

PULMONARY ARTERY HYPERTENSION: NEW DRUG TREATMENT IN CHILDREN

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Pulmonary artery hypertension (PAH) is a rare progressive disease of the pulmonary vasculature. Although it affects fewer than two adults per million population, and probably fewer children, the clinical course can be one of rapid deterioration, with death occurring within three years of diagnosis for adults, and less than one year for children.^{1 2} In the last decade, greater understanding of the disease has led to rethinking the diagnostic classification of pulmonary hypertension, and the identification of therapeutic targets for drug development. A number of new drugs have been studied in randomised controlled trials, and are licensed to treat PAH. A key message from the recent World Symposium on Pulmonary Arterial Hypertension was to refer patients to a centre with expertise in managing PAH; however, paediatricians may encounter patients already commenced on these novel drugs and delivery systems.³ This review will summarise the key trials of the new drugs recently marketed for PAH, some of which are not yet available and none of which are licensed for children in the UK.

DIAGNOSTIC CLASSIFICATION AND DEFINITIONS

Until recently, primary pulmonary hypertension (PPH) was the term used to describe familial disease, or sporadic disease of unknown cause. At the World Pulmonary Arterial Hypertension Symposium in 2003, the term “primary pulmonary hypertension” was officially abandoned and replaced with idiopathic pulmonary artery hypertension (IPAH). This term more accurately indicates that the diagnosis is by exclusion, and exact causes are not known. Where genetic information supports a hereditary basis, the term familial pulmonary artery hypertension (FPAH) is to be used. In this classification, pulmonary artery hypertension (PAH) is differentiated from pulmonary hypertension caused by left heart disease; or chronic lung disease or hypoxaemia; or chronic thrombotic or embolic disorders affecting the lungs; or other infectious or inflammatory triggers (table 1). This classification system is useful in that it provides a rationale for treatment, as reflected in the approval by drug regulating authorities of new drugs for PAH.⁴

The pathogenesis of PAH is complex and not completely understood. Three factors are thought to be important: vasoconstriction of the pulmonary vasculature, remodelling of the pulmonary vessel wall, and thrombosis *in situ*.⁵ Escalating pulmonary vascular resistance (PVR) leads to eventual right heart failure and death. Thus, standard drug treatment for PAH includes vasodilators, diuretics, digoxin, and anticoagulation. A detailed discussion of the pathology and clinical presentation in children is beyond the scope of this review.

The definition of PAH in children is the same as that for adults. It is defined as a mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg at rest, or ≥ 30 mm Hg during exercise, with a normal pulmonary artery wedge pressure, and an increased pulmonary vascular resistance index ≥ 3 Wood units $\times m^2$. Exercise haemodynamics is important for the diagnosis in children, since they may have normal-high pulmonary artery pressure at rest, but an exaggerated increase in response to exertion.⁶

“RESPONDERS” AND “NON-RESPONDERS”

Acute vasodilator testing in the cardiac catheter laboratory is performed to determine the appropriate treatment course. A response is considered to be a decrease in mPAP of at least 10 mm Hg to ≤ 40 mm Hg, with no change or an increase in cardiac output (CO). A higher proportion of children are acute “responders” compared to adults,⁶ and can be effectively managed with calcium channel blockers.⁷ A survival advantage was observed in both adults and children who were “responders” to acute vasodilator challenge and were treated with nifedipine in addition to conventional anti-failure treatment—that is, digoxin, diuretics, and supplemental oxygen.^{7 8} Dihydropyridine calcium channel blockers, such as nifedipine and amlodipine that act on vascular smooth muscle, are the preferred agents. Nifedipine is preferred over amlodipine because of its shorter half life and duration of action, although amlodipine has been used in stabilised patients. Negative inotropic calcium channel blockers, such as verapamil, should be avoided.⁹ The optimum dose of nifedipine or amlodipine in children with PAH is not known. These agents should be introduced cautiously and the dose titrated as tolerated. They should not be started indiscriminately, since in “non-responders” calcium channel

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Table 1 Revised diagnostic classification of pulmonary hypertension (2003)

▶ Pulmonary artery hypertension (PAH)
Idiopathic PAH
Familial PAH
Related to:
Collagen vascular disease
Congenital systemic to pulmonary shunts
Portal hypertension
HIV infection
Drugs and toxins
Others
Associated with significant venous or capillary involvement
Pulmonary veno-occlusive disease
Pulmonary capillary haemangiomas
▶ Pulmonary hypertension with left heart disease
▶ Pulmonary hypertension associated with lung disease and/or hypoxaemia
▶ Pulmonary hypertension caused by chronic thrombotic or embolic disease
▶ Miscellaneous

blockers can cause worsening failure.¹⁰ “Non-responders” treated with intravenous epoprostenol have shown clinical improvement and increased survival¹¹ indicating that a mechanism other than vasodilation is important. Children who were acute “responders” initially, may become “non-responders” over time.¹¹ Periodic repeat acute vasodilator testing is recommended to maintain optimum long term treatment.^{6, 11}

ANTICOAGULATION

Adult studies demonstrated a survival benefit with the addition of warfarin,¹² and subsequently warfarin is commonly given to children. The target international normalised ratio (INR) depends on the risk of benefit and bleeding. In general the INR range is 1.5–2, while children with chronic thromboembolic disease will aim for a higher INR; and active toddlers, and children with thrombocytopenia, would aim for INR < 1.5.⁶ In some small children, the need for ongoing INR blood tests can be problematic for everyone involved, and warfarin is not prescribed.

CLINICAL STUDIES OF NEW DRUGS

All studies enrolled only adults. There are a number of difficulties associated with extrapolating adult data to children. Firstly, children have a longer anticipated lifespan than adults; secondly, children may have a more reactive pulmonary circulation compared to adults, meaning that greater responsiveness could lead to better therapeutic outcomes; and thirdly, children who are not treated show a worse survival compared to adults, despite clinical and pathological studies indicating increased vasoreactivity in children.¹³ In addition, metabolic changes associated with growth and development during infancy and childhood mean that optimum drug doses for children may be different to those in adults. This article will review the studies from the point of view of treating children.

PROSTACYCLIN AND ANALOGUES

Prostacyclin and thromboxane A₂ are products of the arachidonic acid pathway. They have opposing physiological functions: prostacyclin is a short acting vasodilator produced by vascular endothelium with antiplatelet properties. Thromboxane A₂ is a vasoconstrictor and has pro-platelet aggregatory effects. The balance of these two local hormones regulates vasomotor control in many tissues. In PAH, this

balance is lost and may contribute to the overall pathogenesis of PAH.¹⁴

Epoprostenol

Epoprostenol sodium is the synthetic sodium salt of naturally occurring prostacyclin. It is licensed in the UK for the treatment of adults with PAH. When given as a continuous intravenous infusion, epoprostenol improves exercise tolerance, symptoms, haemodynamics, and survival in children^{7, 11} and adults.^{15, 16} Epoprostenol decreases PVR and improves the survival in “non-responders”.^{16–18} Survival in epoprostenol treated adults at one, two, and three years was 87.8%, 76.3%, and 62.8%, respectively, and significantly better than that observed with historical controls, 58.9%, 46.3%, and 35.4%, respectively.¹⁹ This raises the question of a mechanism of action other than vasodilation. Antiproliferative and vascular remodelling effects are proposed.^{17, 20} Side effects associated with epoprostenol treatment include jaw pain, diarrhoea, nausea, light-headedness, and flushing. The usual starting dose in children is the same as in adults: 2 ng/kg/min with up titration until the maximum tolerated dose is reached.⁷ Tolerance frequently develops, and regular dosage adjustment is required to maintain therapeutic response. In children, the maintenance dose is generally higher than adults, and there is considerable interpatient variability for optimum dose. The mean dose for children after one year of treatment is around 50–80 ng/kg/min compared to 20–40 ng/kg/min in adults.⁶ Epoprostenol is the current standard treatment for PAH in patients who do not respond to acute vasodilator challenge, and for those “responders” who have deteriorated on calcium channel blockers. However, there are risks and important considerations for administration, especially with regard to children. The administration of epoprostenol requires the placement of a central venous line and a continuous infusion pump to be worn by the child. Unintentional interruption of the infusion, and pump failure, can lead to life threatening hypertensive crises. Catheter related sepsis and thrombosis are life threatening complications. Epoprostenol is an unstable compound that requires particular and careful reconstitution and dilution. Parents/carers must be competent in the preparation of daily infusions at home. There is a clear need for an alternative mode of drug administration.

Iloprost nebulised

Iloprost is a stable analogue of prostacyclin with a longer half life; 15–30 minutes compared to 2–3 minutes for

Abbreviations

- ▶ **AUC:** area under the curve
- ▶ **ALT:** alanine aminotransferase
- ▶ **cGMP:** cyclic guanosine monophosphate
- ▶ **CO:** cardiac output
- ▶ **ET:** endothelin
- ▶ **FPAH:** familial pulmonary artery hypertension
- ▶ **IPAH:** idiopathic pulmonary artery hypertension
- ▶ **mPAP:** mean pulmonary artery pressure
- ▶ **mPVR:** mean pulmonary vascular resistance
- ▶ **NO:** nitric oxide
- ▶ **NYHA:** New York Heart Association
- ▶ **PAH:** pulmonary artery hypertension
- ▶ **PPH:** primary pulmonary hypertension
- ▶ **SVR:** systemic vascular resistance
- ▶ **6MWT:** six minute walk test

epoprostenol.²¹ The duration of action for iloprost is about 60 minutes, thus frequent nebulisations are necessary.²² Drug delivery direct to the lungs avoids the morbidity associated with a central intravenous catheter, and may also avoid systemic side effects. However, it is not known whether the benefits seen with a continuous infusion will be observed with “pulsed” delivery. Iloprost has a licence in the UK for the treatment of adults with PAH.

Clinical studies

A multicentre, randomised, double blind trial compared nebulised iloprost (2.5–5 µg administered 6–9 times per day) with placebo in 203 patients with IPAH and PAH associated with connective tissue disease or chronic thromboembolic disorder. Only patients with New York Heart Association (NYHA) functional class III or IV disease were included. After 12 weeks there was no significant difference between groups for the primary end point of > 10% increase in baseline walking distance and improvement in NYHA class. However, there was a significant increase in six minute walk test (6MWT) for the iloprost group compared to placebo (overall mean increase 36 m in iloprost group; $p = 0.004$), and there was an overall significant improvement in NYHA class for the iloprost group compared to placebo. There were significant improvements in haemodynamic variables when measured after inhalation compared to placebo. Pre-inhalation values were not different from baseline. In total 17.7% of patients withdrew from the study (13.7% in the placebo group). The most common reason was clinical deterioration. Serious adverse effects were the same for both groups. However, there were significantly more episodes of syncope, jaw pain, and flushing in the iloprost group.²³

Treprostinil sodium subcutaneous infusion

Treprostinil is also a stable analogue of prostacyclin with a longer half life (approximately three hours). Unlike epoprostenol, it is stable at room temperature and has a neutral pH. It has been studied in adults as a continuous subcutaneous infusion, and although it is not yet available in the UK, it has a licence for the treatment of adults with PAH in Europe.

Clinical studies

Treprostinil was compared with placebo in a double blind randomised, multicentred, controlled trial enrolling 470 patients with both IPAH and PAH associated with connective tissue disease or congenital systemic to pulmonary shunts. Patients with NYHA class II, III, or IV disease were included. Subcutaneous treprostinil was given at a starting dose of 1.25 ng/kg/min and incrementally increased until the maximum tolerated dose. Exercise tolerance significantly improved in the active group compared to controls at 12 weeks. The median between group difference was 16 m in favour of treprostinil ($p = 0.006$). There were significant improvements in mPAP, mPVR, and CO for the treprostinil group compared to controls. Eighty five per cent of patients in the treprostinil group reported infusion site pain or erythema. Significantly more patients in the treatment group reported diarrhoea, jaw pain, vasodilation, and oedema.²⁴

Beraprost sodium oral

Beraprost is an orally active prostacyclin analogue with a half life of one hour. Beraprost was designated orphan drug status in the European Union in 2001. It has not been extensively studied in children with PAH.

Clinical studies

There are two studies comparing beraprost to placebo for treatment of PAH. Both studies are double blind randomised and placebo controlled. The first study included 130 patients with NYHA class II or III disease, with IPAH or PAH associated with other diseases. Beraprost was started at 20 µg four times a day, and titrated up to maximum of 480 µg per day as tolerated. After 12 weeks, there was an overall significant improvement in 6MWT in the beraprost group (adjusted mean difference between groups was +25 m in favour of beraprost; $p = 0.036$). However, there were no significant improvements in mPAP, mPVR, or CO in the beraprost group, and changes in NYHA class were not significant.²⁵ The second study was conducted over 12 months and enrolled 116 patients with NYHA class II or III disease. The primary end point was disease progression. Significantly fewer patients in the beroprost group met the criteria for disease progression at six months compared to placebo, but this benefit was not evident beyond six months. Exercise capacity was significantly improved from baseline in the beraprost group up to six months compared to placebo. However, the treatment benefit was not sustained at follow up.²⁶

Limitations

All the trials discussed above were randomised, double blind, and placebo controlled, except for the epoprostenol trials, where a placebo was not used. There were no children included in any of these studies. The studies for both iloprost and treprostinil were not long enough to determine a survival advantage. Although the nebulised route is less invasive and may reduce systemic side effects, small children and very sick children may not be able to manage the mask and nebuliser device, nor the frequency of nebulisations. The high rate of infusion site reactions and pain with subcutaneous treprostinil precludes this treatment option for many children.

Cautions

Iloprost is not recommended for patients with unstable disease and advanced right heart failure. The pulmonary vasodilator effect of nebulised iloprost is of short duration, thus episodes of syncope may reflect therapeutic gaps or insufficient efficacy.²¹ The need for dose adjustment or changing treatment should be continually monitored. Iloprost may exacerbate hypotension in patients with existing low blood pressure. Iloprost is cleared via the liver. In patients with liver dysfunction, iloprost should be started at low dose and increased cautiously. The dosage interval should not be less than three hours.

Parents or carers of children on treprostinil must be skilled in the care of the infusion site and the infusion device. They must also be competent in the preparation of daily infusions at home. Treprostinil is extensively metabolised in the liver. In children with mild hepatic insufficiency, treprostinil sodium should be started at a lower dose and increased cautiously. Beroprost is an attractive alternative because of its oral bioavailability. However, efficacy is yet to be established in adults, and dosage information for children are lacking.

ENDOTHELIN RECEPTOR ANTAGONISTS

Endothelin-1 (ET-1) is a potent vasoconstrictor and smooth muscle mitogen produced by vascular endothelium.²⁷ The

vasoconstrictor effects of ET-1 occur via ET-A receptors, while ET-B receptors on vascular smooth muscle and endothelium are involved with clearance of ET-1 or vasodilation.²⁸ In PAH, endothelin-1 production is increased, and the ET-A vasoconstrictor effect predominates, while ET-B vasodilator mechanisms on endothelium cells are impaired. ET-A receptors and ET-B receptors on vascular smooth muscle are activated causing cell proliferation.²⁹

Bosentan

Bosentan is a competitive ET-A and ET-B receptor antagonist. It is the only oral agent with a licence for the treatment of adult PAH. The licence states efficacy and safety have not been studied in children < 12 years old; however, a pharmacokinetic study has been conducted which indicates doses for children < 40 kg.³⁰

Clinical studies

To date, two randomised studies have been published in adults with PAH. Both trials were multicentre, double blind, and compared bosentan with placebo.

The first study enrolled 32 adults with IPAH, or PAH associated with other aetiologies, with stable World Health Organization functional class III disease. Patients on intravenous epoprostenol were excluded. Bosentan was added to conventional treatment at a starting dose of 62.5 mg twice a day and titrated up to 125 mg twice a day after four weeks. At 12 weeks, there was a significant improvement in the 6MWT in the bosentan group compared to placebo (overall mean difference +76 m in favour of bosentan; $p < 0.021$). Cardiopulmonary haemodynamics and NYHA functional class were also significantly improved from baseline in the bosentan group compared to placebo. Two patients withdrew from the study because of clinical deterioration. Both were in the placebo group. Adverse effects were similar in both groups.³¹

An open label extension of this study enrolled 29 of the 32 patients to monitor ongoing clinical improvement and adverse effects for one year. There were no deaths reported. The most common adverse effects reported were headache, upper respiratory tract infection, dyspnoea, chest pain and aggravated PAH, and sinusitis. Three patients showed elevated hepatic transaminases, although no patient discontinued treatment.³²

The second study enrolled 213 adults using the same inclusion criteria as the first study. Bosentan was started at a dose of 62.5 mg twice a day for the first four weeks, then increased to 125 mg or 250 mg twice a day for the following 12 weeks. There was a significant overall improvement in the 6MWT in bosentan treated patients compared to placebo (mean difference +44 m in favour of bosentan; $p = 0.002$) for the 125 mg twice daily dose. The improvement seen with 250 mg twice daily was not significantly different from the lower dose. There were no significant improvements in NYHA class or Borg dyspnoea scores. The most frequent adverse effects reported were headache and dizziness, with the frequency of each similar in both bosentan and placebo groups. Hepatic dysfunction was more common in the bosentan group compared to placebo, and was most common in the high dose group.³³

Survival has been estimated from both these studies. At 36 months, survival for patients treated with bosentan was 86% compared with predicted survival of 48%.³⁴

Paediatric study

Bosentan has been studied in 19 children aged between 3–15 years with IPAH or PAH related to congenital heart disease. All children were in WHO class II or III. The study was an open label, non-controlled study comparing the pharmacokinetic parameters of single and multiple doses of bosentan with those seen in healthy adults after 12 weeks treatment. Bosentan was added to existing treatment, including intravenous (iv) epoprostenol.

The bosentan dosage was stratified according to weight as follows:

- ▶ 10–20 kg: 31.25 mg daily for four weeks then increase to 32.5 mg twice a day
- ▶ 20–40 kg: 31.25 mg twice a day for four weeks then increase to 62.5 mg twice a day
- ▶ > 40 kg: 62.5 mg twice a day for four weeks then increase to 125 mg twice a day.

The end points were area under the curve (AUC) comparisons, exercise capacity, haemodynamic assessment, and WHO class. The AUC values observed in children were comparable with those measured in healthy adults given 125 mg of bosentan twice a day. Calculated values for the half life of bosentan were not different after single or multiple doses, and were comparable to that calculated in healthy adults. mPAP and PVR index significantly improved for the group. However, change in exercise capacity and WHO class at 12 weeks was not significantly different from baseline. The most frequent adverse effect was flushing, headache, and elevated liver enzymes. One child experienced elevated ALT (alanine transaminase) values to more than three times the upper limit of normal. These resolved upon discontinuation. There were no deaths.³⁵

Bosentan is being used in infants and children with severe disease. The oral dosage form is an enormous advantage in this age group. Clinical improvement has been observed in patients as young as 9 months with severe disease.^{36 37} Endothelium receptor blockers may be beneficial in patients who do not respond to acute vasodilator treatment, or who deteriorate on calcium channel blockers.⁶

Limitations

Paediatric pharmacokinetic studies assume that if AUCs comparable to adult data are measured, comparable efficacy and safety can be expected. This may not be the case if children have a different form of disease. Studies of short duration are insufficient to observe long term adverse effects on growth and development.

Cautions

Bosentan is metabolised by cytochrome P450 isozymes 3A4 and 2C9. Bosentan has inducible metabolism and an active metabolite.³⁰ The effect of these on other drugs metabolised through these same isozymes, such as warfarin, is not known.

Table 2 Drug costs for pulmonary artery hypertension

Drug	Costs/year/child
Epoprostenol sodium + home care delivery costs	£8000–£65000 + ~£15000 = £23000–£80000*
Iloprost trometamol + nebuliser	£438000–£657000* + ~£500
Bosentan	£11500–£23000*
Sildenafil	£6000–£9000*

*Price range reflects the dose increase for different age groups.

Liver dysfunction is reported and monitoring is important especially in the setting of advancing right side failure. Baseline liver function tests should be taken, with discontinuation if liver dysfunction occurs.

PHOSPHODIESTERASE INHIBITORS

In PAH, synthesis of endogenous nitric oxide (NO) is impaired.³⁸ Phosphodiesterase inhibitors boost the effect of NO by inhibiting the breakdown of cyclic guanosine monophosphate (cGMP). In smooth muscle cells, cGMP regulates calcium influx and mediates vasodilation. Sildenafil, a type 5 phosphodiesterase inhibitor, has blocked rebound pulmonary hypertension associated with withdrawal of inhaled NO in infants and neonates.³⁹ In small case series describing children and adults with PAH, sildenafil is reported to improve exercise capacity, decrease PAP, and improve symptoms.^{40–42}

Limitations

Randomised, controlled studies are needed to determine the efficacy and safety of sildenafil in children and adults with PAH.

Cautions

Much of the safety data for sildenafil relates to its use on a "prn" basis. The optimum dosage and long term adverse effects are not known. Sildenafil is metabolised in the liver via CYP450 3A4.⁴³ The clinical importance of drug interactions with other drugs used to treat PAH, such as bosentan, is not known.

COMBINATION THERAPY

Bosentan and epoprostenol combination were assessed in adults with NYHA class III or IV disease in a multicentred, double blind trial. Epoprostenol was commenced in all patients. After two days, patients were randomised to either bosentan or placebo. At 16 weeks, the primary end point of a 30% reduction in total pulmonary resistance was not significantly different between groups. Haemodynamic

parameters and distance covered in 6MWT for the epoprostenol/bosentan combination were not significantly different from the epoprostenol/placebo combination. Four of five patients who withdrew from the study were in the epoprostenol/bosentan arm. Two patients died, one had clinical deterioration, and the final patient withdrew because of adverse effects.⁴⁴

To date, other combinations such as bosentan/sildenafil, sildenafil/prostaglandin analogue have been reported in case series only.^{45–49} There is no evidence so far that combination therapy improves survival or quality of life.

ON THE HORIZON

An imbalance between thromboxane A₂ synthesis and clearance may contribute to the progression of PAH. Thromboxane A₂ inhibitors, such as terbogrel, are in clinical development.⁵⁰ Sitaxentan is a selective ET-A receptor antagonist currently under investigation.⁵¹ Arginine infusion and inhaled NO are being investigated as treatment options.⁹ Lung transplantation may be an option for some children,¹¹ though the donor pool is limited.

COSTS

The treatment of PPH is expensive (table 2).

SUMMARY

The treatment of PAH is complex and involves the use of therapeutic agents with sophisticated delivery systems, which have not been formally studied in children (table 3). Evidence based clinical practice guidelines have been published for the management of PAH in adults, and the treatment of children tends to follow a similar strategy.⁹ However, in all patients, particularly children, careful consideration must be given to the patient and their carers, since the overall benefit of intravenous treatment will depend on their ability to accept and manage drug administration through a central line. Oral therapies are preferable. Until randomised controlled studies have been conducted, the role of sildenafil in PAH is undefined. It is important that both

Table 3 Summary of drugs used to treat pulmonary artery hypertension

Drug	Licence	Doses used in paediatric studies
Epoprostenol	Treatment of patients with PPH in NYHA class III or IV who have not responded to conventional treatment. Administered by continuous iv infusion. Limited published information on use in children	2 ng/kg/min initially. Continuous infusion via central line. Doses increase depending on clinical course and tolerance. At 1 year, doses may be up to 50–80 ng/kg/min for some children. ⁶ Higher doses have been used beyond 1 year ⁸
Iloprost	Treatment of adults with PPH in functional class III by inhalation. Currently no published experience in children and adolescents is available.	NA
Treprostinil	Treatment of PAH in patients with class II–IV symptoms by continuous subcutaneous infusion. Safety and efficacy in paediatric patients has not been established*	NA
Beraprost sodium	Orphan drug. Limited studies in children. Use is experimental	NA
Bosentan	Treatment of PPH and PAH secondary to scleroderma in patients with grade III functional status. Safety and efficacy in patients <12 years old has not been substantially documented	10–20 kg: 31.25 mg daily for 4 weeks then increase to 32.5 mg twice a day 20–40 kg: 31.25 mg twice a day for 4 weeks then increase to 62.5 mg twice a day >40 kg: 62.5 mg twice a day for 4 weeks then increase to 125 mg twice a day
Sildenafil	Not licensed for PPH or PAH. Use is experimental	NA

*Licence in the USA and Europe. Not yet licensed in the UK.

NA, not available; NYHA, New York Heart Association; PAH, pulmonary artery hypertension; PPH, primary pulmonary hypertension.

adults and children are referred to a centre with expertise in the management of PAH, and knowledge of the complex drug delivery systems.

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REFERENCES

- D'Alonso GE, Barst RJ, Ayres SM, *et al*. Primary pulmonary hypertension: a national prospective study. *Ann Intern Med* 1991;**115**:434–49.
- Gaine SP, Rubin LJ. Primary pulmonary hypertension. *Lancet* 1998;**352**:719–25.
- Galie N, Rubin LJ. Introduction: new insights into a challenging disease. A review of the Third World Symposium on Pulmonary Artery Hypertension. *J Am Coll Cardiol* 2004;**43**(12 suppl):15.
- Rubin LJ. Introduction: diagnosis and management of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004;**126**:7S–10S.
- Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary artery hypertension. *N Engl J Med* 2004;**351**:1425–36.
- Rosenzweig EB, Widlitz A, Barst RJ. Pulmonary arterial hypertension in children. *Pediatr Pulmonol* 2004;**38**:2–22.
- Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. *Circulation* 1999;**99**:1197–208.
- Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992;**327**:76–81.
- Badesch DB, Abman SH, Ahearn GS, *et al*. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004;**126**:35S–62S.
- Archer S, Rich S. Primary pulmonary hypertension: a vascular biology and translational research “Work in progress”. *Circulation* 2000;**102**:2781–91.
- Yung D, Widlitz AC, Rosenzweig EG, *et al*. Outcomes in children with idiopathic pulmonary arterial hypertension. *Circulation* 2004;**110**:660–5.
- Fuster V, Steele PM, Edwards WD, *et al*. Primary pulmonary hypertension: natural history and the importance of thrombosis. *Circulation* 1984;**70**:580–7.
- Widlitz A, Barst RJ. Pulmonary arterial hypertension in children. *Eur Respir J* 2003;**21**:155–76.
- Badesch DB, McLaughlin VV, Delcroix M. Prostanoid therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2004;**43**:56S–61S.
- Higenbottam TW, Spiegelhalter D, Scott JP, *et al*. Prostacyclin (epoprostenol) and heart-lung transplantation as treatments for severe pulmonary hypertension. *Br Heart J* 1993;**70**:366–70.
- Barst RJ, Rubin LJ, Long WA, *et al*. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The primary pulmonary hypertension study group. *N Engl J Med* 1996;**34**:296–302.
- McLaughlin VV, Gentner DE, Panella MM, *et al*. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. *N Engl J Med* 1998;**338**:273–7.
- Barst RJ, Rubin LJ, McGoon MD, *et al*. Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. *Ann Intern Med* 1994;**121**:409–15.
- McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension. The impact of epoprostenol therapy. *Circulation* 2002;**106**:1477–82.
- Kim NH, Channick RN, Rubin LJ. Successful withdrawal of long-term epoprostenol therapy for pulmonary hypertension. *Chest* 2003;**124**:1612–1615.
- Schering Health Care Limited. Summary of product characteristics: iloprost (Ventavis®). <http://emc.medicines.org.uk/> (accessed 19 April 2004).
- Goldsmith DR, Wagstaff AJ. Inhaled iloprost: in primary pulmonary hypertension. *Drugs* 2004;**64**:763–73.
- Olschewski H, Simonneau G, Galie N, *et al*. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002;**347**:322–9.
- Simonneau G, Barst RJ, Galie N, *et al*. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2002;**165**:800–4.
- Galie N, Humbert M, Vachiery JL, *et al*. Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2002;**39**:1496–502.
- Barst RJ, McGoon M, McLaughlin V, *et al*. Beraprost therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2003;**41**:2119–25.
- Kim NHS, Rubin LJR. Endothelin in health and disease: Endothelin receptor antagonists in the management of pulmonary artery hypertension. *J Cardiovasc Pharmacol Therapeut* 2002;**7**:9–19.
- Dupois J. Endothelin-receptor antagonists in pulmonary hypertension. *Lancet* 2001;**356**:1113–4.
- Rich S, McLaughlin VV. Endothelin receptor blockers in cardiovascular disease. *Circulation* 2003;**108**:2184–90.
- Actelion Pharmaceuticals UK. Summary of product characteristics: bosentan (Tracleer®). <http://emc.medicines.org.uk/> (accessed 19 April 2004).
- Channick RN, Simonneau G, Sitbon O, *et al*. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001;**358**:1119–23.
- Sitbon O, Badesch DB, Channick RN, *et al*. Effects of the dual endothelin receptor antagonist bosentan in patients with pulmonary arterial hypertension: a 1-year follow-up study. *Chest* 2003;**124**:247–54.
- Rubin LJ, Badesch DB, Barst RJ, *et al*. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;**346**:896–903.
- McLaughlin V, Sitbon O, Rubin LJ, *et al*. The effect of first line bosentan on survival of patients with primary pulmonary hypertension. American Thoracic Society, 99th International Conference, Seattle, 16–21 May, 2003.
- Barst RJ, Ivy D, Dingemans J, *et al*. Pharmacokinetics, safety and efficacy of bosentan in pediatric patients with pulmonary arterial hypertension. *Clin Pharmacol Therapeutics* 2003;**73**:372–82.
- Vogel M, Maiya S, Haworth SG. Current experience with bosentan (Tracleer) in the treatment of pediatric patients with pulmonary arterial hypertension. Association of European Paediatric Cardiology, 38th Annual Meeting, Amsterdam, 28–31 May 2003 Abstract 195.
- Penny DJ, Rose M, Wilson S, *et al*. Preliminary experience with bosentan in children with primary pulmonary hypertension [abstract]. *J Am Coll Cardiol* 2003;**41**(suppl A).
- Cooke JP. A novel mechanism for pulmonary arterial hypertension. *Circulation* 2003;**108**:1420–21.
- Atz AM, Wessel DL. Sildenafil ameliorates effects of inhaled nitric oxide withdrawal. *Anesthesiology* 1999;**91**:307–10.
- Abrams D, Schulze-Neick I, Magee AG. Sildenafil as a selective pulmonary vasodilator in childhood primary pulmonary hypertension. *Heart* 2000;**84**:E4.
- Prasad S, Wilkinson J, Gatzoulis MA. Sildenafil in primary pulmonary hypertension. *N Engl J Med* 2000;**343**:1342.
- Michelakis ED, Tymchak W, Noga M, *et al*. Long-term treatment with oral sildenafil is safe and improves functional capacity and hemodynamics in patients with pulmonary arterial hypertension. *Circulation* 2003;**108**:2066–9.
- Reffelmann T, Kloner RA. Therapeutic potential of phosphodiesterase 5 inhibition for cardiovascular disease. *Circulation* 2003;**108**:239–44.
- Humbert M, Barst RJ, Robbins IM, *et al*. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J* 2004;**24**:353–9.
- Humbert M, Barst RJ, Robbins IM, *et al*. Safety and efficacy of bosentan combined with epoprostenol in patients with severe pulmonary artery hypertension. *Am J Respir Crit Care Med* 2003;**167**:A441.
- Rayburn BK, Benza RL, Tallaj JA, *et al*. The use of bosentan and a prostacyclin analogue in the treatment of primary pulmonary hypertension. *J Heart Lung Transplant* 2003;**22**(1S):abstract 241.
- Bhatia S, Frantz RP, Severson CJ, *et al*. Immediate and long-term hemodynamic and clinical effects of sildenafil in patients with pulmonary arterial hypertension receiving vasodilator therapy. *Mayo Clin Proc* 2003;**78**:1207–13.
- Ghofrani HA, Rose F, Schermuly RT, *et al*. Oral sildenafil as long-term adjunct therapy to inhaled iloprost in severe pulmonary arterial hypertension. *J Am Coll Cardiol* 2003;**42**:158–64.
- Stiebellehner L, Petkov V, Vonbank K, *et al*. Long-term treatment with oral sildenafil in addition to continuous IV epoprostenol in patients with pulmonary arterial hypertension. *Chest* 2003;**123**:1293–5.
- Langleben D, Christman BW, Barst RJ, *et al*. Effects of thromboxane synthetase inhibitor and receptor antagonist terbogrel in patients with primary pulmonary hypertension. *Am Heart J* 2002;**143**:E4.
- Barst RJ, Langleben D, Frost A, *et al*. Sitaxentan therapy for pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2004;**169**:441–7.