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Evidence-Based Treatment for Pulmonary Arterial Hypertension in an Evolving Environment

The clinical classification of pulmonary hypertension was established at a World Health Organization conference in 2003 and has been used by investigators and clinicians since that time. The broad groupings of the 2003 classification are:

- Pulmonary arterial hypertension (PAH)—idiopathic, familial or associated with a pathologic condition such as connective tissue disease, congenital heart disease, portal hypertension, HIV infection, drugs and toxins or “other”;
- Pulmonary venous hypertension with left heart disease;
- Pulmonary hypertension associated with lung disease/hypoxemia;
- Pulmonary hypertension due to chronic thrombotic and/or embolic disease; and,
- Pulmonary hypertension due to miscellaneous causes—e.g., sarcoidosis, histiocytosis X, compression of pulmonary vessels by tumor or fibrosing mediastinitis.

The clinical environment in which pulmonary arterial hypertension (PAH) is diagnosed and treated has been evolving rapidly since 1995. By 1995, the physiology and pathology of PAH was well understood but treatment options were limited. One pharmacologic agent—intravenous epoprostenol—had been approved by the U.S. Food and Drug Administration (FDA) for treatment of PAH. By 2008, six drugs had been FDA-approved for treatment of PAH and additional single and combination drugs were in various stages of development and clinical trial.

Three pathophysiologic pathways are known by which PAH develops:

- Nitric oxide (NO) pathway;
- Endothelin pathway; and,
- Prostacyclin pathway.

All three pathways can be addressed by various drugs and regimens. Clinicians should be knowledgeable regarding the laboratory and clinical trial data of each of the agents. The approach to treatment is made more rational by use of a treatment algorithm developed on the basis of improved clinical data and data from clinical trials of FDA-approved drugs.¹

When a clinician is presented with a patient with diagnosed PAH, two questions immediately arise: (1) When to treat, and (2) How to treat. Because PAH is a progressive disease, the answer to the first question should be “start treatment early”, even if the definition of “early” is not entirely clear by criteria such as World Health Organization (WHO) or New York Heart Association (NYHA) Functional Classifications.^{2,3} Without treatment, PAH will progress more rapidly to deteriorating quality of life and risk for earlier death.

No currently available therapy can cure PAH, but progression of the disease can be slowed, especially in the patient with disease that is “mild” by clinical assessment and by WHO or NYHA Functional Classification as Class I or II. Thus, a useful rule to observe is that the clinician should treat “mild” disease early even if symptoms are minimal, and that not to treat may very well be a mistake.⁴

Determinants for risk of PAH morbidity and mortality are important guides to “when” and “how” to institute and carry out therapy over the short and long term⁴:

- Clinical evidence of right ventricular failure;
- Rate of PAH progression;
- WHO/NYHA Functional Class I, II, III or IV;
- Length of 6-minute walk, monitored at regular intervals;
- Brain natriuretic peptide (BNP) elevation monitored over time;
- Echocardiographic findings monitored over time;
- Right-heart function assessed by right-heart catheterization; and,
- Change in hemodynamics over time.

Before treatment is initiated, goals for treatment outcomes should be established:

- Improvement in hemodynamics;
- Improvement in exercise capacity;
- Improvement in function and quality of life;
- Prevention of clinical worsening; and,
- Decreased risk for death.

Initial treatment strategy should include:

- Initial determination of risk for morbidity and mortality;

- On the basis of risk determination, select oral (usually for “milder” PAH) or non-oral or combination agents (usually for PAH non-responsive to monotherapy or PAH of higher Functional Class);
- Select drugs on the basis of data from clinical trials; and,
- Consider referral of the patient to a PAH center if patient is higher risk or non-responsive to treatment.

Because the 6-minute walk is often the end-point of clinical trials of PAH drugs, the clinician may be tempted to accept improvement in the 6-minute walk distance as an end-point in itself. More realistically, improvement in 6-minute walk distance should be regarded as an indication of improved outcome but not an end in itself. Data from the 6-minute walk should be assessed along with other measures that may be more important, such as improvement in right ventricular function.

No currently available drug will cure PAH. The primary goal of early therapy should be to prevent clinical worsening as measured by criteria such as:

- Decline in function, exercise capacity and symptom severity;
- Necessity for hospitalization;
- Necessity for invasive medical therapy or lung transplantation; and,
- Death.

Clinical trials of PAH drugs have included assessments of clinical worsening, and time to clinical worsening of patients assigned to the placebo or therapeutic arm of the study. What these studies have often not made clear is how the data apply to patients with “mild” disease or “early” disease. Standard classification of disease severity in WHO or NYHA scales may be minimally helpful in assessing the patient with disease that has not yet reached the lowest level of WHO or NYHA classification, or has barely reached Functional Class I or II. Thus, a primary goal of therapy for these patients must be prevention of clinical worsening rather than improvement. Prevention of disease progression improves morbidity and mortality.

The recently published EARLY (Endothelin Antagonist Trial in Mildly Symptomatic PAH Patients)⁴ provides some data indicating that early treatment improves prognosis in mildly symptomatic PAH patients (WHO Functional Class II). Improvement was shown in pulmonary vascular resistance, 6-minute walk and time to clinical worsening over the 6-month trial period.⁵

Definitions of clinical worsening of PAH used in the EARLY study included:

- Symptoms requiring hospitalization, and
- Symptomatic progression defined by (1) appearance or worsening of right heart function, and (2) decrease in two 6-minute walk tests performed 2 weeks apart, by $\geq 10\%$ from baseline or by $\geq 5\%$ with an increase in Borg dyspnea score by ≥ 2 points; the second 6-minute walk test not mandatory if there are overt signs of right heart function.

While the benefits of early treatment are apparent, a number of questions remain to be addressed in future research:

- The long-term effects of PAH therapy on progression of “early” disease;
- Whether combination therapy with two drugs is more effective than monotherapy in preventing disease progression; and,
- What should be done about hemodynamically “mild” disease as may occur in exercise-induced pulmonary hypertension.

After PAH treatment is initiated, the patient is monitored and reassessed at regular intervals or as indicated. Goals monitored include: (1) reversal of vascular injury, (2) normalization of pulmonary artery pressure to prevent ongoing injury, (3) improvement in right ventricular function, and (4) improvement in serologic markers such as BNP elevation.

If any or all of these indicators deteriorate or fail to show improvement, the question arises as to whether therapy should be escalated, and if so, how it should be escalated. Unfortunately, these are questions where consensus on answers is still lacking. Agreement is lacking on the significance of the 6-minute walk—a test that can be influenced by factors such as the patient’s height, weight, age and Functional Class. Right-heart catheterization provides important data but may not in itself be an indicator of disease status in individual patients. The biomarker BNP may be broadly useful, but elevation is influenced by multiple factors such as renal dysfunction that may be minimally related to PAH.

Measurement of pulmonary vascular pressure (PVP) may be less useful than many physicians believe. PVP in itself does not have a strong correlation with disease deterioration and risk for

death. PAH is not a disease of increased pulmonary vascular pressure; rather, it is a disease of cellular proliferation in the vascular bed.

How, then, does the clinician know when a patient is likely to benefit from an escalation of therapy?

Useful indications include:

- Failure to improve on monotherapy;
- Failure to improve to the satisfaction of the patient and/or physician by objective end points such as symptoms and quality of life; and,
- Deterioration in clinical status after a period of improvement.

When these criteria for escalation of therapy are noted, the clinician's options are (1) to switch from the currently prescribed drug to a drug directed toward a higher WHO/NYHA Functional Class, or (2) to initiate combination therapy with two drugs that target different PAH pathways. Benefits of combination therapy also include the potential to reduce the dose of one or both of the drugs, and the positive effect that combination therapy often has on chronic conditions such as chronic obstructive pulmonary disease and cardiovascular hypertension.

The question of when to initiate combination therapy is also one that has no standardized answer.

Options may include:

- Empirically to prevent further deterioration in disease status;
- At baseline in patients with symptoms of severe disease and progression;
- In patients who do not hit treatment targets with a period of monotherapy; and,
- When clinical deterioration is apparent.

Combination therapy may be initiated when clinical deterioration is noted. Another approach takes cancer chemotherapy as a model—i.e., combination therapy is initiated at diagnosis in patients with severe or rapidly progressive disease.

Goal-directed combination therapy offers an approach based upon baseline and 2- to 6-month monitoring of pre-established treatment goals and initiating as indicated (1) oral monotherapy, (2) dual-class oral combination therapy, (3) addition of an inhaled prostanoid, (4) transition to intravenous (IV) prostanoid, and (5) referral for lung transplantation.⁶

In addition to the six drugs currently approved for treatment of PAH, six additional agents are in various stages of trial:

- Imatinib—a platelet-derived growth factor receptor antagonist that has had substantial success in treatment of chronic myelogenous leukemia, also a disease of cellular proliferation;
- Sorafenib—a signal transduction inhibitor currently approved to treat renal and hepatocellular carcinoma;
- Endothelial Progenitor Cells (EPC)—has shown activity in cell regeneration after cellular inactivation;
- Escitalopram—a serotonin transporter that is a specific mitogen for pulmonary artery smooth muscle cells in iatrogenic PAH;
- GR-BH4—a tetrahydrobiopterin essential to nitric oxide formation; and,
- ACT-064992—a tissue selective endothelial receptor antagonist—in Phase III trials as of late 2008.

In addition to agents in various stages of trial, at least three are at early stages of trial development:

- Rho kinase inhibitor (Fasudil)—mediates calcium sensitization involved in cellular contraction, and regulates cell proliferation or apoptosis;
- Vasoactive intestinal peptide (avaptodil)—similarly to epoprostenol, it is an endogenous vasodilator that also inhibits smooth muscle proliferation and platelet aggregation;
- Cicletanine—enhances coupling of endothelial NO synthase, stimulates vascular prostaglandin synthesis and acts as a vasodilator and diuretic; and,
- Riociguat (BAY 63-2521)—stimulates relaxation of vascular smooth muscle via the NO pathway.

Advances in (1) physiologic testing, (2) imaging, and (3) interpretation of biomarkers have the potential to identify PAH earlier and improve opportunities for earlier intervention in the disease process.

References

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Standards of Practice

Pulmonary arterial hypertension (PAH) is a disease of cellular proliferation in the pulmonary vasculature. While this is well recognized by physicians who are experienced and knowledgeable in the treatment of PAH, among physicians in general PAH may be conceptualized and treated as a disease of pulmonary arterial pressure (PAP). Lowering PAP may prevent pressure-associated damage to tissue, but lowering PAP is not necessarily the most desirable end-point of treatment, nor is PAP the most indicative finding for morbidity-mortality risk.

The 6-minute walk test is accepted by many physicians as the gold standard for assessing a PAH patient's clinical status and improvement or decline in functional capacity. Six-minute walk distance is a non-invasive test of functional status that is supported by good-quality evidence in the literature. In addition, it is the end-point of many clinical trials of the efficacy of drugs used to treat PAH, and this may further indicate to physicians the test's ultimate validity for assessing the clinical status of patients. Acceptance of 6-minute walk distance as a gold standard may lead physicians to omit other diagnostic/monitoring tests that provide more specific information regarding clinical status. Of these other tests, right heart catheterization to assess right heart function may be the most important.

When and how to treat mildly symptomatic PAH is difficult to determine from the medical literature. Physicians experienced in the treatment of PAH have the benefit of their experience to guide them in decision-making. Evidence does indicate that "earlier is better" for preventing progression of early, mildly symptomatic PAH.