6MWT or time to clinical worsening despite having smaller doses available for slower uptitration.[44,45] The more recent FREEDOM-EV trial demonstrated lower rates of clinical worsening (26% vs 36% for placebo; $P = .039$) in patients with PAH on background nonprostanoid monotherapy. A post hoc analysis restratified the group into a higher versus lower risk group (defined by at least 2 of 3: WHO functional class I–II, 6MWT >440 m, and *N*-terminal pro brain natriuretic peptide of <300) showing a more pronounced effect of oral treprostinil therapy in the higher risk group with hazard ratio 0.64 (95% confidence interval, 0.46–0.88; $P = .006$)[46] The recommended starting dose for oral treprostinil is 0.250 mg 2 times a day or 0.125 mg 3 times daily and is usually increased by either 0.25 to 0.50 mg 2 times a day or 0.125 mg 3 times daily every 3 to 4 days as tolerated. The maximum dose is determined by tolerability. Assuming a 70-kg patient, 1 mg 2 times a day of oral treprostinil is approximately equivalent to 10 ng/kg/min of infused treprostinil. Similar to other PGI_2 agents, the most common adverse events are headache, diarrhea, flushing, nausea, and vomiting.

Selexipag (Uptravi) is a selective PGI_2 receptor (IP receptor) agonist approved in 2015 based on the GRIPHON trial. The GRIPHON trial demonstrated a composite end point of mortality or morbidity, including disease progression or worsening of PAH resulting in hospitalization, initiation of parenteral prostanoid therapy or long-term oxygen therapy, or need for either lung transplantation or atrial septostomy (**Fig. 2**).[47] The starting dose is 200 μg twice daily, increased by 200 μg at weekly intervals to a maximum of 1600 μg twice daily as tolerated. The maintenance dose is determined by tolerability of side effects, the most common of which are headache, diarrhea, jaw pain, nausea, myalgias, vomiting, extremity pain, and flushing. If side effects cannot be tolerated, then a dose decrease should occur. Ingestion with food increases the time to maximum plasma levels and may improve tolerability. CYP2C8 inhibitors increase exposure of selexipag and its active metabolites, and the drug is dosed only once daily in patients with moderate (Childs–Pugh class B) hepatic impairment, and it should be avoided in patients with severe hepatic impairment.

TREATMENT STRATEGIES

Risk Stratification

After making a diagnosis of PAH, the use of risk stratification in determining the optimal treatment strategy for patients is paramount, and in line

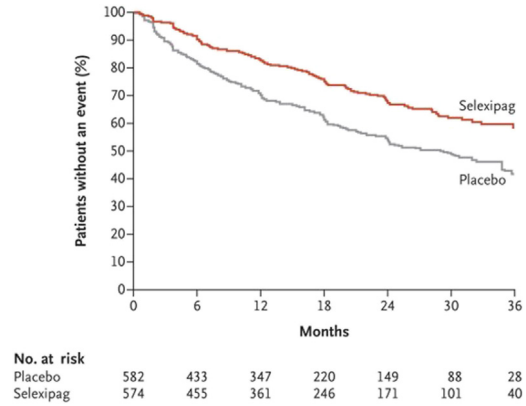


Fig. 2. Effect of selexipag on composite end point of death from any cause or a complication related to PAH (disease progression or worsening of PAH that resulted in hospitalization, initiation of parenteral prostanoid therapy or long-term oxygen therapy, or the need for lung transplantation or balloon atrial septostomy). (*From* Sitbon O, Channick R, Chin KM, et al. Selexipag for the Treatment of Pulmonary Arterial Hypertension. N Engl J Med. 2015;373(26):2522-2533; with permission.)

with recommendations from the World Symposium on Pulmonary Hypertension.[35] There are several registries used for risk stratification including the REVEAL, COMPERA, and French Pulmonary Hypertension Network. Low-risk profiles are associated with improved outcomes and achieving these parameters may serve as a guide for medical therapy.

The REVEAL 2.0 calculator defines low risk patients as 12-month mortality of 2.6% or less and uses a multimodality approach, including clinicodemographic data, vital signs, history of all-cause hospitalizations, 6MWT, brain natriuretic peptide, presence of pericardial effusion on echocardiogram, diffusion capacity for carbon monoxide, and hemodynamic parameters.[48] The COMPERA registry was used to distinguish low-, medium-, and high-risk patients with PAH based on WHO functional class, 6MWT, brain natriuretic peptide or *N*-terminal pro brain natriuretic peptide, right atrial pressure, cardiac index, and mixed venous oxygen saturation.[49] The European Society of Cardiology/European Respiratory Society guidelines use the French registry with 4 criteria defining low risk: WHO functional class I or II, 6MWT of greater than 440 m, right atrial pressure of less than 8 mm Hg, and cardiac index of 2.5 L/min/m^2 or greater. Assessed at baseline and at the first follow-up visit within 1 year, patients who achieved all 4 low-risk criteria had transplant-free survival rate of 91% at 5 years. Patients with 3 or 4 low-risk criteria at first follow-up had a 1-year mortality risk of 0% to 1% compared with those who met zero or 1 low-risk feature with a 1-year mortality of between 13% and 30%.[50]

Combination Therapy Strategies

The majority of patients with PAH will require combination therapy using agents targeting the ERA, PDE5i, and PGI_2 pathways, and there have been several studies examining the tolerability and outcomes associated with combination therapy. In all of the recent large trials, including SERAPHIN[15] and GRIPHON,[47] the majority of the patients were on background PAH therapy. Although these studies examined sequential combination therapy, the landmark AMBITION trial compared upfront combination oral therapy with monotherapy with favorable results, serving as key evidence for the recommendation for upfront dual oral therapy for most patients (**Fig. 3**).[35]

The AMBITION trial examined combination tadalafil and ambrisentan therapy with a combined primary end point of any-cause mortality, hospitalization for worsening PAH, disease progression (worsening WHO functional class and 6MWT), or unsatisfactory long-term clinical response. This study showed that combination therapy had a hazard ratio of 0.5 (95% confidence interval, 0.35–0.72) versus pooled monotherapy, with 18% of combination therapy patients reaching the primary end point versus 34% on ambrisentan monotherapy and 28% on tadalafil monotherapy.[51] **Table 1** summaries the currently available medications for PAH.[52]

Use of Pulmonary Arterial Hypertension Therapy in Non–Group 1 Pulmonary Hypertension

The accurate identification of the underlying etiology is a crucial step in the diagnosis and treatment of PAH. This review discussed the currently approved drugs for the medical management of PAH (ie, group 1 pulmonary hypertension) and how they are used in modern treatment strategies; however, it is essential that targeted therapies are used in patients with appropriate types of pulmonary hypertension. For instance, the most common cause of pulmonary hypertension in developed countries is group 2, owing to left heart disease; however, the FIRST trial was halted early owing to increased mortality in these patients when treated with epoprostenol.[53] Agents targeting the ET and NO pathways have shown mixed results when used in group 2 pulmonary hypertension and targeted PAH therapy is not recommended.[54] As discussed elsewhere in this article, IH treprostinil was recently found to improve 6MWT in patients with

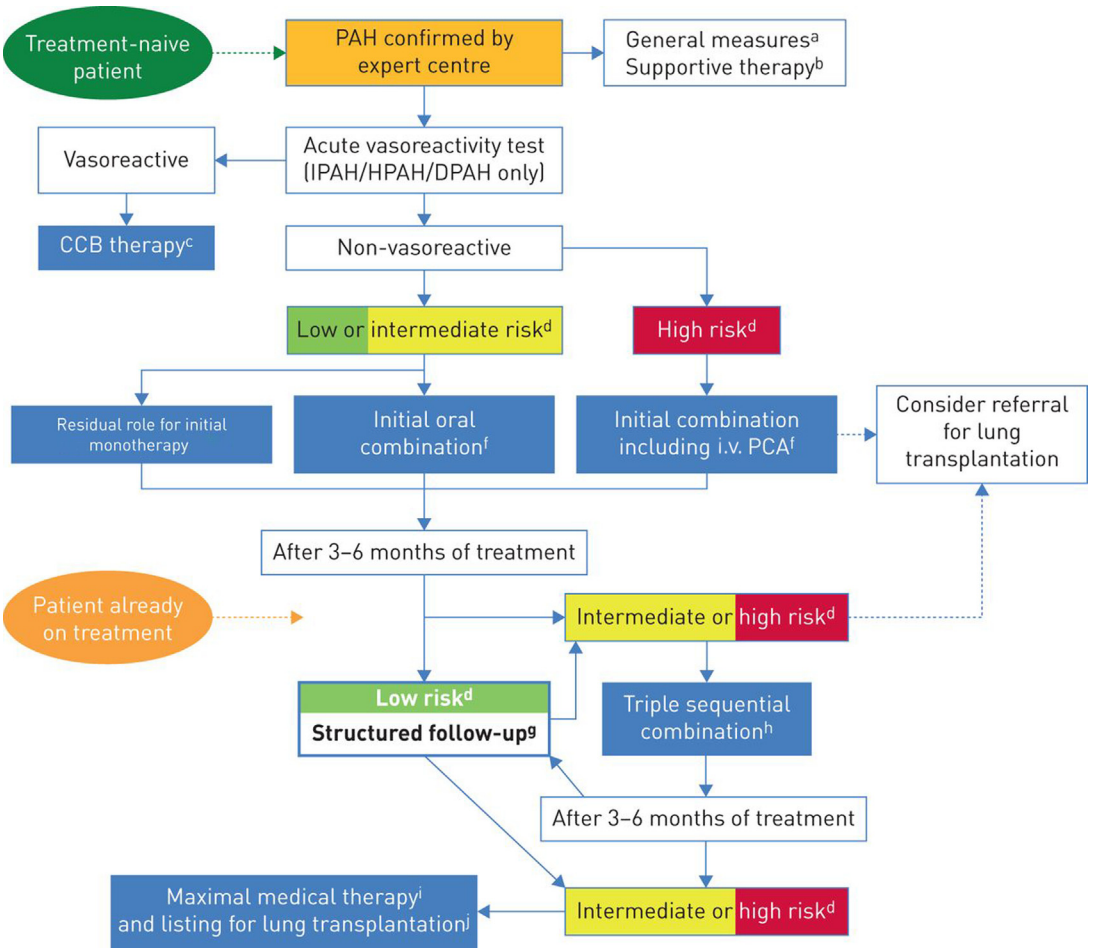


Fig. 3. Treatment algorithm for PAH from the sixth World Symposium on PH. CCB, IPAH/HPAH/DPAH, PCA. [a] 2015 ESC/ERS PH guidelines Table 16; [b] 2015 ESC/ERS PH guidelines Table 17; [c] 2015 ESC/ERS PH guidelines Table 18; [d] 2015 ESC/ERS PH guidelines Table 13; [e] 2015 ESC/ERS PH guidelines Table 19; [f] 2015 ESC/ERS PH guidelines Table 20; [g] 2015 ESC/ERS PH guidelines Table 14; [h] 2015 ESC/ERS PH guidelines Table 21; [i] maximal medical therapy is considered triple combination therapy including a s.c. or an i.v. PCA (i.v. preferred in high-risk status); [j] 2015 ESC/ERS PH guidelines Table 22. (*From* Galiè N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. Eur Respir J. 2019;53(1). Reproduced with permission of the © ERS 2021; DOI: 10.1183/13993003.01889-2018 Published 24 January 2019.)

underlying interstitial lung disease. Treatment with sildenafil is not recommended for patients with group 5 pulmonary hypertension associated with sickle cell disease after sildenafil was associated with increased rates of hospitalization for pain episodes in the Walk-PHaSST trial.[55]

EMERGING THERAPIES AND FUTURE DIRECTIONS

As discussed elsewhere in this article, currently approved medications for PAH target 3 pathways: ET, NO, and PGI_2. Still, the pathogenesis of PAH and its downstream effects leading to pulmonary vascular remodeling and ultimately right ventricular failure are complex and involve inflammation, oxidative stress, growth factor activation, imbalance of proliferative and anti-proliferative signaling, and altered hormonal signaling. New pathways and drugs are under investigation for PAH treatment.[56]

Mutations affecting the bone morphogenetic protein receptor type II are the most common genetic causes of PAH with poorer outcomes compared with other causes of PAH.[57] Bone morphogenetic protein receptor type II mutations lead to transforming growth factor-β receptor overexpression, making it a viable therapeutic target. Sotatercept—a fusion protein that sequesters transforming growth factor-β ligands, thereby

Table 1
Clinical trials of PAH-specific therapies

Clinical Trials	No.	Duration (Weeks)	Background PAH-Specific Therapy	Comparator Group(s)	Primary End Point	Results (S or NS)	PMID
Oral PAH-specific therapies							
Sildenafil							
SUPER 2005	277	12	No	Placebo	Δ 6MWD	6MWD improved (S), TTCW not improved (NS)	16291984
SERAPH 2005	26	16	No	Bosentan	Δ RV mass	Significant reduction in RV mass (S), 6MWD improved (S)	15750042
Singh et al. 2006	20	6	No	Placebo	Δ 6MWD	6MWD improved (S)	16569546
Badesch et al. 2007	84	12	No	Placebo	Δ 6MWD	6MWD improved (S)	17985403
PACES 2008	267	16	Epoprostenol	Placebo	Δ 6MWD	6MWD improved (S), TTCW improved (S)	18936500
Vizza et al. 2017	103	12	Bosentan	Placebo	Δ 6MWD	6MWD not improved (NS)	28874133
Tadalafil							
PHIRST 2009	405	16	No, or bosentan (54%)	Placebo	Δ 6MWD	6MWD improved (S), TTCW improved (S)	19470885
AMBITION 2015	500	78	No (but 1 of the 3 study arms was upfront combination therapy with tadalafil and ambrisentan)	Ambrisentan monotherapy or tadalafil monotherapy	TTCF (including death)	TTCF improved (S), 6MWD improved (S)	26308684
Ambrisentan							
ARIES-1 2008	202	12	No	Placebo	Δ 6MWD	6MWD improved (S), TTCW not improved (NS)	18506008

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Table 1
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Clinical Trials	No.	Duration (Weeks)	Background PAH-Specific Therapy	Comparator Group(s)	Primary End Point	Results (S or NS)	PMID
ARIES-2 2008	192	12	No	Placebo	Δ 6MWD	6MWD improved (S), TTCW improved (S)	18506008
AMBITION 2015	500	78	No (but 1 of the 3 study arms was upfront combination therapy with tadalafil and ambrisentan)	Ambrisentan monotherapy or tadalafil monotherapy	TTCF (including death)	TTCF improved (S), 6MWD improved (S)	26308684
Bosentan							
Channick et al.[11] 2001	32	12	No	Placebo	Δ 6MWD	6MWD improved (S), TTCW improved (S)	11597664
BREATHE-1 2002	213	16	No	Placebo	Δ 6MWD	6MWD improved (S), TTCW improved (S)	11907289
BREATHE-2 2004	33	16	Epoprostenol	Placebo	Δ PVR	PVR not improved (NS), 6MWD not improved (NS)	15358690
BREATHE-5 2006	54	16	No	Placebo	SaO_2, PVR	SaO_2 not reduced, PVR improved (S), 6MWD improved (S)	16801459
EARLY 2008	185	24	No, or sildenafil (16%)	Placebo	Δ PVR and Δ 6MWD	PVR improved (S), 6MWD not improved (NS)	18572079
COMPASS-2 2015	334	16	Sildenafil	Placebo	TTCW (including death)	TTCW not improved (NS), 6MWD improved (S)	26113687
Macitentan							
SERAPHIN 2013	742	115	No, or PDE5i (61%), or oral (5%) or inhaled prostanoid	Placebo	TTCW (including death)	TTCW improved (S)	23984728

MERIT-1 2017	80	16	No, or PDE5i only (46%), or PDE5i + oral or inhaled prostanoid (13%), or oral or inhaled prostanoid alone (3%)	Placebo	Δ PVR	PVR improved (S), 6MWD improved (S)	28919201
Riociguat							
PATENT-1 2013	443	12	No, or ERA (44% - mostly bosentan), or prostanoid (6% - mostly inhaled iloprost)	Placebo	Δ 6MWD	6MWD improved (S), TTCW improved (S), PVR improved (S)	23883378
CHEST-1 2013	261	16	No	Placebo	Δ 6MWD	6MWD improved (S), PVR improved (S)	23883377
PATENT PLUS 2015	18	12	Sildenafil	Placebo	Δ Supine SBP	Terminated owing to excess SAE in the treatment group and no clear benefit	25657022
RESPITE 2017	61	24	ERA	None	Δ 6MWD, Δ NT-proBNP, Δ WHO-FC, Δ hemodynamics	6MWD improved (S), NT-proBNP WHO-FC improved (S), hemody	28889107
REPLACE 2020	226	24	ERA	PDE5i	Clinical improvement	Clinical improvement (S)	33773120
Selexipag							
GRIPHON 2015	1156	71	No, or ERA (15%), PDE5i (32%), or both (33%)	Placebo	TTCW (including death)	TTCW improved (S)	26699168
TRITON 2020	247	26	Macitentan and tadalafil	Placebo	Δ PVR	PVR not improved (NS), 6MWD not improved (NS), TTCW not improved (NS)	NCT02558231

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Table 1
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Clinical Trials	No.	Duration (Weeks)	Background PAH-Specific Therapy	Comparator Group(s)	Primary End Point	Results (S or NS)	PMID
Oral treprostinil							
FREEDOM-C 2012	350	16	ERA and/or PDE-5i	Placebo	Δ 6MWD	6MWD not improved (NS), TTCW not improved (NS)	22628490
FREEDOM-C2 2013	310	16	ERA and/or PDE-5i	Placebo	Δ 6MWD	6MWD not improved (NS), TTCW not improved (NS)	23669822
FREEDOM-M 2013	349	12	No	Placebo	Δ 6MWD	6MWD improved (S), TTCW not improved (NS)	23307827
FREEDOM-EV 2020	690	22	ERA alone (28%), or PDE5i or soluble guanylate cyclase stimulator alone (72%)	Placebo	TTCW	TTCW improved (S), 6MWD not improved (NS)	31765604
Parenteral and inhaled PAH-specific therapies							
Epoprostenol							
Rubin et al.[20] 1990	23	8	No	Conventional therapy[a]	Δ 6MWD and Δ pulmonary hemodynamics	6MWD improved (NS), pulmonary hemodynamics improved (NS)	2107780
Barst et al.[34] 1996	81	12	No	Conventional therapy[a]	Δ 6MWD	6MWD improved (S), PVR and mPAP improved (S), survival improved (S)	8532025
Badesch et al. 2000	111	12	No	Conventional therapy[a]	Δ 6MWD	6MWD improved (S), PVR and mPAP improved (S)	10733441

Treprostinil							
Simnonneau et al. 2002	470	12	No	Placebo	Δ 6MWD	6MWD improved (S), PVR and mPAP improved (S)	11897647
TRUST 2010	44	12	No	Placebo	Δ 6MWD	6MWD improved (S), TTCW improved in a post hoc analysis (S)	20022264
TRIUMPH I 2010	235	12	Bosentan (70%) or sildenafil (30%)	Placebo	Δ 6MWD	6MWD improved (S), TTCW not improved (NS)	20430262
Iloprost							
AIR 2002	203	12	No	Placebo	Δ 6MWD and Δ WHO-FC	6MWD & WHO-FC improved (S), PVR improved (S), TTCW not improved (NS)	12151469
STEP 2006	67	12	Bosentan	Placebo	Δ 6MWD	6MWD improved (S), TTCW improved (S)	16946127
COMBI 2006	40	12	Bosentan	Bosentan monotherapy	Δ 6MWD	Terminated for futility, 6MWD not improved (NS)	17012628

Abbreviations: 6MWD, 6-min walk distance; CCB, calcium channel blocker; IPAH, idiopathic PAH; mPAP, mean pulmonary artery pressure; N/A, not applicable; NS, not statistically significant; NT-pro BNP, *N*-terminal pro brain natriuretic peptide; S, statistically significant; SAE, serious adverse effect; SaO_2, systemic arterial blood oxygen saturation; TTCF, time to clinical failure; TTCW, time to clinical worsening.

[a] Could include CCB, warfarin, supplemental oxygen, digoxin, and/or diuretics, as deemed appropriate.

Adapted from Mayeux JD, Pan IZ, Dechand J, Jacobs JA, Jones TL, McKellar SH, Beck E, Hatton ND, Ryan JJ. Management of Pulmonary Arterial Hypertension. Curr Cardiovasc Risk Rep. 2021;15(1):2; adapted with permission.

decreasing transforming growth factor-β signaling—is being investigated as a novel therapy for PAH. The PULSAR phase II clinical trial (https://clinicaltrials.gov/ct2/show/NCT03496207) enrolled 106 patients with PAH on standard therapy, and preliminary results indicated improvements after 6 weeks in right heart strain, exercise capacity, and a decrease in PVR compared with placebo.[58] SPECTRA (https://clinicaltrials.gov/ct2/show/NCT03738150), a related trial, is examining the effects of sotatercept in adults with PAH and WHO functional class III symptoms.

The role of inflammation in vascular remodeling and progression of PAH is being further recognized, leading to clinical trials targeting signaling factors involved in implicated pathways (eg, IL-1, IL-6, C-reactive protein, tumor necrosis factor-α, monocyte chemoattractant protein-1).[59–61] Anti–IL-1 and anti–IL-6 therapies such as anakinra and tocilizumab have been examined for their use in PAH.[62,63]

Plasmablasts in idiopathic PAH have shown clonality similar to that seen in autoimmune diseases, leading to investigation of rituximab, a B-cell–depleting medication for the treatment of PAH associated with systemic sclerosis. Initial studies have demonstrated safety and biomarkers may identify patients more likely to respond to treatment.[64]

Imatinib, a medication approved for some forms of cancer, has potential benefits on pulmonary blood flow and exercise tolerance, but has only been prescribed for compassionate use owing to safety and tolerability concerns.[65] It remains under investigation, including alternate routes of delivery (ie, inhaled).[66]

SUMMARY

Over the past 25 years, PAH has evolved from an untreatable fatal disease to a highly manageable condition. Translational research has led to breakthroughs in targeted therapies directed toward the ET, NO, and PGI_2 pathways. These treatments produce clinically important benefits, especially when used in combination in a goal-directed approach.

CLINICS CARE POINTS

- Multimodality risk stratification should guide initial therapy for patients with PAH with a goal to achieve low-risk status.
- Combination therapy leveraging the ET, NO, and/or PGI_2 pathways is appropriate for the majority of patients with PAH.
- Individual medications for PAH have varying adverse effect profiles and degrees of patient burden, which should be considered to maximize treatment tolerability.
- Calcium channel blocker therapy provides a sustained hemodynamic benefit in less than 10% of patients, and vasoreactivity testing to identify this uncommon group is recommended in idiopathic PAH, heritable PAH, or drug-induced PAH.
- Intravenous epoprostenol is the recommended therapy for patients with severe PAH and evidence of right ventricular failure given its proven efficacy and mortality benefit.
- Uptitration of PAH therapy, especially for agents acting on the PGI_2 pathway, requires careful attention to adverse side effects.

DISCLOSURE

A.E. Sherman has no relevant financial disclosures. R. Saggar is a consultant for Altavant, Third Pole, Acceleron, Janssen. Consultant and Speaker for United Therapeutics. R.N. Channick is a consultant for several companies producing PAH medications, including Janssen, Bayer, Gossamer, United Therapeutics, and Third Pole. He is a speaker on pulmonary arterial hypertension for Janssen and Bayer.

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