Bone Marrow Cells Boost Left Ventricular Function Post MI

BY MITCHEL L. ZOLER
Philadelphia Bureau

DALLAS — Infusion of bone marrow progenitor cells into a coronary artery after a myocardial infarction led to significantly improved left ventricular function in a controlled study with almost 200 patients.

"This is the first large, proof-of-concept trial to clearly show the benefit of progenitor cells in post–myocardial infarction patients," Dr. Volker Schächinger said at the annual scientific sessions of the American Heart Association.

"Large-scale clinical–end point trials are now needed to assess the effect of intracoronary infusion of bone marrow cells on morbidity and mortality in patients," said Dr. Schächinger, professor of medicine at J.W. Goethe University in Frankfurt.

"The data give compelling evidence of the treatment's benefit," but the new findings conflict with a prior report from Belgian researchers that failed to show increased ventricular function following similar treatment, commented Dr. Philippe Menasche, a cardiovascular surgeon at the Georges Pompidou European Hospital in Paris. Because of these conflicting findings, "additional, large-scale trials are warranted to clarify the efficacy issue," he said.

The study enrolled 204 patients who had an ST-segment elevation MI and were successfully reperfused with either a percutaneous coronary intervention or a thrombolytic drug. The study was done at 16 medical centers in Germany and one in Switzerland. At 3-6 days following the MI, 50 mL of bone marrow was aspirated from each patient and filtered through a ficoll gradient to enrich for progenitor cells, which takes about 90 minutes.

Patients then received an infusion into their infarct-related artery of either the progenitor cells in growth medium, or the medium with no cells, as a control. An average of 236 million cells were infused into each patient who received bone-marrow cells. The cells were introduced with a stop-flow catheter that briefly halted blood flow within the treated artery. Left ventricular ejection fraction (LVEF) was measured at the time of treatment and 4 months later, using left-ventricular angiography.

During follow-up, LVEF increased by an average of 3% over baseline in 92 evaluable control patients and by an average of 5.5% in 95 evaluable patients who received bone marrow cells, a statistically significant effect for the study's primary end point, Dr. Schächinger said.

Two additional analyses were done to identify conditions that were linked to the best outcomes. One divided the patients into the 93 evaluable patients who had an LVEF of less than 49% at baseline and the 94 evaluable patients with LVEF of 49% or greater at baseline.

Among the patients with LVEF of less than 49%, treatment with bone marrow cells led to an average 7.5% boost in LVEF, compared with an average 2.5% improvement in control patients, a statistically significant difference. In patients who had LVEF of 49% or greater at baseline cell treatment led to no significant improvement, compared with the controls.

The other exploratory analysis divided patients based on when they were treated following their MI. Patients who received cell treatment 5 or more days after their infarction had an average 7.0% increase in LVEF, compared with an average 1.9% increase among control patients, a significant difference. Patients treated less than 5 days after their infarction did not have a significant improvement, compared with the controls.

The researchers aren't sure why patients responded better if treatment was delayed a few days. "Early after a myocardial infarction, the myocardium is a hostile environment, with inflammation and oxidative stress. That may be why it's better to delay treatment," Dr. Schächinger said. "We can't draw conclusions now regarding the mechanism of what's happening. But regardless of the mechanism, we clearly showed a benefit that's better than placebo."

"The data are spectacular. They not only showed a positive result, but they identified the patients who got the most benefit," said Dr. Andreas M. Zeiher, professor and chief of cardiology at Goethe University and senior investigator for the study. The Frankfurt researchers are now planning to do a study with about 1,200 patients that will focus on treating patients with an LVEF of less than 50%, and with marrow cell treatment delayed until at least 6 days following an MI, Dr. Zeiher said in an interview. ∎

L-Arginine Given After MI May Elevate Mortality

BY MARTHA KERR
Contributing Writer

The addition of L-arginine to standard post-MI therapy does not decrease vascular stiffness or improve ejection fraction and may be related to an increase in postinfarction mortality, according to the results of the Vascular Interaction With Age in Myocardial Infarction trial.

Dr. Steven P. Schulman and colleagues randomized 153 patients following a first ST-segment elevation MI to receive L-arginine (with a goal dose of 3 g, three times daily) or placebo. Of the patients, 77 were aged 60 years or older. All the patients were followed up at 1, 3, and 6 months.

The amino acid L-arginine is a substrate for nitric oxide synthase. The results of previous studies suggest that it is associated with a reduction in vascular stiffness. As such, the investigators' objective was to establish whether the addition of the amino acid to standard treatment in post-MI patients, and especially older patients, would reduce vascular stiffness and improve left ventricular function (JAMA 2006;259:58-64).

In patients aged 60 years and older, ejection fraction and vascular stiffness did not change during the 6 months of follow-up in either group. However, six (9%) patients who had been randomized to L-arginine died, compared with none of those who received placebo. As a result, the data and safety monitoring board closed enrollment, the authors reported.

The participants had normal L-arginine levels at baseline, and Dr. Schulman, an associate professor of medicine and director of the Coronary Care Unit at Johns Hopkins University in Baltimore, and his associates speculated that the L-arginine level could explain the lack of efficacy.

"The lack of any dose response in plasma L-arginine levels from 0 to 9 g suggests that higher doses of L-arginine would not have resulted in any biological effect in this population," the authors wrote, adding that many of the patients were already taking medications such as ACE to improve vascular function.

The authors attributed the absence of change in ejection fraction and of remodeling possibly to the large proportion of patients who had received "early percutaneous coronary intervention with establishments of coronary patency."

One possible explanation for L-arginine's harmful effects is that instead of generating nitric oxide, it may actually produce reactive oxygen species that create pressure overload. L-arginine also increases homocysteine production.

The authors concluded that "L-arginine therapy should not be given to patients following a myocardial infarction. It neither alters noninvasive measures of vascular stiffness nor improves left ventricular function. L-arginine therapy in older patients with diffuse atherosclerosis may worsen clinical outcomes." ∎

Brief Questionnaire Detects Anxiety After Myocardial Infarction

BY MITCHEL L. ZOLER
Philadelphia Bureau

DALLAS — A quick, six-question survey can diagnose anxiety in patients who've had a myocardial infarction and identify those who need treatment with an anxiolytic.

"The Brief Symptom Inventory [BSI] is performed similarly to the State Anxiety Instrument [SAI]. The brief symptom inventory is a valid instrument for quickly diagnosing anxiety and identifying patients who need anxiolytic therapy," Mohannad Abu Ruz said at the annual scientific sessions of the American Heart Association.

"It's important to treat anxiety during the first 72 hours following a myocardial infarction, but few patients get their anxiety level measured following an infarction," said Mr. Abu Ruz, a nursing-PhD candidate at the University of Kentucky in Lexington. "There is a belief that the diagnostic instruments are time consuming and burdensome to patients, and many physicians rely on physiologic indicators of anxiety such as blood pressure and heart rate."

The study involved 536 patients admitted for an acute MI at any of five participating hospitals in the United States and Australia. MIs were confirmed by ECG and cardiac enzymes. Within 72 hours of admission, all patients were assessed for their anxiety level using the SAI, the standard diagnostic tool for anxiety, and by the BSI, which can be administered in 2-5 minutes.

Questions on the BSI all use simple language and are structured to ask about the patient's mental state at the time of the interview—for example, "Are you nervous at this time?"

Answers are measured on a 0-4 scale, with 0 meaning no anxiety and 4 meaning a high level of anxiety. The ideal is an answer of 0 for all six questions. For this study, a patient who scored 2 or more points on the BSI was considered anxious enough to need treatment.

A total of 261 were diagnosed as anxious using the SAI, and 262 were diagnosed as anxious by the BSI, producing a correlation coefficient of 0.7—a good level of correlation between the two measures, Mr. Abu Ruz said.

Further confirmation of the validity of BSI was based on the mean number of in-hospital complications experienced by the patients diagnosed as anxious or not anxious. Using diagnoses based on the SAI, patients who were anxious had an average of 1.3 complications during hospitalization, compared with 0.8 complications per patient among those who were not anxious. Identical complication rates were seen when patients were categorized by the BSI, Mr. Abu Ruz reported.

In a logistic regression analysis, a diagnosis of anxiety using the BSI was a predictor of subsequent complications independent of other clinical and demographic factors including age, gender, smoking history, comorbidities, left ventricular ejection fraction, and Killip classification.

Patients diagnosed with anxiety immediately after a myocardial infarction should be treated with an anxiolytic drug for the next 3 days, or until they are discharged from the ICU or coronary care unit, Mr. Abu Ruz said. A typical regimen at his institution is 2.5-5 mg of diazepam q.i.d. ∎