Support Device Restored Left Ventricular Shape

Patients with the device had greater quality-of-life improvements and fewer transplants than controls.

BY BRUCE JANCIN
Denver Bureau

NEW ORLEANS — Passive ventricular restraint achieved via a surgically implanted mesh bag fitted around the heart constitutes a novel and effective therapy for systolic heart failure, Douglas L. Mann, M.D., said at the annual scientific sessions of the American Heart Association.

Results of a 300-patient multicenter, randomized trial of Acorn Cardiovascular's investigational CorCap cardiac support device (CSD) showed that it improves left ventricular size and shape and enhances patient quality of life, said Dr. Mann, professor of medicine at Baylor University, Houston.

On the basis of the favorable results of this pivotal trial, in which Dr. Mann served as principal investigator, Acorn plans to petition the Food and Drug Administration for marketing approval in the first quarter of this year.

"This is a breakthrough technology," he said.

He explained that the device provides gentle diastolic support for the heart, encouraging it to return from a dysfunctional spherical shape to a more mechanically efficient and electrically stable elliptical one. It is the first treatment specifically targeting the progressive ventricular enlargement that traditionally has been viewed as a symptom of worsening heart failure (HF) and that only recently has emerged as a therapeutic target in its own right. The degree of improvement in ventricular size and shape with use of the CSD dwarfs that seen in earlier trials of ACE inhibitors, β-blockers, and biventricular pacing, Dr. Mann added.

All participants in the Acorn study were on optimal drug therapy for HF; 81% were New York Heart Association class III. The 193 patients in whom mitral valve repair or replacement was indicated were randomized to undergo surgery with or without CSD placement. The remaining 107 patients were randomized to continued medical therapy alone or to undergo a thoracotomy for placement of the Acorn device, a proprietary synthetic mesh weave.

The primary study end point was a clinical composite of death, change in NYHA class, or need for a major cardiac procedure indicative of disease progression, such as transplantation or implantation of a left ventricular assist device. By these criteria, 37% of CSD-treated patients were blindly rated as worsened after a median 23-month follow-up, significantly less than the 45% rate among controls. Similarly, 38% of CSD-treated patients were judged improved, compared with 27% of controls.

CSD-treated patients showed dramatic improvements in left ventricular structure by three separate indices: reduced end-diastolic volume, reduced end-systolic volume, and a reduced sphericity index indicative of a return to an elliptical ventricle shape. The progressive improvement on these indices over the course of time suggested the mesh sack was encouraging functional unloading of the ventricle and reversing the natural history of the disease, Dr. Mann said.

Patients who received the Acorn device also demonstrated significant quality-of-life improvements on two measures: Minnesota Living With Heart Failure Questionnaire score and the physical functioning domain of the Short Form-36. Moreover, the device group required 19 transplants and other major cardiac procedures, compared with 33 in the control arm.

The benefits of the CSD have been sustained in patients who received theirs up to 4 years ago in the earliest nonrandomized safety studies. No evidence of pericardial constriction has been seen in a total of 540 patient-years of experience.

The CorCap cardiac support device specifically targets the progressive ventricular enlargement as a symptom of worsening heart failure, said Dr. Douglas L. Mann.

Dr. Mann estimated 40%-50% of the nation's 2.5 million patients with systolic HF would be candidates for the Acorn device. Many are also candidates for cardiac resynchronization therapy via biventricular pacing, which entails a far less invasive implantation procedure. But 20%-30% of HF patients who receive biventricular pacing are unresponsive to it, and among patients who do experience marked symptomatic improvement, the benefits often begin to fade after about a year.

Somewhat more measured enthusiasm for the device and its potential role was offered by discussant Bruce R. Rosengard, M.D., the British Heart Society Professor of Cardiac Surgery at University of Cambridge.

Although the CorCap is clearly safe and it does reduce ventricular size, the overall clinical improvement seen in the trial was "modest," he said, noting the device did not improve mortality, NYHA class, or the number or duration of hospitalizations.

"Looking forward, if the procedure is to be carried out as stand-alone therapy, it would be optimal if less invasive surgical approaches could be developed," he added.

"Where does it fit into current management of heart failure? If the study results are durable, and with additional follow-up, passive ventricular restraint would appear to have a useful role in patients with worsening heart failure despite maximal medical therapy and biventricular pacing," Dr. Rosengard continued.

Particularly telling will be the subgroup analysis involving the two-thirds of study participants who underwent mitral valve surgery, which will be completed soon, he said.

Many heart surgeons believe mitral valve surgery in itself induces reverse ventricular remodeling in HF patients, although this is as yet unproven. If the subanalysis shows the CSD augments the benefits obtained with mitral surgery alone, it will become extremely popular with surgeons.

"From a surgeon's point of view, a safe therapy—which this device clearly is—represents an ideal for an adjunctive procedure at the time you're already in the chest," Dr. Rosengard explained. ■

Gout Treatment Aids Cardiac Efficiency in Heart Failure

BY PATRICE WENDLING
Chicago Bureau

TORONTO — Interim data suggest that oxypurinol, a xanthine oxidase inhibitor, significantly increased left ventricular ejection fractions in patients with heart failure after just 4 weeks, Joshua Hare, M.D., reported at the annual meeting of the Heart Failure Society of America.

These are early and provocative data, but they are early human data with the chronic use of oxypurinol, "and I think it's very exciting," Dr. Hare said.

Dr. Hare, director of the heart failure/cardiac transplant program at Johns Hopkins University in Baltimore, is a consultant for and has a financial interest in Cardiome Pharma Corp., which is developing the drug.

Xanthine oxidase is upregulated in heart failure, and is clearly a source of oxidative stress, Dr. Hare said. Targeting xanthine oxidase represents a potential new treatment strategy for patients with heart failure.

Oxypurinol is the active metabolite of allopurinol, a drug that has been used since the early 1960s to suppress uric acid formation in patients with gout. Initial clinical results in nine patients with heart failure showed that allopurinol improved cardiac mechanical efficiency by 40% and cardiac pressure efficiency by 22%.

Left ventricular ejection fractions significantly increased from 35% to 38% in those on oxypurinol and decreased from 30% to 29% in those on placebo.

Oxypurinol may improve myocardial contractility by increasing sensitization of the cardiac myofilaments to calcium. Moreover, it may do so without increasing myocardial oxygen consumption. Most inotropic drugs improve myocardial contractility, but they also increase myocardial oxygen consumption, which worsens the myocardial ischemia and possibly leads to arrhythmias.

"We've traditionally thought of oxidative stress as something that destroys cell membranes and proteins, but as we are clearly uncovering now, there is a critical role for free radicals in nitric oxide and signaling," Dr. Hare said. "And it may be this signaling element that is the target of our therapy."

In a trial conducted in Argentina, 48 patients with heart failure were enrolled in a phase II, proof-of-principle study, and randomized to placebo or 600 mg of oxypurinol daily added to best conventional therapy for 4 weeks.

Interim data from the trial, led by Horatio Cingolani, M.D., of the National University of La Plata (Argentina), showed that left ventricular ejection fractions significantly increased from 35% to 38% in the oxypurinol group and decreased from 30% to 29% from baseline in the placebo group. There was no statistical difference in 6-minute walk scores from baseline between the two groups.

Two ongoing studies should be completed this year, including a phase II trial of oxypurinol infusions in patients with heart failure of ischemic etiology and a 24-week, phase II/III trial of oral oxypurinol in 400 patients with heart failure. ■