New Drugs Enhance Pulmonary Hypertension Tx

BY BRUCE JANCIN
Denver Bureau

SNOWMASS, COLO. — Treatment options in pulmonary arterial hypertension have significantly improved in recent months with the marketing of two useful new agents: oral sildenafil and inhaled iloprost, Dr. Carole A. Warnes said at a conference that was sponsored by the Society for Cardiovascular Angiography and Interventions.

Iloprost (Ventavis), a prostacyclin analog, has several advantages over other available therapies. The inhaled route of administration makes iloprost a topical therapy that selectively causes vasodilation in the pulmonary circulation while minimizing systemic drug effects.

Inhaled therapy also promotes drug deposition in areas of the lung that are well ventilated, with resultant reduced ventilation/perfusion mismatch. "This might be important in patients with associated parenchymal lung disease," noted Dr. Warnes, professor of medicine at the Mayo Medical School, Rochester, Minn.

A source of frustration for many physicians caring for patients with pulmonary arterial hypertension (PAH) is that iloprost, sildenafil, and the other drugs of proven efficacy result in only a modest, albeit clinically meaningful, improvement in 6-minute walk distance, the standard efficacy measure in clinical trials.

For example, in the pivotal randomized, placebo-controlled, double-blind crossover trial—Sildenafil Use in Pulmonary Arterial Hypertension (SUPER)—12 weeks of sildenafil (Revatio) at 20 mg t.i.d. resulted in a mean placebo-corrected 45-meter gain in 6-minute walk distance, compared with baseline (N. Engl. J. Med. 2005;353:2148-57). Twelve weeks of iloprost brought a 36-meter gain in another randomized trial. An ongoing major trial combining the two agents with their differing mechanisms of action aims to learn whether efficacy is enhanced.

Inhaled therapy deposits the drug in well-ventilated areas of the lung, reducing ventilation-perfusion mismatch.

DR. WARNES

Recent developments in PAH involved a rat model of the disease, in which inhaled iloprost induced remodeling of the vascular structure of the pulmonary arteries (Am. J. Respir. Crit. Care Med. 2005;172:358-63). The prostacyclin analog resulted in reduced right ventricular systolic pressure, regression of right ventricular hypertrophy, attenuation of matrix metalloproteinase-2 and -9 expression, and decreases in the degree of muscularization and the medial wall thickness of the small pulmonary arteries in this German study.

That's a first for any drug. The animal data raise the possibility that damage to the pulmonary vascular circuit in patients with PAH may not be irreversible. "There is a structural change in the rat model. Perhaps we can regress PAH, not just hemodynamically, but structurally," Dr. Warnes said.

But inhaled iloprost is a complicated therapy. Patients self-administer it using a special device six to nine times per day, with each session taking about 10 minutes.

Iloprost is approved for patients with New York Heart Association functional class III or IV PAH.

Sildenafil, on the other hand, is the first oral agent approved for early-stage PAH. In the SUPER trial, it not only improved 6-minute walk distance by 13% over baseline, it also lowered pulmonary artery pressure. Improvements were maintained at 12 months.

The near-term drug development pipeline includes more endothelin-receptor antagonists and prostanoids. But there is also an opportunity to test entirely new therapeutic approaches targeting abnormalities in PAH that have not yet been addressed, Dr. Warnes continued.

For example, PAH is associated with serotonin transporter-gene polymorphisms and increased circulating serotonin levels, raising the possibility that SSRIs might be beneficial. Potassium channels are downregulated on the pulmonary artery smooth muscle cells of patients with PAH, suggesting a therapeutic role for a potassium channel opener. The disease is also marked by increased circulating cytokines, autoantibodies, and chemokine expression, pointing to a potential application for immunosuppressive agents.

Patients with PAH have reduced vascular levels of vasoactive intestinal peptide; perhaps administration of vasoactive intestinal peptides would provide benefit. PAH is also marked by increased vascular endothelial growth factor activity, which could be addressed by antiangiogenesis agents. And even though warfarin has been standard therapy in PAH for decades, the effect of aspirin has never been studied, Dr. Warnes noted. ■

Obesity, Hypertension, Apnea Confound Diagnosis of PAH

BY BRUCE K. DIXON
Chicago Bureau

MONTREAL — Obese patients often have a constellation of physiological problems that together can lead to a mistaken diagnosis of pulmonary artery hypertension, according to researchers at Duke University Medical Center in Durham, N.C.

The presence of exertional dyspnea in these patients often leads to an echocardiogram and a finding of elevated right ventricular systolic pressure.

"Often the pressure is just mildly elevated, and these patients don't really have pulmonary arterial hypertension but are referred for evaluation anyway," Dr. Terry A. Fortin said at the annual meeting of the American College of Chest Physicians.

To assess diagnostic strategies for pulmonary arterial hypertension (PAH) in this often very symptomatic population, Dr. Fortin and her colleagues at Duke University retrospectively assessed consecutive cardiac catheterization data on patients referred for suspected PAH.

Suspected PAH was defined as mean pulmonary arterial pressure (mPAP) greater than 25 mm/Hg, pulmonary capillary wedge pressure (PCWP) less than 15 mm/Hg, and pulmonary vascular resistance (PVR) greater than 3 Wood units. Patients with left ventricular systolic dysfunction, PAH clearly associated with a known syndrome, or significant valve or lung disease of sufficient severity to explain PH were excluded. That left 78 obese patients with mild pulmonary hypertension (PH) with mPAP greater than 25 mm/Hg and PVR less than 5 Wood units, said Dr. Fortin of Duke University Medical Center.

Of those 78 patients, 40 had baseline syndromes or conditions that the investigators believed adequately explained the patients' PH after workup. Those conditions included connective tissue disease, congenital heart disease, chronic thromboembolic disease, portopulmonary disease, severe lung disease, high-output arteriovenous shunts, and left-sided valve disease.

Eliminating these patients left 38 patients with elevated mPAP associated with a constellation of factors that together resulted in PH, although maybe not PAH, Dr. Fortin said.

Most were women with a mean age of 60 years. All were hypertensive, and virtually all had a body mass index greater than 30; half had a body mass index (BMI) greater than 40. Nearly two-thirds had diabetes and/or a sleep disorder.

"The precatheterization diagnostic tests often showed elevated right ventricular systolic pressures on referral cardiac echo, and that was typically the reason that the patients were sent to us," Dr. Fortin explained. Many of the patients did have increased artery sizes, and their right atrium size or decreased contractility in the right ventricle was of concern. About half the patients were hypoxemic, and some were hypercarbic, "which is not necessarily what we would expect in pulmonary hypertension," she added.

'It should not be assumed that patients with an elevated right ventricular systolic pressure by echo' have PAH.

DR. FORTIN

Low lung volume was common, and many patients had reduced diffusion capacity of carbon monoxide (DLCO). Two patients had only increased right ventricular systolic pressures.

"Looking at the cardiac cath data, PVRs were not quite 3 [Wood units] in most patients, and if you break them down into those with enlarged and normal right ventricles, they're slightly different, but not statistically so," Dr. Fortin said. The investigators also found a slight but statistically nonsignificant difference in mean pulmonary pressures, with a predominance of elevated pressures—as expected in bigger right ventricles. Overall, the patients had normal cardiac indices and were not very sick.

Only one patient had pulmonary arterial hypertension based upon a PCWP less than 15 mm/Hg and a PVR greater than 3, Dr. Fortin said. Hypoxemia, hypercarbia, low total lung capacity, and DLCO were all related to obesity, hypoventilation, and sleep disorders, she added.

"Lest you think that obese people do not ever have pulmonary hypertension, I was quickly able to glean 13 patients … who were morbidly obese with BMIs greater than 40 who were seen in our clinic," Dr. Fortin said. "All had mPAPs greater than 25 with elevated pulmonary vascular resistances. In fact, their average pulmonary artery pressure was 60, and their PVR was 12, while their cardiac indices were very low; these were very sick patients."

The study's researchers concluded that a number of factors can contribute to a mistaken diagnosis of PAH. They include systemic hypertension, obesity, sleep-disordered breathing and hypoventilation, and elevated pulmonary capillary wedge pressure.

"It should not be assumed that patients with an elevated right ventricular systolic pressure by echo have pulmonary arterial hypertension," Dr. Fortin cautioned. "Pulmonary capillary wedge pressure and diastolic dysfunction may be causative."

Aggressive management of weight, sleep disorders, hypertension, hypoxemia, and diabetes may limit the development of diastolic dysfunction and secondary pulmonary hypertension, though that's easier said than done, she added.

"Patients with this complex of disorders often have findings similar to those in full-blown PAH, and thus cardiac catheterization is necessary to help sort this out," Dr. Fortin said. "I think that diagnostic testing also should definitely include sleep studies, as 70% of these patients had sleep disorders that were not necessarily diagnosed at the time of presentation."

It's not necessary to go right to a diagnostic test, Dr. Fortin said, "as long as you're following the patient carefully; try to fix these other factors first before going to cardiac catheterization." ■