DISEASE MANAGEMENT

Recently approved drugs offer significant improvements for treatment options in pulmonary arterial hypertension

Treatment of pulmonary arterial hypertension (PAH) has come a long way in the last decade, with new and emerging options for treatment, including prostanoids, endothelin receptor antagonists and phosphodiesterase type 5 inhibitors. While none of these agents can cure this life-threatening condition, they improve clinical status and health-related quality of life.

New treatments increase hope

Advances in therapy for pulmonary hypertension over the last decade have seen the condition shift from one in which lung or heart-lung transplantation provided the only hope of survival for many patients to one that can be pharmacologically managed to provide improvements in health-related quality of life and survival.[1]

Diagnoses of pulmonary hypertension can be classified into several categories, including pulmonary arterial hypertension (PAH; table I; focus of this article) and pulmonary hypertension secondary to other conditions (e.g. left heart disease, lung disease, hypoxaemia, or chronic thrombotic or embolic disease).[2] Treatments for PAH may not be suitable, and may in fact be deleterious, in patients with forms of pulmonary hypertension secondary to other conditions, so it is important that patients are classified correctly.[1]

Stratify patients by function

Patients with PAH should also be stratified according to their functional capacity.[1] The New York Heart Association classification for left heart disease has been modified for patients with PAH and consists of the following four functional classes based on limitations of physical activity due to symptoms of undue dyspnoea or fatigue, chest pain or near-syncope.[1]

Table I. Types of pulmonary arterial hypertension[2]

Idiopathic (primary pulmonary hypertension)
Familial
Associated with congenital left-to-right shunt, portal hypertension (portopulmonary hypertension), collagen vascular disease, HIV infection, drugs/toxins and various other conditions
Associated with substantial venous or capillary involvement (e.g. pulmonary veno-occlusive disease, pulmonary capillary haemangiomatosis)
Persistent neonatal pulmonary hypertension

- Class I. PAH without a resulting limitation of physical activity (ordinary physical activity does not cause symptoms)
- Class II. PAH resulting in a slight limitation of physical activity (the patient is comfortable at rest, but ordinary physical activity causes symptoms)
- Class III. PAH resulting in a marked limitation of physical activity (the patient is comfortable at rest, but less than ordinary activity causes symptoms)
- Class IV. PAH resulting in a marked limitation of physical activity (the patient is comfortable at rest, but less than ordinary activity causes symptoms).

This functional classification is important to help guide therapy and is also a good indicator of prognosis.[1] Most patients (70–90%) are not diagnosed until their condition has reached the severity of functional classes III or IV. Risk stratification by noninvasive measures (e.g. 6-minute distance walking test, brain natriuretic peptide and serum uric acid levels, cardiopulmonary exercise testing and echocardiography) are useful in assessing disease severity and predicting patient outcomes.[3]

Therapy established for classes III and IV

Evidence-based recommendations for treating patients diagnosed with functional class III and IV idiopathic PAH or PAH associated with scleroderma have been established.[4-6] These guidelines should be regarded as a general recommendation only, and other patient factors should be taken into consideration when deciding the most appropriate course of therapy.

Insuffiencient data are currently available to make specific recommendations for the treatment of functional class I or II PAH.[1]

Begin with supportive therapy

Once a patient has been diagnosed with functional class III or IV PAH, patients should receive general medical care, oral anticoagulation therapy and other appropriate therapies.[1,3-6]

Although there are no randomised, placebo-controlled studies demonstrating the benefits of anticoagulation in patients with PAH, a retrospective analysis has suggested survival is improved when oral anticoagulants are given.[7] This finding is supported by a prospective study examining calcium channel antagonist therapy in PAH.[8] It is, therefore, recommended that warfarin be given to all patients with PAH, unless there are other

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contraindications.[3] Heparin may be more efficacious because of its ability to inhibit smooth muscle proliferation, but this has not yet been ascertained.

Diuretics may be given to patients with right heart failure to provide symptom relief by reducing the elevated intravascular volume.[3] However, excessive diuresis must be avoided, as this can lead to reduced cardiac output. Digoxin may also have a role in PAH therapy, particularly in patients who also have atrial fibrillation or biventricular failure.[3,9] Supplemental oxygen may alleviate arterial hypoxaemia and attenuate pulmonary vasoconstriction in patients with PAH.[3]

Test for vasoreactivity

In order to identify patients who may benefit from treatment with a calcium channel antagonists, vasoreactivity testing should be performed before initiating targeted treatment of PAH.[1] A right heart catheter is inserted, and patients are challenged with a short-acting pulmonary vasodilator (e.g. inhaled nitric oxide or iloprost, or intravenous epoprostenol or adenosine).[1] Patients who exhibit a positive acute response to vasodilators (i.e. reduction in mean pulmonary arterial pressure of 10–40mm Hg with normal cardiac output) may be considered for a trial of calcium channel antagonist therapy.

A sustained benefit from calcium channel antagonist therapy is seen in <10% of patients with idiopathic PAH, and less frequently in patients with other forms of PAH; however, those that do benefit can remain in functional class I or II for many years.[1] There are no studies that have investigated which calcium channel antagonists offer the best outcome in PAH, but nifedipine and diltiazem are the agents typically used, and others (e.g. amlodipine) may be equally beneficial.[1]

Most patients require more

As most patients will not fulfil the criteria for calcium channel antagonist treatment, patients who present in functional class III PAH should receive the oral endothelin antagonist bosentan, a non-parenteral prostanoid (i.e. inhaled iloprost or subcutaneous treprostinil) or intravenous epoprostenol.[4-6] Once evidence from randomised, controlled trials of sildenafil in PAH is incorporated into guidelines, the role of this agent as another option in the treatment of PAH will become established.[1]

Intravenous epoprostenol therapy is generally considered first-line therapy for patients who present in or progress to functional class IV disease, particularly if they exhibit signs or symptoms of haemodynamic instability.[4-6] Intravenous iloprost or treprostinil may someday emerge as acceptable first-line alternatives to epoprostenol because of their superior stability and longer half-lives; intravenous iloprost is already used instead of epoprostenol for first-line therapy in some European countries, with reportedly similar results. Haemodynamically stable patients with functional class IV PAH can be given bosentan or a non-parenteral prostanoid, but they should be carefully monitored during such treatment and switched to intravenous epoprostenol if their condition does not improve or worsens. If the condition of patients receiving intravenous epoprostenol deteriorates or does not improve, atrioseptostomy and/or lung transplantation should be considered.[4-6]

Refer to local prescribing information for details on approved dosages, indications, cautions and contraindications.

Prostanoids have primary place

Prostanoid treatment plays a fundamental role in the treatment of PAH, as the synthesis of endogenous prostacyclin (a potent vasodilator in both the pulmonary and systemic circulation) is markedly diminished in the pulmonary endothelium of patients with PAH.[1] Adverse events associated with prostanoids include vasodilation-related events (e.g. flushing, headache and hypotension).

Epoprostenol surpassed expectations

Intravenous epoprostenol (*Differential features* table) represents a major development in the management of severe PAH.[1] It was introduced as a bridge to lung transplantation in the 1980s, but it became apparent that many patients receiving it for this purpose experienced significant, long-term improvements that eliminated the need for the transplant procedure.

Epoprostenol, which has been approved for treating idiopathic PAH and PAH associated with scleroderma, has been shown to improve haemodynamics, exercise capacity and survival in patients with PAH.[13,14] It has been postulated that in addition to pulmonary vasodilation, epoprostenol may also affect pulmonary vascular remodelling by inhibiting pulmonary smooth muscle cell proliferation, modulating endothelial cell proliferation and angiogenesis, and possibly other mechanisms.[1]

Continuous epoprostenol treatment is effective in patients with functional class III or IV idiopathic PAH at baseline.[15,16] In one study,[15] survival rates at 1, 2, 3 and 5 years with epoprostenol treatment were 85%, 70%, 63% and 55%, respectively, which were significantly better than the expected survival rates of 58%, 43%, 33% and

Differential features

Selected features of currently recommended drug therapies for managing pulmonary arterial hypertension (PAH)[1,10-12]

Drug	Dosage and administration		Half-life	Comments
	usual route	dosage		
Endothelin receptor (A and B) antagonist				
Bosentan	Oral	62.5mg twice daily Increase to 125mg twice daily after 4wk if liver enzyme levels are not elevated	5h	Monthly hepatic aminotransferase level monitoring is necessary ≈3% of patients had to discontinue treatment due to elevated liver enzyme levels, but no cases of permanent liver dysfunction have been reported to date
Prostanoid				
Epoprostenol	Continuous infusion via permanent central venous catheter delivered by portable pump	Usual starting dosage: 2 ng/kg/min Dosage gradually titrated depending on symptoms and adverse effects Average dosage at 1y: 20–35 ng/kg/min	2–3 min	Most adverse effects are preventable or manageable with careful dose adjustment Pump failure or catheter dislocation can cause rapid, life-threatening haemodynamics deterioration Sepsis at the catheter site is a serious complication
Iloprost	Inhalation (must be administered with an appropriate nebuliser to maximise alveolar deposition)	5.0μg 6–12 times per day Some patients only require 2.5μg doses	20–30 min	Even with frequent inhalations, cover is not provided for 24h per day Long-term efficacy is not yet established
Treprostinil	Subcutaneous (via microinfusion pump similar to that used for insulin delivery)	Usual starting dosage: 1.25 ng/kg/min Dosage gradually titrated depending on symptoms and adverse effects	30–45 min (after intravenous administration)	Infusion-site pain is common (85% of patients) Switching patients from epoprostenol to treprostinil should only be performed under careful clinical and haemodynamic scrutiny Long-term efficacy not yet established
Phosphodiesterase type 5 inhibitor				
Sildenafil	Oral	20mg three times daily	3–5h	Most frequent adverse effects are headache, dyspepsia, facial flushing, epistaxis and insomnia Must consider whether the mild and transient vasodilatory effecfts will adversely affect the patients Cannot be taken concomitantly with organic nitrates

28%. The other study reported similar survival rates with epoprostenol at 1, 2 and 3 years of 88%, 76% and 63%.[16]

Inhaled iloprost convenient

Inhaled iloprost (*Differential features* table) is approved for the treatment of functional class III idiopathic PAH.[1] It produced significant improvements in functional class, exercise capacity, haemodynamics and clinical outcomes relative to placebo.[17]

Treprostinil administered subcutaneously

Subcutaneous treprostinil (*Differential features* table) is indicated in the treatment of functional classes II–IV PAH.[1] Dose-dependent improvements in several haemodynamic variables relative to placebo have been reported, but improvements in survival and number of patients with clinical deterioration have not been seen.[18] While some guidelines suggest that subcutaneous treprostinil be used as first-line therapy in patients with functional class III PAH,[4] some experts believe it should only be considered if other options are not available.[1]

Inhaled treprostinil is currently under evaluation in clinical trials, and may emerge as a more convenient and/or efficacious option than inhaled iloprost due to its longer half-life.[1]

Beraprost fails to impress

Beraprost can be taken orally, and it has a half-life of 30–45 minutes.[1] However, it appears to have only limited short-term benefits in the treatment of PAH and frequent adverse effects. Consequently, it is not widely recommended for the treatment of PAH.[1]

Endothelin receptor antagonists block vasoconstriction

Patients with PAH have increased plasma levels of endothelin-1, a potent vasoconstrictor.[1] Endothelin-1 activates two distinct G-protein coupled membrane receptors, designated type A (ET_A; mediate

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vasoconstriction and hypertrophy) and type B (ET_B; stimulation causes the release of prostacyclin and nitric oxide, resulting in vasodilation).

Oral bosentan (*Differential features* table), a dual ET_A/ET_B receptor antagonist, improves 6-minute walk distances, Borg dyspnoea index, functional class, haemodynamics, right heart function and clinical status.[19,20] Data on long-term survival with bosentan have shown impressive survival rates of 96% at 1 year and 89% at 2 years, but these data must be interpreted cautiously since nearly a quarter of these 169 patients also received intravenous epoprostenol.[21] With the exception of reversible elevated aminotransferase levels, bosentan has been found to be well tolerated.[1]

Sitaxsentan sodium and ambrisentan, which are selective ET_A antagonists with relatively long half-lives (≈5–7 hours), are undergoing clinical trials.[1] Initial results with sitaxsentan sodium have demonstrated improvements in 6-minute walking tests and haemodynamics.

Sildenafil finds a new purpose

Sildenafil is a phosphodiesterase type 5 (PDE5) inhibitor (*Differential features* table) that has recently been approved to increase exercise ability in functional class I (US)[11] or III (Europe) PAH.[12] Due to a current lack of data, sildenafil is not indicated in patients with functional class IV PAH.[22] PDE5 is abundantly expressed in the lung, where it inactivates cyclic guanosine monophosphate, thereby inhibiting the vasodilatory effects of nitric oxide and atrial natriuretic peptides.[1]

In a large, well designed 12-week study, 277 patients with primarily functional class II or III idiopathic PAH received sildenafil 20, 40 or 80mg three times a day or placebo.[22] All three treatment groups showed significant improvements in exercise capability (6-minute walk distance), functional class and mean pulmonary-artery pressure relative to placebo recipients. However, differences between active treatment groups were not significant, leading to an approved dosage of 20mg three times daily. In an open-label 1-year extension trial, sildenafil maintained improvements in walk distance and cardiac function, and recipients had a 96% survival rate (expected survival rate 71%).[22]

Other PDE5 inhibitors have not yet been evaluated in patients with PAH and their pulmonary vasorelaxing properties may differ from those of sildenafil.[1]

Vasodilatory peptides look promising

Among agents that have a potential role in PAH therapy are vasoactive intestinal peptide (demonstrated clinical and haemodynamic improvement in a preliminary case series) and adrenomedullin, another vasodilatory peptide (lowered pulmonary vascular resistance in patients with idiopathic PAH).[1]

In animal studies, simvastatin inhibited pulmonary vascular remodelling, but there are no published reports of improvement in PAH with statins in patients.[1]

Combination therapy makes sense

While various drug monotherapies have been shown to improve the symptoms of PAH, none so far has provided a cure, and the disease will continue to progress, albeit more slowly, in most patients.[1] Combination therapy seems a logical and attractive option for these patients.

The only randomised trial that has examined combination therapy in PAH was underpowered, but there was a trend towards greater haemodynamic improvement with epoprostenol plus bosentan than with epoprostenol plus placebo.[23] Successful use of bosentan as adjunctive therapy in patients who experienced deterioration while receiving inhaled iloprost or beraprost has also been reported.[24] Open-label studies have reported promising results with the combination of iloprost and sildenafil.[1]

Combining a PDE5 inhibitor with an endothelin receptor antagonist is an attractive option, as their mechanisms of action differ and both can be taken orally. There has been some concern about liver toxicity as a result of drugs from these two classes interacting, but a case series has reported that sildenafil was both well tolerated and efficacious when added to bosentan in patients not responding well to monotherapy.[25]

Guidelines lacking for other PAH types

There is little evidence-based data for the treatment of types of PAH other than idiopathic PAH or PAH associated with scleroderma. Other forms of PAH and their treatment options are briefly discussed in table II.[1]

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Table II. Treatment of patients (pts) with forms of pulmonary arterial hypertension (PAH) other than idiopathic PAH or PAH associated with scleroderma[1]
PAH associated with congenital right-to-left shunt
Open-label studies indicate that epoprostenol, bosentan and sildenafil may be effective Pts with simple cardiac defects can generally be treated according to the guidelines for idiopathic PAH Pts with complex defects must be referred to a specialised centre for treatment
PAH associated with portal hypertension (portopulmonary hypertension)
Treatment is often complex Currently insufficient data to make evidence-based recommendations Epoprostenol and bosentan have been shown to be effective in case series, but the latter's propensity to cause liver toxicity is an important consideration in pts with compromised liver function Pts should be referred to centres with experience in treating both liver and lung disease
PAH associated with HIV infection
A small proportion (0.5%) of pts with HIV infection develop PAH Antiretroviral therapy results in improvement in some cases, but pts with advanced PAH need targeted therapy Available data suggest that pts are treated in a specialist environment with bosentan (functional class III) or epoprostenol (functional class IV)
Pulmonary veno-occlusive disease or pulmonary capillary haemangiomatosis
Very rare disorders with a distinct pathology, but similar clinical presentation As these are generally considered to be fatal conditions for which there is no effective medical treatment, eligible pts should be referred for lung transplantation Epoprostenol has been associated with some improvement, but also with fatal pulmonary oedema in pts with these conditions; therefore, if this agent is used, pts must be monitored with great care

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