

Comparative Analysis of Clinical Trials and Evidence-Based Treatment Algorithm in Pulmonary Arterial Hypertension

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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. Both uncontrolled and controlled clinical trials with different compounds and procedures are reviewed and compared in order to define the efficacy-to-side-effect ratio of each treatment. A grading system for the level of evidence of treatments based on the number of favorable controlled clinical trials performed with a given compound is adopted; a treatment algorithm based on the evidence derived by clinical trials is proposed. It includes drugs approved by regulatory agencies for the treatment of patients with PAH and/or drugs available on the market for other indications. The algorithm is restricted to patients in New York Heart Association (NYHA) functional class III or IV because they represent the largest population included in controlled clinical trials. In addition, 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 the other PAH subgroups should be done with caution. Oral anticoagulation is proposed for all patients, whereas diuretic treatment and supplemental oxygen are indicated in cases of fluid retention and hypoxemia, respectively. High doses of calcium channel blockers are indicated only in the minority of patients who are responders to acute vasoreactivity testing. Nonresponders to acute vasoreactivity testing, or responders who remain in NYHA functional class III, should be considered candidates for treatment with either an endothelin receptor antagonist or a prostanoid. Continuous intravenous administration of epoprostenol is proposed as rescue treatment in NYHA functional class IV patients. Phosphodiesterase-V inhibitors should be considered in patients who have failed or are not candidates to other therapies. Combination therapy can be attempted in selected cases. Both balloon atrial septostomy and lung transplantation are indicated for refractory patients or where medical treatment is unavailable. (J Am Coll Cardiol 2004;43:81S–88S) © 2004 by the American College of Cardiology Foundation

Treatment of pulmonary arterial hypertension (PAH) has shown a dramatic change from the slow progress in the past decades to the remarkable number of randomized controlled trials (RCTs) accomplished in the past few years.

Initially, up to the 1980s, attempts to reduce pulmonary arterial pressure were performed with various vasodilators. Favorable and sustained results were convincingly shown only by the use of high doses of calcium-channel blockers (CCBs), but only in the minority of patients who responded to acute vasoreactivity testing. Also, oral anticoagulant treatment was considered effective based on retrospective or uncontrolled studies. Finally, in the 1990s, the complex treatment with continuous intravenous (IV) administration of epoprostenol was shown in three non-blinded RCTs to consistently improve symptoms and survival in the more severe cases. In the same period, favorable results of different

uncontrolled series of PAH patients who underwent balloon atrial septostomy or lung transplantation were also reported.

Recently, three phase II studies and nine phase III RCTs with new compounds have been completed in PAH patients and six more are ongoing or planned. In addition, three RCTs testing the combination of new compounds with epoprostenol have been completed or planned. More than 2,500 patients have been or will be involved in this unprecedented effort to find effective treatments and, ultimately, a cure for PAH.

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. The purpose of the present report is to compare the RCTs performed in PAH and to propose an evidence-based grading system and a treatment algorithm that incorporate the currently available therapies.

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UNCONTROLLED CLINICAL STUDIES IN PAH

Anticoagulants. The evidence for favorable effects of oral anticoagulant treatment in patients with idiopathic pulmonary arterial hypertension (IPAH) or PAH associated with

Abbreviations and Acronyms

CCB	= calcium channel blocker
ERA	= endothelin-1 receptor antagonist
ET _A	= endothelin receptor A
IPAH	= idiopathic pulmonary arterial hypertension
IV	= intravenous
NYHA	= New York Heart Association
PAH	= pulmonary arterial hypertension
RCT	= randomized controlled trial

anorexigens is based on retrospective analysis of single-center studies (1–3). The survival of anticoagulated patients, selected on the basis of clinical judgment, was improved as compared to a concurrent population that was not treated with oral anticoagulants. Three-year survival improved from 21% to 49% in the series reported by Fuster et al. (1) and from 31% to 47% in the series of Rich et al. (2). The design of these studies was not randomized, and one can argue that the lower survival of the control groups could be related to comorbidity that precluded the use of anticoagulation in the untreated patients. In addition, only IPAH and anorexigen-related PAH patients were included in the studies. In recent RCTs, oral anticoagulants were administered in 51% to 86% of subjects at study entry. Interestingly, the highest prevalence of oral anticoagulant treatment was seen in the trials involving mainly IPAH patients in New York Heart Association (NYHA) functional class III and IV, whereas the lowest prevalence was observed in the trial of patients with scleroderma. It should be emphasized that there is no evidence of any difference in efficacy of oral anticoagulant therapy based on functional class severity.

Diuretics, digoxin, and oxygen. The clear symptomatic and clinical benefits of diuretic treatment in right heart failure preclude the need for controlled trials to show efficacy in PAH. In the recent RCTs on new treatments, 49% to 70% of patients were treated with diuretics. However, the lack of trials with specific classes of diuretics in PAH and the individual variability in responses leave the choice of the type and the dose of drug to be used in individual cases to the experience of the physician.

Short-term IV administration of digoxin in IPAH produces a modest increase in cardiac output and a significant reduction in circulating norepinephrine; however, no data are available on the effects of long-term treatment. Accordingly, the use of digitalis in PAH patients is based primarily on the judgment of the physician rather than on scientific evidence of efficacy. Digoxin was administered to 18% to 53% of patients upon entering recent RCTs in PAH.

No consistent data are currently available on the effects of long-term oxygen treatment in PAH. Although improvement in pulmonary hypertension with low-flow supplemental oxygen has been reported in some PAH patients, this has not been confirmed in controlled trials. In a controlled study of Eisenmenger syndrome, nocturnal oxygen therapy had no

effect on hematologic variables, quality of life, or survival (4).

Calcium channel blockers. Favorable clinical and prognostic effects of high doses of calcium channel blocker (CCB) drugs in vasoreactive patients with IPAH have been shown in single-center, nonrandomized, noncontrolled studies (2,5–8). In these studies, the control group consisted of nonvasoreactive patients who may have a poorer prognosis as compared to vasoreactive individuals (6). Conversely, the demonstration of a consistent reduction of pulmonary artery pressure by acute pharmacological testing in vasoreactive patients raises ethical questions on the appropriateness of performing a placebo-controlled clinical trial in these patients.

According to the definition of “a positive acute vasoreactive response” proposed in this Supplement (reduction of mean pulmonary arterial pressure ≥ 10 mm Hg to reach a mean pulmonary arterial pressure ≤ 40 mm Hg with a increase or unchanged cardiac output with acute pulmonary vasodilator challenge), only about 10% to 15% of IPAH patients will meet these criteria (8). In addition, only about one-half of these will manifest a sustained response to high doses of CCB therapy as defined by a long-term hemodynamic (assessed after at least three months) and functional (NYHA functional class I and II) improvement in the absence of additional treatments (8).

Favorable results of long-term administration of high doses of CCBs have also been shown in children with IPAH (7). In contrast, the effects of high-dose CCBs on associated forms of PAH have not yet been clearly demonstrated (9).

Balloon atrial septostomy. The role of balloon atrial septostomy in the treatment of PAH patients is uncertain because its efficacy has been reported only in small series and case reports, totalling approximately 120 published cases (10,11). In most circumstances, this intervention has been performed in severely ill patients as a bridge to lung transplantation, which may explain a procedure mortality rate ranging from 5% to 15%. In addition to symptomatic and hemodynamic improvement, an increase of survival as compared with historical control groups has also been shown (12). At present, balloon atrial septostomy is indicated for advanced NYHA functional class III and class IV patients who are refractory to all available medical treatments; septostomy is used either as a bridge to lung transplantation or as the sole treatment modality when other options are not available (11).

Lung transplantation. As with many other surgical procedures performed in severely ill patients, lung transplantation in PAH has been assessed only in prospective uncontrolled series, because formal RCTs are considered unethical in the absence of alternative treatment options (11). The three- and five-year survival after lung transplantation is approximately 55% and 45%, respectively (13). Accordingly, lung transplantation is indicated in PAH patients with advanced NYHA functional class III and IV symptoms that are refractory to available

Table 1. Controlled Clinical Trials With Epoprostenol in Patients With Pulmonary Arterial Hypertension

Trial	Epoprostenol IPAH (Ref. 14)	Epoprostenol IPAH (Ref. 15)	Epoprostenol Scleroderma (Ref. 16)
Patients (n)	23	81	111
Trial type	Controlled	Controlled	Controlled
Drug/route	Epoprostenol/IV	Epoprostenol/IV	Epoprostenol/IV
Duration (months)	2	3	3
Primary end points	Hemodynamics	Hemodynamics	6-min walk
NYHA functional class (%) [*]			
II	9	—	5
III	65	75	78
IV	26	25	17
Etiology (%)			
IPAH	100	100	—
CTD	—	—	100
CHD	—	—	—
HIV	—	—	—
Treatment effect			
Peak VO ₂ (% predicted)	N/A	N/A	N/A
6-min walk change (m)	+45	+47	+94
Hemodynamics	Improved	Improved	Improved
Clinical events	Reduced	Reduced (improved survival)	No change

^{*}Sum of percentage may not be 100% for rounding to the nearest unit; 0.5 is rounded to the upper unit.

CHD = congenital heart disease (congenital systemic-to-pulmonary shunts); CTD = connective tissue disease; IPAH = idiopathic pulmonary arterial hypertension; IV = intravenous; N/A = not available; NYHA = New York Heart Association.

medical treatments. The unpredictability of the length of time on the waiting list and of donor organ shortage complicate the decision making regarding the appropriate timing of listing for transplantation.

CONTROLLED CLINICAL TRIALS IN PAH

Synthetic prostacyclin and prostacyclin analogues. The efficacy of continuous IV administration of epoprostenol (synthetic prostacyclin, Flolan) has been tested in three unblinded, controlled clinical trials in IPAH (14,15) and in PAH associated with the scleroderma spectrum of diseases (16), and the results are summarized in Table 1. Epoprostenol improves symptoms, exercise capacity, and hemodynamics in both clinical conditions, and it is the only treatment to be shown in RCTs to improve patient survival in IPAH.

Four RCTs have been performed with prostacyclin analogues and results are summarized in Table 2.

The effects of continuous subcutaneous administration of treprostinil in PAH were studied in the largest worldwide RCT performed in this condition, and improvements in exercise capacity, hemodynamics, and clinical events were shown (Table 2) (17). One additional pilot controlled study was performed with treprostinil in 26 PAH patients and showed trends in the improvement of 6-min walk distance and in the reduction of pulmonary vascular resistance (18).

The orally active prostacyclin analogue beraprost has been evaluated in PAH patients in two RCTs in Europe (19) and in the U.S., respectively (20) (Table 2). In the first study, an

increase in exercise capacity was seen in IPAH subjects after three months. In the second randomized trial that lasted 12 months, improvement in exercise capacity was observed at six months but not thereafter. No hemodynamic improvements were observed in the long-term study, and clinical events were reduced only at the six-month evaluation.

Inhaled iloprost has been evaluated in one RCT that enrolled both patients with PAH and chronic thromboembolic pulmonary hypertension (21) (Table 2). The study showed an increase in exercise capacity and improvement in symptoms, pulmonary vascular resistance, and clinical events in IPAH patients only. Continuous IV administration of iloprost has been shown to be effective in a small series of patients with PAH and chronic thromboembolic pulmonary hypertension (22).

Endothelin-1 receptor antagonists. Three RCTs with endothelin-1 receptor antagonists (ERAs) have been performed in PAH patients (Table 3). The orally active, dual ERA bosentan has been evaluated in PAH patients in two RCTs that have shown improvement in exercise capacity, functional class, hemodynamics, echocardiographic and Doppler variables, and time to clinical worsening (23–25).

Sitaxsentan, a selective orally active endothelin A receptor (ET_A) antagonist has been assessed in PAH patients in one RCT that demonstrated improvement in exercise capacity, hemodynamics, and clinical events (only for the lower dose tested) (26,27). An additional pilot study with this compound in 20 PAH patients has shown similar results (28).

Ambrisentan, a selective, orally active ET_A receptor antagonist, has thus far been evaluated only in a pilot blinded, dose-comparison study in 64 PAH patients. Pre-

Table 2. Controlled Clinical Trials With New Prostacyclin Analogues in Patients With Pulmonary Arterial Hypertension

Trial	Treprostinil (Ref. 17)	ALPHABET (Ref. 19)	Beraprost— Long Term (Ref. 20)	AIR (Ref. 21)
Patients (n)	469	130	116	203
Trial type	Controlled	Controlled	Controlled	Controlled
Drug/route	Treprostinil/sc	Beraprost/os	Beraprost/os	Iloprost/inh
Duration (months)	3	3	12	3
Primary end points	6-min walk	6-min walk	Disease progression	6-min walk† NYHA*
NYHA functional class (%)				
II	11	49	53	—
III	82	51	47	59
IV	7	—	—	41
Etiology (%)†				
IPAH	58	48	74	54
CTD	19	7	10	17
CHD	24	21	16	—
CTEPH	—	—	—	28
HIV	—	7	—	—
P-PH	—	16	—	—
Treatment effect				
Peak VO ₂ (% predicted)	N/A	N/A	Trend to increase	N/A
6-min walk change (m)	16‡	25	31‡§	36
Hemodynamics	Improved	No change	No change	Improved
Clinical events	Reduced	No change	Reduced§	Reduced

*Combined end point of an improvement in NYHA functional class and a >10% improvement in 6-min walk. †Sum of percentage may not be 100% for rounding to the nearest unit; 0.5 is rounded to the upper unit. ‡Median change. §Statistically significant at six months. ||Only pulmonary vascular resistance improved in preinhalation period, and a more consistent improvement of other parameters is observed in postinhalation period.

AIR = Aerosolised Iloprost Randomized Study; ALPHABET = Arterial Pulmonary Hypertension And Beraprost European Trial; CHD = congenital heart disease (congenital systemic-to-pulmonary shunts); CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; IPAH = idiopathic pulmonary arterial hypertension; inh = inhaled; N/A = not available; NYHA = New York Heart Association; os = oral; P-PH = porto-pulmonary hypertension; sc = subcutaneous.

liminary results show improvements in exercise capacity and hemodynamics that appear similar to the results observed with other ERAs (29).

Additional phase III RCTs with sitaxsentan and am-

brisentan are ongoing or are planned; these trials will further explore both the efficacy and side effects profile of selective ET_A receptor antagonists and allow comparisons with bosentan.

Table 3. Controlled Clinical Trials With Endothelin-1 Receptor Antagonists in Patients With Pulmonary Arterial Hypertension

Trial	Bosentan Pilot (Ref. 21)	BREATHE-1 (Ref. 24)	STRIDE-1 (Ref. 27)
Patients (n)	32	213	178
Trial type	Controlled	Controlled	Controlled
Drug	Bosentan	Bosentan	Sitaxsentan
Duration (months)	3	4	3
Primary end points	6-min walk	6-min walk	Peak VO ₂
NYHA functional class (%)			
II	—	—	33
III	100	91	66
IV	—	9	1
Etiology (%)*			
PPH	85	70	53
CTD	15	30	24
CHD	—	—	24
HIV	—	—	—
Treatment effect			
Peak VO ₂ (% predicted)	N/A	N/A	+3%†
6-min walk change (m)	+76	+44	+34
Hemodynamics	Improved	N/A	Improved
Clinical events	Reduced	Reduced	Reduced‡

*Sum of percentages may not be 100% for rounding to the nearest unit; 0.5 is rounded to the upper unit. †Only for 300-mg dose.

‡Only for 100-mg dose.

BREATHE-1 = Bosentan Randomized trial of Endothelin Antagonist Therapy for pulmonary hypertension; CHD = congenital heart disease (congenital systemic-to-pulmonary shunts); CTD = connective tissue disease; IPAH = idiopathic pulmonary arterial hypertension; N/A = not available; STRIDE-1 = Sitaxsentan to Relieve Impaired Exercise study.

Phosphodiesterase-V inhibitors. A number of uncontrolled studies have reported favorable effects of the orally active phosphodiesterase-V inhibitor sildenafil in PAH (30–32). A RCT with a cross-over design has been recently published: sildenafil 25 to 100 mg tid administered in 22 NYHA functional class II and III PAH patients has improved after six weeks' symptoms, the exercise capacity as assessed by the Naughton protocol on the treadmill, and the hemodynamics (33). Results of a pivotal RCT on approximately 300 PAH patients are expected in the second quarter of 2004; the findings of this major trial will define the precise role of sildenafil in the treatment algorithm of PAH.

Combination therapy. Combination treatment is an attractive option to address the multiple pathophysiologic mechanisms that are present in PAH. Both the efficacy and the safety of the combination of bosentan and epoprostenol were investigated in a study of 33 patients with severe PAH enrolled in a placebo-controlled, prospective study (BREATHE-2). Improved hemodynamics, exercise capacity, and functional class were observed in both groups. A preliminary report shows that there was a trend for a greater (though nonsignificant) improvement in all hemodynamic parameters in the combination treatment group (34). Additional RCTs that are ongoing or planned will explore the effects of combinations using epoprostenol with sildenafil, sitaxsentan, and ambrisentan, respectively.

In patients with PAH who are deteriorating despite chronic treatment with nonparenteral prostanoids, addition of bosentan (35) or sildenafil (36) to the ongoing treatment resulted in favorable improvements of pulmonary hemodynamics and exercise capacity in uncontrolled studies.

General comments on controlled clinical trials. The RCTs in PAH have produced a tremendous increase of both knowledge and therapeutic options in PAH. Although these studies have similar designs, treatment duration, and end points, close analyses of baseline NYHA functional class and etiology profiles (Tables 1 to 3) show substantial differences. Accordingly, comparisons may be misleading; improvement, albeit to different degrees, of the mean exercise capacity as assessed by the 6-min walk distance has been observed in all these studies. Peak VO_2 was assessed only in two trials, and the results were not completely consistent with changes in the 6-min walk distance. In evaluation of the clinical relevance of exercise capacity improvements, additional elements should be considered such as baseline functional class, effects on combined clinical events (i.e., hospitalizations, mortality, rescue therapies), and hemodynamic effects (Tables 1 to 3). As mentioned previously, a survival benefit has been demonstrated in only one controlled, unblinded study using epoprostenol in patients with severe IPAH. Because epoprostenol is considered rescue therapy based on these results, the more recent RCTs could not be ethically performed to assess mortality as an end point. Furthermore, severely ill subjects requiring epoprostenol treatment were excluded in the recent RCTs, resulting in an overall low mortality of these study populations.

Table 4. Grading of Evidence for Efficacy

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

LEVEL OF EVIDENCE FOR EFFICACY

Various grading systems for the definition of the level of evidence of treatments have been proposed. Table 4 shows the grading system adopted in the current review, which is based on the number of favorable RCTs performed with a given compound. The analysis takes into consideration the studies reported and the RCTs presented in Tables 1 to 3. The grading system was adapted from the European Society of Cardiology recommendation for guidelines (37). The only difference is that we did not include in category B “nonrandomized studies” because all these studies in PAH are rather small; therefore, they are included in category C (Table 4). In category B, we included the wording “multiple randomized clinical trials with heterogeneous results” because this situation may happen (and has happened) and this definition is more comprehensive even if the outcome is that “a single randomized clinical trial” resulted positive.

This approach may present some limitations that should be taken into account:

1. The level of evidence may change over time as a result of additional studies performed.
2. The grading system does not address the sample sizes of the RCTs.

Table 5. Grading of Evidence for Efficacy and Regulatory Approval Status of Selected Treatments

Treatment	No. of RCTs*	Grading of Evidence	Regulatory Approval
Oral anticoagulants	3†	C	—
Diuretics	—	C	—
Digoxin	—	C	—
Oxygen	—	C	—
Calcium channel blockers	5†	C	—
Epoprostenol	3	A	Europe, U.S., Canada
Treprostinil	2	B	U.S.
Iloprost (inhalation)	1	B	Europe, Australia
Iloprost (IV)	1†	C	New Zealand
Beraprost	2	B	Japan
Bosentan	2	A	Europe, U.S., Canada
Sitaxsentan	1	B	—
Ambrisentan	1†	C	—
Sildenafil	1	B	—
BAS	Multiple†	C	—
Lung transplantation	Multiple†	C	—

*See appropriate paragraph of the text for references. †Uncontrolled and/or retrospective study.

BAS = balloon atrial septostomy; IV = intravenous; RCT = randomized controlled trials.

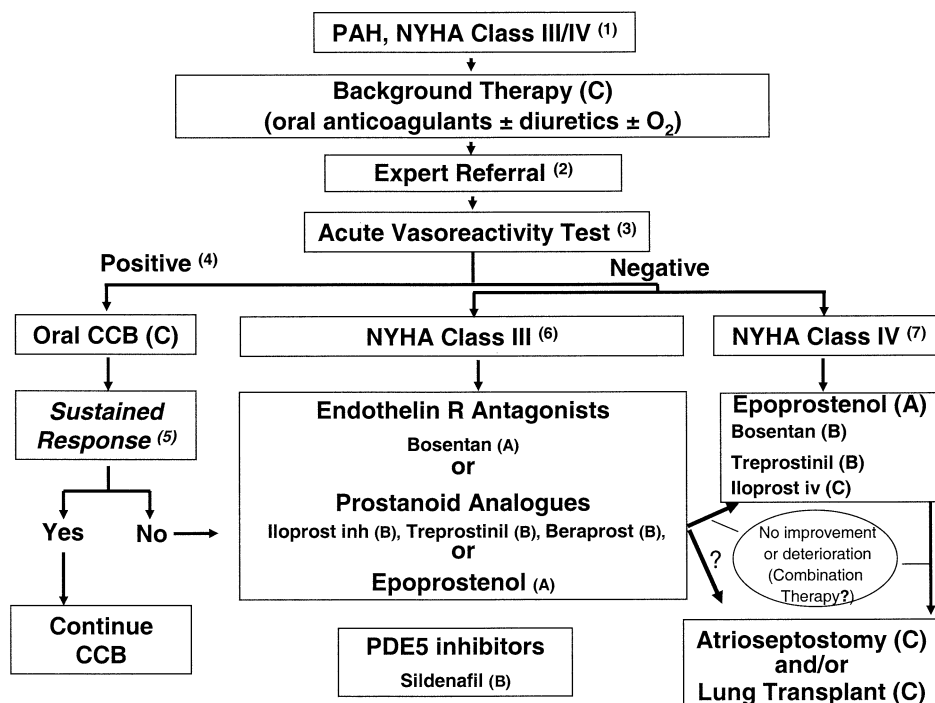


Figure 1. Evidence-based treatment algorithm. Levels of evidence A, B, and C grading according to Tables 4 and 5; inh = inhaled; iv = continuous intravenous. (1) The algorithm is restricted to patients in New York Heart Association (NYHA) functional class III or IV because they represent the largest population included in controlled clinical trials. For NYHA functional class I or II, very few data are available. In addition, the different treatments have been evaluated mainly in sporadic idiopathic pulmonary arterial hypertension (IPAH) patients, and in pulmonary arterial hypertension (PAH) associated with scleroderma or to anorexigen use. Extrapolation of these recommendations to the other PAH subgroups should be done with caution. (2) Owing to the complexity and dangers of the acute vasoreactivity tests, and to the treatment options available, it is strongly recommended that consideration be given to referral of patients with PAH to a specialized center. (3) The acute vasoreactivity test should be performed in all patients with PAH even if the greater incidence of positive response is achieved in individuals with IPAH and PAH associated to anorexigen use. (4) A positive acute response to vasodilators is defined as a drop in mean pulmonary artery pressure of at least 10 mm Hg to ≤ 40 mm Hg, with an increase or unchanged cardiac output during acute challenge with inhaled nitric oxide (NO), IV epoprostenol, or IV adenosine. (5) Sustained response to calcium channel blockers (CCBs) is defined as patients being in NYHA functional class I or II with near-normal hemodynamics after several months of treatment. (6) In patients in NYHA functional class III, first-line therapy may include oral endothelin receptor antagonists, chronic IV epoprostenol, or prostanoid analogues. Phosphodiesterase-V (PDE5) inhibitors should be considered in patients who have failed or are not candidates to other therapies. (7) Most experts consider that NYHA functional class IV patients in unstable condition should be treated with IV epoprostenol (survival improvement, worldwide experience, and rapidity of action).

3. The *level of evidence* for efficacy should not be confused with the *strength* of clinical efficacy, which depends on the pharmacodynamic effects of the compound and on patient response. For example, a compound that increased the 6-min walking distance in two controlled clinical trials by 40 m will be rated with a Level of Evidence A (Table 4). If a more potent compound increased the 6-min walking distance by 80 m in only one controlled clinical trial it will be rated Level of Evidence B even though the clinical relevance of the effect is greater.
4. Regulatory agencies may grant approval to a given treatment on the basis of a single RCT with an appropriate sample size and prespecified adequate statistical requirements.

Table 5 shows the grading of evidence for efficacy and regulatory approval status of selected treatments.

EVIDENCE-BASED TREATMENT ALGORITHM

A treatment algorithm based on the evidence derived by clinical trials is depicted in Figure 1. The algorithm is restricted to patients in NYHA functional class III or IV because such patients represent the predominant population

included in RCTs. For NYHA functional class I or II, very few data are available, and the most appropriate strategy has still to be determined and possibly validated by specific studies. In addition, the different treatments have been evaluated mainly in sporadic IPAH, and in PAH associated with scleroderma or to anorexigen use. Extrapolation of these recommendations to the other PAH subgroups should be done with caution.

The suggested initial approach, after the diagnosis of PAH, is to treat patients with oral anticoagulant drugs (if no contraindication exists), diuretics (in cases of fluid retention), and supplemental oxygen (in cases of hypoxemia) even though RCTs with these compounds are lacking. The patient should then be referred to a center experienced with vasoreactivity testing and the treatment of pulmonary vascular diseases. Acute vasoreactivity testing should be performed in all patients with PAH, although patients with IPAH and PAH associated with anorexigen use are the most likely to exhibit a positive response. Vasoreactive patients, as defined above, should be treated with optimally tolerated doses of CCB; maintenance of the response (defined as NYHA functional class I or II with

near-normal hemodynamics) should be confirmed after three to six months of treatment. Nonresponders to acute vasoreactivity testing, or responders who remain in NYHA functional class III, should be considered candidates for treatment with either an ERA or a prostanoid. At present, the only commercially available and approved ERA is the oral active dual-antagonist bosentan. Among prostanoids, treprostinil is administered subcutaneously and has been approved in the U.S.; iloprost, administered by aerosol, has been approved in Europe, whereas beraprost is approved in Japan. Continuous IV administration of epoprostenol may also be used in NYHA functional class III patients who are refractory to ERAs or other prostanoids.

The choice of drug is dependent on a variety of factors, including the approval status, route of administration, side-effect profile, and the physician's experience. The orally active phosphodiesterase-V inhibitor sildenafil is not approved for the treatment of PAH, and its use should be considered in patients with PAH, who have failed or are not candidates for other available therapy. The role of this drug will be better defined after the evaluation of the pivotal RCT that is currently ongoing.

Continuous IV epoprostenol, approved in the U.S. and Europe, may be considered as first-line therapy for IPAH patients in NYHA functional class IV because of the demonstrated survival benefit in this subset.

Although both bosentan and treprostinil are approved for this population, only a small number of NYHA functional class IV patients were included in the clinical trials of these agents. Accordingly, most experts consider these treatments as a second line for severely ill patients. Although no RCTs have been performed with the continuous IV delivery of iloprost this prostacyclin analogue, administered intravenously is approved in New Zealand for PAH patients.

Combination therapy (e.g., ERA + prostanoids) may be considered for patients who fail to show improvement or who deteriorate with first-line treatment, even though data on this specific strategy are limited and largely uncontrolled at this point. Appropriate protocols for timing and dosing to limit possible side effects of the combination have still to be implemented.

Finally, both balloon atrial septostomy and lung transplantation are indicated for refractory PAH or where medical treatments are unavailable. These procedures should be performed only in experienced centers.

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