Oral treatments for pulmonary arterial hypertension

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Abstract

The management of pulmonary arterial hypertension (PAH) has changed dramatically over the last decade. Where once the physician had only limited tools to combat this devastating condition, recent randomised controlled trials have shown that there are now treatments that both prolong the rate of progression and improve survival. The 'gold standard' of treatment, due to its beneficial effect on survival, is epoprostenol, a prostacyclin analogue. However, there are a number of problems with the prostacyclin analogues, mainly centred on their administration and cost, which led to their use only in severely ill patients. A better understanding of the pathophysiology of PAH has led to a number of other pharmacological targets, namely antagonism of endothelin (ET) receptors and increasing local levels of nitric oxide (NO) via inhibition of phosphodiesterase 5.

The successful treatment of PAH means that there is now a growing population of patients on disease-modifying agents, so it is essential that physicians are aware of their use, benefits and side effects.

Key words: pulmonary arterial hypertension, bosentan, sildenafil, endothelin, nitric oxide.

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Introduction

Pulmonary arterial hypertension (PAH) is a condition of the small pulmonary arteries, characterised by vasoconstriction, inflammation and thrombosis, which involves smooth muscle cell proliferation and endothelial dysfunction. The resulting increase in pulmonary vascular resistance leads to right ventricular failure and, ultimately, death. Pulmonary hypertension can occur at any age.

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Table 1. Revised clinical classification of pulmonary hypertension (Venice 2003)

1. **Pulmonary arterial hypertension (PAH)**
   - 1.1 Idiopathic (IPAH)
   - 1.2 Familial (FPAH)
   - 1.3 Associated (APAH):
     - 1.3.1 Collagen vascular disease
     - 1.3.2 Congenital systemic-to-pulmonary shunts
     - 1.3.3 HIV infection
     - 1.3.4 Drugs and toxins
     - 1.3.5 Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders, splenectomy)
   - 1.4 Associated with significant venous or capillary involvement
     - 1.4.1 Pulmonary venous occlusive disease (PVOD)
     - 1.4.2 Pulmonary capillary haemangiomatosis (PCH)
   - 1.5 Persistent pulmonary hypertension of the newborn
2. **Pulmonary hypertension with left heart disease**
   - 2.1 Left-sided atrial or ventricular heart disease
   - 2.2 Left-sided valvular heart disease
3. **Pulmonary hypertension associated with lung diseases and/or hypoxaemia**
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Sleep-disordered breathing
   - 3.4 Alveolar hypoventilation disorders
   - 3.5 Chronic exposure to high altitude
   - 3.6 Developmental abnormalities
4. **Pulmonary hypertension due to chronic thrombotic and/or embolic disease**
   - 4.1 Thromboembolic obstruction of proximal pulmonary arteries
   - 4.2 Thromboembolic obstruction of distal pulmonary arteries
   - 4.3 Non-thrombotic pulmonary embolism (tumour, parasites, foreign material)
5. **Miscellaneous**
   Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumour, fibrosing mediastinitis)

The pathophysiological features are seen in a number of forms of PAH, and recently the classification of pulmonary hypertension has been changed to reflect this. In the revised clinical classification of pulmonary hypertension (table 1), PAH is further subdivided into idiopathic (IPAH), familial (FPAH), associated (APAH), and PAH associated with significant venous or capillary involvement.

For the purposes of this review the treatment options will be

Table 2. WHO functional classification of pulmonary arterial hypertension

Class I Pulmonary arterial hypertension without a resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near-syncope

Class II Pulmonary arterial hypertension resulting in a slight limitation of physical activity. The patient is comfortable at rest, but ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near-syncope

Class III Pulmonary arterial hypertension resulting in a marked limitation of physical activity. The patient is comfortable at rest, but less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near-syncope

Class IV Pulmonary arterial hypertension resulting in an inability to carry out any physical activity without symptoms. The patient has signs of right heart failure. Dyspnoea, fatigue or both may be present even at rest, and discomfort is increased by any physical activity

limited to IPAH, FPAH and APAH, in particular that associated with collagen vascular disorders. It is also limited to trials in adults. It is important to remember that treatment has to be individualised, as the response to different treatments varies according to the underlying pathology. Intravenous epoprostenol can be detrimental in patients with PAH associated with significant venous involvement.[1,2]

Idiopathic PAH, previously known as primary pulmonary hypertension, accounts for approximately 70% of all cases of PAH. A significant proportion of patients with APAH have collagen vascular disease, mainly scleroderma. Both of these conditions are more common in females. Untreated, the median lifespan from diagnosis is 2.8 years;[3] with a median age at time of diagnosis of the fourth and fifth decade, the statistic becomes all the more depressing. Conventional treatment for PAH was limited until the last decade. The treatment was mainly directed at the consequences of right ventricular failure, such as diuretics for fluid retention and digoxin.[4] Warfarin is used to prevent further vascular occlusion within the pulmonary arterioles, based on a few studies.[5,6]

The intravenous prostacyclin analogue, epoprostenol, revolutionised the treatment of IPAH in the 1990s, improving symptoms, quality of life and survival. It remains the only agent that has a proven survival benefit in the treatment of PAH[7] and the first-line therapy for patients with severe symptoms in New York Heart Association World Health Organisation (NYHA/WHO) functional class IV. Table 2 details the WHO functional classification of PAH. There is no upper dose limit, and symptoms and haemodynamics can be successfully titrated against side effects, which may transiently increase with dose escalation.

There are a number of limitations to its use. The main problem relates to the delivery system and its short half-life. As prostacyclin analogues are inactivated by low pH, they must be administered either by continuous intravenous infusion (epoprostenol), continuous subcutaneous infusion (treprostinil) or in aerosolised form (iloprost) between six and 12 times a day. In the case of epoprostenol this necessitates the use of a permanent tunnelled venous catheter, and the rate of serious catheter-related sepsis even in experienced centres is 0.1–0.6 cases per patient year.[8,9] In addition, withdrawal of the drug (as with all PAH therapies) can be life-threatening, and since the half-life of epoprostenol is only about six minutes, patients need to be well trained and able to problem-solve quickly. These drawbacks, along with the significant cost implications of treatment, have pushed forward a number of trials of oral agents for the treatment of PAH.

The endothelin receptor antagonists

Endothelin-1 (ET-1) is a potent vasoconstrictor and vascular smooth muscle mitogen.[10] ET-1 is secreted from vascular endothelial cells and is found at higher concentrations in the serum of patients with IPAH;[11] in addition, it is found at higher concentrations in the muscular pulmonary arteries from patients compared to control specimens.[12] Its actions are mediated via two receptors, ET_A and ET_B.[13] The ET_A receptor is found on vascular smooth muscle cells in the lung whilst the ET_B receptor is found on vascular smooth muscle cells and endothelial cells within the lung. When ET-1 activates the ET_A receptor there is an increase in intracellular calcium via a cyclic guanosine monophosphate (cGMP) pathway, resulting in vasoconstriction.[14] In comparison, when ET-1 activates the ET_B receptor on endothelial cells, there is vasodilation, mediated by increased prostacyclin and nitric oxide (NO) release.[15] However, activation of the ET_B receptor can also result in vasoconstriction when the receptor is located on vascular smooth muscle cells.[16]

A number of ET receptor antagonists have been developed, with differing specificities for the two receptors. Bosentan is a dual receptor antagonist that has only marginally more affinity for the ET_A receptor, whereas sitaxsentan has 6,500-fold greater affinity for the ET_A receptor. In addition, ambrisentan is a further ET_A-specific antagonist that is currently undergoing clinical evaluation. All of the endothelin receptor antagonists undergo hepatic metabolism via cytochrome p450.

Clinical trials

There have been two multicentre, randomised, placebo-controlled, double-blind trials using bosentan. The first pilot study included 32 patients with a 2:1 randomisation protocol to the bosentan group.[17] All patients were in functional class III (table 2), and had to have either IPAH (approximately 80%) or PAH associated with scleroderma. The primary end point was a change in submaximal exercise capacity at 12 weeks, as measured by the unencouraged six-minute walk test, which is known to correlate with survival. Patients receiving bosentan started at a dose of 62.5 mg twice daily for four weeks before increasing the dose to 125 mg twice daily for the remainder of the study. The results of this study were very encouraging, with a significant improvement in the mean increase in exercise capacity from 360 m to 430 m, compared to a decrease of 6 m in the untreated group. As the six-minute walk test has been shown to correlate with cardiac index, there was a corresponding improvement in cardiac

index when compared to placebo. These improvements in exercise capacity, NYHA/WHO functional class and haemodynamics were still seen at one year.

Following this pilot study, BREATHE-1 (Bosentan Therapy for Pulmonary Arterial Hypertension) enrolled 213 patients, including patients in NYHA/WHO functional class IV (6% in the placebo group compared to 10% in the combined bosentan group).[18] The demographics of the patients were broadly similar to the earlier pilot study, but patients were randomised to either 125 mg or 250 mg bosentan. The primary end point was change in exercise capacity; secondary end points were change in NYHA/WHO functional class, time to clinical worsening and change in the Borg dyspnoea index.

At 16 weeks there was a significant improvement in the six-minute walk test in both bosentan-treated groups compared to deterioration in the placebo group, a difference of 44 m for the 250 mg dose and 35 m for the 125 mg dose. Whilst there was a trend towards an increase in exercise capacity with the 250 mg dose, no dose-response relationship could be found. In addition, the time to clinical worsening, defined as death, hospitalisation, rescue therapy with epoprostenol, lung transplantation or atrial septostomy, was also significantly improved in both bosentan groups. Side effects were few, but the higher dose of bosentan did result in hepatic dysfunction in 14% of patients. A further 48 patients continued their treatment in a double-blind manner up to 28 weeks, and the improvements were sustained.[18] The benefits of bosentan appeared also to be sustained for at least a year in an open-label extension of the first pilot study (n=29).[19]

Following these trials, the Federal Drug Administration (FDA) and European agency for the evaluation of medicinal products (EMEA) licensed the use of bosentan, at a maximum dose of 125 mg twice daily, for use in patients in NYHA/WHO functional class III and IV, with monthly liver function and pregnancy testing.

It is unknown whether the use of a selective ET_A receptor antagonist should be beneficial as, in addition to blocking the vasoconstrictor effects mediated via ET_A receptors, the vasodilator and ET-1 clearance effects mediated via endothelial ET_B receptors might be preserved. STRIDE-1 (Sitaxsentan Therapy for Pulmonary Arterial Hypertension)[20] was a placebo-controlled, randomised controlled trial similar in design to the earlier BREATHE-1 study. A total of 178 patients were randomised to either 100 mg or 300 mg of sitaxsentan or placebo. The primary outcome measure, in contrast to BREATHE-1 and earlier trials with epoprostenol, was maximal exercise capacity measured by predicted peak VO_2, with submaximal exercise capacity as measured by the six-minute walk test, NYHA/WHO functional class, and time to clinical worsening among the secondary end points.

A significant improvement in the predicted peak VO_2 was seen in the 300 mg group, although this was only 3.1%, and no improvement at the 100 mg dose was observed. However, exercise capacity measured by six-minute walk test did improve at both doses, as in the earlier open-label pilot study,[21] with an improvement compared to placebo of approximately 30 m. The changes in the six-minute walk test were mirrored with favourable haemodynamic improvements measured at cardiac catheterisation. A third of the patients in STRIDE-1 were in WHO functional class II, as seen by the average distance walked in the six-minute walk test at baseline being approximately 400 m. Post-hoc analysis indeed confirms that when only class III patients are studied there is a significant improvement in exercise capacity. Recently, a follow-up study has been published and in a small group of patients (n=11) the improvements have been sustained at one year.[22] Neither the FDA nor the EMEA has yet approved sitaxsentan for use in PAH.

Phosphodiesterase 5 inhibitors

Nitric oxide (NO), a potent vasodilator, is produced in the airway epithelial cells and vascular endothelium via various NO synthases, acting through a cGMP-dependent pathway. In the normal lung it plays a key role in the regulation of ventilation: perfusion matching.[23] In patients with PAH this NO-dependent vasodilation pathway has been shown to be depressed.[24] Whilst inhaled NO can be used to assess response in a vasodilator challenge at cardiac catheterisation,[25] its short half-life and mode of delivery make this rather impractical for long-term treatment (which has nevertheless been tried). Cyclic GMP and cAMP are degraded by the phosphodiesterases, of which 11 different isoforms with differing tissue and substrate specificities have so far been identified.[23] Phosphodiesterase 5 (PDE5) is the most abundant isoform found in the lung and shows specificity for cGMP. Sildenafil is a selective PDE5 inhibitor, used in the treatment of erectile dysfunction.

Clinical evidence

Currently there is limited published evidence for the use of sildenafil and other PDE5 inhibitors in the treatment of PAH, and appropriately they are not licensed for this indication yet. However, there have been a few small studies that have shown promise and larger trials have been reported recently at international conferences.

In a pilot study, sildenafil was given to five consecutive patients in a single centre at a dose of 50 mg eight-hourly for three months.[26] Four of the patients had IPAH, and the other patient had PAH associated with Eisenmenger's syndrome. At three months all of the patients had improved from baseline, with increased six-minute walk test and cardiac index, and decreases in functional class and pulmonary vascular resistance.

There is one published, small, randomised, double-blind, crossover design trial for the use of sildenafil in patients with IPAH.[27] In this study 22 patients were enrolled to take either sildenafil or placebo for six weeks prior to crossing over to the alternate treatment for a further six weeks. Patients had to be in either NYHA/WHO functional class II or III, and were excluded if they had PAH associated with other causes. The primary outcome was exercise time on a treadmill, using the Naughton protocol, with secondary end points of cardiac index (measured by Doppler echocardiography) and quality of life (QOL) score. Exercise time increased in all patients, from a mean of 475 $\pm$ 168 seconds to 686 $\pm$ 224 seconds ($p<0.0001$). Accordingly, there was also a significant increase in cardiac index and the QOL score.

A trial of the use of sildenafil in pulmonary hypertension was presented in a late-breaking trials session at CHEST 2004. The SUPER-1 trial (Sildenafil Use In Pulmonary Arterial Hypertension) enrolled 278 patients in a randomised, placebo-controlled, double-blind trial. Patients, 75% of whom were female with a mean age of 49, were randomised to one of three doses of sildenafil 20 mg (n=69), 40 mg (n=68) or 80 mg (n=71) three times daily, or to placebo (n=70). The majority (58%) of patients were in NYHA/WHO functional class III at baseline, with 38% in class II. At 12 weeks the distance walked on a six-minute walk test had improved from a pooled baseline of 344 m to 394 m for patients receiving 80 mg of sildenafil three times a day, and to 390 m and 389 m in the groups receiving 40 mg and 20 mg three times a day, respectively. This result was statistically significant at $p<0.01$. This trial is yet to be published, but there is already a long-term trial in progress for patients on the 80 mg dose of sildenafil.

At the American Heart Association scientific sessions, 2004, the SERAPH study (Sildenafil Versus Endothelin Receptor Antagonist For Pulmonary Hypertension) was presented in abstract form. This was a double-blind, randomised trial that compared bosentan and sildenafil in NYHA/WHO functional class III patients. Despite its very limited size (14 patients in the sildenafil group and 12 patients in the bosentan group), improvement was seen in the six-minute walk test at 12 weeks of therapy with both treatments. In summary, evidence is mounting that sildenafil has a role in the treatment of PAH but definitive data have not yet been published in peer-reviewed journals.

Oral prostacyclin analogues

Prostacyclin, the main product of arachidonic acid metabolism, is a non-selective vasodilator; it inhibits the growth of smooth muscle cells via a cAMP-mediated pathway and inhibits platelet aggregation.[4] Its role in the treatment of PAH has already been established with the use of intravenous epoprostenol, a prostacyclin analogue (as discussed earlier). An orally active analogue of prostacyclin has been developed, beraprost sodium, which is stable at low pH due to its cyclopentabenzofuranyl skeleton.[28] The half-life is longer than intravenous epoprostenol, at 35–40 minutes, and it is conventionally given four times a day.

Clinical evidence

Little evidence supports the use of beraprost in PAH, and it only has a licence for use in Japan. In a small, non-randomised study beraprost was given to 12 patients with IPAH, three of whom were in NYHA/WHO functional class III, the remainder in class IV.[28] Unfortunately, in this trial no objective measure of exercise capacity was published, but eight patients improved their functional class with a mean follow-up of five months.

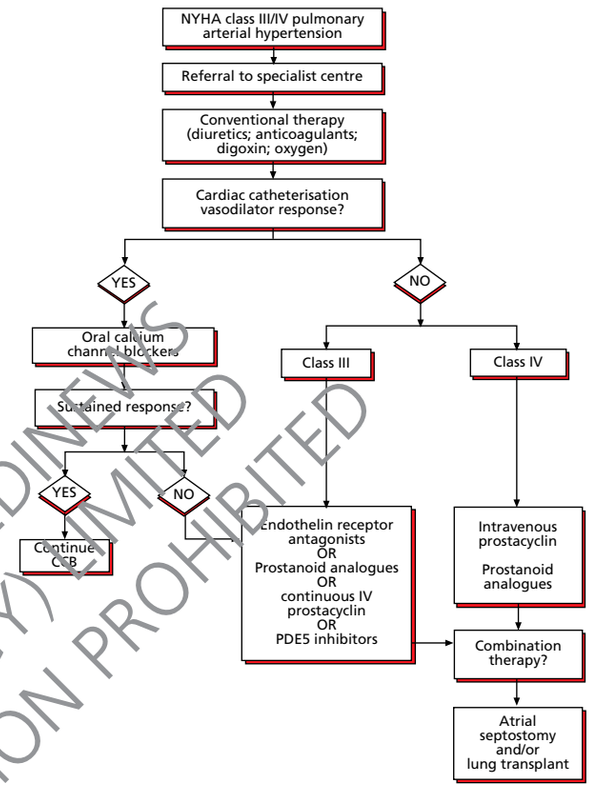
The ALPHABET (Arterial Pulmonary Hypertension And Beraprost European) study group investigated the effect of beraprost in a heterogeneous population of patients with PAH (n=130), all of whom were in NYHA/WHO functional class II or III.[29] There was a significant improvement of the primary end point (distance walked in the six-minute walk test at 12 weeks) in the treated group; this was more pronounced in patients with a diagnosis of IPAH (mean increase of 46 m compared to 25 m in all patients).

However, a further group studied the effect of beraprost in a double-blind, randomised, placebo-controlled trial for 12 months with patients in NYHA/WHO functional class II or III (n=116).[30] Although an improvement in six-minute walk test, a secondary end point, was seen at three and six months, no difference was seen at nine and 12 months, suggesting its main action was limited to vasodilatation. In addition, disease progression, the primary end point, was only significantly improved at six months, but not at earlier or later timepoints.

The future

Many patients with PAH have a poor prognosis without treatment. Delays in making a diagnosis, determining the aetiology and severity of PAH, and starting treatment may result in unnecessary deaths. Oral therapies represent a further step forward in

Figure 1. Treatment algorithm for pulmonary arterial hypertension based on European for Society of Cardiology guidelines. These guidelines apply to idiopathic, familial pulmonary hypertension and that associated with collagen vascular disease, as discussed in the text



Modified from the New York Heart Association (NYHA) classification of patients with cardiac disease. It is adapted from the executive summary of the World Symposium on Primary Pulmonary Hypertension in Evian, France, in 1998

Key messages

- The treatment for pulmonary arterial hypertension has changed dramatically over the last decade so prompt referral to a specialist centre is necessary
- More patients are on disease-targeted therapy so physicians need to be aware of the use of these agents and their common side effects
- Bosentan is a dual endothelin receptor antagonist that improves exercise tolerance in patients with pulmonary arterial hypertension
- Sildenafil is a phosphodiesterase type 5 inhibitor; mounting evidence suggests that this has a significant role in patients with pulmonary arterial hypertension

disease management but they are not necessarily first-line treatments in all patients and they form part of a larger armamentarium. Physicians treating PAH patients must have expertise in managing all the therapies, whether oral or parenteral. If one therapy fails then another may need to be started with minimal delay. To improve patient care, referral to pulmonary hypertension specialists is recommended in the latest European Society of Cardiology guidelines (figure 1). In the UK the Department of Health has already designated specialist centres to manage pulmonary hypertension.

Combination therapy is now being used but which combinations are optimal and when treatment should be augmented remain to be determined. The combination of sildenafil and bosentan appears attractive but bosentan, being both a substrate and inducer of CYP3A4, has been shown to reduce the effective dose of sildenafil significantly when the two are given together. Several new agents are under investigation since current therapy is still associated with appreciable mortality and residual symptoms.

While most evidence supports the treatment of patients in NYHA/WHO functional classes III and IV, data from the treprostinil and sildenafil trials have been collected for functional class II patients. Oral disease-modifying therapy would be attractive in patients with milder symptoms, with the hope of delaying disease progression, but the value of this approach will require evidence: large mortality trials are probably not practical.

The indications for treatment are now extending beyond the idiopathic, familial and connective tissue disease patient groups. There are anecdotal data and small clinical series in patients with congenital heart disease, HIV infection and portal hypertension. There is increasing interest in investigating such treatments in patients with other conditions where pulmonary hypertension increases mortality, such as sickle cell disease and some lung diseases.

A new era in the management of PAH has dawned; the physician who previously had to stand by helpless now has questions to ask: When is the ideal time to start disease-targeted therapy? Which agent to choose first? Single or multiple agents? The answers to these questions will be answered with upcoming studies, but a cure for PAH remains an elusive goal.

Conflict of interest

None declared.

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