ative to metoprolol. Mortality was reduced from 39.5% with metoprolol to 33.9% with carvedilol (OR, 0.87; 95% CI, 0.74-0.93; P <.0017). The annual mortality rate was reduced from 10% in the metoprolol group to 8.3% in the carvedilol group. The survival advantage with carvedilol translated to a prolongation of median survival by an extra 1.4 years. The co-primary, composite endpoint of all-cause mortality or all-cause hospitalization was not statistically different between the 2 medications. Similar reductions were observed in the risk for sudden death and progressive heart failure deaths with carvedilol. There was no significant heterogeneity in response between clinically relevant subgroups of patients, including men and women, those with and without coronary artery disease, and diabetics and nondiabetics.

The favorable outcome with carvedilol could be attributed to blockade of both ß-1 and ß-2 adrenergic receptors, inhibition of α-1 adrenergic receptors, a greater antiischemic effect, inhibition of apoptosis, or an antioxidant action. This trial convincingly demonstrates that carvedilol produces benefits in patients with heart failure beyond those of ß-1 blockade alone. The calculated number of patient-years of treatment to save one life is 59. While it has been suggested that the use of the metoprolol CR/XL preparation at higher doses may have produced different results, this possibility remains speculative and would need to be demonstrated in a prospective, randomized mortality trial. COMET has clearly demonstrated the superiority of carvedilol for the treatment of chronic heart failure. Every effort should be made to translate this significant research finding into routine clinical practice and ensure that patients with systolic-dysfunction heart failure are treated with carvedilol, in the absence of contraindications or intolerance. ■

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Cardiomyopathy

Feasibility and Safety of Skeletal Myoblast Transplantation

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Autologous Skeletal Myoblast Transplantation for Severe Postinfarction Left Ventricular Dysfunction

Menashe P, Hagege A, Viliquin JT, et al.

J Am Coll Cardiol. 2003;41:1078–83.

Menashe and coworkers report the clinical outcome of a phase I study to assess the feasibility and safety of autologous skeletal myoblast transplantation in patients with severe ischemic cardiomyopathy.

Ten patients with left ventricular (LV) systolic dysfunction with an ejection fraction of less than 35% were recruited for the study. The patients all had LV scar documented by the use of low-dose dobutamine and positron emission tomography and were undergoing coronary artery bypass surgery to the non-scar areas.

Ten to 15 g of vastus lateralis muscle was removed and digested using collagenase and trypsin. After a mean period of 16 days of expansion, 871×10^6 cells in 5.7 mL of saline were injected over 37 sites throughout the scar area. Two bypass grafts were done in all but 1 patient. One patient died before cardiopulmonary bypass was initiated. The rest of the patients were followed for an average of 10.9 months (range, 5 to 17.5 months).

The major adverse event was the development of ventricular tachycardia in 4 patients 11 to 22 days after transplantation. All 4 received an automatic implantable cardioverter-defibrillator (AICD). However, the recurrence of AICD-triggered shock was rare after implantation.

LV function improvement can be distinguished in those segments injected with cells and those segments that were bypassed. Fourteen of 22 (63%) transplanted segments improved (6 of 8 patients). Twenty-six noninjected but bypassed segments also improved. The overall ejection fraction improved from 23.8% to 32.1%, and the NYHA class improved from 2.7 to 1.6. One patient died subse-

quently of a stroke, and autopsy found clusters of myotubes embedded in the scar tissue. There was no cardiomyogenic differentiation as reflected by the lack of gap junction formation.

Comment

This is the first study and follow-up by the Menashe group. This study addresses the feasibility of such an approach in patients with severe LV dysfunction. However, it is unknown at this time whether the transplanted cells contribute to the overall contractility of the ventricle or whether it is due to the overall improved contraction of the adjacent segments. Substantial work remains to evaluate the time course of survival of these transplanted cells and to determine whether they actually contribute to contraction. More sophisticated molecular imaging will be needed to test these hypotheses in the future. Of particular concern is the incidence of ventricular tachycardia post-transplantation. Whether this condition indicates the development of ventricular foci at the site of implantation, resulting in re-entry pathways, is still to be determined. ■

Statins

Statin Therapy and Timing

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Several decades of observational studies have revealed that cholesterol levels are directly related to the prevalence of coronary artery disease.[1,2] More recent large-scale randomized trials have taught us that lowering cholesterol with statin therapy reduces subsequent cardiac events for patients with chronic coronary artery disease.[3] However, several questions concerning the timing of therapy with statins in other clinical settings remain. Two recent reports attempt to address these issues.

Early Statin Initiation and Outcomes in Patients with Acute Coronary Syndromes

Newby LK, Kristinsson A, Bhapkar MV, et al.
JAMA. 2002;287:3087–3095.

To assess the value of initiating statin therapy early in patients with acute coronary ischemia, an observational study was conducted in 15,900 patients in two Sibrafiban vs Aspirin to Yield Maximum Protection from Ischemic Heart Events Post-acute Coronary Syndromes (SYMPHONY) trials. The trials were designed to determine the efficacy of using an oral glycoprotein IIb/IIIa platelet receptor inhibitor in patients with acute coronary syndromes.

The 12,365 patients who did not take a statin before the index coronary event were divided into those who started a statin early after the acute event (median, 2 days; n = 3952) and those who never received statin therapy and survived more than 5 days after the acute event (n = 8413).

The authors concluded that there was no relationship between early initiation of statin therapy and improved outcomes for patients with acute coronary syndromes.

The primary composite endpoint for the trial was death, recurrent myocardial infarction, or severe recurrent ischemia at 90 days.

The average age was 58 years, and 75% of the patients were men. Revascularization was performed in 32.8% of the patients who received early statin therapy and in 19.4% of patients who did not get the statin. Patients who received early statin therapy were more likely to be younger, to have a history of elevated cholesterol or infarction as the index event, to be receiving ß-blockers, heparin, or glycoprotein IIb/IIIa platelet receptor inhibitors, and to be living in North America. Early statin therapy was less likely to be initiated in patients with an S3 gallop sound, atrial fibrillation, hypertension, previous stroke, prior angiography or coronary revascularization, and in patients receiving aspirin and nitrates.

The 90-day and 1-year unadjusted mortality was 1.2% for patients who received early statins versus 2.1% for patients who received no statins. However, there was no difference in the composite endpoint between the groups after adjustment for statin propensity and covariates. Interestingly, there were significantly fewer strokes at 90 days in the early-statin group. Among the 2711 patients with available lipids, early statin therapy was associated with a higher adjusted risk for death or myocardial infarction at cholesterol levels below treatment guidelines, but was more favorable at higher levels. The authors concluded that there was no relationship between early initiation of statin therapy and improved outcomes for patients with acute coronary syndromes. The authors' subset analysis suggests, however, that early statin therapy may be of benefit for patients with elevated cholesterol levels.