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### **Controversies in Clinical Pulmonary Arterial Hypertension**

Pulmonary arterial hypertension (PAH) is clinically classified by the scheme adopted in 2003 at the Third World Symposium on Pulmonary Arterial Hypertension in Venice. The Venice Classification, as it is generally known today:

- Idiopathic PAH (IPAH), also called sporadic PAH
- Familial PAH (FPAH)
- PAH associated with other conditions—e.g., connective tissue disease, congenital heart disease, portal hypertension, HIV infection, drugs and toxins, other conditions including sarcoidosis, histiocytosis X, tumor, mediastinitis;
- PAH with significant venule and/or capillary involvement—e.g., pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis; and,
- Persistent fetal circulation.

The most current update of evidence-based guidelines for treatment of PAH are those of the American College of Chest Physicians.<sup>1</sup> The 2007 update of the ACCP guidelines recommend a trial of calcium channel blockers (CCB) for patients with symptomatic PAH uncomplicated by right-heart failure, who demonstrate a favorable acute response to vasodilation testing defined by criteria recommended in the guidelines. A sustained response to CCB therapy is an indication to continue the patient on a CCB regimen. Lack of a sustained response is an indication to determine the World Health Organization (WHO) and/or New York Heart Association (NYHA) Functional Class (I, II, III or IV) into which the patient may be classified. Study of 557 consecutive IPAH patients receiving CCB therapy found that 93.2% were non-responders, while 38 of the 557 patients went on to become long-term responders to CCB therapy. Long-term CCB response was associated with long-term survival, and long-term CCB failure was associated with increased risk for earlier death.<sup>2</sup>

The definition of a CCB responder in the ACCP evidence-based guidelines state that the patient should show:

- Fall in mean pulmonary artery pressure (PAP) by at least 10 mm Hg, to an absolute PAP mean of  $\leq 35$ -40 mm Hg, and,
- Unchanged or increased carbon dioxide (CO) level.

The treatment algorithm developed from the ACCP guidelines directs the physician to selection of advanced therapy for the patient who did not respond to a trial of CCB. Choices of advanced therapy are made from three classes of drugs:

*Prostacyclin analogues*

- Epoprostenol (IV);
- Treprostinil (IV or SC); and,
- Iloprost (inhaled).

Epoprostenol has the longest clinical history, having been approved in 1995 for treatment of PAH. Iloprost is the most recently approved agent, in 2002. Epoprostenol and iloprost are approved for use in WHO Functional Class III and IV patients, treprostinil for use in WHO Functional Class II, III and IV patients.

*Endothelin receptor antagonists*

- Bosentan (oral), approved for use in treatment of IPAH and PAH associated with scleroderma, and WHO Functional Class III and IV patients; and,
- Ambrisentan (oral), approved for use in WHO Functional Class III and IV patients.

*Phosphodiesterase-5 inhibitors*

- Sildenafil (oral), approved for use in WHO Functional Class II, III and IV patients. The phosphodiesterase inhibitors function via the nitric oxide (NO) pathway to mediate pulmonary arterial vasodilation and decrease pulmonary vascular resistance.

All of these agents are associated with side effects that vary in intensity from patient to patient. All are costly and therapy with an agent must often be pre-approved by the patient's health insurance carrier.

Before any advanced PAH therapy is undertaken, right-heart catheterization should be performed and wedge pressure measured to determine the status of right-heart function. Choice of advanced therapy should include the patient in decision-making. The patient should be fully informed regarding (1) the rationale for proposed advanced therapy, (2) the potential side effects associated with proposed agents, (3) the cost of therapy with each agent proposed for use, and (4) end-points of proposed therapy. The desired end-points of patients may be somewhat different from those proposed by the physician—e.g., the patient may want to be able to climb stairs to the second floor of his/her home or make a trip to the grocery store.

When a patient does not improve on first-line monotherapy, combination therapy may be considered. Failure to improve may be due to more than one PAH pathway being involved in the disease process. A single drug addresses only one of the three PAH pathways: endothelin pathway, nitric oxide pathway or prostacyclin pathway.

Combination therapy for PAH was first studied in the BREATHE-2 trial of combined bosentan and epoprostenol in 30 patients.<sup>3</sup> The trial showed that combination therapy was well tolerated in patients with severe PAH, and resulted in greater improvement than monotherapy although this finding did not achieve statistical significance.

The more recent (2006) randomized, placebo-controlled STEP trial evaluated combination therapy with oral bosentan and inhaled iloprost in patients with NYHA Functional Class III and IV PAH.<sup>4</sup> The study showed that the combination of bosentan and iloprost improved disease status by clinical measures including 6-minute walk distance, change in Functional Class, change in Borg dyspnea score, time to clinical worsening, proportion of responders and change in hemodynamics.

The TRIUMPH-1 randomized, placebo-controlled, double-blind study looked at the efficacy/safety of inhaled treprostinil added to therapy of 235 NYHA Functional Class III and IV patients who were receiving bosentan or sildenafil. By all measures including the primary end-point of 6-minute walk distance, efficacy of the combination therapy was demonstrated.<sup>5</sup>

Major unanswered questions regarding combination therapy for PAH remain to be addressed:

- Is the strategy to target more than one PAH pathway by combination therapy clearly superior to monotherapy?
- Would patients do better if they were started on combination therapy, rather than waiting for them to fail monotherapy?
- Do the combined side effects of drugs in combination therapy pose risk for patients, or make therapy intolerable for patients?
- Which are the most effective/safe combinations of agents?
- What are the optimal end-points by which to assess combination therapy?
- Should combinations of drugs be studied as starting therapy?

Choice of therapy for diagnosed PAH is based on a number of criteria derived from monitoring of patients under treatment. The physician must determine what patient parameters to monitor, and when and how to monitor them. The physician's own experience is important to making rational choices. There are few randomized studies in the literature to help the physician make monitoring decisions.

PAH is a disease of decline and deterioration of the patient's physical status and quality of life. A number of prognostic indicators are predictive of poor outcome and survival:

- Diagnosis of underlying scleroderma;
- Poor or absent response to vasodilation;
- Poor hemodynamic profile—e.g., increased right arterial pressure, decreased cardiac index;
- Worsening echocardiographic finding;
- Poor exercise tolerance;
- Worsened Functional Class; and
- Increased brain natriuretic peptide (BNP) level.

The objective goals of therapy are to improve symptoms, hemodynamics, right ventricular function and survival. A patient's goals may be less comprehensive and more subjective—e.g., improved ability to carry out activities of daily living. Improvement is the only goal attainable with current therapy; no therapy cures the disease.<sup>6,7</sup>

BNP has been emerging as a prognostic indicator of disease status in patients with PAH and right-heart dysfunction. In general, studies have shown, BNP at baseline and at follow-up examination is an independent predictor of mortality. A less elevated BNP level is association with a patient doing better over time.<sup>8</sup>

Echocardiography is often regarded as a definitive monitoring procedure. There is, however, no consensus in the literature on the absolute value of echocardiography in monitoring the status of PAH. If echocardiography is used for monitoring of a PAH patient, the physician should compare all data derived from the procedure. Relevant changes may be occurring in more than cardiac parameter—e.g., heart valve function, atrial or ventricular chambers or right ventricular function. The tricuspid annular plane systolic excursion (TAPSE) test strongly predicts mortality and can be used to complement echocardiographic findings.

Monitoring of right ventricular function is the single most important indicator of change in disease severity and risk for death. The procedure is not difficult to perform and the cost is well justified by the data retrieved. If an individual practitioner is hesitant to do the procedure, the patient should be referred to a center where pulmonary hypertension is treated.

Treatment of PAH may improve in the future, with the introduction of newer and/or novel therapies. The pace of new drug development is not rapid, however. As of 2008, the last new drug introduction occurred in 2002. A very fundamental difficulty is the lack of a satisfactory animal model for human PAH. In the standard monocrotaline rat model, PAH is a curable disease whereas it is incurable in humans. Some interventions that are effective in the rat model are ineffective in humans.

Novel therapies currently being investigated for effectiveness in treating PAH include:

- Tyrosine kinase inhibitors;
- Non-prostenoic PGI-2 receptor agonists;
- Vasoactive intestinal peptide;
- Tissue dual endothelin receptor antagonists; and,
- Serotonin antagonists.

Imatinib, a platelet-derived growth factor inhibitor, has been shown in animal trials to reverse pulmonary vascular remodeling.<sup>9</sup> In human trial, it has improved clinical outcomes in PAH resistant to other therapies.<sup>10,11</sup>

Further in the future, approaches to treatment of PAH may be derived from genetics of PAH and pharmacogenomics that target drugs to specific genetic targets. A conundrum of PAH is that disease-causing genetic mutations are known and characterized, but their penetrance is low. It would be helpful to know what protective factors keep PAH from developing in the preponderance of patients who carry the disease-causing polymorphisms.

Other entities that may hold promise for improved treatment of PAH include:

- Better methods for assessing right ventricular function;
- Determining the pathway(s) by which PAH progresses;
- Stem cell therapy; and,

- Improving end-points for therapeutic trials and assessing therapies in trials that are larger in size and longer in duration than has been the case to date.

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### Standard of Practice

Diagnosing the clinical status of patients with pulmonary artery hypertension (PAH), preparing an appropriate treatment plan, selecting appropriate pharmacotherapy and monitoring the patient's response to therapy presents a number of potential pitfalls for the clinician. The clinician's approach to the problems

posed by PAH is more systematic when current evidence-based guidelines and algorithmic approaches to treatment are consulted.

Clinical trials over the past decade have been accumulating evidence regarding the safety and efficacy of three classes of drugs that have their therapeutic effect via three PAH pathways. Selection of monotherapy and combination therapy may be based, in part, on the pathway by which drugs have their therapeutic effect.

The question of when to initiate combination therapy, with which agents, is one not answerable by evidence from trials alone. While combination therapy is usually started only after monotherapy has failed to elicit a satisfactory response, an outstanding question is whether some patients would have a better response if combination therapy was initiated as starting therapy. Few studies have addressed that question: most studies of combination therapy add a drug to the drug with which the therapy was initiated.

Monitoring of clinical status relies on standard methods including 6-minute walk distance, pulmonary artery pressure measurements, pulmonary vascular resistance, oxygen saturation, cardiac output/cardiac index and echocardiography. Monitoring should essentially include right-heart catheterization. Although the procedure is not difficult to perform and is safe for the patient, general physicians who do not routinely treat PAH may be reluctant to do it. The value of right-heart catheterization in terms of information returned emphasizes the necessity for general physicians to refer patients to a PAH treatment center that can provide advanced diagnostic, treatment and monitoring services.