

Pulmonary arterial hypertension: therapeutic algorithm

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The numerous controlled clinical trials performed recently in pulmonary arterial hypertension (PAH) can allow us to abandon a clinical-based treatment strategy and adopt an evidence-based therapy. The treatment algorithm is restricted to patients in NYHA class III or IV. The different treatments have been evaluated mainly in sporadic, idiopathic PAH and in PAH associated with scleroderma or to anorexigen use. Extrapolation of these recommendations to other PAH subgroups should be done with caution.

High doses of calcium channel blockers are indicated only in the minority of patients who are responders to acute vasoreactivity testing. Patients in NYHA class III should be considered candidates for treatment with either an endothelin receptor antagonist, a prostanoid or a type 5 phosphodiesterase inhibitor. Continuous intravenous administration of epoprostenol is proposed as rescue treatment in NYHA class IV patients. Combination therapy can be attempted in selected cases. Balloon atrial septostomy and/or lung transplantation are indicated for refractory patients or when medical treatments are unavailable.

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The treatment of pulmonary arterial hypertension (PAH) has been traditionally characterized by few and difficult options¹. Recently, we have faced a dramatic change from the slow progress in the past decades to the remarkable number of randomized controlled trials (RCT) accomplished in the last few years. The impressive amount of knowledge derived from these studies can allow us, for the first time in the history of PAH therapy, to shift from a clinical-based to an evidence-based treatment strategy. However we have also inherited different treatments that are generally accepted to be efficacious (e.g. oral anticoagulants, oxygen, calcium channel blockers) although not supported by RCT and not formally approved by Regulatory Agencies for the specific PAH indication. The purpose of the present article is to compare the RCT performed in PAH and to propose an evidence-based grading system and a treatment algorithm that incorporate the currently available therapies.

The grade of recommendation (I: general agreement of efficacy; II: divergence of opinion for efficacy; IIa: weight of opinion in favor of usefulness; IIb: weight of opinion less well established) and the level of evidence for efficacy (A: data derived from multiple randomized clinical trials; B: data derived from a single randomized clinical

trial; C: consensus of the expert and/or non-randomized small studies, registries) of the treatments for PAH are based on the suggestions of the Committee for Practice Guidelines of the European Society of Cardiology^{2,3}. The treatment algorithm is shown in figure 1³⁻⁵. The algorithm is appropriate for NYHA class III or IV idiopathic PAH or PAH associated with connective tissue disease patients. Extrapolation of these recommendations to other subgroups should be done with caution.

Traditional therapy

The suggested initial approach is the adoption of the general measures and initiation of the supportive therapy. Due to the complexity of the evaluation and the treatment options available, it is strongly recommended that PAH patients are then referred to a specialized center. General measures include adjustments (reduction) of daily activities, avoiding altitudes > 1500 m, pulmonary infection prevention, birth control, pregnancy termination, psychological assistance and appropriate management of elective general surgery.

The rationale for the use of oral anti-coagulant treatment in patients with PAH is based on the presence of traditional risk

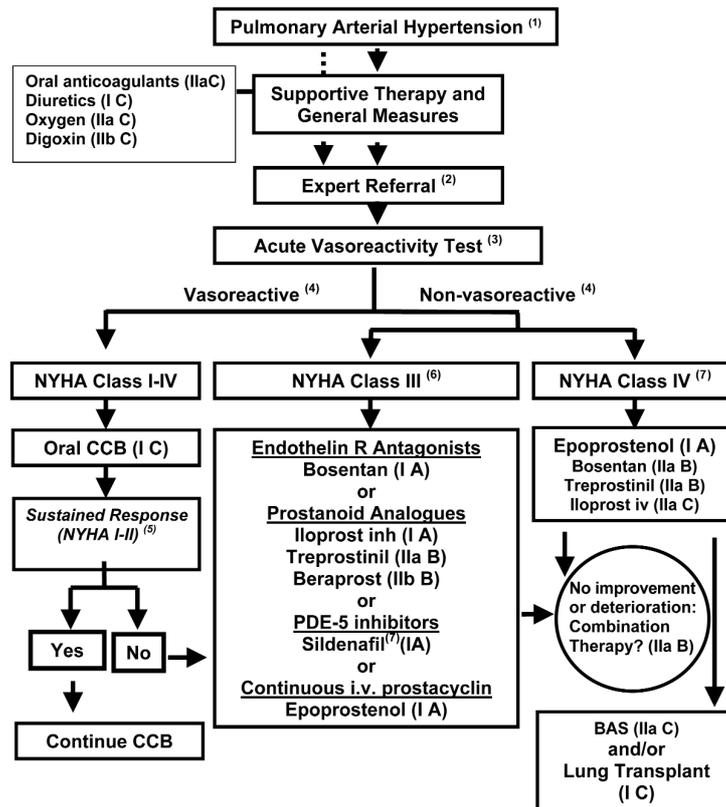


Figure 1. Treatment algorithm. 1 = the algorithm is restricted to patients in NYHA class III or IV because they represent the largest population included in controlled clinical trials. For NYHA class I or II very few data are available. In addition the different scleroderma treatments have been evaluated mainly in sporadic idiopathic pulmonary arterial hypertension (PAH) patients, and in PAH associated with scleroderma or to anorexigen use. Extrapolation of these recommendations to other PAH subgroups should be done with caution. 2 = due to the complexity of the acute vasoreactivity tests, and of the treatment options available, it is strongly recommended that consideration be given to referral of patients with PAH to a specialized center. 3 = acute vasoreactivity test should be performed in all patients with PAH even if the greater incidence of positive response is achieved in patients with idiopathic PAH and PAH associated with anorexigen use. 4 = a positive acute response to vasodilators is defined as a fall in mean pulmonary artery pressure of at least 10 mmHg to ≤ 40 mmHg, with an increase or unchanged cardiac output during acute challenge with inhaled nitric oxide, intravenous epoprostenol, or intravenous adenosine. 5 = sustained response to calcium channel blockers (CCB) is defined as patients being in NYHA class I or II with near-normal hemodynamics after several months of treatment. 6 = in patients in NYHA class III, first-line therapy may include oral endothelin receptor antagonists, chronic intravenous epoprostenol, or prostanoid analogues. 7 = most experts consider that NYHA class IV patients in unstable conditions should be treated with intravenous epoprostenol (survival improvement, worldwide experience and rapidity of action). I, IIa, IIb = grade of recommendation; A, B, C = grading of level of evidence; BAS = balloon atrial septostomy; PDE = phosphodiesterase; R = receptor.

factors for venous thromboembolism like heart failure and sedentary lifestyle as well as on the demonstration of thrombophilic predisposition and of thrombotic changes in the pulmonary microcirculation and in the elastic pulmonary arteries. Oral anticoagulant treatment should be initiated in patients with idiopathic PAH and the proposed target INR varies somewhat being 1.5 to 3.0. Anticoagulation of other forms of PAH is also suggested if no bleeding risk factors are present. Appropriate diuretic treatment in case of right heart failure allows clear symptomatic and clinical benefits. Although no consistent data are currently available on long-term oxygen treatment in PAH, it is generally considered important to maintain oxygen saturation $> 90\%$ at all times. The usefulness of digoxin is controversial and intravenous inotropes such as dobutamine may be used in end-stage right heart failure.

An acute vasodilator challenge performed during right heart catheterization^{6,7} can identify patients who

may benefit from long-term calcium channel blocker treatment. Acute vasodilator testing should only be done using short-acting pulmonary vasodilators in experienced centers to minimize the potential risks. Currently the agents used in acute testing are intravenous prostacyclin or adenosine and inhaled nitric oxide^{5,8,9}. Generally, only about 10 to 15% of idiopathic PAH will meet these criteria^{7,8}. Treatment with high doses of calcium channel blockers is mandatory in responders to acute vasoreactivity tests. Careful titration to optimally tolerated doses (up to 120-240 mg/day for nifedipine and 240-720 mg/day for diltiazem) may be required. Long-term response (after 3-6 months) needs to be evaluated and subjects on NYHA class I-II and with marked hemodynamic improvement can continue calcium channel blockers as monotherapy.

Non-responders to acute vasoreactivity testing who are in NYHA class I and II should continue with general measures and supportive therapy under close clinical follow-up.

Targeted therapies

Non-responders to acute vasoreactivity testing or responders who remain in NYHA class III should be considered candidates for treatment with either an endothelin receptor antagonist¹⁰, a prostanoid¹¹ or a cyclic guanosine monophosphate (cGMP)-type 5 phosphodiesterase inhibitor¹².

Endothelin receptor antagonists¹⁰. Endothelin-1 (ET-1), a peptide produced primarily by vascular endothelial cells, is a powerful vasoconstrictor and mitogen for smooth muscle. ET-1 binds to two types of receptors, ET_A and ET_B: ET_A receptors are found in smooth muscle cells whereas ET_B receptors are localized on both endothelial cells and in smooth muscle cells. Activation of ET_A and ET_B receptors on smooth muscle cells mediate the vasoconstrictive and mitogenic effects of ET-1. Stimulation of endothelial ET_B receptors promote ET-1 clearance and activation of nitric oxide and prostacyclin release. An activation of the ET-1 system has been demonstrated in both plasma¹³ and lung tissues of PAH patients. Although it is not clear if the increases in ET-1 plasma levels are a cause or a consequence of PAH, studies on tissue endothelin system expression support a prominent role of ET-1 in the pathogenesis of PAH. The clear evidence of the activation of the endothelin system in PAH provides a sound rationale for testing ET-1 antagonists in PAH patients. The most efficient way to antagonize the ET-1 system is the use of ET-1 receptor antagonists that can block either ET_A or both ET_A and ET_B receptors.

At present, the only approved drug of the first class is the orally active dual ET_A and ET_B receptor antagonist bosentan. Bosentan has been evaluated in two randomized trials that have shown improvement in exercise capacity, functional class, hemodynamics, echocardiographic and Doppler variables, and time to clinical worsening. Increases in hepatic aminotransferases occurred in 10% of the subjects treated with 125 mg bid, were found to be dose-dependent and reversible after dose reduction or discontinuation. Additional long-term studies have shown persistent efficacy over time. Bosentan was shown to be effective also in an uncontrolled study in patients with HIV-associated PAH and in pediatric patients with idiopathic PAH or PAH associated with congenital heart defects. The results of a placebo-controlled study on the effects of bosentan in adult patients with PAH associated with congenital heart defects will be soon released. Bosentan has been approved for the treatment of NYHA class III and IV PAH patients in the United States and Canada. In Europe it has been approved by the European Agency for the Evaluation of Medicinal Products (EMA) for the treatment of NYHA class III PAH patients.

Two selective orally active ET_A receptor antagonists are currently under evaluation: sitaxentan (100 mg/day)

has been assessed in two phase III trials who have demonstrated efficacy on exercise capacity, hemodynamics and time to clinical worsening; ambrisentan has been evaluated in a phase II study which has shown improvements in exercise capacity and hemodynamics. Two additional phase III studies are ongoing. Incidence of abnormal liver function tests was apparently 3-4% with both drugs.

Prostanoids¹¹. Prostacyclin is produced predominantly by endothelial cells and it induces potent vasodilation of all vascular beds studied. This compound is the most potent endogenous inhibitor of platelet aggregation and it appears also to have both cytoprotective and antiproliferative activities¹⁴. A dysregulation of the prostacyclin metabolic pathways has been shown in patients with PAH as assessed by a reduction in prostacyclin synthase expression in the pulmonary arteries and in prostacyclin urinary metabolites¹¹. Although it remains to be clarified whether dysregulation of the prostacyclin metabolic pathways has a causative role or it is merely a consequence of PAH, it represents a convincing rationale for the therapeutic use of prostacyclin in PAH patients.

Among prostanoids, treprostinil is administered subcutaneously by micro-infusion pumps and small subcutaneous catheters. The effects of treprostinil in PAH patients were studied in the largest worldwide study performed in this condition, and showed improvements in exercise capacity, hemodynamics and clinical events. In 2002 the Food and Drug Administration (FDA) approved the use of treprostinil in NYHA class II, III and IV patients with PAH. Treprostinil subcutaneous treatment has recently been approved by the French Regulatory Agency in PAH patients. Infusion site pain was the most common side effect of treprostinil. Trials on the intravenous and inhaled use of this compound are ongoing.

Inhaled iloprost (6-9 daily repetitive inhalations) has been evaluated in one clinical trial which demonstrated an increase in exercise capacity, an improvement of symptoms, pulmonary vascular resistance and clinical events. A second study on 60 patients already treated with bosentan has shown an increase of exercise capacity in the subjects randomized to the addition of inhaled iloprost in comparison with placebo. Inhaled iloprost treatment has been approved by EMA in Europe for NYHA class III idiopathic PAH and in Australia and New Zealand for PAH and non-operable chronic thromboembolic pulmonary hypertension class III and IV. Inhaled iloprost has been approved for the treatment of PAH also by the FDA.

Beraprost is the first chemically stable and orally active prostacyclin analogue. Two clinical studies have shown an improvement of exercise capacity that unfortunately persists only up to 3-6 months. Beraprost sodium has been approved in Japan and South Korea for idiopathic PAH but its development seems to be stopped

in the United States and in Europe. Inhaled iloprost treatment has been approved by EMEA in Europe for NYHA class III idiopathic PAH and in Australia and New Zealand for PAH and non-operable chronic thromboembolic pulmonary hypertension class III and IV. Inhaled iloprost has been approved by the FDA.

The efficacy of continuous intravenous administration of epoprostenol has been tested in three unblinded clinical trials in idiopathic and associated with scleroderma PAH. Epoprostenol improves symptoms, exercise capacity and hemodynamics in both clinical conditions, and is the only treatment to be shown in clinical trials to improve survival in the idiopathic form. Epoprostenol has been shown to be effective also in pediatric patients and in patients with PAH associated with congenital heart defects with porto-pulmonary hypertension and HIV infection. Optimal dose is variable between individual patients ranging in the majority between 20 and 40 ng/kg/min. Serious adverse events related to the delivery system include pump malfunction, local site infection, catheter obstruction and sepsis. Epoprostenol may also be used in NYHA class III patients who are refractory to endothelin receptor antagonists or other prostanoids. Some authors still use first-line epoprostenol in NYHA class III patients, due to its demonstrated survival benefits. Epoprostenol in Europe has not been registered through the centralized procedure of the European Union (EMA) but is approved in different European countries on a local basis for idiopathic PAH in NYHA class III and IV. Epoprostenol is approved by the FDA in the United States and Canada for idiopathic PAH and PAH associated with connective tissue disease in NYHA class III and IV.

Cyclic guanosine monophosphate-type 5 phosphodiesterase inhibitors¹². Type 5 phosphodiesterase physiologically induces the degradation of cGMP. The inhibition of type 5 phosphodiesterase increases the intracellular concentration of cGMP thereby enhancing cGMP-mediated relaxation and growth inhibition on pulmonary vascular smooth muscle cells¹⁵.

The orally-active cGMP-type 5 phosphodiesterase inhibitor sildenafil has been evaluated in a clinical study with a cross-over design showing improvement in symptoms, exercise capacity and Doppler-derived pulmonary pressure. A pivotal study on 278 patients treated with sildenafil 20, 40 or 80 mg tid has shown improvement in exercise capacity, functional class and hemodynamics with the three doses. Sildenafil has recently been approved by the FDA for the treatment of PAH patients. A preliminary approval (PAH in NYHA class III) has also been granted by the EMA. Uncontrolled studies have reported favorable effects of the orally active type 5 phosphodiesterase inhibitor sildenafil in patients with chronic thromboembolic pulmonary hypertension and in PAH associated with lung fibrosis.

In NYHA class III patients the choice among an endothelin receptor antagonist, a prostanoid or a cGMP-type 5 phosphodiesterase inhibitor is dependent on a variety of factors, including the approval status, route of administration, side effect profile, patient's preference and physician's experience. As head-to-head comparisons are not available a first-line therapy based on efficacy cannot be scientifically defined.

In contrast, continuous intravenous epoprostenol may be considered as first-line therapy for patients in NYHA class IV because of the demonstrated survival benefit in this subset. However, these patients should be concurrently listed for lung transplantation and subsequently delisted in case of improvement. Although both bosentan and treprostinil are approved in NYHA class IV patients, most experts consider these treatments as a second line for severely ill patients. Although no controlled trials have been performed with the intravenous delivery of iloprost, this prostacyclin analogue has been approved in New Zealand.

Combination therapy

Combination therapy is an attractive option to address the multiple pathophysiologic mechanisms of PAH. Combination therapy can be pursued by the simultaneous initiation of two (or more) treatments or by the addition of a second (or third) treatment to a previous therapy that may be considered insufficient. Which is the best choice between these two strategies is currently unknown.

Combination therapy (e.g. bosentan + prostanoids) has been currently tested in two clinical trials combining respectively bosentan to epoprostenol (32 patients) and bosentan to inhaled iloprost (64 patients). The efficacy and safety of the concurrent initiation of bosentan and epoprostenol were investigated in 33 NYHA class III and IV PAH randomized either to an epoprostenol + placebo group or an epoprostenol + bosentan group (BREATHE-2)¹⁶. Improved hemodynamics, exercise capacity and functional class were observed in both groups. Data show that there was a trend for a greater (though non-significant) improvement in all hemodynamic parameters in the epoprostenol + bosentan group. However, an increase of adverse events was observed in the combination group as compared to epoprostenol alone.

The STEP study has been performed in PAH patients treated with bosentan who were randomized to receive either inhaled iloprost or inhaled placebo in combination with bosentan for 12 weeks (32 iloprost and 33 placebo). Combination-treated patients (iloprost plus bosentan) at the 6-min walk test walked a mean difference of 26 m farther than patients treated only with bosentan ($p = 0.051$). Other important clinical endpoints, including change in NYHA functional class, reduction in mean pulmonary artery pressure and delay

in clinical deterioration were statistically significant (p values range from 0.02 to < 0.0001). In patients with PAH, deteriorating despite chronic treatment with non-parenteral prostanoids, addition of bosentan or sildenafil to the ongoing treatment resulted in favorable improvements in pulmonary hemodynamics and exercise capacity in uncontrolled studies.

Interventional and surgical therapies¹⁷

Balloon atrial septostomy is performed in severely ill patients as a palliative bridge to lung transplantation. The role of this procedure in the treatment of PAH patients is uncertain because its efficacy has been reported only in small series and case reports, totaling approximately 120 published cases.

Lung and heart-lung transplantation in PAH has been assessed only in prospective uncontrolled series, since formal RCT are considered unethical in the absence of alternative treatment options. The 3- and 5-year survival after lung and heart-lung transplantation is approximately 55 and 45%, respectively. Both single and bilateral lung transplantation have been performed for idiopathic PAH and these operations have been combined with repair of cardiac defects for the Eisenmenger syndrome. For some complex defects and in cases of ventricular septal defects, a survival advantage of heart-lung transplantation has been shown.

Double lung or heart-lung transplantation is indicated in patients with advanced NYHA class III and IV symptoms that are refractory to available medical treatments. The unpredictability of the period on the waiting list and donor organ shortage complicate the decision-making regarding the appropriate timing of listing for transplantation.

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