

Current Therapeutics for Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) is characterized by a progressive rise in pulmonary vascular resistance resulting from vascular remodeling, vasoconstriction, and cellular proliferation. For patients diagnosed with PAH, the prognosis is poor, with an approximate 9-15% annual mortality rate. The goal of medical therapy is to improve survival and patients' quality of life. Although PAH is an incurable orphan disease with a high mortality rate, current treatment strategies have led to considerable gains, including exercise capacity, hemodynamic and time to clinical worsening. General disease management options include avoidance of salt in the diet, oxygen, appropriate vaccinations and routine health maintenance, and avoidance of pregnancy. Traditional treatments include warfarin, diuretics, and calcium channel blockers (if patients are deemed "responders" during cardiac catheterization). Currently, three classes of drugs are approved for the treatment of PAH based on results from clinical trials – prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors. Clinical practice patterns have shifted in favor of earlier diagnosis, aggressive front line treatment, and upfront versus stepwise combination therapy. Future drug development targeting other molecular pathways of pulmonary vascular disease is essential for advancing our understanding of this disease. The purpose of this review is to summarize recent guidelines for the management of pulmonary arterial hypertension, and highlight clinical topics for the primary care physician.

Key Words: Current therapy • Pulmonary artery hypertension

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a complex disorder in which pulmonary arterial obstruction leads to elevated pulmonary arterial resistance and right ventricular dysfunction. The prognosis of PAH is poor, with an approximate 9-15% annual mortality rate utilizing contemporary therapy.¹⁻³ The goal of medical therapy is to improve survival and patients' quality of life. General

disease management includes avoidance of salt in the diet, oxygen, appropriate vaccinations and general health maintenance, and avoidance of pregnancy. Traditional treatments include warfarin, diuretics, and calcium channel blockers (if patients are deemed "responders" during cardiac catheterization). Based on core scientific research and clinic trials, several targeted therapies are now approved, including prostanoids, endothelin receptor antagonists (ERA) and phosphodiesterase (PDE) inhibitors. Our review seeks to summarize recent guidelines for PAH management, and underscore useful clinical topics for the primary care physician.

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NEW CLASSIFICATION OF PULMONARY HYPERTENSION

There are 5 groups of pulmonary hypertension (PH) based on the most recent 2008 Dana Point classification:

(1) PAH; (2) PH associated with left-side heart disease; (3) PH associated with lung disease/hypoxia; (4) chronic thromboembolic PH (CTEPH); and (5) miscellaneous.⁴

DEFINITION

PAH is defined by a resting mean pulmonary artery pressure (PAP) ≥ 25 mmHg, pulmonary vascular resistance (PVR) > 3 Wood units, and pulmonary capillary wedge pressure < 15 mmHg.⁵ The normal mean PAP at rest is 14 ± 3 mmHg, with an upper limit normal of 20 mmHg.^{6,7}

EPIDEMIOLOGY

Comparative epidemiological data on the prevalence of the different groups of PH is currently based on registry data from around the world. The registry to evaluate early and long-term PAH disease management (REVEAL) and the pulmonary hypertension connection (PHC) are both United States (US) based registries and, despite their differences in size, report similar findings.⁸ In an echocardiographic survey of 4579 patients, the prevalence of PH (defined as systolic pulmonary pressure > 40 mmHg) was 10.5%.⁹ Among the PH patients, 78.7% had group 2 PH, 9.7% group 3, 4.2% group 1, and 0.6% group 4. This review will focus on group 1 PH, which includes idiopathic, heritable, and anorexigen-associated PAH, as well as PAH associated with a variety of conditions [including connective tissue disease (CTD), congenital heart disease (CHD)], portopulmonary hypertension (PoPH), and rare conditions such as pulmonary venoocclusive disease (PVOD), pulmonary capillary hemangiomatosis (PCH), and persistent pulmonary hypertension of the newborn.

PAH is a rare disease with a prevalence of about 15 cases per million.¹⁰ The global prevalence of PAH is hard to estimate because an accurate diagnosis relies on right heart catheterization for confirmation, which is not possible in many areas of the world.

PAH has an incidence of 2.4 cases per million per year.⁹ PAH associated with HIV is more prevalent in France, and PAH associated with connective tissue disease is more prevalent in the US.⁸

PROGNOSIS

PAH is a fatal disease and, when left untreated, is associated with mortality statistics that are quite similar to many cancers. The one-year incident mortality rate of PAH remains high (15%) even under modern therapy protocols.¹⁻³ The prognosis of PAH appears to vary according to etiology, with CTD-associated PAH (APAH) having the worst prognosis and CHD-APAH having the best prognosis.^{1,8,11} Predictors of poor prognosis of PAH include advanced functional class, poor exercise capacity, high right atrial pressure, significant right ventricular dysfunction, evidence of right ventricular failure, syncope, low cardiac index, elevated brain natriuretic peptide (BNP), pericardial effusion and tricuspid annular plane systolic excursion (TAPSE) > 1.5 cm by echocardiography (Table 1).¹²⁻¹⁶

Risk estimation utilizing risk modeling equations may help physicians better predict individual patient prognosis. REVEAL is a prospective registry study that enrolled patients with a diagnosis of world health organization (WHO) group 1 PH at 54 PAH specialty care facilities in the US.¹⁷ Nineteen parameters were independently associated with survival, with PoPH, a family history of PAH, men > 60 years of age, modified New York Heart Association (NYHA)/WHO Functional Class (FC) IV, and PVR > 32 Wood units associated with > 2 -fold increase in the hazard ratio. Four variables were associated with an increase in 1-year survival: modified NYHA/WHO FC I, 6-minute walk test distance (6MWD) ≥ 440 m, BNP < 50 pg/mL and percent predicted diffusing capacity of the lung for carbon monoxide (DLCO) $\geq 80\%$.¹⁸

Recent validation of this equation in the REVEAL incident cohort permits its use now in the clinic and in research trials to determine its clinical applicability. In addition, the PHC and the French group equations, developed independently, have now been validated in an external cohort of 5 randomized placebo-controlled trials.¹⁹ All of these equations will need adaptation to improve clinical applicability.

GENERAL MEASURES

Diet

For patients with diagnosed PAH, a sodium re-

Table 1. Parameters with established importance for assessing disease severity, stability and prognosis in PAH

Better prognosis	Determinants of prognosis	Worse prognosis
No	Clinical evidence of RV failure	Yes
Slow	Rate of progression	Rapid
No	Syncope	Yes
I, II	WHO FC	IV
Longer (> 500m)	6 minute walk distance	Shorter (< 300 m)
VO ₂ max > 15 mL/min/Kg	Cardiopulmonary exercise testing	VO ₂ max < 12 mL/min/Kg
Normal or near-normal	BNP/NT-proBNP plasma level	Very elevated and rising
No pericardial effusion	Echocardiographic findings	Pericardial effusion
TAPSE > 2.0 cm		TAPSE < 1.5 cm
Right atrial pressure < 8 mmHg and cardiac index ≥ 2.5 L/min/m ²	Hemodynamics	Right atrial pressure > 15 mmHg or cardiac index ≤ 2.0 L/min/m ²

Adapted from ESC/ERS/ISHLT guideline (reference 16).

BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; TAPSE, tricuspid annular plane systolic excursion; WHO-FC, world health organization functional class.

stricted diet (less than 2400 mg per day) and fluid restriction are advised. Additionally, avoidance of fluid retention is important in PAH patient care. Patients should be instructed to weigh themselves every day and to contact their doctor if weight gain of 3-4 pounds (1.4-1.8 kg) over 1 or 2 days is observed.⁵

Oxygen

All patients should maintain systemic oxygen saturation greater than 92% at rest, during sleep, and with exercise. Oxygen is often underutilized due to social embarrassment. Furthermore, sleep oximetry and formal sleep studies to best understand individual patient circumstances are recommended.⁵

Physical activity

Patients with PAH should be encouraged to be active within symptom limits. A pivotal study done in Germany demonstrated an improvement in exercise capacity in PAH patients on PAH specific therapy in an intensive cardiopulmonary inpatient training program.²⁰ Mild breathlessness is acceptable, but patients should avoid exertion that induces severe breathlessness, dizziness or chest pain. Patients should be limited to lifting no more than 10 lbs (4 kg) in each arm to avoid straining and should always maintain adequate hydration.

Pregnancy

The hemodynamic fluctuations caused by pregnancy, labor, delivery, and the postpartum period are stressful to PAH

patients. Pregnancy is associated with a high maternal mortality in PAH patients (30-50%).²¹ Current guidelines recommend that pregnancy should be avoided or terminated early in women with PAH. Some patients, despite counseling by their physician, choose to continue with their pregnancy. In addition, some women first present with PAH during pregnancy. When a patient becomes pregnant, close follow-up in a medical center by a multidisciplinary team with the ability to prescribe PAH therapy is imperative.²²

Travel

Exposure to high altitudes may contribute to hypoxia induced pulmonary vasoconstriction and may not be well tolerated by PAH patients. In-flight oxygen (O₂) support should be considered for patients classified as FC III/IV and for those with arterial O₂ tension < 60 mmHg. Patient should not travel at altitudes above 1500-2000 meters without a supplemental O₂ supply. And when traveling, written information about the disease and how to contact a doctor should be kept with patients.²³

Immunization

Pneumonia is the cause of death in 7% of PAH patients. Yearly influenza and pneumococcal pneumonia vaccinations (every 5 years) are recommended.²³

GUIDELINES FOR DRUG THERAPY

Traditional PAH therapy includes diuretics, digoxin,

vasodilators, and warfarin (Table 2).²⁴⁻²⁹ Since 1990, nine therapeutics have been approved for the treatment of PAH by the US Food and Drug Administration (FDA) (Tables 3 and 4).¹⁶

Specific PAH-drug therapies

Prostanoids

Prostacyclin is produced predominantly by endothelial cells and induces vasodilatation of all vascular beds. This compound is the most potent endogenous inhibitor of platelet aggregation, appearing to have both cytoprotective and antiproliferative activities.³⁰ There is evidence that a relative prostacyclin deficiency may contribute to the pathogenesis of PAH.

Epoprostenol

Intravenous epoprostenol (synthetic prostacyclin) was the first prostacyclin analogue used for the treatment of PAH and is a first-line therapy for patients with severe PAH. Epoprostenol is available as a stable freeze-dried preparation that needs to be dissolved in alkaline buffer for intravenous infusion. Epoprostenol has a short half-life (3-5 minutes) and a rapid onset of action, reaching plasma steady-state concentrations within 15 minutes. It is stable at room temperature for only 8 hours after dissolved in a buffer. It needs to be given continuously by an infusion pump and a permanent catheter. Continuous intravenous administration of epoprostenol improves survival in patients with idiopathic PAH (IPAH)^{31,32} and in those with PAH associated with the scleroderma spectrum of diseases.³³ Epoprostenol improves symptoms, exercise capacity and hemodynamics, and is the only treatment shown to improve survival in

IPAH.³² It was approved by the FDA in 1995 for the long-term treatment of IPAH and PAH associated with scleroderma in functional class (FC) III/IV patients.³⁴ Long-term efficacy has also been shown in open label registries of IPAH,^{13,14} as well as in other APAH conditions³⁵⁻³⁷ and inoperable CTEPH.^{34,38} Treatment with epoprostenol begins at a dose of 2-4 ng·kg⁻¹·min⁻¹, and is increased gradually if no severe side effects arise. Potential side effects include flushing, headache, jaw pain, diarrhea and leg pain. For the majority of patients, the optimal dose of epoprostenol varies between individual patients, ranging between 20 and 40 ng·kg⁻¹·min⁻¹.^{13,14}

Serious adverse events related to the delivery system include pump malfunction, local site infection, catheter obstruction and sepsis. However, guidelines for the prevention of central venous catheter bloodstream infections have been proposed.³⁹ Abrupt discontinuation of the epoprostenol infusion should be avoided as it may lead to rebound increases in pulmonary arterial pressure with severe symptomatic deterioration, and even death.

Because of the complexity of its administration, epoprostenol is generally reserved for patients with advanced PAH and those who have had poor response to oral therapies.

Iloprost

Iloprost is a synthetic analogue of prostacyclin available for intravenous, oral and inhaled administration. Inhaled iloprost was approved in 2004 by the FDA for the treatment of FC III/IV PAH and has the theoretical advantage of being selective for the pulmonary circulation with less systemic hypotension. Inhaled iloprost has been evaluated in one randomized control trial (RCT) in which daily repetitive iloprost inhalations (6-9

Table 2. Traditional PAH therapies

Therapy	Suggestions
Oxygen	Ambulatory O ₂ may be considered when there is evidence of symptomatic benefit and correctable desaturation on exercise
Diuretics	It is necessary to monitor renal function and electrolyte in patients to avoid hypokalemia and pre-renal failure
Digoxin	Heart failure treatment and rate control
Anticoagulation	The potential benefits of oral anticoagulation should be weighed against the risks in patients when there is an increased risk of bleeding. Advice regarding the target international normalized ratio (INR) in patients with IPAH varies from 1.5-3.0
Calcium channel blockers	use of an oral CCB in patient without right-heart failure who has a positive vasodilator test response

CCB, calcium channel blocker; IPAH, idiopathic pulmonary artery hypertension; PAH, pulmonary artery hypertension.

Table 3. Specific PAH-drug therapies

Medication	Approved indications	Dose	Side-effect
Prostacyclin			
Epoprostenol (intravenous)*	PAH (Europe) IPAH and PAH-CTD (USA, Canada)	Initiated at a dose of 2-4 ng·kg ⁻¹ ·min ⁻¹ , and increased gradually if no severe side effects. The optimal dose varies between individual patients, ranging in the majority between 20 and 40 ng·kg ⁻¹ ·min ⁻¹	Flushing, headache, jaw pain, diarrhea and leg pain
Iloprost (inhalation)*	IPAH (European Union) PAH(USA)	Initiated at a dose of 2.5 µg/inhalation and increased to 5 µg/the maximum recommended dose is 45 µg/d. inhalation	Flushing, jaw pain
Iloprost (intravenous)	IPAH, PAH-CTD and CTEPH (New Zealand)		
Treprostinil (subcutaneous)*	PAH (USA, Canada) IPAH (European Union)	Initiated at a dose of 1-2 ng·kg ⁻¹ ·min ⁻¹ , the optimal dose between 20 and 80 ng·kg ⁻¹ ·min ⁻¹	Infusion site pain
Treprostinil (intravenous)*	PAH (USA, Canada)	Dose is between two and three times higher than Epoprostenol	Flushing, headache, jaw pain, diarrhea and leg pain
Treprostinil (inhaled)	PAH (USA)	Start by taking 3 breaths four times a day with a goal of nine breath four times a day	
Beraprost	PAH (Japan, Korea)	120 mcg four times a day	Headache, flushing, jaw pain and diarrhea
Endothelial receptor antagonist			
Ambrisanten*	PAH (USA, Canada, European Union)	5 mg once daily which can be increased to 10 mg once daily	Include low extremity edema and nasal congestion, testicular atrophy, male infertility
Bosentan*	PAH (USA, Canada, European Union)	Started at the dose of 62.5 mg twice daily and titrated to 125 mg twice daily after 4 weeks	Potential hepatotoxicity and anemia, testicular atrophy, male infertility
Phosphodiesterase type-5 inhibitor			
Sildenafil [†]	PAH (USA, Canada, European Union)	20 mg orally 3 times daily	Headache, flushing, dyspepsia and epistaxis
Tadalafil	PAH (USA)	40 mg daily	Headache, flushing, dyspepsia and epistaxis

* Taiwan health insurance approved medication for idiopathic pulmonary arterial hypertension; [†] Taiwan health insurance approved medication for idiopathic or connective tissue disease-associated pulmonary arterial hypertension.

IPAH, idiopathic pulmonary artery hypertension; PAH, pulmonary artery hypertension; PAH-CTD, connective tissue diseased associated PAH; USA, United States of America.

times, 2.5-5 mg·inhalation⁻¹, median 30 mg daily) were compared with placebo inhalation in patients with PAH and CTEPH.⁴⁰ The study showed an increase in exercise capacity and improvement in symptoms, PVR and clinical worsening events in enrolled patients. A second RCT with 60 patients on background oral bosentan did not reach its endpoint, but did demonstrate safety in those study subjects randomized to the addition of inhaled

iloprost in comparison with placebo.⁴¹ After these 2 trials, the FDA approved iloprost for PAH. Overall, inhaled iloprost was well-tolerated, with flushing and jaw pain being the most frequent side effects. Inhalation of iloprost is initiated at a dose of 2.5 µg/inhalation and increased to 5 µg/inhalation as tolerated. The maximum recommended dose is 45 µg/d. Because of iloprost's short half life (20-30 minutes), the full inhalation course

Table 4. Evidence-based treatment algorithm for group 1 pulmonary hypertension patients

Recommendation-evidence	WHO-FC II	WHO-FC III	WHO-IV
I-A	Ambrisentan Bosentan Sildenafil	Ambrisentan Bosentan Sildenafil Epoprostenol i.v. Iloprost inhaled	Epoprostenol i.v.
I-B	Tadalafil	Tadalafil Treprostinil s.c., inhaled	
IIa-C		Iloprost i.v. Treprostinil i.v.	Ambrisentan Bosentan Sildenafil Tadalafil Iloprost inhaled, i.v. Treprostinil s.c., i.v., inhaled Initial combination therapy
IIb-B		Beraprost	

Adapted from ESC/ERS/ISHLT guideline (reference 16).

i.v., intravenous; s.c., subcutaneously; WHO-Fc, World Health Organization functional class.

per prescription usually involves 6 to 9 separate inhalation events per day. Continuous intravenous administration of iloprost appears to be as effective as epoprostenol in a small series of patients with PAH and CTEPH.⁴² Effects of oral iloprost have just been under clinical assessment of its safety and efficacy in PAH.

Treprostinil

Treprostinil is a tricyclic benzidine analogue of epoprostenol, with sufficient chemical stability to be administered at room temperature. This characteristic allows administration of the compound by the intravenous as well as the subcutaneous (SC) route. The effects of SC treprostinil in PAH were studied in the largest worldwide RCT, and showed improvements in exercise capacity, hemodynamics and symptoms.⁴³ The greatest exercise improvement was observed in patients who were more compromised at baseline, and in subjects who were able to tolerate the upper quartile dose ($> 13.8 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Infusion site pain was the most common adverse effect of treprostinil. Further support of its efficacy was reported in a large open-label study in patients with IPAH or CTEPH followed up for a mean of 26 months.⁴⁴ Treatment with SC treprostinil is initiated at a dose of $1\text{-}2 \text{ ng}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, with doses increasing at a rate limited by the extent and nature of any side effects (local site pain, flushing, headache). The optimal dose varies be-

tween individual patients, ranging between 20 and 80 $\text{ng}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in the majority of patients.

Bioequivalence data on intravenous versus SC treprostinil prompted clinical trials to explore dosing and safety in PAH.⁴⁵ Tapson et al. reported that newly diagnosed patients started on intravenous therapy dramatically improved 6MWD and hemodynamics.⁴⁶ Gomberg-Maitland et al. transitioned 31 FC II/III PAH patients from intravenous epoprostenol to intravenous treprostinil to determine dose equivalence, safety, and feasibility of transition. Twenty-seven patients completed the transition.⁴⁷ The data suggest that transition from intravenous epoprostenol to intravenous treprostinil is safe and effective. The effects of intravenous treprostinil appear to be comparable with those of epoprostenol, but at a dosage which is between two and three times higher.⁴⁶⁻⁴⁸ It is, however, more convenient for the patient because the reservoir can be changed every 48 hours as compared with 24 hours with epoprostenol due to its elimination half-life (about 4.5 hours). The FDA approved the use of intravenous treprostinil in FC II, III and IV PAH patients in whom subcutaneous infusion is not tolerated.

Inhaled treprostinil sodium in patients with severe pulmonary arterial hypertension (TRIUMPH), a phase 3 RCT, proved that inhaled treprostinil improved exercise capacity and quality of life, and is safe and well-toler-

ated in patients on background therapy with either the ERA bosentan or the PDE type-5 inhibitor.⁴⁹ Oral treprostinil is currently being evaluated in RCTs in PAH.

Beraprost

Beraprost is the first oral prostacyclin analogue. It is approved for the treatment of PAH in Japan, but not in the US. There are few published randomized trials which examine beraprost in PAH. Two RCTs^{50,51} with this compound have shown an improvement in exercise capacity, but this exercise effect only persists up to 3-6 months without hemodynamic benefits. The most frequent adverse events were headache, flushing, jaw pain and diarrhea.

Endothelin receptor antagonists

Activation of the endothelin system has been demonstrated in both plasma and lung tissue of PAH patients.⁵² Endothelin-1 is a vasoconstrictor and a smooth muscle mitogen that produces an effect by binding to two distinct receptor isoforms in the pulmonary vascular smooth muscle cells, endothelin-A and endothelin-B receptors. The efficacy in PAH of the dual endothelin-A and endothelin-B receptor antagonist drugs and of the selective endothelin receptor antagonist (ERA) compounds appears to be comparable based on clinical trial data in PAH.^{53,54}

Bosentan

Bosentan is an oral active dual endothelin-A and endothelin-B receptor antagonist and the first molecule of its class that was synthesized. Bosentan has been evaluated in PAH (idiopathic, CTD-APAH and Eisenmenger's syndrome) in five RCTs [Pilot, Bosentan Randomised trial of Endothelin Antagonist Therapy (BREATHE)-1, BREATHE-2, BREATHE-5, and Endothelin Antagonist trial in mildly symptomatic pulmonary arterial hypertension patients (EARLY)], which have shown significant improvement in exercise capacity, functional class, hemodynamics, echocardiographic and Doppler variables, and time to clinical worsening (TCW).⁵⁵⁻⁵⁸ Two RCTs have enrolled exclusively patients classified as WHO FC II⁵⁸ or patients with Eisenmenger's syndrome.⁵⁹ This has resulted in regulatory authority approval for the use of bosentan in the treatment of WHO FC II PAH patients and also in patients with PAH associ-

ated with congenital systemic-to-pulmonary shunts and Eisenmenger's syndrome. Bosentan treatment is started at the dose of 62.5 mg, twice daily, and titrated to 125 mg twice daily after 4 weeks. In pediatric patients doses are adjusted according to body weight. Long-term observational studies have demonstrated the durability of the effect of bosentan in adult IPAH patients over time.^{12,34,60} Bosentan is widely used in patients with PAH. Due to potential hepatotoxicity and anemia, the FDA requires that liver function tests be administered monthly, and a hematocrit test given every 3 months. Increases in hepatic aminotransferases occurred in about 10% of the subjects but were found to be dose-dependent and reversible after dose reduction or discontinuation. Fatal hepatotoxicity case reports after years on therapy mandate the continuance of monthly testing indefinitely. The development of edema is another side effect, but should improve with diuretic therapy. Contraception is recommended due to potential teratogenicity. There is concern that the ERA may cause testicular atrophy and male infertility. There is potential for drug interactions due to its induction of cytochrome P450 (CYP) 2C9 and 3A4 isozymes.

Ambrisentan

Ambrisentan is a relatively selective antagonist for the endothelin-A receptor. Ambrisentan has been evaluated in a pilot study⁶¹ and in two large RCTs [Ambrisentan in pulmonary arterial hypertension, Randomized, double-blind, placebo-controlled, multicentre, Efficacy Study (ARIES) 1 and 2], which demonstrated symptom improvement, improved exercise capacity and hemodynamics, and TCW of patients with IPAH and CTD-APAH and HIV infection-APAH.⁶² Ambrisentan was approved by the FDA in 2007 for the treatment of FC II and III PAH patients. The current approved dose is 5 mg once daily, which can be increased to 10 mg once daily if the drug is tolerated at the initial dose.

Ambrisentan at a dose of 5 mg was well-tolerated in a small group of patients in which treatment with either bosentan or sitaxsentan was discontinued due to liver function test abnormalities.⁶³ The FDA recently removed the risk of possible liver injury from the Boxed Warnings and Precautions section of the 2011 Ambrisentan Prescribing Information.⁶⁴ Monthly testing for serum liver enzymes is no longer required for distribution of

ambrisentan, but monthly pregnancy testing in women of child bearing age is still required. Potential side effects include low extremity edema and nasal congestion. Precautions regarding contraception and testicular atrophy are similar to bosentan.

Sitaxsentan

Sitaxsentan is a selective endothelin-A receptor antagonist, which has been assessed in two RCTs,^{65,66} where improvements in both exercise capacity and FC were demonstrated. In 2010, following two cases of fatal liver toxicity, it was announced that sitaxsentan would be removed from the market and all clinical study use.

Phosphodiesterase type-5 inhibitors

Cyclic guanosine monophosphate (GMP) causes vasorelaxation through the nitric oxide/cGMP pathway, but its effects are short-lived due to the rapid degradation of cGMP by phosphodiesterase (PDE). PDE-5 inhibitors, such as sildenafil and tadalafil, might therefore be expected to enhance or prolong the effect of vasodilatation. In addition, PDE-5 inhibitors exert antiproliferative effects.^{67,68} Since the pulmonary vasculature contains substantial amounts of PDE-5, the potential clinical benefit of PDE-5 inhibitors has been investigated in PAH and the results have been promising.⁶⁹

Sildenafil

There have been reported effects of sildenafil in IPAH, CTD-, CHD-APAH and CTEPH.⁷⁰⁻⁷² The SUPER-1 (Sildenafil Use in Pulmonary arterial hypertension) study was a randomized, double-blind, placebo-controlled trial that enrolled 278 PAH patients (IPAH, CTD- and corrected CHD-APAH), treated with placebo or sildenafil at a dosage of 20, 40, or 80 mg orally, 3 times daily for 12 weeks. Favorable results on exercise capacity, symptoms and hemodynamics were noted in all active doses.⁷³ The FDA approved dose is 20 mg orally 3 times daily based on the 6MWD results at 12 weeks. Notably, all of the open label extension data is based on a dosage of 80 mg orally 3 times daily. Side effects include headache, flushing, dyspepsia and epistaxis. However, pre-dose acetaminophen for the first week after treatment initiation helps alleviate the headache.

Tadalafil

The Pulmonary arterial Hypertension and ReSponse to Tadalafil (PHIRST) trial tested long-acting PDE-5 inhibitors in PAH. Four hundred and six PAH patients (~50% were on background bosentan therapy) were treated with tadalafil at doses of 5, 10, 20 or 40 mg orally once daily. Exercise capacity, symptoms, hemodynamics and TCW improved most significantly at the highest dose (40 mg).⁷⁴ The side-effect profile is similar to that of sildenafil. The FDA approved the 40 mg dose for FC II-IV PAH patients in May 2009.

Combination therapy and goal-oriented therapy

The term combination therapy describes the simultaneous use of more than one PAH-specific class of drugs, e.g. ERAs, PDE-5 inhibitors, prostanoids and investigational therapies. The goal of combination therapy is to maximize efficacy and minimize toxicity. As the field of PAH progresses, combination therapy has become the standard of care in many PAH centers. Numerous case reports have suggested that various drug combinations appear to be safe and effective.^{41,49,57,75-79} Hoepfer et al. demonstrated that the use of combination therapy according to predefined treatment goals proved to be better in all objective outcomes compared with a historical control group from their practice.⁷⁸

The results of several RCTs evaluating combination therapy for PAH have been published. The relatively small BREATHE-2 study⁵⁷ showed a trend to an improved hemodynamic effect of the initial combination epoprostenol-bosentan as compared to epoprostenol alone, but the trial was halted due to futility. Apparently, there were 2 deaths in this study. The STEP-1 study⁴¹ addressed the safety and efficacy of 12 weeks of therapy with inhaled iloprost in addition to bosentan, and found a marginal increase in the post-inhalation 6MWD, therefore not reaching its endpoint. Additionally, Hoepfer et al. demonstrated that this same combination was not effective in a randomized unblinded trial.⁷⁶ It is unclear if all combinations are good and who will benefit most.⁸⁰ The Pulmonary Arterial hypertension Combination study of Epoprostenol and Sildenafil (PACES) trial is the best completed combination trial in this disease state.⁸¹ PACES addressed the effects of adding sildenafil to epoprostenol in 267 FC III PAH patients. The most pertinent findings of this study were significant improve-

ments after 12 weeks in 6MWD, TCW, and survival, with all seven deaths occurring in the placebo group. TRIUMPH studied the effects of inhaled treprostinil in patients already treated with bosentan or sildenafil.⁸² The primary end-point, median change in 6MWD at peak exposure, improved by 20 meters compared with the placebo ($p < 0.0006$). There were no significant differences in Borg dyspnea index, FC and TCW. Additional data from RCTs are available for the combination of ERAs and PDE-5 inhibitors. In the subgroup of patients enrolled in the EARLY study,⁵⁸ (bosentan in FC II PAH patients) who were already on treatment with sildenafil, the hemodynamic effect of the addition of bosentan was comparable with that achieved in patients without background sildenafil treatment.

Drug-drug interactions are not well-studied in PAH. A pharmacokinetic interaction exists between bosentan and sildenafil, acting as inducers and inhibitors of cytochrome P450 CYP3A4, respectively. The co-administration of both substances results in a decline of sildenafil plasma levels and in an increase in bosentan plasma levels.⁸³ So far, there is no indication that these interactions are associated with reduced safety,⁸⁴ but the issue of whether the clinical efficacy of sildenafil is significantly reduced is still under debate. No pharmacokinetic interactions have been reported between sildenafil and ambrisentan. A pharmacokinetic interaction is known with tadalafil and bosentan (citation needed).⁸⁵ The PHIRST study's⁷⁴ substudy of subjects on background bosentan appears to demonstrate clinical improvements despite this interaction.

There are many open questions regarding combination therapy, including the choice of combination medications, when to switch and when to combine medications. Goal-oriented strategies may provide predefined, structured, and reproducible ways for clinicians to assess response to therapy. Goal-oriented therapy is becoming a standardized treatment strategy, but the choice of goals requires refinement to correlate closely with clinical outcome.

CONCLUSION

PAH is a rare fatal disease with a number of therapeutic options. Prostacyclin infusion should be utilized

in severe disease and perhaps earlier to improve outcomes, but this will require more specific goal-oriented trials. If patients are failing monotherapy, combination therapy should be considered. Lung transplantation, not discussed in this review, is a final option if available and the patient is suitable for transplantation. Risk prediction equations help define prognosis but need further study before its utility can be understood. Identification of new therapeutic targets and a better understanding of disease mechanisms will help further advance this field.

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