Fetal Stem Cells Reported to Boost Failing Hearts

A small pilot study in Ecuador finds benefits in patients with nonischemic dilated cardiomyopathy.

BY MITCHEL L. ZOLER
Philadelphia Bureau

NEW YORK — Intracardiac injections of human fetal stem cells led to rapid improvements in heart function in a pilot study of 10 patients with nonischemic cardiomyopathy.

The promising results mean that the research should progress to larger, controlled studies, Valavanur A. Subramanian, M.D., said at the annual meeting of the International Society for Minimally Invasive Cardiothoracic Surgery.

The study, which was done at the Hospital Luis Vernaza in Guayaquil, Ecuador, used stem cells harvested from fetuses that had been either spontaneously or electively aborted at 5-12 weeks' gestation. Prior to 12 weeks, fetal cells contain no histocompatability antigens, so tissue matching wasn't necessary.

All 10 patients in the study had primary dilated cardiomyopathy that was not caused by ischemia or Chagas' disease. Five of the patients had New York Heart Association class III heart failure, and the other five had class IV disease. The average left ventricular ejection fraction of the entire group was 27.6%.

Each patient received 60-80 million stem cells that were suspended in 80 mL of saline solution and delivered in a series of 80 injections through the heart's surface. The injections were done using a 25-gauge butterfly needle and were placed 3 mm into the heart, said Federico Benetti, M.D., a cardiothoracic surgeon at the Benetti Foundation in Rosario, Argentina, who led the clinical team that did this work. Each injection delivered 1 mL, and the injections were spaced 1 cm apart. In nine cases, a sternotomy with general anesthesia was performed to expose the patient's heart. The 10th patient received the cell injections via a minithoracotomy.

The treatment did not result in any intraoperative or postoperative deaths by 90 days of follow-up, said Dr. Subramanian, chairman of the department of cardiothoracic surgery at Lenox Hill Hospital in New York. (Dr. Subramanian was not directly involved in the clinical work, but he helped analyze the results and he presented the findings at the meeting with Dr. Benetti.)

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Two patients developed a temporary bradycardia following treatment, one patient had episodes of ventricular fibrillation, and one patient had an ischemic stroke 3 days after receiving the injections.

At 90 days after treatment, the eight patients who could be evaluated had New York Heart Association class II disease on average, compared with class III/IV at baseline. In these patients, the average left ventricular ejection fraction rose from 27.5% at baseline to 37.5% after 90 days. The average distance walked during a 6-minute walking test increased from 275 m at baseline to 553 m after 90 days.

Echocardiographic examination of treated patients showed a thickening of the myocardium, with increased muscle mass that began to be apparent by a week after treatment. This pattern of response differed from that described in previous reports of patients with ischemic cardiomyopathy treated with intracardiac injections of autologous stem cells, in whom angiogenesis seemed to be the main mechanism of action. In the current study, patients seemed to respond more quickly and by a different process than angiogenesis, Dr. Subramanian said. ■

Cochrane Review Finds Role For Digoxin in Heart Failure

BY BRUCE JANCIN
Denver Bureau

VANCOUVER, B.C. — The latest Cochrane systematic review of digoxin for treatment of heart failure patients in sinus rhythm paints a picture of a more than 200-year-old drug that's still clinically useful, although it has no effect on mortality, William B. Hood Jr., M.D., said at a meeting sponsored by the International Academy of Cardiology.

"It's probably not first-line therapy. It's not very powerful. But it's available for patients who are not fully responsive to other agents that have become first-line treatments, such as the ACE inhibitors, β-blockers, spironolactone, and the angiotensin receptor blockers," added Dr. Hood, lead author of the recent Cochrane review and a cardiologist at the University of Washington, Seattle.

The metaanalysis was restricted to randomized, double-blind, placebo-controlled trials involving adults followed for at least 7 weeks. A total of 13 trials involving nearly 7,900 patients qualified, including the largest of all digoxin studies: the 6,800-patient, 3-year Digitalis Investigation Group (DIG) trial (N. Engl. J. Med. 1997;336:525-33).

Why even bother doing a metaanalysis when one trial is so dominant in size? Dr. Hood explained that the smaller trials are helpful in that each consistently reached the same conclusion as DIG regarding the effect of digoxin on mortality—namely, there is none—thereby reinforcing the finding. The drug didn't lessen mortality, nor did it significantly worsen it. Indeed, the odds ratio for mortality was 0.98 in heart failure patients randomized to digoxin, compared with placebo. In the DIG trial, however, there was a nonsignificant trend for fewer deaths from heart failure in digoxin-treated patients and a hint that the inotrope may have caused more arrhythmia deaths, although this wasn't a prespecified study end point.

Digoxin's effect on deterioration in clinical status was more clearcut in the metaanalysis. The odds ratio for that end point was 0.31, meaning patients randomized to digoxin were 69% less likely to show clinical deterioration than were control patients. The third end point used in the metaanalysis was hospitalization for worsening heart failure. Patients on digoxin were 32% less likely to experience it.

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Two studies included in the metaanalysis were designed to learn whether concomitant ACE inhibitor therapy mattered in patients randomized to digoxin or placebo. Both showed that patients on an ACE inhibitor plus digoxin did better than those on an ACE inhibitor plus placebo.

However, the effects of digoxin in patients on other agents that have become first-line therapies in heart failure more recently than the ACE inhibitors, including β-blockers and aldosterone antagonists, haven't been systematically studied. For ethical reasons, such trials are highly unlikely to ever be done, Dr. Hood said. ■

Cardiac MRI Beats Echocardiography In Diagnostic Subtleties of Heart Failure

BY ROBERT FINN
San Francisco Bureau

SAN FRANCISCO — Cardiac MRI with late gadolinium enhancement is the imaging technique of choice when the goal is tissue characterization and infarct detection in heart failure, Christopher M. Kramer, M.D., said at a cardiovascular imaging conference sponsored by the American College of Cardiology.

While echocardiography—especially 3-D echocardiography—does have its advantages, cardiac magnetic resonance (CMR) provides outstanding image quality, excellent quantification, and tissue characterization, said Dr. Kramer of the University of Virginia, in Charlottesville.

Gadolinium contrast, which is easy to use and safe with CMR, also offers the ability to assess intramural function.

On the other hand, CMR devices are not portable, are quite expensive, and are not readily available. Physicians need extensive training in the use of CMR and the technique is suitable for patients with implanted metallic devices such as pacemakers and implantable cardioverter defibrillators. Furthermore, assessment of diastolic function is not routine with CMR.

Echocardiography does have a number of advantages. The devices are portable, relatively inexpensive, and readily available. Generations of cardiologists have established its validity, and all cardiologists become proficient in the use of echo during their training. Contrast can be added to echocardiography, and the assessment of diastolic function has become routine.

But echocardiography is subject to variable image quality and poor windows. Results tend to be qualitative, and quantitation can be difficult. Newer 3-D echocardiographic techniques address some of these issues, but these devices are not widely available.

Gadolinium-enhanced CMR has proved to be especially useful in determining whether cardiomyopathy is ischemic or nonischemic. In one study of 90 patients (63 with dilated cardiomyopathy and 27 with coronary artery disease) and 15 controls, none of the controls showed any hyperenhancement. All the patients with coronary artery disease showed hyperenhancement. And among the patients with dilated cardiomyopathy, 59% had no hyperenhancement, 13% had hyperenhancement consistent with coronary artery disease, and 28% had midwall hyperenhancement (Circulation 2003;108:54-9).

Enhanced CMR is also useful as a marker of late-stage myocarditis. In a study of 32 patients with myocarditis, investigators noted enhancement in 28 (88%) of them, with the lateral free wall the most common site.

Twenty-one of the patients had biopsy in the area of enhancement, and active myocarditis was detected in 19. Of the other 11 patients, only 1 had active disease (Circulation 2004;109:1250-8).

Other studies have shown the value of enhanced CMR in hypertrophic cardiomyopathy, amyloidosis, sarcoidosis, and Chagas disease.

Dr. Kramer concluded that echocardiography is fine in several circumstances, especially for diastolic function and when "quick and easy" is adequate. CMR, on the other hand, is best for regional systolic function, for differential diagnosis and tissue characterization, and whenever quantitation is needed and 3-D echo is unavailable. ■