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Original Article

Conventional and targeted medical therapies

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Pulmonary hypertension is a progressive disease with a poor prognosis if left untreated. It is defined as pulmonary vascular obstructive disease. For patients with congenital cardiac disease, increased pulmonary vascular resistance is observed in addition to increased pulmonary arterial pressure. Pulmonary arterial hypertension may be either idiopathic/familial, or related to congenital cardiac disease, connective tissue disease, portal hypertension, human immunodeficiency virus infection, ingestion of drugs and toxins. It also includes pulmonary occlusive venopathy, pulmonary capillary hemangiomatosis, and the persistent pulmonary hypertension of the newborn. Similarities in terms of clinical features, pathobiology and histopathology, has led to the development of similar treatment approaches for pulmonary arterial hypertensive patients. However, prognosis may be very different, e.g. whereas the natural history of the idiopathic form is most often rapidly progressive and fatal with a median survival of 2.8 years, patients with congenital cardiac disease considered inoperable due to pulmonary vascular disease, i.e. Eisenmenger's syndrome, can survive for decades (Fig. 1). Natural history studies report five-year survival of 80% and 25-year survival of 40%.[1,2]

The overall goal for treating pulmonary arterial hypertensive patients, including those with congenital cardiac disease, is to improve functional class III/IV to II, and at a minimum, maintain patients at functional class II as so. Several studies "suggest" successful therapeutic strategies in the management of congenital cardiac disease-associated pulmonary arterial hypertension. Unfortunately, clinical data is limited and often extrapolated from trials involving other forms of the disease. The selection of the optimal therapy is complex, as there are no consistently successful treatments. Some agents may involve complicated delivery systems, specific dosing regimens, side effects and potential complications. As the disease progresses, the treatments may have to be revised based on individualized risk/benefit considerations. The 2007 treatment algorithm for pulmonary arterial hypertension[3] may thus provide guidance for the treatment of the disease associated with congenital cardiac anomalies (Fig. 2); however, there is little evidence-based data for this specific group.

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General measures

Patients with pulmonary arterial hypertension usually maintain physical activities that are appropriate to their capabilities. Patients are instructed to self-limit if they become symptomatic, and to avoid heavy activities, particularly if a history of syncope is present.[4] Due to the potentially devastating effects of respiratory tract infections, pneumococcal and influenza immunizations are recommended.[5]

Other general measures include avoiding pregnancy by using effective contraception (progesterone derivatives or low-dose estrogens in patients with no history of thromboembolic disease). Intrauterine devices or surgical sterilization may not be advised in severely compromised patients because of the increased risk of bleeding.[6] Additional contraceptive measures may also be indicated for patients

being treated with agents such as bosentan due to the concern about decreased effectiveness of oral birth control pills.

Oxygen, diuretic and digoxin

Oxygen therapy is indicated in cases of chronic hypoxemia to maintain systemic arterial oxygen saturation above 90%.[5] Supplemental oxygen should be considered in the following instances: 1) systemic arterial desaturation during sleep or an upper respiratory tract infection; 2) during exercise, if it causes significant desaturation; 3) resting hypoxemia due to heart failure. 4) right-to-left shunting through a patent foramen ovale or congenital cardiac defect, to reduce erythrocytosis. The long-term effects of oxygen therapy still need to be confirmed; improved survival has been reported in a small group of patients with Eisenmenger's syndrome,[7] although not confirmed in a more recent study.[8]

Diuretics are used to control peripheral edema and/or ascites in patients with right heart failure. Treatment with digitalis is controversial;[9] however, it may benefit patients with right ventricular dysfunction.

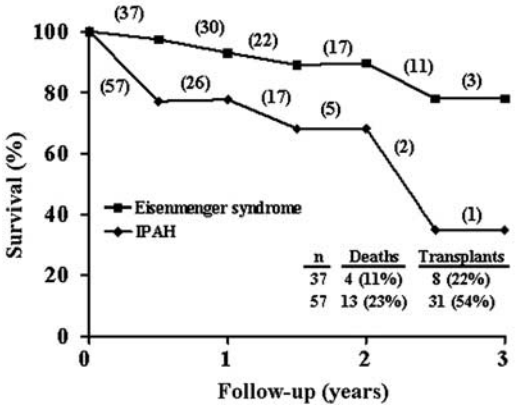

Figure 1.
Non-transplantation survival in 94 adults with Eisenmenger's syndrome or severe idiopathic pulmonary arterial hypertension (IPAH). The number of patients is shown for each follow-up interval (reproduced with permission from [65]).

Anticoagulation

The rationale for anticoagulation therapy in pulmonary arterial hypertension associated with congenital cardiac disease is based on the increased risk of thrombosis *in situ* due to sluggish pulmonary blood flow, dilation of the right heart and a sedentary lifestyle. Improved survival has been reported in non-randomized clinical trials with oral anticoagulation in adult patients with idiopathic

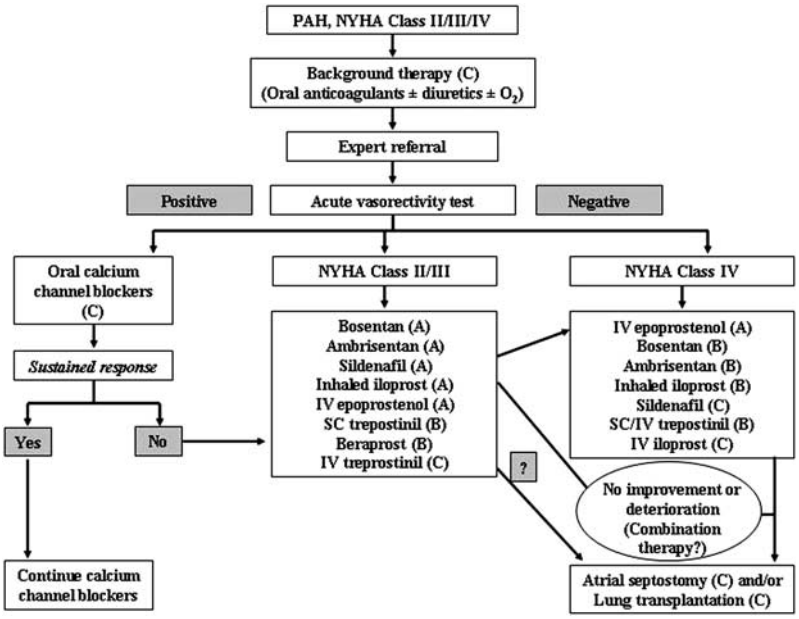

Figure 2.
The pulmonary arterial hypertension treatment algorithm developed at the 2003 World Symposium on Pulmonary Hypertension with an update in 2007[3] for adult patients may provide guidance for the treatment of patients with the congenital cardiac disease-associated form. The recommended therapies presented in this algorithm have been evaluated mainly in patients with idiopathic pulmonary arterial hypertension or those with connective tissue disease or anorexigen use. Extrapolation to other forms of the disease should be made with caution. Grading of evidence for efficacy in adult patients:

- *A: Data derived from multiple randomized clinical trials or meta-analyses.*
- *B: Data derived from a single randomized clinical trial or from multiple randomized clinical trials with heterogeneous results.*
- *C: Data derived from small nonrandomized studies and/or consensus opinion of experts.*

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pulmonary arterial hypertension.[10,11] Because thrombosis *in situ* is also observed in patients with congenital cardiac disease, these results have often been extrapolated to support anticoagulation. However, the risk/benefit ratio should be carefully considered in these patients since anticoagulation may be detrimental.[12]

The target international normalized ratio in pulmonary arterial hypertensive patients treated with warfarin is approximately 1.5 to 2.5.[13] A higher level may be advised in certain clinical conditions (e.g. documented chronic thromboembolic disease, antiphospholipid antibody syndrome),[14] while a lower level may be recommended for patients at a higher risk of bleeding (e.g. patients with significant thrombocytopenia).[15] Alternatively, heparin can be used when anticoagulation with warfarin is contraindicated or when adjustments of doses are difficult, although long-term use of heparin can be associated with osteoporosis.[16]

In advanced pulmonary hypertension associated with congenital heart disease, anticoagulation with warfarin may be considered, although the effectiveness is not established.

Class: IIb. *Level of evidence: C.*

Calcium channel blockers

Calcium channel blockers may be beneficial in pulmonary arterial hypertension because of their pulmonary vasodilatory properties. Acute testing of pulmonary vasoreactivity with inhaled nitric oxide or intravenous prostacyclin is necessary to determine if the patient is a 'responder' and may benefit from long-term therapy with this class of drugs. In adults, an acute response (to predict long term response with chronic calcium channel blockers) is currently defined by a decrease in mean pulmonary arterial pressure of at least 10 mmHg to a final value of 40 mmHg or less, with increased or unchanged cardiac output.[17] However, in contrast to patients with the idiopathic form, adults with pulmonary hypertension associated with congenital cardiac disease rarely show acute vasodilator responsiveness and thus, overall, are unlikely to be candidates for chronic calcium channel blocker therapy. Because of significant side effects, treatment with these drugs (in particular at high doses) is not recommended for patients who are not acute responders, or for those who have significant right cardiac failure.

Epoprostenol and prostacyclin analogues

The rationale for the use of epoprostenol or other prostacyclin analogues in the treatment of pulmonary arterial hypertension associated with congenital cardiac disease is based on the imbalance between thromboxane and prostacyclin[18,19] and the decreased expression of prostacyclin synthase[20] observed in the idiopathic form of the disease. Deficient prostacyclin synthesis may also play a role in the development of pulmonary vasculopathy in congenital cardiac shunts.

Although rare, patients who are acute responders to pulmonary vasoreactivity testing could be considered for treatment with high dose calcium channel blockers. This applies to post-operative (either complete or partial repair) patients that have persistent pulmonary vascular disease, or patients with trivial congenital heart defects that are not considered causally related to pulmonary vascular disease.

Class: I. *Level of evidence: C.*

Continuous intravenous infusion of epoprostenol, has been associated with improvement of exercise capacity and hemodynamics in pulmonary arterial hypertension either idiopathic or associated with scleroderma.[21–25] Epoprostenol is the only treatment shown to prolong survival in idiopathic pulmonary hypertension in a randomized controlled trial.[21] McLaughlin et al. reported significant hemodynamic improvement after chronic intravenous epoprostenol in seven patients with congenital cardiac disease.[26] In the study of 20 younger patients, Rosenzweig et al. also showed significant hemodynamic improvement and increased exercise capacity after one year.[27]

The starting dose of epoprostenol is 2 ng/kg/min and is uptitrated by increments of 1 to 2 ng/kg/min based on side effects and symptoms of pulmonary hypertension, with the most rapid increases implemented during the first several months of treatment. Epoprostenol has a number of side effects that tend to be dose-dependent and often respond to reduction of the dosage. The short half-life of epoprostenol (3–6 min) renders interruptions of treatment, due to pump malfunction or line dislodgement, potentially life-threatening.

Treprostinil sodium is a stable prostacyclin analogue with a longer half-life than epoprostenol which can be infused intravenously or subcutaneously. Intravenous treprostinil has similar effects on hemodynamics as epoprostenol, and induces comparable short-term decreases in pulmonary vascular resistance as subcutaneous treprostinil.[28] Subcutaneous treprostinil improved exercise capacity, indices of dyspnea, and hemodynamics in a 12 week randomized controlled trial (which included patients with congenital cardiac disease).[29] Pain at the site of infusion is reported in more than 80% of patients. Side effects also include headache, diarrhea, nausea, rash, and jaw pain. Treprostinil (for subcutaneous or intravenous infusion) is currently approved in the United States for pulmonary arterial hypertensive patients with class II–IV symptoms.

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Iloprost is a stable prostacyclin analogue that can be used intravenously or by inhalation. The hemodynamic efficacy and side effects of intravenous iloprost are similar to those seen with epoprostenol.[30,31] Inhaled iloprost is an appealing therapy, given the selectivity for the pulmonary vascular bed. It improved exercise capacity, hemodynamics, the functional class and quality of life in the 12 week randomized controlled trial.[32] Sustained beneficial effects were reported after one year of treatment in adult patients with idiopathic pulmonary hypertension.[33] Common side effects are headache, flushing, nausea and dizziness. Syncope has also been reported in patients who do not have an inhalation upon arising in the morning. In view of the short duration of action, six to nine inhalations a day (2–5 mcg per inhalation) are currently recommended. It is approved in Europe for idiopathic pulmonary arterial hypertension in class III (New York Heart Association), and in the United States for pulmonary arterial hypertension in class III–IV.

Beraprost sodium is a stable and orally active prostacyclin analogue. In the first randomized controlled study (12 weeks), only patients with idiopathic pulmonary hypertension treated (median oral dose, 80 mcg 4 times a day) significantly improved their exercise capacity and symptoms, but not hemodynamics.[34] The second study[35] included patients with pulmonary arterial hypertension, either idiopathic or associated with connective tissue disease or congenital cardiac disease treated for 12 months (median oral dose, 120 mcg 4 times a day). The exercise capacity improved at 3 and 6 months, with no benefit at 9 and 12 months; hemodynamics and survival rates did not change significantly. Frequent side effects reported with beraprost are headache, nausea, and dizziness. Beraprost is an approved therapy for pulmonary arterial hypertension in Korea and Japan.

With respect to the more recently developed prostacyclin analogues, including inhaled iloprost, subcutaneous treprostinil and oral beraprost, the number of patients with pulmonary arterial hypertension associated with congenital cardiac disease enrolled in the randomized trials has been quite small and thus do not permit definitive conclusions of the benefits.

Endothelin receptor antagonists

Endothelin, a naturally occurring peptide, is one of the most potent vasoconstrictors known to date. It has essential role in a number of physiological and pathological conditions such as normal development, vasoconstriction, hypertrophy, fibrosis, and inflammation.[36] It is present at elevated concentrations in the plasma and lung tissue of patients with pulmonary arterial hypertension,[37–42] and correlates with indices of severity of disease,[43] and inversely with survival in patients with the idiopathic form.[44]

Bosentan is an oral nonselective endothelin receptor antagonist that binds to both ET_A and ET_B receptor subtypes. Bosentan (62.5 mg b.i.d. for first four weeks with uptitration to 125 mg b.i.d. thereafter) has been evaluated in two randomized clinical trials (12 and 16 weeks)[45,46] in patients with pulmonary arterial hypertension, either idiopathic or related to connective tissue disease, with improvements in exercise capacity, hemodynamics, functional class and symptoms. In the second study, a decreased rate of clinical worsening was also observed. Patients with the idiopathic form (169 individuals from these 2 trials), treated with bosentan, were followed for up to three years.[47] Kaplan-Meier survival estimates were 96% at one year and 89% at two years. Bosentan is an approved therapy for pulmonary arterial hypertension in New York Heart Association class III or IV in the United States. and in Europe. More recently, bosentan was demonstrated to be safe and efficacious in a 16 week randomized clinical trial in patients with the Eisenmenger syndrome,[48] demonstrating improved exercise capacity and hemodynamics, without deterioration in systemic arterial oxygen saturation. This raises the possibility of antiproliferative effects and restoration of apoptosis by at least some treatment modalities in patients who were considered to have a chronic and "fixed" elevation of pulmonary vascular resistance.

Sitaxsentan is an oral ET_A selective endothelin receptor antagonist. The rationale for selective ET_A receptor blockade is based on blocking the vasoconstrictor effects of the ET_A receptors while maintaining the vasodilator and clearance effects of the ET_B receptors. In two randomized clinical trials (12 and 18 weeks)[49,50] in patients with pulmonary arterial hypertension, either idiopathic or associated with connective tissue disease or congenital cardiac disease, 100 mg once daily sitaxsentan improved exercise capacity, hemodynamics, and functional class. Sitaxsentan (100 mg) is currently approved in the European Union for idiopathic pulmonary arterial hypertension with class III symptoms.

Ambrisentan, another oral ET_A selective endothelin receptor antagonist improved exercise capacity, functional class and time to clinical worsening (5 mg and 10 mg once daily);[51,52] in addition, hemodynamics improved in an earlier pilot study. Ambrisentan is currently approved by the United

States Food and Drug Administration for New York Heart Association class II, III and IV pulmonary hypertensive patients (5 mg and 10 mg).

Adverse effects associated with endothelin receptor antagonists include acute hepatotoxicity (dose-related), teratogenicity, and possible male infertility. Common side effects are headache, flushing and dose-related decreases in hemoglobin. The clinical experience with endothelin receptor antagonists is promising. Furthermore, the possibility of combined therapy with other therapeutic agents may lead to treatment regimens with an overall enhanced efficacy and reduced dosage for each agent.

Phosphodiesterase inhibitors

The vasodilator effects of nitric oxide are mediated in smooth muscle cells by cyclic guanosine monophosphate which is rapidly inactivated by phosphodiesterases.[53] In chronic pulmonary arterial hypertension, phosphodiesterase type 5 gene expression and activity are increased.[54] Inhibitors may prevent the breakdown of cyclic guanosine monophosphate, thus potentiating pulmonary vasodilation. Vasoreactivity studies in pulmonary arterial hypertension suggest that sildenafil, an oral phosphodiesterase type 5 inhibitor, may have greater acute hemodynamic effects than inhaled nitric oxide and may further reduce pulmonary vascular resistance in patients already demonstrating a benefit from chronic intravenous epoprostenol.[55] Sildenafil may be particularly beneficial to prevent rebound pulmonary hypertension upon withdrawal of inhaled nitric oxide.[56] In combination with inhaled iloprost, sildenafil produces a greater and more prolonged decrease in pulmonary arterial pressure and pulmonary vascular resistance than either agent alone, although acute hemodynamic improvement is more pronounced with inhaled iloprost than with oral sildenafil.[57,58]

Sildenafil improved exercise capacity, hemodynamics, and functional class in pulmonary arterial hypertensive patients (idiopathic form or associated with connective tissue disease or congenital cardiac disease) in a 12 week randomized clinical trial (20, 40 or 80 mg sildenafil t.i.d. vs. placebo).[58] Sildenafil is approved (20 mg t.i.d.) for class II-III pulmonary arterial hypertension in the United States and in the European Union. Several small studies have reported clinical benefits with a phosphodiesterase type 5 inhibitor in pulmonary arterial hypertension associated with repaired congenital cardiac defects.[59] A randomized controlled trial has demonstrated beneficial effect with the addition of sildenafil to chronic intravenous epoprostenol in pulmonary arterial hypertension.[60]

1. *Patients who are nonresponders to acute pulmonary vasodilator testing, or responders who remain in New York Heart Association functional class III, should be considered for treatment with either an endothelin receptor antagonist (e.g. bosentan) (Class I, Level of evidence A), a phosphodiesterase type 5 inhibitor (e.g. sildenafil) (Class I, Level of evidence A) or a prostacyclin analogue (e.g. inhaled iloprost) (Class I, Level of evidence A), or subcutaneous treprostinil (Class I, Level of evidence B).*

2. *Functional class IV patients, and those with class III symptoms who do not improve with an endothelin receptor antagonist, phosphodiesterase type 5 inhibitor or with subcutaneous or inhaled prostacyclin analogues should be strongly considered for treatment with an intravenous prostanoid (epoprostenol (Class I, Level of evidence A), treprostinil (Class I, Level of evidence B), or iloprost (Class I, Level of evidence C)).*

3. *Combination therapy may become an attractive option for patients who fail to improve or deteriorate with a single vasoactive agent, although clinical data are currently limited (Class IIa, Level of evidence C).*

Atrial septostomy

Patients with pulmonary arterial hypertension associated with a corrected congenital cardiac defect (no residual shunt) presenting with syncope and right cardiac failure despite medical treatment may benefit from atrial Septostomy.[61,62] The procedure can reduce right atrial pressure, increase cardiac output and systemic oxygen transport, improving exercise capacity and survival in pulmonary arterial hypertensive patients.[63] It may serve as a palliative bridge to heart-lung or lung transplantation. However, the procedure carries a significant risk and should only be performed in experienced centers as well as in selected patients (without severe right ventricular failure). Although a Potts shunt (surgical anastomosis of the left pulmonary artery to the descending aorta) is an alternative to performing an atrial septostomy,[64] data with this are even more limited.

Atrial septostomy should be considered for refractory pulmonary arterial hypertensive patients without an adequate residual pulmonary to systemic shunt.

Class: IIa. *Level of evidence: C.*

Future considerations

The treatment algorithm continues to evolve as additional treatments become available. In the future, new approaches with agents under investigation, including gene and cell therapy as well as a number of exciting new pharmacological approaches, may further increase options of treatment for this challenging disease. Why patients respond to various drugs differently from one another

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remains an enigma. This may be due, in part, to the many polymorphisms that exist in the human genome. By stratifying targeted therapeutic agents by relevant polymorphisms, i.e. genetic variants, we may one day be able to predict responders versus nonresponders (to various vasoactive agents) using pharmacogenomics. Undoubtedly, this will help to determine optimal medical treatment regimens for patients with various forms of pulmonary arterial hypertension, including the congenital cardiac disease-associated form.

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