

# Pulmonary hypertension

## — treatment options

By Neil Hamilton, Dip Clin Pharm, MRPharmS and Charlie Elliot, MB ChB, MRCP

Treatment of pulmonary hypertension can be complex and depends on the cause of the condition. This article describes the drug treatment options for the disease based on the experiences from a specialist treatment centre



CT scans are used to investigate the cause of pulmonary hypertension

**T**reating patients with pulmonary arterial hypertension (PAH) is demanding but also rewarding. Treatments are often complex and side effects are a limiting factor. Ideally patients should be treated in a specialist centre where staff have experience in the initiation, continued use and monitoring of targeted drug treatments.

The right ventricle of the heart has a great potential to remodel if the pulmonary vascular resistance can be reduced. In patients with chronic thromboembolic pulmonary hypertension (CTEPH) vascular resistance can be reduced surgically, by performing a pulmonary endarterectomy (see Panel 1, p13). In patients with PAH, pharmaceutical intervention is used. The past few years have seen significant advances in the types of treatment used for PAH, both standard and targeted. It should be noted that targeted treatments are expensive, costing up to £38,000 per patient year, depending on the agent used and the dose required. Approval from the referring primary care trust is therefore needed before targeted treatment can be initiated for patients.

**Neil Hamilton** is specialist clinical pharmacist and **Charlie Elliot** is clinical lecturer respiratory medicine, both at the Pulmonary Vascular Disease Unit at the Royal Hallamshire Hospital, Sheffield.

Standard treatments for PAH include warfarin, diuretics, digoxin and oxygen therapy where appropriate.

### Standard treatments

**Anticoagulation** Oral anticoagulation is used in the majority of patients with pulmonary hypertension. Obviously, patients with CTEPH need anticoagulation treatment to reduce further clot formation, but in PAH the rationale is less clear. Benefit may be drawn in part from reducing in situ thrombus formation.

Evidence for treating patients who have idiopathic primary arterial hypertension (IPAH) with oral anticoagulation is based on data from single centre, retrospective studies showing that when warfarin treatment was selected by clinical judgement, three-year survival rates improved in the groups that were anticoagulated. Recent randomised controlled trials have shown that up to 85 per cent of patients were receiving anticoagulation on entry to the trial.<sup>1</sup> This perceived benefit of anticoagulation is often extrapolated to other forms of PAH, although these groups have not been studied separately. At the pulmonary vascular disease unit at the Royal Hallamshire Hospital in Sheffield patients are routinely maintained on an INR of 2–3, in the absence of complication or contraindications.

**Diuretics** There is no evidence to demonstrate a benefit of diuretic therapy in patients with PAH. However there is a clear need to reduce afterload on the right side of the heart and treat the symptoms of heart failure and fluid overload. Recent randomised controlled trials have shown that up to 70 per cent of patients were prescribed diuretic therapy on entry.<sup>1</sup> Diuretic treatment is, however, indicated if investigation shows that there is any evidence of right heart failure. Loop diuretics are most commonly prescribed, usually given orally but given intravenously to patients with severe decompensated right heart failure with gross peripheral oedema. Potassium sparing diuretics such as amiloride or spironolactone may also be indicated. Close monitoring of urea and electrolytes is essential, particularly for the elderly and patients on high doses of diuretics.

**Digoxin** No long-term data exist to demonstrate the effectiveness of digoxin in patients with PAH. It is suggested that digoxin may improve cardiac output. However practice at the Royal Hallamshire Hospital mirrors that seen in recent randomised controlled trials, where less than 53 per cent patients were prescribed digoxin on entry.<sup>1</sup> It is not clear if all the patients in the trial who were prescribed digoxin had co-existing atrial fibrillation,

but it is in this group where it would be most appropriate to use digoxin.

**Oxygen therapy** There is also a lack of clear evidence with regard to the benefits of long-term oxygen therapy. Some clinicians consider oxygen therapy to be an integral part of the long-term management plan for patients with PAH. However, there are no randomised controlled studies to confirm that low flow oxygen improves PAH. As part of the investigations at the Royal Hallamshire Hospital, patients undergo an overnight oximetry trace. If this illustrates significant hypoxia (<92 per cent PaO<sub>2</sub>) on air, with no other obvious contraindication, then long-term oxygen therapy is considered.

**Targeted therapies** Over the past five years the number of targeted pulmonary vascular therapies has increased markedly following the completion of several phase III randomised controlled trials.

In the UK currently licensed treatments for PAH are prostacyclin (epoprostenol), its analogue, iloprost (for nebulised administration), and the endothelin receptor antagonist bosentan. Significant experience with the phosphodiesterase inhibitor sildenafil and the prostacyclin analogue treprostinil, (now both now licensed for PAH in the US) has been gained at the Royal Hallamshire Hospital through clinical trials and unlicensed use. These treatments have also been used off-label in other categories of the disease including CTEPH as a bridge to pulmonary endarterectomy, or as a definitive treatment in inoperable disease. Other treatments under investigation are sitaxsentan and ambrisentan — orally active endothelin receptor antagonists that are currently the subject of phase III randomised controlled trials.

**Epoprostenol** Intravenous epoprostenol improves life expectancy, haemodynamics, six-minute walk test results and quality of life in patients with severe idiopathic PAH of New York Heart Association class III and IV<sup>2</sup>. It is the only prostaglandin analogue licensed in the UK for intravenous use. Originally this treatment was seen as a bridge to transplantation. However survival figures have shown that it is at least as effective as transplantation

#### Do you receive your own copy of *Hospital Pharmacist*?

All hospital pharmacists in Great Britain and members of the Royal Pharmaceutical Society's Hospital Pharmacist Group are entitled to receive a free copy of *Hospital Pharmacist*. If you do not receive your own copy, please e-mail your name, address and Society registration number to [jo.cook@rpsgb.org](mailto:jo.cook@rpsgb.org)

## Panel 1: Surgical options

Other than transplantation, which is usually reserved for patients deteriorating on pulmonary vascular directed therapy, other surgical options are available in patients with pulmonary hypertension. Patients with chronic thromboembolic pulmonary hypertension and surgically accessible disease can potentially be “cured” by pulmonary endarterectomy. There is a 5–10 per cent operative mortality compared with a 5-year survival of less than 10 per cent in this form of the disease once the mean pulmonary artery pressure exceeds 50mmHg.

Balloon atrial septostomy is another option. This procedure can be performed at cardiac catheterisation and involves controlled perforation of the inter-atrial septum. Its exact place in pulmonary hypertension treatment is yet to be defined since its efficacy has only been demonstrated in case reports. It has mainly been used in severely ill patients awaiting transplantation and has a reported mortality of 5–15%. It appears to be an effective way of off-loading the right ventricle, improving haemodynamics and symptoms. It is currently reserved for those patients with severe disease, failing on medical therapy as a bridge to transplantation.

in terms of extending a patient's life. Unfortunately, this form of therapy requires continuous infusion via a central line, with can cause the patient significant body image problems and also introduces a high risk of infection.

From a patient's point of view, one disadvantage is that a reconstituted syringe of epoprostenol is only stable at room temperature for eight to 12 hours. Practice varies, with some centres changing the pumps twice or even once a day although with the latter approach there may be a loss of efficacy towards the end of the 24 hours and symptoms of flushing and headache may be experienced by the time the pump is changed. Cold packs may be used to enhance the stability of the solution.

**Iloprost** Iloprost is a prostacyclin analogue commonly used to treat pulmonary hypertension. It is more stable at room temperature than epoprostenol, with the reconstituted solution remaining stable over 24 hours. Intravenous iloprost is also delivered via a central line, although this is an unlicensed use. As a result of the better stability, the syringe only needs to be changed once a day. Unlike epoprostenol, iloprost can also be given via a nebuliser. The latter device has been shown to be an effective treatment for idiopathic PAH in the context of a multi-centre randomised controlled trial,<sup>3</sup> and has recently gained a licence for this indication. The problem is that due to its short half life, patients need to nebulise around six to nine times per day. At the Royal Hallamshire Hospital, approximately 50 patients are currently managed on iloprost via both intravenous and nebulised routes. Iloprost is generally well tolerated although common side effects include headache, flushing, jaw pain and gastrointestinal upset.

It is critical to be aware of the risk of line infection in these patients since the typical features of sepsis are often absent and patients usually present with a non-specific

worsening of dyspnoea and lethargy. There is significant mortality associated with this complication.

**Treprostinil** Treprostinil is another prostacyclin analogue that has been shown to be efficacious in the largest randomised controlled trial conducted in pulmonary hypertension.<sup>4</sup> Treprostinil is licensed in the US for the treatment of PAH in patients with NYHA class II–IV symptoms. Treprostinil is currently licensed in 12 European countries and it is expected to be licensed in the UK shortly. The drug can be infused subcutaneously into the abdomen, thighs or arms using a MiniMed infusion pump.

The main problem associated with this form of therapy is infusion site pain, which is the primary cause for discontinuation. The Royal Hallamshire Hospital was involved in a multi-centre study evaluating treprostinil in the treatment of pulmonary hypertension. Including the trial population, 48 patients have been managed on this therapy to date. Of these, 21 per cent have discontinued the drug due to site pain. It is thought that the site pain results from a “pooling” effect under the skin. Increasing the concentration used (with decreased volume) improved symptoms in a few cases. Research is currently under way into the use of intravenous treprostinil. The inhalation route is also being investigated, an attractive option owing to the longer half-life of this prostaglandin.

**Calcium channel blockers** Although unlicensed for pulmonary hypertension, calcium channel blockers are often advocated as a cheap treatment for PAH. No large scale randomised controlled trials investigating these agents have been carried out in pulmonary hypertension, and their use is limited to a small minority of patients with idiopathic PAH who demonstrate a significant vasodilator response at cardiac catheterisation (approximately 10 per cent

of IPAH patients).<sup>5</sup> Only half of these will have a sustained clinical benefit from calcium channel blockers. It is suggested that high doses (up to 720mg of diltiazem or 180mg of nifedipine per day) may be beneficial but these doses are associated with a significant frequency of adverse effects. The most common problem with high dose calcium channel blockers is dose-dependant ankle swelling. In patients with significantly impaired right ventricular function their use can be dangerous.

**Beraprost** Beraprost is an orally active prostaglandin with orphan drug status. It has been shown to be effective in terms of improvements in the six-minute walk test in patients with milder disease (NYHA class II and III). However, evidence on the long-term benefit of this medicine as monotherapy is conflicting and it is therefore not currently prescribed in the UK.

**Bosentan** The endothelin receptor antagonist bosentan is currently the only licensed oral treatment for PAH in the UK for patients in NYHA class III. In addition to the vasodilative properties demonstrated by the prostacyclin analogues, bosentan has been shown to be an anti-fibrotic, anti-proliferative agent. It has been shown to improve the symptoms of pulmonary hypertension, physiological markers of disease severity and delay clinical worsening.<sup>6</sup> Compared with historical controls, bosentan appears to offer a survival advantage. Recently published data show Kaplan Meier survival estimates of 89 per cent at two years, compared with a predicted survival of 57 per cent (n=113). Sixteen patients have been followed to three years with a survival estimate of 86 per cent compared with a predicted survival of 48 per cent.<sup>7</sup>

As an oral preparation, bosentan avoids the difficulties and complications of parenteral administration. The vast majority of patients receive 125mg twice daily. It is not certain whether increasing the dose has any additional benefits, although higher doses appear to be associated with an increased incidence of liver function test abnormalities. Patients all have monthly LFT monitoring at their local GP practice. Other targeted therapies require no routine laboratory tests.

At the Royal Hallamshire Hospital, over 130 patients are currently managed on bosentan and it has been found to be well tolerated. The only significant adverse effect is abnormal hepatic function with an incidence of approximately 7 per cent. This effect is dose-related, abnormalities are usually reversible on withdrawal and not always recurrent on rechallenging therapy after normalisation of the LFTs.

**Sildenafil** The results of the SUPER-1 (sildenafil use in pulmonary arterial hyper-

tension) study have recently been published. Results presented at the 70th annual meeting of the American College of Chest Physicians and later in literature showed that sildenafil improves symptoms, six-minute walking test results and pulmonary haemodynamics in patients with pulmonary arterial hypertension compared with placebo. As a result, sildenafil is now licensed in the US under the proprietary name Revatio at a standard dose of 20mg three times a day. Clinical trials are ongoing in the UK with patients continuing on a dose of 80mg three times a day.

Pooling the sildenafil data from the three different doses used, the study showed that 35 per cent of the sildenafil patients improved by one functional class versus a seven per cent improvement in the placebo group. At the Royal Hallamshire Hospital, experience of sildenafil is limited to the treatment of around 120 patients. Eighty per cent of these are still receiving sildenafil and the drug is well tolerated. The most common side effect is headache, although trial data suggest an incidence not significantly greater than that in the placebo arm. Patients are currently started on sildenafil at a dose of 25mg three times a day and this may be titrated up to 100mg three times a day, depending on the patient's symptomatic benefit and adverse effects.

## Combination therapy

In other disease states such as essential hypertension, combination therapy is a recognised approach. At the Royal Hallamshire Hospital, combination therapy has been used in a small number of patients with PAH with varying results. One of the most successful combinations appears to be that of sildenafil and prostaglandin. The combination of prostaglandin and bosentan has also been explored and a small pilot study has suggested a trend towards a reduction in the PVR in the group treated with epoprostenol plus bosentan compared with epoprostenol alone.

An interesting potential combination would be bosentan and sildenafil and, although limitations exist, it appears to be a well-tolerated combination. The individual agents, however, are expensive and in the absence of randomised multicentre controlled studies it is not possible to demonstrate the cost-benefit of combination therapy.

This is an exciting and evolving area and multicentre studies are awaited, as theoretically combination therapy would be a rational treatment option.

## Conclusion

The past 20 years have seen significant developments in the understanding of pulmonary hypertension. Patient assessment and disease classification has become much

more standardised globally and, crucially, effective treatments are now available. Despite this, the diagnosis is often only made once the disease has become well established.

An increased awareness of pulmonary hypertension and its associations should enable the diagnosis to be made more readily. The increase of research in this area and a significant increase in therapeutic options should improve the prognosis for this increasingly recognised group of patients.

**Meeting report, p20**

## References

1. Galie N, Seeger W, Naeije R, Simmoneau G, Rubin L. Comparative analysis of clinical trials and evidence-based treatment algorithm in pulmonary arterial hypertension. *Journal of the American College of Cardiology* 2004;12(5):815-885.
2. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al. A comparison of continuous intravenous epoprostenol with conventional treatment for primary pulmonary hypertension. *New England Journal of Medicine* 1996;334:296-301.
3. Olschewski H, Simonneau G, Galie N, Higenbottam T, Naeije R, Rubin LJ, et al. Aerosolized Iloprost randomized study group. Inhaled Iloprost for severe pulmonary hypertension. *New England Journal of Medicine* 2002;347: 322-9.
4. Simonneau G, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC, et al. Treprostinil study group. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized controlled trial. *American Journal of Respiratory and Critical Care Medicine* 2002;165: 800-4.
5. Rich S, Brundidge B. High-dose calcium channel-blocking therapy for primary pulmonary hypertension: Evidence for long-term reduction in pulmonary arterial pressure and regression of right ventricular hypertrophy. *Circulation* 1987;76:135-41.
6. Rubin L, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, Pulido T, Frost A, Roux S, Leconte I, Landzberg M, Simonneau G. Bosentan therapy for pulmonary arterial hypertension. *New England Journal of Medicine* 2002;346:896-903.
7. VV McLaughlin. Survival with first line bosentan in patients with PPH. *European Respiratory Journal* 2005;25:1-6.