Ambrisentan Safer in PAH Than Others in Its Class

BY BRUCE JANCIN
Denver Bureau

SALT LAKE CITY — The investigational endothelin receptor antagonist ambrisentan appears to provide a more favorable risk/benefit ratio than current therapies do for pulmonary artery hypertension, Dr. Lewis J. Rubin said at the annual meeting of the American College of Chest Physicians.

Results of the phase III randomized double-blind ARIES-I trial demonstrate that ambrisentan has good efficacy as once-daily oral therapy. What sets it apart from other effective endothelin receptor antagonists is that it displayed no liver toxicity in ARIES-I. Indeed, the incidence of liver function test abnormalities in the trial was zero, noted Dr. Rubin, professor of medicine at the University of California, San Diego.

Ambrisentan is a high-affinity propanoic acid–class endothelin receptor type A–selective agent with no interactions with warfarin or sildenafil. Its dosing is 10-100 times less than with bosentan—the endothelin receptor antagonist now on the market—and sitaxsentan, now under FDA review. Bosentan and sitaxsentan are oral twice-daily sulfonamide-class agents, and both are associated with dose-dependent increases in liver function abnormalities that can force treatment discontinuation.

ARIES-I involved 202 patients with pulmonary artery hypertension (PAH) who were randomized to 12 weeks of double-blind placebo or once-daily ambrisentan at 5 or 10 mg. Roughly two-thirds had idiopathic PAH. Most others had PAH associated with connective tissue disease. Most subjects had moderate disease; 58% of patients were WHO class III, while 32% of patients were class II. The mean baseline 6-minute walk distance was 341 m, indicative of moderate impairment.

The primary study end point was change in 6-minute walk distance over 12 weeks. It increased by 43.6 m with 10 mg/day of ambrisentan and 22.8 m with 5 mg, and it decreased by 7.8 m on placebo, suggesting a possible dose-response effect.

ARIES-I broke new ground as the first trial in PAH to use change in plasma brain natriuretic peptide (BNP) as a secondary end point. BNP is a marker of right heart stress. It reflects severity of PAH and is predictive of long-term outcome. BNP dropped by a mean of 62.5 and 149.3 pg/mL in patients on 5 and 10 mg/day of ambrisentan, respectively, while climbing 11.8 pg/mL with placebo.

Unlike other effective endothelin receptor antagonists, ambrisentan displayed no liver toxicity.

DR. RUBIN

In terms of other secondary end points, the Borg dyspnea index showed significant improvement in ambrisentan-treated patients. They were also only half as likely to experience clinical worsening during the study period. The ambrisentan arms showed nonsignificant trends for improvement in WHO functional class and on the Short Form-36 physical function scale.

Ambrisentan's chief side effects were peripheral edema, occurring in more than one-quarter of patients, and nasal congestion, in 9%. The edema is an endothelin receptor antagonist–class effect. It is typically mild and readily managed with low-dose diuretics without need for dose adjustment of the anti-PAH drug, Dr. Rubin said.

With a mean extended follow-up of 1.4 years and a maximum of 2.8 years, the incidence of confirmed liver function test abnormalities in ambrisentan-treated ARIES-I participants was 0.5%. That's less than the 3% incidence noted in the placebo arm during the 12-week double-blind treatment period.

Several audience members who have used ambrisentan said it's their impression there is a dose-response effect, although that hasn't been proven. Dr. Rubin agreed.

"I don't think that 10 mg is clearly superior to 7.5 mg, but my sense is that 5-7.5 mg is better than 2.5 mg. My guess is there's a potential advantage to having a range of doses with this drug, so you can start on the low side with the ability to increase," he said.

Dr. Rubin is a consultant to Myogen Inc., which sponsored ARIES-I and was recently acquired by Gilead Sciences Inc. Giliad filed a new drug application with FDA in December, according to a statement. GlaxoSmithKline will market ambrisentan outside the United States. ■

Half of Heart Failure Is Diastolic, Not Systolic

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — A majority of patients presenting to emergency departments with pulmonary edema have diastolic heart failure, also known as heart failure with preserved ejection fraction, Dr. William Grossman said.

A recent analysis of data from more than 100,000 hospitalizations in the Acute Decompensated Heart Failure Registry (ADHERE) showed that 51% of patients with heart failure had preserved ejection fractions, and 49% had depressed ejection fractions, also called systolic heart failure (J. Am. Coll. Cardiol. 2006;47:76-84). In-hospital mortality rates were 3% with diastolic heart failure and 4% with systolic heart failure, he said at a meeting sponsored by the California chapter of the American College of Cardiology.

That finding may surprise many people who attribute death from heart failure mainly to systolic dysfunction, said Dr. Grossman, chief of cardiology at the University of California, San Francisco. Many patients have both types of heart failure.

Compared with the systolic heart failure group, patients who had diastolic heart failure were more likely to be women and less likely to have a prior MI or to be taking ACE inhibitors or angiotensin receptor blockers (ARBs).

In a separate recent study, investigators from the Mayo Clinic, Rochester, Minn., followed 556 patients with heart failure in the community for 6 months. The mortality rate was 16% both in the 55% of patients with diastolic heart failure and in the rest of the cohort, who had systolic heart failure, Dr. Grossman noted.

Diastolic heart failure patients were more likely to be women and less likely to have a prior MI or to be taking ACE inhibitors or ARBs, vs. systolic heart failure patients.

"The prognosis is really not much better than for classic systolic heart failure," he said at the meeting, also sponsored by the university.

In the Mayo Clinic study, diastolic dysfunction and the patient's ejection fraction independently predicted elevation of brain natriuretic peptide (BNP).

"When patients come to the emergency ward with acute shortness of breath, many of us look to the BNP to tell us, is this pneumonia? Is this asthma? Is this hypertension? BNP is elevated in heart failure whether it's systolic or diastolic," an important fact to recognize, he said.

If diastolic heart failure is so widespread, what's causing it? It's not all caused by amyloidosis, and is unlikely to be due to untreated hypertension in so many cases, Dr. Grossman believes.

German investigators performed cardiac biopsies and other tests on 70 patients hospitalized with diastolic heart failure and found that 84% were infected with parvovirus B19. Presence of the virus was strongly associated with coronary endothelial dysfunction (Circulation 2005;111:879-86).

"I'm not saying this is what's going on in our emergency wards, but it's certainly something that I would never have thought to look for. We should pay attention. There may be increased information about this in the future," Dr. Grossman commented.

There are few data from randomized trials to guide treatment of diastolic heart failure. Dr. Grossman approaches management much as he would for patients with systolic heart failure. ■

Most PAH Patients Are on Dual Therapy

BETHESDA, MD. — More than half of patients in the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) are on two or more medications to treat their disease, said Dr. Michael McGoon, who is chairman of the registry's steering committee.

"One of the revealing outcomes early on … is that already 54% of the 460 patients on any pulmonary arterial hypertension medication are on two or more medications," said Dr. McGoon, at a meeting on pulmonary hypertension sponsored by the National Institutes of Health.

The REVEAL registry is designed to look at the clinical course and medical management of pulmonary arterial hypertension. Researchers hope to enroll 3,000 patients with PAH, who will be followed for at least 5 years, regardless of their therapy. The registry is intended to capture demographic data and clinical treatment patterns and factors associated with improved clinical outcomes.

As of October 2006, 545 patients had been enrolled. Of these, slightly less than half (46%) had idiopathic PAH. Roughly half (51%) had PAH associated with other diseases. Of those enrolled, 71% also had cardiovascular disease, said Dr. McGoon, who is also director of the pulmonary hypertension clinic at the Mayo Medical School, Rochester, Minn.

The registry is sponsored by CoTherix Inc., which makes Ventavis (iloprost) for the treatment of pulmonary arterial hypertension. Dr. McGoon disclosed that he has financial ties to several pharmaceutical companies, including CoTherix.

—Kerri Wachter