Pulmonary Hypertension Treatment Looking Up

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

Iloprost (Ventavis), a prostacyclin analogue, 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.

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, noted Dr. Warnes, professor of medicine at the Mayo Medical School, Rochester, Minn.

Inhaled iloprost, an approved prostacyclin analog, has advantages over other therapies.

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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.

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 analogue 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, 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.

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, he 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.

PAH patients have reduced vascular levels of vasoactive intestinal peptide; administration of vasoactive intestinal peptides may 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. ■