Sildenafil, Iloprost Expand PAH Treatment Options

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 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.

"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.

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. "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.

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DR. WARNES

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. ■

Thyroid-Related Cardiovascular Concerns Limited to AFib

BY KATE JOHNSON
Montreal Bureau

Subclinical hyperthyroidism was linked to atrial fibrillation but not to other clinical cardiovascular conditions or deaths in a new study.

"We report an independent association of subclinical hyperthyroidism with incident atrial fibrillation but not with other clinical cardiovascular conditions or mortality," reported Dr. Anne R. Cappola from the University of Pennsylvania in Philadelphia and her colleagues (JAMA 2006;295:1033-41).

The study examined the link between unrecognized thyroid dysfunction and cardiovascular risk, including atrial fibrillation, coronary heart disease, cerebrovascular disease, and death (cardiovascular and all-cause) in a subgroup of 3,233 participants in the population-based, longitudinal Cardiovascular Health Study. The study subjects were community-dwelling older adults with a mean age of 73 years who were followed for an average duration of 12.5 years.

At baseline, 82% of the cohort were euthyroid, 15% had subclinical hypothyroidism (TSH above 4.5 mU/L and below 20 mU/L with a normal FT_4 concentration), 1.6% had overt hypothyroidism (TSH of at least 20 mU/L or TSH of more than 4.5 mU/L with a low FT_4), and 1.5% had subclinical hyperthyroidism (TSH of 0.10-0.44 mU/L or less than 0.10 mU/L with a normal FT_4). Individuals with overt hyperthyroidism, or thyrotoxicosis (TSH below 0.10 mU/L with an elevated FT_4 level) were excluded because of the small sample size.

Because the aim of the study was to detect previously unrecognized thyroid dysfunction, potential subjects were excluded if they were taking thyroid medication at baseline. However, once thyroid dysfunction was identified, medication use was included in the analysis because of its potential effect on subsequent cardiovascular risk.

The study found no differences in cardiovascular events at baseline between the euthyroid group and any of the three groups with thyroid dysfunction.

However, over the 12.5-year follow-up period, subclinical hyperthyroidism emerged as a risk factor for atrial fibrillation, but for no other clinical cardiovascular conditions. Subjects with subclinical hyperthyroidism had a greater incidence of atrial fibrillation than did euthyroid subjects (67 vs. 31 events per 1,000 person-years). After adjustment, this risk was nearly double (hazard ratio, 1.98). None of the other thyroid abnormalities were associated with increased CVD risk.

The findings do not support thyroid screening in older adults simply to prevent atrial fibrillation, since the estimated number needed to screen would be 2,500 to detect 1 case of atrial fibrillation, the authors noted.

However, the data do support the treatment of subclinical hyperthyroidism when it is detected.

The authors disagree with an earlier expert panel report that cited insufficient evidence to treat patients with TSH levels of 0.1 mU/L-0.45 mU/L and recommended treating only those patients with TSH levels below 0.1 mU/L (JAMA 2004;291:228-38). ■

Postop Neurocognitive Decline Tied To Elevated Inflammatory Markers

SAN DIEGO — Increased levels of C-reactive protein and other markers of perioperative inflammatory response are associated with neurocognitive decline following cardiac surgery, Dr. Basel Ramlawi said at a congress sponsored by the Association for Academic Surgery and the Society of University Surgeons.

Dr. Ramlawi and his associates prospectively evaluated 41 patients who underwent coronary artery bypass graft and/or valve procedures that used cardiopulmonary bypass. The patients' mean age was 67 years. All patients had neurocognitive testing preoperatively, postoperatively at day 4, and at 3 months. The validated tests took 45 minutes to administer and covered memory, executive function, naming, attention, fluency, and premorbid intelligence, said Dr. Ramlawi of the division of cardiothoracic surgery at Harvard Medical School, Boston. Neurocognitive decline was defined as performing one standard deviation from baseline on at least 25% of tasks.

Participants underwent serum testing preoperatively, postoperatively at 6 hours, and at 4 days. Levels of C-reactive protein (CRP) and of interleukin 1β, IL-6, and IL-10 were assessed, and an increase of serum tau protein after surgery was used as a marker of axonal central nervous system damage.

Of the 41 patients, 7 (17%) developed neurocognitive decline. Baseline characteristics and predictors of neurocognitive decline such as age, education level, and perioperative temperature did not differ significantly between patients with and without postoperative neurocognitive decline.

However, patients who experienced postoperative neurocognitive decline had significantly greater increases of CRP, IL-1β, and IL-10 than those who had no decline.

In addition, the level of tau protein was increased 78% in patients with neurocognitive decline, compared with 29% in their counterparts who did not show a decline.

"There exists a significant association [between] the magnitude and persistence of the perioperative inflammatory response and neurocognitive decline in this cohort," Dr. Ramlawi said. "This association is likely mediated by axonal damage."

According to the medical literature, the incidence of neurocognitive decline is 20%-60% in the first 2 weeks after cardiac surgery. "It can range from 5% to 40% for periods up to 5 years after surgery," he said, adding that the etiology of this complication is not known.

"It is likely a multifactorial problem," Dr. Ramlawi said. "Several theories have been assessed. The most obvious one is ischemia. Any microemboli might cause this."

Other possible factors include anesthesia, perioperative hypothermia, and low level of education.

—Doug Brunk