Novel Agent Eases Acute Heart Failure Symptoms

Dyspnea was improved in 53% of the rolofylline group compared with 37% of the placebo group.

BY BRUCE JANCIN
Denver Bureau

CHICAGO — It's full speed ahead for a pivotal phase III clinical trial of the novel drug rolofylline in patients with acute decompensated heart failure and renal dysfunction, on the basis of its impressive performance in a 301-patient pilot study.

In the preliminary round, the selective adenosine A_1 receptor blocker rapidly improved acute heart failure symptoms, prevented further worsening of renal function, and reduced the combined rate of death or hospital readmission within 60 days, Dr. Barry M. Massie reported at the annual meeting of the American College of Cardiology.

"This is the first evidence that an intervention to prevent renal impairment may positively affect acute symptoms and intermediate-term outcomes in patients hospitalized with acute heart failure. These pilot data have important therapeutic implications. Better treatment of acute heart failure patients with progressive renal dysfunction requiring diuresis is a significant unmet medical need," said Dr. Massie, professor of medicine at the University of California, San Francisco, and chief of cardiology at the San Francisco VA Medical Center.

Heart failure is the No. 1 cause of hospitalization in patients aged older than 65 years. Guidelines call for the routine use of diuretics in these acutely decompensated patients. But diuretics can be associated with worsening renal function, especially in patients with underlying chronic kidney disease. And worsening renal function is itself associated with a worse prognosis.

Adenosine stimulates sodium reabsorption in the proximal tubule. In the setting of increased sodium load presented to the distal tubule during diuresis, adenosine also mediates reduced renal blood flow and renal function. Rolofylline has the opposite effects.

In the pilot dose-finding study, 301 patients were randomized to intravenous rolofylline at 10, 20, or 30 mg or to placebo infused daily with loop diuretics over a 4-hour period on the first 3 days of hospitalization.

The primary study end point was therapeutic success defined as patient-reported moderate or marked improvement in dyspnea on day 2 or 3. The dose-related success rate ranged from 37% with placebo to 53% with rolofylline at 30 mg/day. The failure rate (defined as worsening heart failure symptoms or renal function) ranged from 38% on placebo to 16% with high-dose rolofylline.

The 60-day combined end point of death or rehospitalization for renal or cardiovascular causes was 33% with placebo, 32% with rolofylline at 10 mg, 24% at 20 mg, and 19% at 30 mg.

Rolofylline's seizure potential was a potential concern because the adenosine A_1 receptor downregulates electrical activity in the CNS. Patients at high seizure risk because of past history were excluded from the trial, and those deemed at intermediate risk received daily prophylactic lorazepam. No seizures occurred in the study. Indeed, rolofylline's side effect profile was essentially the same as placebo, according to Dr. Massie.

The phase III trial, called PROTECT, is ongoing. To date, roughly 900 of a planned 2,000 patients have been enrolled. Only the 30-mg dose of rolofylline is being used, and trial end points are the same as in the pilot study.

Rolofylline is being developed by Merck & Co. following its purchase of NovaCardia Inc., the drug's original developer. Dr. Massie is a consultant to the company. ■

Heart Failure Patients Greatly Overestimate Life Expectancy

BY MARY ANN MOON
Contributing Writer

Ambulatory patients with heart failure tend to substantially overestimate their life expectancy, especially those who are younger or who have severe disease, according to the findings of a survey.

Their misperception could "fundamentally influence medical decision making regarding medications, devices, transplantation, and end-of-life care," said Dr. Larry A. Allen of Duke Clinical Research Institute, Durham, N.C., and his associates.

Patients with advanced disease might opt for comfort measures over enhanced survival.

DR. YANCY

The researchers surveyed 122 patients with a broad spectrum of heart failure severity to determine their understanding of their prognoses. "Despite advances in care, the prognosis for patients with symptomatic HF remains poor, with a median life expectancy of less than 5 years," they noted.

Most of the study subjects had long-standing chronic heart failure and comorbid conditions such as hypertension and diabetes. The sample was racially diverse and included a large number of elderly people.

The patient predictions were compared with those obtained using the Seattle Heart Failure Model, a prognostic tool that calculates life expectancy based on clinical characteristics, medications, device use, and results of diagnostic testing.

A total of 9% of the subjects believed their heart failure would be cured, and another 51% believed they would always have heart failure but nevertheless would have a normal life expectancy. Only 36% indicated that heart failure would likely shorten their lives.

A total of 63% of patients markedly overestimated their life expectancy, thinking they'd survive a median of 40% longer than predicted by the clinical prognostic tool, Dr. Allen and his associates said (JAMA 2008;299:2533-42).

Patients also predicted they would live a median of another 13 years. In contrast, the clinical model predicted a median survival of 10 years. The model came close to predicting actual survival rates at 1 and 3 years of follow-up. Mortality at 3 years was 29%.

The younger the patient, the longer they estimated their life expectancies to be. However, the model predicted similar life expectancies across all age groups.

Similarly, patients who had advanced symptoms gave themselves the same prognosis, as did patients with minimal symptoms, predicting great longevity despite the objective severity of their disease.

There was no difference in the accuracy of patient predictions between the 45 patients who reported they had discussed a prognosis with their clinicians and the 76 patients who said they had not.

The study could not address the reasons for the disconnect, but it seems likely that inadequate communication between providers and patients plays a role. Also, "individuals' predictions of longer life expectancy for themselves may simply reflect hope," they added.

Whatever the reason, patient perception of prognosis warrants further attention, because it "may refine decision making around resuscitation preferences, adherence to medical therapy, and consideration of advanced HF therapies such as implantable cardioverter-defibrillators, cardiac transplantation, or mechanical cardiac support," Dr. Allen and his associates noted.

In an editorial accompanying the report, Dr. Clyde W. Yancy agreed. "Another reason precise awareness of survival may be important is embedded in the 'time trade-off' construct," noted Dr. Yancy of the heart and vascular institute at Baylor University Medical Center, Dallas. "Knowing that survival is limited, patients with advanced disease might opt for comfort measures or an enhanced quality of life, even at the expense of shortened survival" (JAMA 2008;299:2566-7). ■

Atenolol Edged Out Carvedilol for Systolic Heart Failure

BY MITCHEL L. ZOLER
Philadelphia Bureau

CHICAGO — Atenolol may be about as effective as carvedilol for improving survival and reducing hospitalizations in patients with systolic heart failure, based on a retrospective review of more than 1,000 patients who did not undergo randomization.

The finding suggests that atenolol should be tested in a prospective, randomized study to definitively test whether it works as well as carvedilol in patients with heart failure, Dr. John R. Kapoor and his associate said in a poster presented at the annual meeting of the American College of Cardiology.

Currently, the only β-blockers approved by the Food and Drug Administration for use in patients with heart failure are carvedilol and metoprolol succinate, an extended-release formulation of metoprolol, said Dr. Kapoor, a cardiologist at Stanford (Calif.) University. Another β-blocker, bisoprolol, has also proved to help patients with heart failure, but in the United States bisoprolol is approved only to treat hypertension. Atenolol, another β-blocker that is often prescribed in the United States for treating heart failure, is not approved by the FDA for treating the indication, noted Dr. Kapoor.

The Stanford researchers reviewed 1,385 consecutive patients who had their left ventricular ejection fraction measured by echocardiography at the VA Palo Alto Health Care System during 1998 and 2004 and were found to have an ejection fraction of 40% or less. The study then focused on the 1,162 patients from this group who were treated with either carvedilol, atenolol, or metoprolol tartrate (an immediate-release formulation of metoprolol). The primary outcome of the analysis was death within the following 6 months; secondary end points were heart-failure hospitalization, and death plus hospitalization during 6 months of follow-up. The average age of the patients was 68, and nearly all were men.

The mortality rate was lowest, 1.3%, among the 251 patients (22%) treated with atenolol. Among the 611 patients (53%) treated with carvedilol, 2.5% died; and among the 300 (26%) treated with metoprolol, 6% died.

After adjustment by a propensity score analysis, patients treated with atenolol had a slightly reduced risk of death compared with patients treated with carvedilol, but the difference between the two drugs was not statistically significant. After propensity score adjustment, patients treated with metoprolol tartrate were about twice as likely to die as were patients treated with atenolol.

Adjusted analyses were not reported for the secondary end points. But the unadjusted findings showed that the patients treated with atenolol consistently fared better than did those treated with either carvedilol or metoprolol tartrate for both heart failure hospitalizations and for hospitalizations plus deaths. Atenolol treatment was linked with superior outcomes at 90 days, 1 year, and 2 years after the start of treatment, Dr. Kapoor reported in his poster. ■