Bone Marrow-Derived Cell Transplantation for Acute Myocardial Ischemia

To the Editor:

We read with interest the report on transcatheter intracoronary transplantation of autologous mononuclear bone marrow-derived cell transplantation by Strauer et al., which is a timely addition to the literature of cell transplantation for myocardial repair. From our own experience of bone marrow transplantation into the myocardium of patients undergoing coronary artery bypass graft surgery (El Oakley et al., unpublished data, 2003), we agree with the probable safety and the potential benefits of this approach. However, we wish to highlight a few important issues that need to be addressed before this treatment has wider application.

First, revascularization by thrombolysis, angioplasty, or surgery is not widely accepted as a standard treatment for patients presenting 12 hours after uncomplicated acute myocardial infarction (AMI). The main role of cell transplantation after AMI, however, is to prevent ventricular remodeling, which is the inevitable outcome of AMI presenting more than 6 to 12 hours after onset of symptoms. The acute nature of coronary occlusion in an end artery system does not allow the native stem cells, if they exist in the heart, or the circulating stem cells to achieve satisfactory tissue regeneration. This is made worse by the absence of an open artery to the infarcted myocardium. With increasing evidence to support the "open artery hypothesis," the proposal of coronary revascularization coupled with cell transplantation may be the future standard therapy for these cases. Whether cell transplantation will also be beneficial to patients presenting within 6 to 12 hours after AMI and/or patients with long standing myocardial dysfunction remains to be seen.

Second, the use of total versus a subset(s) of bone marrow, the in-vitro propagation versus drug-mediated cell differentiation, and the ideal time for cell transplantation require further systematic experimental and clinical studies before this is accepted as a treatment for myocardial infarction.

Third, the potential risk of life-threatening ventricular arrhythmias, observed after clinical skeletal myoblasts transplantation into the heart (Menache et al., unpublished data, 2003), was not addressed in this study. It is important to know the outcome of Holter monitoring and the signal averaged ECG in both groups after 6 to 12 months follow-up.

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Response

The letter by Alsmehri and El Oakley that comments on our novel catheter-based stem cell therapy in acute myocardial infarction (AMI) contains some misconceptions.

One of the well-known aims in the treatment of AMI is the early (4 to 6 hours) recanalization of the infarct-related artery, preferably by angioplasty. Also, in the post-acute phase (6 to 12 hours), angioplasty may be beneficial in preventing ventricular remodeling. However, cell repair in our patients was not performed during these acute phases of AMI (4 to 6 or 6 to 12 hours), but 6 to 7 days thereafter, ie, in the postinfarction period.

Also, treatment of AMI by stem cells depends on the availability of cells in the area of interest, ie, the infarcted zone. This cannot be achieved by surgery, but may be best realized by the intracoronary transplantation route, because all cells that are antegradely injected in the infarcted artery must directly pass through the infarct and the peri-infarct tissue. This novel catheter-based procedure was first described by our group.

Further, except for hematopoietic and mesenchymal stem cells, many other bone marrow-derived cell types as well as primitive bone marrow cells may participate in organ repair with regard to neovascularization (bone marrow hemangioblasts) and to endothelial (mesodermal progenitor cells) and to cardiomyocyte (endothelial progenitor cells) cell transdifferentiation. In this regard, therapeutic use of mononuclear cell populations of bone marrow may be more useful and promising than single isolated cell fractions alone. The effect manifested by more heterogeneous bone marrow cell populations, which contain very small numbers of stem cells, may also suggest the importance of an entire array of bone marrow-derived growth factors and cytokines that may also regulate cellular growth and regeneration via cellular secretion mechanisms.

Nevertheless, experimental studies are needed to differentiate between the therapeutically most successful kind of bone marrow cells: global bone marrow containing all bone marrow cells or specifically selected subfractions, as isolated cell fractions containing preferably CD34+, CD34-/CD45-, or CD133+/H11001 cells.

After surgery for intramyocardial cell transplantation, severe cardiac arrhythmias have been observed that require intensive antiarrhythmic therapy or implantation of implantable cardioverter-defibrillators. In contrast, using our intracoronary transplantation technique in 24 patients with AMI with a maximum follow-up of 18 months, aggravation or induction of cardiac arrhythmias after cell therapy has been detected in none of the patients.

Thus, in contrast to surgical intervention, the use of mononuclear bone marrow cells by intracoronary cell transplantation represents a beneficial and safe procedure for myocardial healing after AMI.

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