NATIONAL INSITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Drugs for the Treatment of Pulmonary Arterial Hypertension

Personal Comment

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Pulmonary hypertension is a progressive disease that leads to disabling symptoms of breathlessness and exercise limitation and when untreated leads to early death. It may occur as a primary disease process and this is known as idiopathic pulmonary hypertension. This disease is also known to run in families when it is known as familial pulmonary hypertension.

Both idiopathic and familial pulmonary hypertension are forms of pulmonary arterial hypertension and this also includes pulmonary hypertension secondary to collagen vascular disease, congenital systemic to pulmonary shunts, portal hypertension, HIV infection and exposure to various drugs or toxins.

Importantly the development of pulmonary arterial hypertension in association with these other diseases leads to further disabling symptoms of breathlessness and exercise limitation and is recognised as an independent adverse prognostic sign. In connective tissue disease, and in particular systemic sclerosis, the development of pulmonary arterial hypertension is clearly associated with decreased survival and indeed now represents the leading cause of premature death in such patients.

Pulmonary arterial hypertension is therefore a serious disease and complication of disease which if untreated leads to severe morbidity and early mortality

Prior to the development of targeted medical therapy which is the topic for this Health Technology Appraisal, the only potential treatment for such patients was consideration of heart lung or bilateral lung transplantation.

A very small minority of patients with idiopathic pulmonary arterial hypertension who showed a major vasodilator response during right heart catheterisation may be successfully treated by calcium channel blockers, however, the vast majority of patients are not suitable for consideration of this therapy. Calcium channel blockers cause systemic hypotension and a negative inotropic effect may be adverse when right ventricular function is already damaged. As a consequence, calcium channel blockers should not be started before performance of an acute vasodilator study in patients with idiopathic pulmonary arterial hypertension.

Right heart failure gives rise to fluid retention which is improved by diuretics which are regarded as key supportive medical therapy. Hypoxaemia also increases pulmonary vaso constriction and may worsen pulmonary hypertension and therefore patients with hypoxaemia and pulmonary arterial hypertension are generally given oxygen as further supported medical therapy.

Finally pulmonary arterial hypertension is associated with pulmonary arterial thrombosis and a hypercoagulable state associated with a fibrinolytic defect and haemostatic disturbance. Anticoagulation may reduce thrombosis and slow progression of some forms of the disease. Warfarin therapy has been shown in clinical trial to increase survival in idiopathic pulmonary hypertension. There are no published data on the use of Warfarin in other forms of pulmonary hypertension. As a consequence all patients with idiopathic pulmonary hypertension should be treated lifelong with Warfarin to achieve an international normalised ratio of 2-3. Warfarin should be seriously considered in other types of pulmonary arterial hypertension where there are no contra-indications.

Despite supportive medical therapy the prognosis of severe pulmonary arterial hypertension is poor and therefore the development of specific targeted therapy for the treatment of such patients which forms the basis of this Health Technology Appraisal represents a major step forward in healthcare.

1. Prostaglandin Therapy

Prostaglandins are potent endogenous vasodilators which inhibit platelet aggregation and have anti-proliferative and cyto-protective properties. An important part of their action also appears to be associated with remodelling of the pulmonary vascular bed and subsequent reduction in endothelial cell injury and hyper-coagulability. There are three agents currently available for clinical use comprising epoprostenol, iloprost and trepostenil. All three drugs appear to be effective but the greatest experience is will continuous intravenous epoprostenol. In addition to continuous intravenous therapy, iloprost may be delivered via nebulisers and trepostenil via a nebulisers or continuous subcutaneous infusion.

Intravenous therapy is delivered as a continous intravenous infusion using a portable infusion pump via a Hickman line. Safe management of this system in an out patient setting clearly demands a degree of competency that not all patients are capable of. All three drugs have been shown in clinical trials to be effective in terms of improving exercise performance and survival. The majority of the data is in patients with NYHA Functional Class III and IV.

Major complications of continuous intravenous therapy relates to catheter infections and the risk of septicaemia. Epoprostenol cannot be delivered by any means other than the intravenous route and therefore there is clear need to have a range of prostenoids available for the management of these patients offering different delivery systems. These include the nebulised and subcutaneous routes because of significant numbers of patients who would otherwise be suitable for prostaglandin therapy would not be able to manage continuous intravenous infusion.

2. Endothelin Antagonists

Bosentan an ETA and ETB receptor blocker and Sitaxentan a selective ETA receptor blocker are available in the UK. Both drugs have been investigated and been shown to improve symptoms including exercise tolerance, quality of life and survival in both randomised trials and non-randomised trials.

Patients taking endothelin receptor antagonists and in particular Bosentan require monitoring liver function tests to monitor transaminases which may rise and progress to

liver damage unless the dose is reduced or the drug discontinued. There is significantly less hepatotoxicity associated with Sitaxentan.

3. Phospherodiesterase V Inhibitors

PD5 inhibitors are the newest class of disease targeted therapy in pulmonary arterial hypertension and there is less long term experience than with prostenoids or the endothelin receptor antagonist Bosentan. Only Sildenafil is available for use in pulmonary arterial hypertension in the UK with Tadalafil currently in trials.

Whilst Sildenafil has been licensed for use at 20 mg three times a day, longer term survival data has been collected at 80 mg three times per day. There are both randomised and non-randomised clinical trials indicating improved exercise performance and survival.

Combination Therapy

The optimum management for those patients who exhibit clinical deterioration despite targeted mono-therapy remains a matter of debate. In the event of worsening functional status in haemodynamics the approach of combining different agents to augment the clinical response has a strong rationale and it has already been widely accepted by clinicians in the UK, rest of Europe, USA and Australia. The concept of combination therapy has appeared in published guidelines and is based on three rational considerations.

Firstly, the notion that a unifying molecular mechanism may be critical to the development of PAH seems improbable given the distinct pathways that have proved amenable to targeted therapies in such patients. It is unlikely therefore that employing treatments that act on a single pathway will be consistently successful whereas there is theoretical advantage to a strategy of combining different molecular targets or different aspects of the same target.

Secondly, combination therapy is often necessary in order to optimally control systemic hypertension and a variety of other diseases such as cardiac failure, cancer and HIV infection where combination therapy has become standard care supported by the highest level of evidence. The potential for targeting multiple pathways at the time of the initial diagnosis for patients with advanced disease makes intuitive sense.

Finally, many patients will have a suboptimal response or develop tolerance to an initial therapeutic approach. By exploiting molecular inter-relationships between individual therapeutic targets overall treatment of efficacy is likely to be improved with minimal risk of toxicity. For example, the addition of Sildenafil in patients refractory to Epoprostenol is associated with enhanced levels of cyclic AMP an effect mediated by inhibition of PDE3 by cyclic GMP. The effect in turn causes up-regulation of NO production and further increases in cyclic GMP concentrations.

To date there have been relative few prospective trials conducted to appraise the merits of combining drugs with different modes of action for the treatment of PAH. Most of the clinical studies currently available are of a retrospective or observational nature describing experiences with small numbers of heterogenous patients without matched controls. The most commonly applied combination therapy approach to date has involved the addition of a second drug where patients deteriorate or fail to sufficiently improve despite optimal doses of initial therapy.

In the UK the most common combination is the addition of a second oral agent (Sildenafil to an endothelial receptor antagonist or endothelin receptor antagonist to Sildenafil). In small studies this approach has been shown to be effective in improving functional class and exercise performance.

The second most common approach to combination therapy is combined prostenoid with Sildenafil and this has been demonstrated to confer added clinical benefits to mono therapy compared to either class of drugs alone.
Finally the addition of Bosentan to Trepostenol has been shown to improve functional class, exercise capacity and haemodynamics.

In conclusion therefore, individuals who demonstrate an inadequate response to mono therapy should be considered for a combination of two or more disease targeted therapies. There are a number of active on-going clinical trials in this area which will help clarify the situation in due course. There is an evidence base that supports the use of targeted medical therapy as indicated above both as mono therapy or as in combination in all forms of pulmonary arterial hypertension including idiopathic, familial and secondary pulmonary arterial hypertension relating to a connective tissue disease, HIV infection and porto-pulmonary hypertension. In addition these agents have been shown to be effective in patients with chronic thromboembolic pulmonary hypertension and pulmonary hypertension associated with sickle cell disease.

The treatments have also been shown to be effective in children with pulmonary hypertension and in common with adult patients all drugs should be available for use in children though it is recognised that subcutaneous trepostenil causes site pain which is poorly tolerated and small sick children cannot reliably inhale an adequate dose of iloprost at two to three hourly intervals. Combination therapy is often necessary to maximise benefits in children.

In conclusion the specific disease target therapies under review in this Health Technology Appraisal have all been demonstrated in clinical trial to benefit patients with all forms of pulmonary arterial hypertension. A satisfactory range of drugs are required to ensure maximum benefit for the maximum number of patients and the role of combination therapy has a clear rationale.