Tolvaptan Safely Improves Heart Failure Symptoms

BY MARY ANN MOON
Contributing Writer

NEW ORLEANS — The investigational agent tolvaptan relieves core symptoms of acute decompensated heart failure without inducing adverse effects, but had no impact on all-cause mortality, according to researchers in the multinational EVEREST clinical trials.

The oral vasopressin antagonist also had no effect on the combined end point of cardiovascular mortality or subsequent hospitalization for worsening heart failure, study investigators reported at the annual meeting of the American College of Cardiology.

After one dose, significantly more patients reported improvement in dyspnea scores after taking tolvaptan, compared with placebo. Changes in body weight due to reduced fluid overload were also significant at day 1 and day 7, and were sustained during a median 9.9 months of follow-up, study investigator Dr. Marvin A. Konstam reported at the meeting.

"I, as a clinician, can say I have something new to offer patients," said Dr. Konstam, chief of cardiology and professor of medicine at Tufts–New England Medical Center, Boston, during a press briefing.

However, Dr. Konstam acknowledged he was "disappointed" that the agent failed to reduce mortality or heart failure–related morbidity either during hospitalization or at 1-year follow-up.

In an editorial comment accompanying simultaneous publication of trial data, Dr. Clyde W. Yancy of Baylor Heart and Vascular Institute, Dallas, applauded the "noteworthy findings" on symptomatic improvement, but said the lack of impact on global clinical status, subsequent hospitalizations, or mortality must temper enthusiasm for the EVEREST findings.

"To the extent that it helps patients do better, that's a good thing," Dr. Yancy said at the ACC press briefing. He called the lack of safety signals in the follow-up study "comforting."

But neither physician suggested that the trial points to an improvement in the progression of heart disease in a patient group Dr. Konstam termed "daunting."

He specifically said it should not be used indiscriminately or indefinitely in patients with worsening heart failure, although he said he might reinstate it if a patient's fluid overload worsened upon discontinuation of short-term use of the drug.

The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial comprised two identical short-term trials and one long-term safety trial conducted at 359 sites in North America, South America, and Europe between 2003 and 2006. All were funded by Otsuka Inc., the drug's manufacturer.

In the two short-term trials, the clinical effects of tolvaptan were compared with those of placebo when added to optimal medical therapy during hospitalization for acute decompensated heart failure (HF) with impaired left ventricular ejection fraction (LVEF). In trial A, 1,018 subjects were randomly assigned to receive tolvaptan and 1,030 to receive placebo, while in trial B the numbers were 1,054 and 1,031, respectively, wrote Dr. Mihai Gheorghiade of Northwestern University, Chicago, and associates (JAMA 2007;297:1332-43).

In both short-term trials, patients in the active drug group showed decreases in body weight as early as the first day of treatment, which persisted as long as the drug was administered (7 days or until hospital discharge, whichever came first). Dyspnea and rales, fatigue, jugular venous distension, and pedal edema all improved in a similar fashion.

Tolvaptan improved or normalized serum sodium concentrations in hyponatremic patients. It also allowed all patients to reduce their use of furosemide.

"These positive effects were achieved without adversely affecting heart rate, blood pressure, or serum electrolytes," and there was no adverse effect on liver or renal function, Dr. Gheorghiade and associates wrote.

The long-term trial was primarily designed to assess the drug's safety in the same patients from hospital discharge through 1-year of follow-up. Unlike other agents previously used to treat the disorder, "Long-term tolvaptan treatment had no effect, either favorable or unfavorable, on all-cause mortality or the combined end point of cardiovascular mortality or subsequent hospitalization for worsening HF," wrote Dr. Konstam, the lead investigator in this trial, and his associates.

"Overall, the benefits on short-term symptoms, together with the demonstrable short-term and long-term safety profile, support the usefulness of tolvaptan treatment for patients manifesting volume overload during hospitalization for HF," the researchers wrote (JAMA 2007;297:1319-31).

Tolvaptan's safety record stands in contrast to nesiritide, which has been associated with increased mortality and renal dysfunction in two meta-analyses.

In his editorial comment, Dr. Yancy noted that there were no differences in global clinical status, nor in rates of recurrent HF hospitalization or mortality. And rates of adverse events—especially thirst and dry mouth—were "high" in all three EVEREST trials, he said.

Moreover, the trial results apply only to patients with profiles like those of the study subjects, and cannot be extrapolated to other groups.

"Clinicians should be encouraged to continue to use diuretics judiciously as needed. ... Adjunctive short-term arginine vasopressin antagonism may be considered for the patient with established low [ejection fraction]," Dr. Yancy wrote. ■

Betsy Bates contributed to this report from New Orleans.

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