Cell Therapy for Acute Myocardial Infarction
Curb Your Enthusiasm?

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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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(Circulation. 2006;113:1272-1274.)

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Circulation is available at http://www.circulationaha.org
DOI: 10.1161/CIRCULATIONAHA.105.613034

In 1960, McCulloch and Till identified a bone marrow stem cell capable of reconstituting hematopoiesis in mice, later documenting the clonality of these cells. The concept of the adult stem cell thus was born.

More than 3 decades later, Asahara et al extended this concept to include the formation of vascular elements from bone marrow–derived, circulating endothelial progenitors. Although controversial at the outset, the endothelial progenitor cell, or EPC, has now established itself within the lexicon of cardiology: At the 2005 Scientific Sessions of the American Heart Association, more than 100 abstracts contained the words “stem cell” in the title and an additional 75 contained the term EPC.

The escalating interest in stem cells within cardiovascular medicine could be said to be the result of a growing body of evidence that suggests that stem cells may represent therapeutic entities. More than this, however, the concept of stem cell therapy has generated excitement by challenging the long-held paradigm that the heart cannot be repaired. In classic experiments in the laboratory of John Ross in the 1970s (Maroko et al and Ginks et al), the extent of myocardial necrosis was shown to be inextricably linked to the time of coronary occlusion. These studies were not only critical in driving forward the field of reperfusion therapy but also were taken to indicate that the fate of the myocardium was irreversibly determined by this single factor. The field of cardiac stem cell therapy has reopened this question and ignited interest in the previously unthinkable notion of cardiac regeneration.

Preclinical studies in a variety of animal models have provided evidence that both autologous and heterologous cells can contribute to vascular and cardiac repair after myocardial ischemia. For the purposes of this editorial, we will restrict our comments to studies in the myocardium and focus on the use of bone marrow or circulating cells.

Human observational studies have indicated that in the setting of myocardial injury, the mobilization of progenitor cells is a natural response and that the magnitude of mobilization correlates with long-term outcome. Most compelling is a series of pilot human clinical studies that use cell-based approaches to cardiac therapy, yielding promising data. The latter of these reports, by Wollert et al, described the initial findings of the BOner MarOw Transfer to Enhance ST-Elevation Infarct Regeneration (BOOST) trial, indicating a favorable outcome in patients after myocardial infarction who received an intracoronary infusion of unselected, autologous, bone marrow mononuclear cells.

In this issue of Circulation, Meyer et al discuss the long-term (18 months) follow-up of patients in the BOOST trial. In this trial, patients with acute myocardial infarction (AMI) were randomly assigned to receive either an intracoronary bone marrow cell (BMC) infusion or placebo 4.8 ± 1.3 days after having undergone successful percutaneous coronary intervention. The BMC infusion was documented to contain 24.6 ± 9.4 × 10⁶ nucleated cells, 9.5 ± 6.3 × 10⁶ CD34⁺ cells, and 3.6 ± 3.4 × 10⁶ hematopoietic colony-forming cells. Using cardiac magnetic resonance imaging to evaluate ventricular function, the authors reported a statistically significant improvement in ventricular function in the patients assigned to BMC infusion at 6 ± 1 month after random assignment (0.7% improvement in mean left ventricular ejection fraction [LVEF] in the control group versus 6.7% in the BMC transfer group). At the 18-month evaluation, however, the difference between groups was no longer significant (3.1% improvement in mean LVEF in the control group versus 5.9% in the BMC transfer group). Although the authors report that the speed of LVEF recovery was significantly higher in the BMC transfer group, they conclude that a single dose of intracoronary BMCs does not provide long-term benefit on left ventricular systolic function after AMI as compared with a placebo.

Like many good investigations, this report helps to sharpen our focus on the important questions that face the nascent field of cardiac stem cell therapy. Which disease should we be treating? At what point in the disease process should we treat? Which cells should be injected? How should these cells be treated? At what point in the disease process should we treat? How should these cells be delivered? What are the mechanisms by which transplanted cells exert influence, if they do?

Hints to the answers of these questions can be gleaned from preclinical data. For example, in the groundbreaking study by Orlic et al showing the improvement in outcome after myocardial infarction with mobilization of stem cells, the authors found it necessary to pretreat the mice with a mobilization agent before the onset of injury, an indication that the timing of therapy was critical.

Meyer et al reference 4 articles describing preclinical work as background for their clinical trial. Of these 4 referenced articles, all of them used direct injection of cells into infarcted myocardium of animals immediately after onset of ischemia. The potential impact of route of delivery was nicely shown by Aicher et al who used indium labeling of EPCs, documenting the very low myocardial uptake of cells when administered by intraventricular...
injection. These studies also showed enhanced myocardial uptake in the presence of acute ischemia. It is noteworthy that this group used a novel technique of transient coronary occlusion for cell delivery in their clinical trial.28

The selection of cell type is perhaps one of the central issues in the field. The use of an unselected bone marrow mononuclear cell preparation is based on the fact that various stem and progenitors cells will be contained within this population and that the “manufacturing” process does not require expensive equipment or that the cell products meet specifications before administration, thus streamlining the procedure. The liabilities inherent in this strategy include the variability of the therapeutic being administered and the possibility that cells that may inhibit repair, or even potentially worsen outcome, might be present in varying quantities from patient to patient. Again, preclinical data are potentially informative in this regard. For example, Uribch et al29 showed that phenotypic modulation of cells in culture resulted in significant differences in the potency of cells for therapeutic neovascularization, and Kawamoto et al30 showed that only EPCs selected using surface expression of endothelial specific markers exhibited potency for myocardial revascularization. Kajstura et al31 used c-kit+ cells, whereas Yoon et al30 identified a previously unrecognized human bone marrow stem cell population isolated through single cell culture. Clearly, there are major differences between these preclinical studies and the methods used in the BOOST trial, and how these are related to the eventual lack of improvement seen in the BOOST trial are unknown.

One concern that arises when a negative trial results occur in a high profile field is whether there will be a disproportionate reaction and a loss of support for a promising therapeutic. Put another way, will unreasonable expectations of immediate success lead to disappointment and abandonment of a potentially revolutionary technology? In the case of the present study,24 the authors must be credited with carefully collecting and reporting the clinical trial data, despite the disappointing final results, providing the entire field with the opportunity to learn. What have we learned? Here, it is critical that our conclusions are precise: Intracoronary infusion of unselected bone marrow mononuclear cells did not demonstrate significant benefit in left ventricular functional recovery versus placebo in a 60-patient, randomized clinical trial. One could certainly ask whether a 60-patient trial is sufficiently powered to answer such a question—probably not. Tens of thousands of patients were enrolled in clinical trials of thrombolytic agents, and it is worth remembering that t-PA was originally approved on the basis of a 4% improvement in LVEF. Another question is whether the use of unselected bone marrow mononuclear cells is optimal—the overwhelming evidence would argue that this is inconceivable. Pragmatic matters undoubtedly played a significant role in the design of this study—the relatively straightforward preparation of the cells made it tempting to test this approach. Now, however, we must look to preclinical models to guide us in developing the next phase of investigation. There is no perfect model for studying human disease, but one of the advantages of cell-based therapies is that human cells can actually be tested for potency. Thus, the identification of subpopulations of cells with enhanced potency is possible. We can phenotypically characterize cells that work versus those that don’t31 and ultimately modify the cells to enhance their potency for specific indications.32,33

These latter points, of course, address the issue of mechanism. Human observational and animal data suggest that bone marrow–derived cells play a role in the repair process after injury, but the precise means by which the repair process is effected remains incompletely defined. The contribution of circulating and resident cells to neovessel formation and to replacement of cardiomyocytes has been elegantly shown though not universally accepted, whereas paracrine mechanisms and fusion continue to be debated.34,35

A vexing issue in the field is the pharmacokinetics/pharmacodynamics of cell therapy. Dosing of cells is not straightforward. What does dosage mean in terms of cell delivery? Should it refer to the number of cells delivered, the number of cells initially retained within tissue, or the number of cells eventually incorporated into myocardial structures? How should we measure the retention of cells in human trials? Additionally, although multiple small clinical trials have showed short-term benefit, the article by Meyer et al24 suggests that this may be a short-lived effect after a single treatment. Importantly, previous trial data have included follow-up typically of 6 to 9 months. An exception is the Transplantation Of Progenitor Cells And Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI) trial. In this trial, 12-month follow-up suggests a preservation of benefit in LVEF observed 4 months after intracoronal transfer of culture-selected, bone marrow–derived cells or circulating progenitor cells.28

More than a decade into research regarding cell-based therapy for cardiovascular disease, these are just some of the unanswered questions dogging the field. These and other questions are sure to be raised in response to the report of Meyer et al24 in this issue of Circulation.

We have restricted our discussion to trials associated with AMI. However, clinical trials have been completed or are underway for other conditions including chronic ischemic angina without conventional revascularization option, chronic ischemic heart failure, and nonischemic heart failure. Despite the myriad questions raised above, there have been multiple studies that have suggested clinical benefit from cell therapy for cardiac conditions, and these propel the field forward. However, the larger question remains. Do we have sufficient preclinical data to understand pharmacokinetics, pharmacodynamics, and mechanism to give this field the best chance for success with the most efficient use of resources?

We remain optimistic regarding the future of cell therapy for cardiac disease. However, we suggest that the field requires a recommitment to preclinical investigation as a means of better understanding basic mechanisms and clinical trial design based on these preclinical data. The publication of negative clinical data are equally important to publication of data from positive trials, and it is therefore gratifying to see the BOOST trial results published. We hope that insight from this “failure” will lead to an eventual better understanding of this exciting therapeutic option.

Acknowledgments

A PubMed search with the terms (stem cell) and (heart) resulted in 3600 hits; we request the understanding of the many authors whose excellent work is not cited here.
Disclosures

Dr Losordo has received research grants from Baxter Inc, Coraautis, Cordis, Curis, AnorMed, and Boston Scientific Corp, consulting fees from Baxter, Cordis, and AnorMed, and stock options from AnorMed. Dr Welt reports no conflicts.

References


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Circulation. 2006;113:1272-1274
doi: 10.1161/CIRCULATIONAHA.105.613034

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