Levosimendan No Home Run in ADHF Studies

Some cite lethality as a reason to consider using the drug; whereas others point to concerns about safety.

BY BRUCE JANCIN Denver Bureau

DALLAS — The investigational acute decompensated heart failure drug levosimendan garnered mixed reviews for its less-than-stellar performance in two large, multinational, double-blind, randomized clinical trials presented at the annual scientific sessions of the American Heart Association.

Levosimendan has both inotropic and vasodilator properties. But unlike other positive inotropes, whose action is mediated by increased intracellular calcium, levosimendan enhances cardiac myofilament sensitivity to an unchanged concentration of calcium. The drug also possesses peripheral vasodilator action mediated by an agonist effect on potassium channels.

Dr. Milton Packer reported on 600 patients in the Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE II) trial who were hospitalized for acute decompensated heart failure (ADHF) not adequately responsive to intravenous diuretics. They were randomized to a 24-hour infusion of levosimendan or placebo, with intensification of standard background therapies as needed.

The primary end point in REVIVE II was a composite measure of clinical status during the first 5 days of hospitalization. The levosimendan group fared significantly better in this regard than did the controls, even though levosimendan had been stopped after the first 24 hours. Of those in the levosimendan arm, 76% showed moderate or marked improvement in a composite global assessment score, compared with 65% of controls. In the levosimendan arm, 15% required rescue therapy because their condition worsened, compared with 26% in the placebo arm. Levels of brain natriuretic peptide, a surrogate for heart failure severity, were halved in the levosimendan group and stayed low. Patients treated with Levosimendan felt better in as little as 6 hours, and that feeling persisted through 5 days.

But 28 levosimendan-treated patients developed atrial fibrillation and 72 experienced ventricular arrhythmias, compared with 6 and 51, respectively, on placebo. Symptomatic hypotension and headaches were also more common with levosimendan. There were 49 deaths within 90 days with levosimendan and 40 with placebo, said Dr. Packer, professor of medicine and director of the Center for Biostatistics and Clinical Science at the University of Texas Southwestern Medical Center, Dallas.

He stressed that intravenous diuretics—a fast-acting, safe, and relatively inexpensive treatment—will remain the initial intervention for patients who present with ADHF. He estimated, however, that this therapy achieves an adequate response—relief of shortness of breath at rest—in only about half of the 3 million U.S. hospitalizations per year with ADHF as the primary or secondary diagnosis. It's in the other half that he sees levosimendan as potentially playing a major role. Dr. Alexandre Mebazaa presented the re-

sults of the Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) study, the first large-scale study to examine the survival impact of medications used to treat ADHF. SURVIVE involved 1,327 patients in eight countries who were randomized to levosimendan or dobutamine along with standard background treatments.

In SURVIVE, the primary end point was 6-month all-cause mortality, which was 26% in the levosimendan arm and

28% with dobutamine, a nonsignificant difference. But it was unrealistic to expect a mortality difference so long after a single 24hour drug infusion, said Dr. Mebazaa, professor and director of the depart-

ment of anesthesia and critical care medicine at Lariboisière Hospital, Paris.

The results were more impressive closer to the treatment period. At day 5, for example, mortality was 4.4% in the levosimendan group and 6.0% with dobutamine, a 28% reduction in relative risk. As in RE-VIVE II, there was an increased incidence of atrial fibrillation with levosimendan, he said.

Some audience members were enthused that the levosimendan trials had raised the bar in terms of the rigor with which ADHF drugs are evaluated. All currently available drugs were approved on the basis of hemodynamic gains rather than evidence of the more meaningful end points of improved clinical status or outcomes.

Dr. Gordon F. Tomaselli, vice chairman of the AHA scientific sessions program committee, said in an interview that given the high lethality of ADHF (more than onequarter of SURVIVE participants died within 6 months) and the very limited current treatment options, levosimendan "probably does have a place in the armamentarium."

But Dr. Gregg C. Fonarow was skeptical. "It's hard to conceive that with this dosing regimen this would be a treatment that

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DR. PACKER

physicians would want to use for their patients. A reduction in symptoms is not going to be acceptable if it comes at a price of substantial increased risk of severe adverse events," said Dr Fonarow, profes-

sor of medicine at the University of California, Los Angeles, and director of the Ahmanson-UCLA Cardiomyopathy Center.

"If you compare the serious adverse events seen in REVIVE II with what was observed in the largest trial with nesiritide, levosimendan comes nowhere close to being as safe as nesiritide," he said. Nesiritide (Natrecor) has come under fire in the past year after assertions it may worsen renal function and increase mortality.

Dr. Packer is a consultant to Abbott Laboratories and Orion Pharma, which funded REVIVE II and SURVIVE. Dr. Mebazaa is a consultant to Abbott.

Obesity Paradox in Acute HF Broadens Therapeutic Possibilities

BY BRUCE JANCIN Denver Bureau

DALLAS — The obesity paradox previously described in patients with chronic systolic heart failure has, for the first time, been shown to be strikingly evident in acute heart failure as well, Dr. Gregg C. Fonarow reported at the annual scientific sessions of the American Heart Association.

An analysis of 108,927 hospitalizations recorded in the Acute Decompensated Heart Failure Registry (ADHERE) showed that in-hospital mortality decreased in near-linear fashion with increasing body mass index (BMI) quartile. (See box.)

The same marked reduction in in-hospital mortality that was seen in heavier ADHERE participants who had reduced systolic function was also seen in those with preserved systolic function, added Dr. Fonarow, professor of medicine at the University of California, Los Angeles, and director of the Ahmanson-UCLA Cardiomyopathy Center.

The paradox lies in the fact that obesity is a well-recognized independent cardiovascular risk factor in the general population, yet in the setting of chronic or acute heart failure, it is somehow protective.

The bottom line is that the paradox in

acute heart failure is a real phenomenon. "Given the huge number of hospital episodes we're looking at here, the results are irrefutable," Dr. Fonarow said.

The obesity paradox has potentially enormous clinical implications for the management of acute decompensated heart failure, a condition that constitutes the primary or secondary diagnosis in an estimated 3 million hospitalizations annually in the United States. The next step in the research is to provide acute nutritional support when normal-weight or underweight patients—those with, say, a BMI below 27 kg/m²—present at the hospital in acute heart failure, and then to study whether their short-term mortality is reduced as a consequence.

"The broad implication is that this represents half of all acute heart failure hospitalizations, and they could potentially be amenable to having their acute mortality rates cut by one-third to one-half if this therapy pans out," Dr. Fonarow said in an interview.

"We're seriously thinking of doing some pilot studies looking at whether we can improve measures of cardiac function and nutritional status in these patients through acute nutritional support—and if that looks promising, to go forward with an interventional trial," he said.

Only through such studies will physicians learn whether obesity is causative of reduced mortality in acute heart failure patients or whether it is merely a marker for lower risk. It is worth noting, though, that even after adjustment for known predictors of in-hospital mortality in acute heart failure-including age, gender, blood urea nitrogen, creatinine, blood pressure, and dyspnea

at rest—patients in the lowest BMI quartile had a highly significant 46% greater inhospital mortality than did those in the top quartile, who had a BMI of at least 33.4.

The same held true when patients were grouped by World Health Organization BMI category rather than by quartile. Underweight patients—those with a BMI less than 18.5—had an in-hospital mortality of 6.3%. The rate was 4.6% in normal-weight patients (BMI 18.5-24.9), 3.4% in over-

In-Hospital Mortality by BMI in ADHERE 5.0% 3.9% 2.8% 2.2% 16.0-23.6 23.7-27.7 27.8-33.3 ≥ 33.4 BMI (kg/m2)Mote: Based on data from 108,927 patients hospitalized with acute decompensated heart failure. Source: Dr. Fonarow

weight patients (BMI 25.0-29.9), and 2.4% in obese patients.

The obesity paradox in acute heart failure cannot be explained merely as a reflection of cachectic patients being unable to handle the stress of acute illness. After all, in-hospital mortality was increased even in normal-weight patients, compared with those who were overweight or obese, Dr. Fonarow said.

ADHERE is funded by Scios Inc.