

Current Medical Treatment of Pulmonary Arterial Hypertension

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Abstract

Primary pulmonary hypertension is a rare disease of the pulmonary vasculature manifested by dyspnea on exertion, syncope, and signs and symptoms of right heart failure. In the absence of adequate treatment, primary pulmonary hypertension has a grave prognosis, with a median survival of 2.8 years. Pulmonary arterial hypertension develops in association with known risk factors and predisposing clinical conditions, and shares many clinical, pathological and therapeutic characteristics with primary pulmonary hypertension. Therapeutic choices in pulmonary arterial hypertension depend on the etiology of the disease, severity of functional impairment and hemodynamic response following acute vasodilator administration during right heart catheterization. Agents currently approved for the specific treatment of pulmonary arterial hypertension are continuous intravenous epoprostenol, subcutaneous treprostinil and oral bosentan. A small group of patients who demonstrate true acute vasoreactivity at right heart catheterization may be chronically treated with oral calcium channel blockers. In addition, most patients with pulmonary hypertension receive conventional treatment, represented by anticoagulants, diuretics, inotropic medication or oxygen supplementation. Treatment of pulmonary arterial hypertension has significantly altered the natural course of the disease, with pronounced symptomatic, functional and survival benefit. Current clinical research focuses on the discovery of new targets of therapy and the use of a combination treatment approach, which will offer hope and valuable insight into the pathogenetic basis of this devastating illness.

Key Words: Primary pulmonary hypertension, pulmonary arterial hypertension, treatment, prostacyclin, endothelin receptor antagonist, epoprostenol, treprostinil, bosentan.

Introduction

PULMONARY HYPERTENSION (PH) is a heterogeneous group of disorders characterized by increased pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR). Without intervention, PH has a progressive downhill course, leading to right ventricular failure and death. Diagnostic classification of PH includes five major categories of diseases, based on similar biologic, etiologic, clinical and therapeutic characteristics (1) (Table 1). Primary pulmonary

TABLE 1

Diagnostic Classification of Pulmonary Hypertension

Pulmonary Arterial Hypertension

Primary Pulmonary Hypertension (PPH):
sporadic
familial

Related to:

Collagen vascular disease
Congenital systemic-to-pulmonary shunts
Portal hypertension
HIV infection
Drugs/toxins: anorexigens and others
Persistent pulmonary hypertension of the newborn

Pulmonary Venous Hypertension

Pulmonary Hypertension Associated with Disorders of the Respiratory System and/or Hypoxemia

Pulmonary Hypertension due to Chronic Thrombotic and/or Embolic Disease

Pulmonary Hypertension due to Disorders Affecting the Pulmonary Vasculature

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hypertension (PPH) has no apparent cause, while other forms of PH are associated with known risk factors or develop as a consequence of other co-existing disease states. All forms of diseases included under the pulmonary arterial hypertension (PAH) category have similarities with PPH in terms of pathologic characteristics, clinical presentation, diagnostic modalities and therapeutic options. If PPH remains untreated, its prognosis is extremely poor, with an estimated median survival, based on the National Institutes of Health (NIH) Registry of 194 patients, of 2.8 years and 1-, 3-, and 5-year survival rates of 68%, 48% and 34%, respectively (2). The most important determinant of survival is the level of right ventricular function, and the most common cause of death is right ventricular failure (2–4).

The pathologic hallmark of PAH consists of the triad of vasoconstriction, vascular wall remodeling and thrombosis (5, 6). Pulmonary vascular endothelium dysfunction plays a crucial role in the pathogenesis of pulmonary hypertension. Specifically, there is an imbalance between endothelial mediators with opposing actions on pulmonary vasculature (7–11). There is an overexpression and/or activation of vasoconstricting, mitogenic and prothrombotic factors (endothelin-1, thromboxane and serotonin) and a decrease in prostacyclin, nitric oxide and heparin-like substances, which promote vasodilatation and have antiproliferative and antithrombotic properties. Current treatment of PAH focuses on either replacing deficient vasodilating factors and growth factor inhibitors, or inhibiting mediators that induce vasoconstriction and vascular proliferation and remodeling (Fig. 1).

Therapeutic choices in pulmonary hypertension depend on the etiology of the disease, the severity of functional impairment and the presence or absence of acute vasoreactivity at right heart catheterization. The only agents currently FDA-approved for the specific treatment of PAH are continuous intravenous epoprostenol (prostacyclin, prostaglandin I₂, Flolan®), continuous subcutaneous treprostinil (prostacyclin analogue, Remodulin®) and oral bosentan (dual endothelin receptor antagonist, Tracleer®) (12–26). Other drugs recently investigated or currently being studied in clinical trials of PAH include inhaled iloprost, oral beraprost, oral sildenafil, inhaled nitric oxide, oral L-arginine, thromboxane synthetase inhibitors and selective endothelin receptor antagonists, such as sitaxsentan (27–43). A very small group of pa-

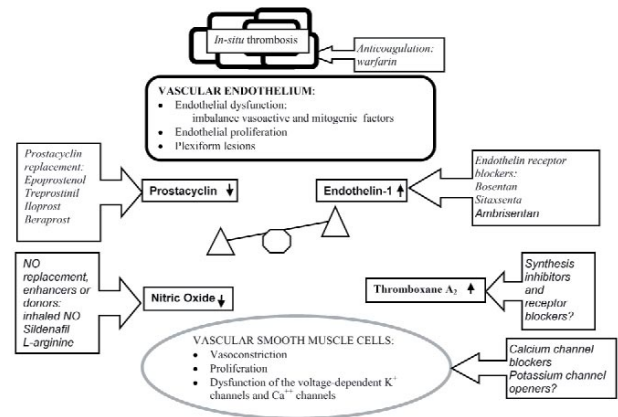


Fig. 1. Specific therapy for pulmonary hypertension is directed at excessive production of endothelium-derived vasoconstrictors and proliferative factors, such as endothelin-1, and reduced production of substances with beneficial vasodilatory properties, such as prostacyclin and nitric oxide.

tients who demonstrate true acute vasoreactivity at right heart catheterization may be chronically treated with oral calcium channel blockers (44–47). In addition, most patients with PH receive conventional heart failure treatment, represented by anticoagulants, diuretics, inotropic medication and oxygen supplementation (45, 48, 49) if necessary.

Recent trends in the comprehensive management of patients with PAH focus on the introduction of new drugs with different intracellular mechanisms of action or alternative routes of administration, and on the use of combination therapy for cases unresponsive to monotherapy. The currently available therapeutic options have been clearly shown to improve outcome and survival. However, the invasive nature of follow-up evaluation by right heart catheterization has created major challenges for the design of therapeutic trials in PAH because of potential ethical and logistical dilemmas. Ethical difficulties may arise from enrolling patients in double-blind, placebo-controlled, randomized studies and from establishing endpoints of death and survival. A widely used clinical endpoint for many evidence-based trials is the time to clinical worsening, defined as a composite of death, transplant or need for rescue (by intravenous epoprostenol) from the time the investigational treatment was initiated. Use of follow-up right heart catheterization to document treatment effect, although objective and accurate, may jeopardize the safety of study participants and unduly increase the cost of investigation. Recent trials are focusing more on

TABLE 2
Functional Assessment and Prognosis

Functional Class	Description	Median Survival (months)
WHO class I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.	58.6
WHO class II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.	58.6
WHO class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.	31.5
WHO class IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.	6

Adapted from the Executive Summary — World Symposium on PPH 1998 (1).

clinically relevant endpoints, such as improvement in the 6-minute walk test (6MWT) distance or in symptoms (Borg score) and in the general clinical status (such as dyspnea-fatigue rating) (15, 21, 24–27). In particular, the 6MWT, if performed in accordance with published guidelines (50), is a relatively objective, reliable and clinically meaningful measure of outcome. In deciding the type of treatment, it is important to evaluate the baseline prognostic factors of clinical outcome. These factors include hemodynamic parameters of right ventricular function, extent of symptoms as assessed by the WHO functional class, and overall exercise capacity. Right atrial pressure greater than 15–20 mm Hg and cardiac index less than 2 L/min/m² obtained at right heart catheterization are associated with increased mortality. Depending on the degree of physical limitation by symptoms, the functional level of patients with PH is graded from I to IV, with higher grades indicating more severe disease and worse prognosis (1) (Table 2). This is known as the WHO functional classification and represents an adaptation of the NYHA functional classification in congestive heart failure. Distance walked during 6 minutes is an accurate and reproducible indicator of the overall exercise capacity. The distance and degree of oxygen desaturation during the 6-minute walk test correlate with prognosis and survival in patients with primary pulmonary hypertension (51, 52).

Specific Therapy for Pulmonary Artery Hypertension

Epoprostenol

Epoprostenol (Flolan[®], prostacyclin, prostaglandin I₂) was approved in 1995 for the treatment of patients with PPH and PAH related to connective tissue disease. Prostacyclin (epoprostenol), a metabolite of arachidonic acid, is produced primarily in the vascular endothelium, induces direct vasodilatation of both pulmonary and systemic arterial vascular beds, inhibits platelet aggregation and increases cardiac output. In addition to direct pulmonary vasodilatation, prostacyclin probably has a chronic remodeling effect in the pulmonary vasculature; in long-term therapy, both mean pulmonary arterial pressure and pulmonary vascular resistance decrease substantially more than they do during acute testing in the catheterization laboratory (12). The long-term beneficial effect of prostacyclin in PH is probably related to a combination of these pharmacologic properties.

Prostacyclin, the most effective therapeutic agent currently available, is used for patients with World Health Organization (WHO) class III and IV and it is the only option available for patients with class IV and severe right ventricular dysfunction. For patients with PPH and most other forms of PAH, prostacyclin improves exercise capacity, pulmonary hemodynamics, right ventricular function and survival rate (12–23). Earlier

studies of patients with PPH, comparing the effect of intravenous prostacyclin therapy with conventional treatment over 8–12 weeks, have showed significant improvement in hemodynamics and exercise capacity, which were sustained in long-term follow-up at 6 and 18 months (13–15). When the 6-minute walk test was used to gauge the prostacyclin effect on exercise capacity, PPH patients treated with prostacyclin had an improvement in the median walk distance of 47 m at 12 weeks and could walk over 100 m farther at both 6 and 18 months, while patients receiving conventional therapy had both hemodynamic and functional deterioration (13–15). For patients with PPH treated with intravenous prostacyclin, the clinical and functional improvements were associated with a survival benefit, when compared with historical controls from NIH data (14, 17). Recent studies evaluating the long-term outcome of prostacyclin treatment have documented symptomatic, hemodynamic and survival benefits for patients with PPH and other types of PAH (18–20). Clinical response to long-term prostacyclin therapy is predicted by the age at onset of the disease, the presence of acute vasoreactivity, the level of functional impairment as determined by WHO functional class, exercise capacity or history of right heart failure either at baseline or follow-up, and the etiology of PAH (18–20). Younger PPH patients with less functional impairment and good hemodynamic and clinical response at follow-up have better outcomes from long-term prostacyclin therapy (18–20). Decision for lung transplant referral is influenced by clinical and hemodynamic response after 3–12 months of epoprostenol therapy (18–20). Transition from intravenous prostacyclin to either subcutaneous treprostinil or oral bosentan is feasible and safe. Such transition may be a treatment alternative for stable patients or in cases of intolerable or life-threatening adverse effects from epoprostenol (53–56).

Prostacyclin has a short half-life (1–2 minutes) and requires a complicated delivery system and continuous intravenous administration. Once reconstituted for infusion, prostacyclin is unstable at room temperature and has to be preserved with ice packs. Moreover, this form of treatment requires placement of permanent central venous access, which is cumbersome and carries the risk of catheter-related infection (with a rate of 0.22–0.68 per patient per year of local central line infection and 0.39 per patient per year of bacteremia) and thrombosis (57). The drug is delivered using a battery-operated pump. Pump malfunctioning or catheter dislo-

cation may result in life-threatening complications from rebound pulmonary hypertension, with acute worsening of right heart failure, syncope and sudden death. Other adverse effects of prostacyclin, probably a consequence of prostaglandin excess, are headache, nausea, diarrhea, rashes, pruritus, jaw pain (usually occurring during the first bite of a meal), neuropathic pain, hypotension, dizziness and vasodilatation. Other chronic side-effects described for patients receiving chronic prostacyclin therapy are thrombocytopenia, weight loss and ascites. Currently, there is no uniform consensus regarding the exact dosing regimen of prostacyclin. In most centers, however, treatment starts with initial doses of 2–4 ng/kg/min. Afterwards, the dose is increased by 1 ng/kg/min each week depending on the clinical response and prostacyclin-associated adverse effects, until a total dose of about 20 ng/kg/min is reached, or until repeat right heart catheterization is performed. Studies have showed that a follow-up right heart catheterization is required 3–12 months after initiation of therapy for prognostic purposes, dose adjustments and further management recommendations such as listing for lung transplantation (18–20). Soon after the introduction of this form of therapy, it seemed that a degree of tolerance to the beneficial effect of prostacyclin develops, which leads to rapid dose escalation. Excessive doses of prostacyclin, however, have deleterious effects on the right heart function, with induction of a hyperdynamic and high output state (58). Dosing of prostacyclin is tailored to keep cardiac index above 2 L/min/m², but below 4 L/min/m², and to minimize adverse effects.

Treprostinil

Treprostinil (Remodulin®), a longer acting prostacyclin analogue, was approved in 2002 for treatment of PAH patients with WHO class II-IV symptoms. Treprostinil has pulmonary vasodilatory and antithrombotic properties. *In vitro* studies have also showed a potent antiproliferative and remodeling pulmonary vascular effect. Treprostinil has prolonged bioavailability (3-hour half-life), is stable at room temperature, and is administered by continuous subcutaneous infusion through a battery-operated pump similar to that used for insulin administration. Recent placebo-controlled trials of treprostinil administration for 8–12 weeks in patients with PAH have documented improvement in exercise capacity, symptoms and hemody-

namics (24, 59). Exercise capacity was evaluated by the change in the mean 6-minute walk distance, with an overall treatment effect of 36 meters in a pilot study which included only patients in WHO functional classes III and IV, and 16 meters in a larger study which evaluated 470 patients with PAH in WHO functional classes II–IV (24, 55). Clinical efficacy of treprostinil is more pronounced in patients with more severe disease, as judged by lower 6-minute walk distance, higher WHO functional class and reduced mixed venous oxygenation (24, 59). Patients who were in WHO functional class IV at study entry had an average treatment effect of 54 meters (59).

In addition, the effect of treprostinil on the exercise capacity is dose-dependent, although dose escalation may be hampered by development of pain and reactions at the infusion site, as proved by the average dose of 9.3 mg/kg/min at 12 weeks instead of 22.5 ng/kg/min allowed by the study design. Ability to reach a dose of about 14 ng/kg/min after 12 weeks of treatment was associated with a mean improvement in the 6-minute walk distance of 36 meters (24). Retrospective data suggest survival advantage in PAH patients treated with treprostinil compared to expected survival from the NIH predictive equation (60).

Most common adverse events encountered in more than 80% of treated patients, are pain and reactions at the infusion site, requiring drug interruption in about 15% of cases (24, 59). Various pain management strategies have been developed to control adverse effects at the infusion site, including the local administration of pluronic lecithin organogel (PLO gel), which has been shown to provide symptomatic relief and reduce healing time over a one-month period (61). Adverse effects reflecting prostacyclin excess have been also described with treprostinil. Although complications related to malfunction of pump or infusion set are frequent, these problems are easily resolved by the patients themselves and usually result in adverse effects rated as mild to moderate in severity; no fatalities have been reported (24, 59).

Recommended initial dose of subcutaneous treprostinil is 1.25 ng/kg/min, with increments of no more than 1.25 ng/kg/min per week for the first four weeks and then no more than 2.5 ng/kg/min per week for the remaining duration of infusion, depending on the clinical response and severity of adverse effects. A small European study has demonstrated that rapid dose escalation to reach a target dose of 10–15 ng/kg/min within

2–3 weeks is safe and effective, and does not increase the frequency of local pain and adverse reactions (62). Transition from intravenous prostacyclin to subcutaneous treprostinil is feasible and safe, and may be warranted in cases of intolerable or life-threatening adverse effects from prostacyclin (53). A phase IV trial of treatment transition from intravenous prostacyclin to subcutaneous treprostinil is currently ongoing.

Bosentan

Bosentan (Tracleer®), a dual endothelin receptor antagonist, is the first oral agent specifically approved by the FDA (in 2001) for the treatment of PAH patients with WHO class III–IV symptoms. It represents an entirely new class of drugs in the therapeutic armamentarium of patients with PAH. Endothelin-1 is a potent vasoconstrictor, a vascular growth factor and a neurohormonal activator. Endothelin system activation is common to most forms of pulmonary vascular disease. In animal models and *in vitro* studies, endothelin receptor blockade has been associated with pulmonary vasodilatory and vascular remodeling effects and improvement in the right ventricular pathophysiologic consequences. In two randomized, double-blind, placebo-controlled clinical trials of patients with PAH, bosentan administration was associated with improved exercise capacity, symptoms and hemodynamics, and increase in the time to clinical worsening (25, 26). Clinical benefit was evident at 4–8 weeks and sustained at 20 weeks or more (25, 26). In the 12-week pilot study, which included 32 patients with PAH in WHO functional class III, bosentan treatment effect, as judged by the change in the mean 6-minute walk distance, was 76 meters (25). In the larger study, which included 213 PAH patients in WHO classes III and IV, treatment effect of bosentan was 44 meters at 16 weeks (26). Most favorable therapeutic benefit from bosentan is derived for patients with PPH compared to patients with scleroderma spectrum of disease (26). An open-label extension to the 12-week pilot study has shown that the improvement in exercise capacity was sustained for an additional 6 months. In addition, one year treatment with Bosentan is associated with persistent reduction in pulmonary vascular resistance and increasing cardiac index (63).

Furthermore, long-term bosentan therapy has been shown to have a positive effect on echocardiographically determined parameters of pulmonary hypertension and right ventricular

dysfunction for patients with PAH (64). Retrospective data from patients who were treated with bosentan and followed up for 26 months demonstrated improved survival compared to historical controls (65). Oral administration of bosentan probably has a positive effect on the quality of life of patients with pulmonary hypertension, due to ease of administration, and it is sometimes the only viable therapeutic option for patients ineligible for prostacyclin treatment.

Bosentan administration was associated with dose-related liver injury in 10–11% of study patients (25, 26). Liver injury is manifested by elevation in the hepatic aminotransferase levels, which is reversible upon dose reduction or treatment discontinuation. Mechanism of aminotransferase increase is uncertain, but it may result from competitive inhibition of bile salt elimination from hepatocytes. During bosentan therapy, liver enzymes must be monitored on a regular basis, and dose adjustments made or treatment discontinuation guidelines followed in cases of detected abnormalities. To date, no fatalities secondary to liver insult have been reported (personal communication, Actelion). Nevertheless, initiation of bosentan therapy in patients with pre-existing liver disease is not recommended. Bosentan has teratogenic potential and is contraindicated in pregnancy. Other adverse effects reported with bosentan include headache, nasopharyngitis, flushing, lower extremity edema, hypotension, palpitations, dyspepsia, fatigue and pruritus. Lower extremity edema may be a local phenomenon and not a reflection of worsening in the right ventricular function, and may be readily reversible with diuretics. Bosentan treatment is initiated after baseline liver function test is performed, at a 62.5 mg bid oral dose for one month. After one month, if the aminotransferase levels are stable, dose is increased to 125 mg po bid, which has the most favorable risk-benefit ratio. Clinical trials have suggested that a 250 mg po bid dose is more efficacious in improving exercise capacity of bosentan-treated patients, but the incidence of adverse effects increased as well (26). Therapeutic efficacy of bosentan treatment is evaluated by patients' symptoms and by periodic 6-minute walk test performance, with repeat right heart catheterization every 6–12 months or as dictated by the clinical status. In the absence of a favorable clinical and hemodynamic response, transition to intravenous epoprostenol may be considered. Administration of bosentan in combination with intravenous prostacyclin or subcutaneous treprostinil appears safe and, in certain cases, al-

lows transition from parenteral prostacyclin therapy to oral treatment (54–56).

Treatment of Other Forms of Pulmonary Arterial Hypertension

Connective Tissue Disease

Development of pulmonary hypertension in various connective tissue disorders is associated with increased morbidity and mortality. PAH in connective tissue diseases is often an isolated phenomenon, which bears pathogenetic or management similarity with PPH. In other cases, however, PH appears as a consequence of other pulmonary pathologic processes such as pulmonary fibrosis or chronic thromboembolism. A large multicenter, randomized, placebo-controlled trial of prostacyclin treatment for patients with the scleroderma spectrum of disease has demonstrated symptomatic, functional and hemodynamic benefit from prostacyclin administration at 12 weeks, compared with conventional therapy (21). The difference between the treatment groups in the median 6-minute walk distance was 108 meters (21). Beneficial use of prostacyclin has been demonstrated in PAH associated with other forms of connective tissue disease, such as systemic lupus erythematosus (66, 67). Multicenter randomized trials of treprostinil and bosentan included patients with PAH associated with connective tissue disease. Group subset analyses showed that specific treatment of pulmonary hypertension is less effective in both short-term and long-term follow-up for patients with connective tissue disease PAH compared to PPH, while most benefit is derived from apparent halting of the disease progression (26).

End-Stage Liver Disease

Presence of portopulmonary hypertension increases morbidity and mortality of patients with end-stage liver disease and has an important impact on their eligibility for liver transplantation. Patients with moderate-to-severe pulmonary hypertension have unacceptably high perioperative mortality. Evidence exists for favorable hemodynamic response to chronic prostacyclin therapy, which can be used perioperatively to decrease pulmonary pressure and improve right ventricular function (68, 69). Chronic intravenous prostacyclin therapy may also decrease cardiovascular mortality of patients with portopulmonary hypertension (69). A side effect of prostacyclin

therapy often found in patients with portopulmonary hypertension is thrombocytopenia, probably from hypersplenism or immune causes (70). There are reports of the safe use of treprostinil by patients with portopulmonary hypertension, and in the near future, treprostinil may become a suitable alternative for patients who are not prostacyclin candidates (71). Bosentan is not recommended for patients with severe liver disease.

HIV Infection

In HIV-related pulmonary hypertension, viral infection and secondary inflammation may have a direct or indirect effect on pulmonary vessels. In a small-series study of patients with HIV-related PAH, intravenous prostacyclin therapy has been associated with symptomatic and hemodynamic benefit (72, 73). A recently published case series of patients with HIV-associated PAH has demonstrated that continuous intravenous prostacyclin and highly active antiretroviral therapies were independent predictors of improved survival (74).

Congenital Heart Disease

In a series of patients with congenital heart disease unresponsive to conventional therapy, long-term administration of intravenous prostacyclin induced hemodynamic, symptomatic and functional improvement at one year (75).

Oral Calcium Channel Blockers

Chronic administration of oral calcium channel blockers (OCCB) is beneficial in fewer than 10% of PPH patients who demonstrate acute vasoreactivity during testing in the catheterization laboratory with short-acting agents, such as inhaled NO, and intravenous adenosine or prostacyclin. Patients with true acute vasoreactive response demonstrate a substantial reduction in the mean pulmonary artery pressure of more than 10 mm Hg to reach a level lower than 40 mm Hg, in the absence of a significant decrease in the cardiac output or systemic arterial pressure (47). Initiation of OCCB therapy must be undertaken under close hemodynamic monitoring until the highest dose devoid of adverse effects is reached (46). This restricted group of patients, who respond acutely to pulmonary vasodilators, derive long-term hemodynamic and survival benefit from OCCB treatment (44, 45, 47). Patient selection and long-term monitoring for both safety and effi-

cacy represent a challenging aspect in the management of patients with PH, since indiscriminate use of OCCB may result in worsening right heart failure and death. Patients who initially respond to OCCB therapy but subsequently develop disease progression should be treated with alternative agents, and OCCB should be discontinued. There are no available large-scale studies of OCCB treatment in PAH other than PPH.

Combination Therapy for PAH

Since multiple and complex pathogenetic mechanisms are implicated in the development and progression of pulmonary arterial hypertension, it is possible that treatment combining various classes of vasodilator drugs will be used for those PAH patients who are refractory to the standard treatment protocol. Prostacyclins, endothelin-receptor antagonists and drugs acting through a NO-dependent pathway (such as sildenafil, a phosphodiesterase inhibitor) have different intracellular signal transduction pathways, with multiple cross-talk mechanisms that may have synergistic beneficial effects in the treatment of PAH. There is evidence from *in vitro* and animal studies that combining classes of drugs with different mechanism of action enhances the effect on the pulmonary vasculature. Although small human clinical trials on various combinations of drugs effective in PAH management have been reported (54–56), at the present time, the absence of efficacy and safety data in large clinical trials precludes the widespread recommendation of combination PAH therapy as an initial treatment approach. Preliminary results from a 12-week multicenter clinical trial on the combined use of prostacyclin and bosentan initiated simultaneously have demonstrated that the combination is well tolerated and that bosentan may provide a small additional benefit to patients with severe PAH who require prostacyclin treatment (54). In retrospective studies of PAH patients chronically treated with either prostacyclin or treprostinil, subsequent addition of bosentan was safe and effective, allowing for prostacyclin dose reduction or even discontinuation (55).

Small series from other countries have demonstrated acute and chronic benefit from combined use of various investigational drugs for PAH, such as inhaled iloprost, a long-acting prostacyclin analogue, inhaled NO and oral sildenafil or from addition of sildenafil for patients with suboptimal response to chronic prostacyclin (76–81).

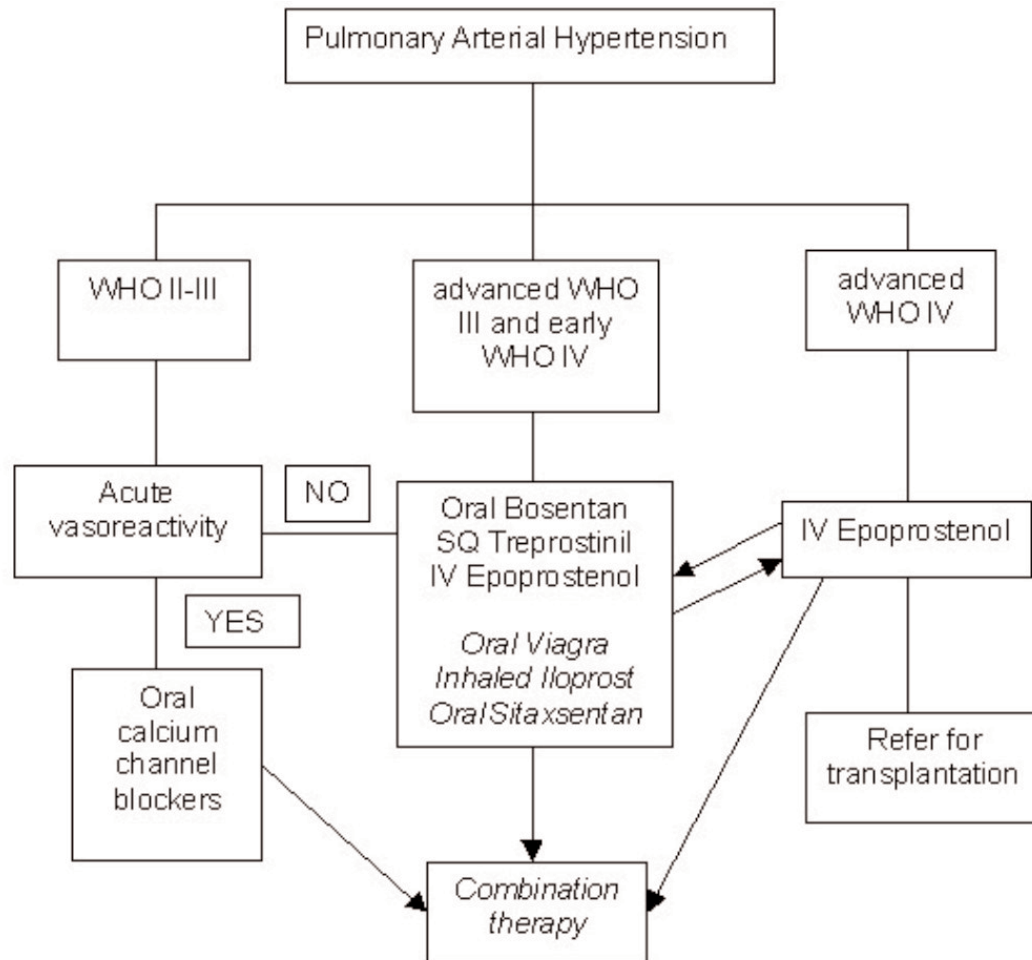


Fig. 2. For patients with early disease and positive acute vasodilatory response, a trial of oral calcium channel blockers is indicated. For most patients who do not respond acutely to vasodilator challenge, treatment depends on the WHO functional class. Most appropriate treatment strategy for patients with WHO I and II class symptoms is not yet determined. Endothelin receptor antagonist bosentan and prostanoids, such as treprostinil and epoprostenol, are indicated for patients in WHO functional class III and stable patients in class IV. The only option for severely ill patients or patients with rapidly progressive disease in the WHO functional class IV is intravenous epoprostenol. Selective ET_A receptor antagonists, prostanoids with alternate route of administration and different classes of drugs are currently investigated. Combination therapy may be considered in case of no improvement or deterioration with primary treatment.

Conventional Therapy

Anticoagulant Therapy

Treatment with warfarin has been associated with improved survival in retrospective and prospective studies of patients with PPH (45, 49). Survival benefit was most pronounced for patients unresponsive to OCCB (45). Likely benefit from anticoagulation in PAH is related to the effect on the *in-situ* thrombosis and possibly occurs by counteracting the effects of thrombin activation (80) in the pulmonary vascular bed. In the absence of contraindications, anticoagulation is recommended for all patients

with PH. The goal of warfarin therapy in PAH is to keep INR between 2 and 3 (83).

Diuretics

Diuretics are used to reduce the fluid overload state, a condition commonly encountered in patients with PAH and right ventricular failure. Hemodynamic optimization in these cases requires reduction in peripheral edema, ascites and hepatic congestion, with the goal of keeping the fluid balance slightly on the dry side, but without compromising right ventricular filling. Diuretic combinations or intravenous agents may be necessary in refractory cases.

Inotropes

Digoxin may be used in cases of right ventricular dysfunction; however, its long-term benefit is uncertain. A short-term study of a few patients with PPH demonstrated that digoxin increases the cardiac output and reduces neurohormonal activation (48).

Supplemental Oxygen

Home oxygen therapy is recommended for patients who develop hypoxemia at rest, with exercise or during sleep, with the goal of keeping O₂ saturation above 90–92%, to reduce any potential component of hypoxic vasoconstriction.

Treatment Algorithm for Pulmonary Arterial Hypertension

Factors that influence treatment decisions for patients with PAH include the etiology of the disease, the presence or absence of acute vascular reactivity during right heart catheterization, and the degree of functional impairment. The treatment algorithm for PAH has undergone major modifications in the past year, to include the agents newly approved by the FDA (Fig. 2), and further changes are expected in the near future to reflect the continuous expansion of the therapeutic armamentarium for pulmonary hypertension.

For patients with early disease in WHO classes I–II and selected, clinically stable patients in class III in whom acute vasoreactivity has been demonstrated in the laboratory, a trial of oral calcium channel blocker therapy under close hemodynamic monitoring is indicated. Until recently, intravenous epoprostenol was the first-line treatment for PAH patients with WHO class III and IV symptoms who were unresponsive to the acute vasodilator trial. Currently, in the absence of acute vasoreactivity, initial therapy for WHO class III and stable WHO class IV patients consists of subcutaneous treprostinil or oral bosentan. Treprostinil is the only FDA-approved agent for patients with WHO class II symptoms and no acute vasodilator responsiveness. Intravenous prostacyclin is still considered the most effective therapeutic option available and is reserved for patients in WHO class IV with severe functional impairment and for patients who fail treprostinil or bosentan therapy. Selected patients who are stable on intravenous epoprostenol or who develop complications related to intravenous

treatment may be transitioned to other forms of therapy, such as subcutaneous treprostinil or oral bosentan. Combination therapy and use of investigational agents such as inhaled iloprost or orally administered sildenafil and sitaxsentan are promising treatment options that need further validation.

Conclusion

There has been significant progress in the treatment of pulmonary hypertension in the past decade. Intravenous prostacyclin has been the standard for treatment of patients with advanced disease. However, the risks associated with this intravenous treatment have limited its popularity and clinical usefulness. The advent of the oral endothelin-receptor antagonist has dramatically altered the treatment options available to patients with less advanced symptoms. The introduction of the subcutaneous form of the longer-acting prostacyclin analogue allows greater treatment flexibility. Treatment of pulmonary hypertension has evolved from adopting the standard treatment regimen of congestive heart failure to the current use of selective pulmonary vasodilators and growth inhibitors. Future advances in the understanding of the genetic and molecular basis of this elusive disease will provide new hope for a cure.

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