EDITORIAL COMMENT

Long-Term Outcome of Stem Cell Therapy for Acute Myocardial Infarction

Right Results, Wrong Reasons*

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In this issue of the Journal, Yousef et al. (1) present the first 5-year follow-up of intracoronary autologous bone marrow mononuclear cell (BMC) infusion after acute myocardial infarction (AMI). An equal number of myocardial infarction (MI) patients who were offered the procedure but declined served as control subjects. An early significant improvement in ejection fraction (EF) and infarct size at 3 months and 1 year was followed at 5 years by greater exercise capacity and lower mortality (1 death vs. 7 deaths) in the treated patients.

Assessing the Current Status of Cardiac Stem Cell Therapy

The earliest clinical experience with intracoronary BMC infusion was nonrandomized, so this report is subject to the substantial limitations of matched control study design, which include potential selection bias and retrospective analysis. However, the 1-year follow-up result of this study is consistent with that of both randomized trials (2,3) and meta-analyses (4). Thus, these data allow us the reasonable conclusion that the procedure is safe and offers a small long-term improvement in cardiac function. The results also suggest an additional unanticipated speculation: a small long-term improvement in cardiac function is a sufficiently sensitive measure of therapeutic outcome, given the many physiologic compensatory mechanisms that stabilize resting function. In support of this idea, it is worth noting that the EF benefit of prompt reperfusion is small (on average) but the clinical benefits are large.

The clinical outcome data, however, should not be used to obscure a central issue in cell therapy of AMI: bone marrow cells do not reproducibly generate new myocardium (5), and the observed benefit is most reasonably attributed to paracrine effects. To achieve genuine cardiac regeneration, it seems we might have to return to first principles to understand the natural impediments to stem cell therapy (6). These barriers exist at the level of the pluripotent cell, its environmental regulators, and the tissue into which the cell is delivered (7).

Cells

Although venerable and convenient, BMC might not be the ideal cell for cardiac regeneration. A large number of alternative candidate cell types are being tested. Although no consensus has yet emerged, a desirable cell type would be autologous, capable of differentiating into all the adult cell types in the heart, and highly resistant to malignant transformation. Arguably the 2 most promising types are induced pluripotent stem cells (iPS) derived from the patient’s own tissue and the patient’s own cardiac stem cells.

Induced pluripotent cells are derived from skin fibroblasts by nuclear reprogramming, which involves insertion of specific transgenes into the fibroblast nucleus (8,9). The resultant pluripotent cells, which very closely resemble embryonic stem cells, can then be directed into the specific cell lines of different organs. “Guided cardiopoiesis” uses cocktails of proteins that regulate embryonic cardiovascular differentiation and diversification (10) to create cardiac cells in vitro, including beating cardiomyocytes (11). Although not yet reported in cardiovascular application, iPS cells have been used to markedly ameliorate Parkinson’s disease (12) and diabetes in animal models. The use of iPS in clinical trials, however, will probably face significant regulatory hurdles, because in addition to their potential benefits, the methods for nuclear reprogramming carry the potential to induce euplastic transformation.

Closely to clinical application is the use of the patient’s own stem cells cultured from a cardiac biopsy. Two methods are in current use. In 1 such method, enzymatically dissociated myocardial samples are enriched in cardiac stem cells by cell sorting with xenogenic antibodies to a stem cell antigen before culture (13). This method purposely limits the cell types selected and requires several months to yield sufficient cells for therapeutic applications, even with source tissues as large as atrial appendages. An alternative method is to culture the biopsy material first, allowing the spontaneous outgrowth of cells that can then be harvested to form additional data as it becomes available in the next few years. If validated, we might need to question whether global function is a sufficiently sensitive measure of therapeutic outcome, given the many physiologic compensatory mechanisms that stabilize resting function. In support of this idea, it is worth noting that the EF benefit of prompt reperfusion is small (on average) but the clinical benefits are large.

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*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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multicellular structures called cardiospheres; cardiospheres are then propagated in monolayer culture to yield the final product (14). These cardiosphere-derived cells (CDC) might represent a broader spectrum of cardiac cell precursors. Tens of millions of CDC can readily and reproducibly be produced from tiny endomycocardial biopsies within a matter of weeks. We have found that intracoronary infusion of approximately $10^7$ CDC in an autologous pig infarct model induces new myocardial tissue formation as well as a significant decrease in relative infarct size (19.2% to 14.2%) and improved hemodynamic status compared with control subjects (15). A first-in-human trial of CDC in patients after MI has received Food and Drug Administration approval and is anticipated to begin shortly.

### Cell Environment

Creation of a receptive cell environment is a second central issue in cardiac stem cell therapy. When labeled human cardiomyocytes derived from embryonic stem cells are engrafted in uninjured rat hearts, 90% survive, whereas when the same human cells are injected into a peri-infarct area, they typically fail to engraft (16). This resistance to human stem cell engraftment can be overcome by a pro-survival cocktail, resulting in the appearance of segments of human myocardium within the infarcted area and a 2.5-fold increase in regional wall thickening (17).

Insight into the mechanisms responsible for resistance to cell engraftment after infarction comes from the wound-healing published data. Early in embryologic development, injured tissue heals without scar formation. The transition to adult-type scar formation coincides with the appearance of the inflammatory process. Several recent studies suggest that the embryologic healing response is activated after MI. Embryologic transcription factors are upregulated 2- to 5-fold in infarcted rat myocardium, accompanied by as much as an 18-fold increase in their respective proteins at 14 days (18) and 90-fold increase in the embryonic protein periostin. Progenitor cells are increased 4-fold in both the systemic circulation and tissue after infarction in humans (19,20). These data suggest a strategy aimed at tipping the cell environment from that favoring adult scarring to one favoring scarless healing.

Although the necessary and sufficient environmental factors for optimal stem cell survival and proliferation are as yet undefined, some of these factors are prominent in embryologic healing after injury. Critical environmental modifiers seem to include those that inhibit inflammation and apoptotic cell death and factors that promote cell growth. For instance, in rats with hind limb paralysis, function was restored by embryonic stem cell-derived motor neurons only when anti-apoptotic adenosine derivatives were combined with neurotrophic growth factors, whereas the cells alone did not restore function (21). Indeed, in our own unpublished clinical trial of intracoronary BMC infusion, 4 of 5 patients who responded with >15% increase in EF at 4-month follow-up received adenosine during the procedure. Conversely, in the porcine MI model, adding basic fibroblast growth factor to human CDC increases donor-cell engraftment and enhances cardiomyocyte differentiation in the transplanted hearts, resulting in improvements in global ventricular function, regional wall motion, and infarct size (22,23). Taken together, the available data suggest that future cell therapy will include both pluripotent cells and a receptive cell environment.

### Timing and Method of Delivery

Timing of stem cell therapy remains a conundrum, because the early inflammatory response creates an environment hostile to cell engraftment, whereas evolving fibrosis could inhibit later therapy in the subacute and chronic phase of healing. In this report and the randomized clinical trials, BMC infusion typically was delayed for 5 to 7 days after infarction. This reasonable speculation that further delay might impede therapy, however, will have to be tested. We have found that delaying delivery of BMC in the porcine infarct model until 1 month after infarction resulted in stabilization of cardiac function, with statistically significant difference from untreated control subjects (24), and others have reported similar outcomes with CDC (15). In chronic stable ischemic heart failure, a randomized trial of intracoronary BMC therapy showed EF increased by 2.9%, whereas in those receiving no infusion, it fell by 1.2% at 3-month follow-up. Thus, a small body of data suggests similar outcomes when cell therapy is delayed for longer intervals after infarction.

The present study and the others principally reviewed here rely on intracoronary delivery of cells into a recanalized infarct-related artery. Although this delivery method is convenient, there is no evidence to suggest that it is preferable to direct injection or to other approaches (e.g., topical cell-embedded scaffolds and image-controlled direct intramyocardial delivery) (25).

### Patient Population

Finally, it is worth noting that the patient population used here and in most subsequent clinical BMC trials has been a first-infarct population with little ventricular dysfunction at baseline, with a projected low mortality and morbidity even without adjunctive biological therapy. Perhaps we cardiologists would be well-advised to take a page from the oncology handbook and focus on critically ill patients who stand to benefit dramatically, not incrementally, from these experimental treatments.

Therefore, this publication of the first long-term results of BMC therapy in AMI serves as both a significant milestone and a pivot point in cardiovascular research. The therapy can now be considered safe and modestly efficacious. Conversely, there is little evidence that it has achieved either the biologic goal of regenerating new myocardium or the clinical goal of efficacy sufficient to justify widespread use. As a consequence, we must focus on the barriers to stem cell therapy at level of the
cell, its environment, and the recipient tissue. Identification of these barriers provides both a stimulus to ongoing research and a justification for the hope that stem cell therapy will ultimately achieve its much-anticipated potential. The race is on to find better cell types, create a receptive cell environment, optimize delivery strategies, and identify the patient populations most likely to benefit from our ministrations.

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Key Words: acute myocardial infarction • intracoronary cell therapy • remodeling.