Published in final edited form as:

JAMA. 2011 November 16; 306(19): 2156–2157. doi:10.1001/jama.2011.1686.

Bone Marrow Therapy for Myocardial Infarction

Joshua M. Hare, MD

Interdisciplinary Stem Cell Institute, University of Miami, Miami, Florida

The results of the latetime study,¹ reported by Traverse and colleagues in this issue of *JAMA*, appear 1 decade after the publication of the landmark study by Orlic et al.² The authors conducted a rigorous clinical trial to test the hypothesis that intracoronary infusion of autologous bone marrow mononuclear cells (BMCs) in patients with myocardial infarction (MI) would improve left ventricular function. The rationale for using whole bone marrow in this setting derives from numerous sets of experimental studies showing that bone marrow contains cellular constituents that have cardiac reparative ability.^{2,3} The authors found that among 87 patients with MI and left ventricular dysfunction following reperfusion with percutaneous coronary intervention, compared with placebo intracoronary infusion, intracoronary infusion of BMCs 2 to 3 weeks after percutaneous coronary intervention did not improve global or regional ventricular function at 6 months.

Given its rigorous design with placebo control, blinding, and sophisticated magnetic resonance imaging (MRI), the LateTIME trial results are compelling, arguing against the value of intracoronary bone marrow infusion administration 2 to 3 weeks following acute MI. The results of the LateTIME trial are in contrast with several other rigorous clinical trials, notably the Reinfusion of Enriched Progenitor Cell and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) published in 2006,⁴ which showed a statistically significant increase in ejection fraction (EF) in response to intracoronary bone marrow given within 3 to 7 days of MI. In that study, the authors found that the benefit increased among patients treated toward the end of the 7-day time frame, with an enhanced effect in the subgroup of patients with EFs less than the median of 48.9%.

The results of a meta-analysis⁵ substantiated the finding that intracoronary BMCs are associated with an improvement in EF by approximately 3% to 4%. Additionally, a potentially important analysis from the REPAIR-AMI data suggests that intracoronary BMCs may have clinical benefits that exceed those predicted by the increase in EF.⁶ Importantly, 2 ongoing current trials—TIME⁷ and BAMI (Bone marrow-derived mononuclear cells [BM-MNC] on all-cause mortality in Acute Myocardial Infarction)—will offer important information. The TIME study,⁷ conducted by the same investigators as the LateTIME study, will compare the efficacy of bone marrow therapy at 3 vs 7 days, and the

Corresponding Author: Joshua M. Hare, MD, Interdisciplinary Stem Cell Institute, Biomedical Research Bldg, University of Miami, 1501 NW Tenth Ave, PO Box 016960 (R125), Room 824, Miami, FL 33101 (jhare@med.miami.edu).

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Hare reported receiving consulting fees from Osiris Therapeutics, Kardia, and Teva; receiving a grant from Biocardia; having stock in Kardia; and being an inventor on a patent in the area of cell therapy.

BAMI study is a planned 3000 patient trial evaluating all-cause mortality that will be conducted in Europe.

The idea of treating chronic disorders characterized by tissue destruction with a cell-based and potentially regenerative strategy is one of the most exciting possibilities on the horizon in medicine. However, just like any new treatment strategy, well-designed clinical trials are required to assess safety and efficacy and to determine the parameters that characterize the effective use of the new approach. As with any emerging approach, early clinical testing is plagued by the problem of surrogate efficacy (ie, a correct surrogate end point has been chosen that will accurately reflect important clinical outcomes). The LateTIME trial is clear that intracoronary BMCs delivered at a “late time point” of 2 to 3 weeks lack efficacy to improve the surrogate of EF.

To date, most investigations of cell therapy for acute MI have used EF as the surrogate end point. However, an increasing consensus holds that direct determination of injured tissue and ventricular remodeling more directly measures the phenotype targeted by the therapy,^{8,9} and the LateTIME study is strengthened by its use of cardiac MRI to determine infarct size and regional ventricular wall motion. Failure to identify reductions in infarct size using MRI in the LateTIME study provides added evidence that the therapy did not have the hypothesized biological effect.

The value of a rigorously conducted negative trial in a new area is that it allows focus on the therapeutic approach. For instance, forthcoming data will help determine whether earlier time points for BMC administration show enhanced efficacy, or if other administration approaches are required, such as intramyocardial delivery. In this regard, ongoing and early studies using intramyocardial delivery for patients with MI in both acute and chronic settings have reported positive results for surrogate end points, including infarct size, regional wall motion, and ventricular chamber size.^{8,10}

An important consideration is that the LateTIME study may not have demonstrated a significant effect because the time frame of 2 to 3 weeks may have extended beyond a window in which “injury signals” that recruit and retain stem cells are released. Moreover, the heterogeneous mixture of whole bone marrow may not be an optimal therapeutic cellular agent and could vary from patient to patient. Thus, the ongoing series of clinical trials testing cell therapy for patients with heart disease will be highly informative in revealing clinical efficacy with novel cell formulations. These include mesenchymal stem cells,¹¹ mesenchymal precursor cells,³ cardiac stem cells,¹² cell mixtures, and possibly pluripotent stem cells.¹³

Mechanistic studies are crucial for advancing cell-based therapies for chronic disorders characterized by tissue loss. Much attention has focused on the ability of bone marrow cells to differentiate into contractile myocardium, and diametrically opposite findings are reported. The quest for finding a cell with the capability for forming large numbers of integrating cardiomyocytes drives the field of induced pluripotent cells.¹³ Additional studies are highlighting other mechanisms of action with potential importance; for example, an increasing number of studies identify the importance of endogenous reservoirs of cardiac

stem cells.¹² These cells may be activated by pharmacologic approaches, other exogenous cell therapies, or amplified ex vivo and used as a therapy. With regard to activation by exogenous cell therapy, several studies suggest that mesenchymal stem cells may recruit endogenous cardiac c-Kit stem cells.^{14,15}

The LateTIME trial offers important take-home messages. To the extent that intracoronary infusions of BMCs prove to offer clinical benefit for patients with heart disease, there is most likely a therapeutic window of opportunity that does not exceed 2 to 3 weeks following ischemic injury. For later time points, trials should use intramyocardial delivery systems that have documented efficacy in early studies. Ongoing research is essential to obtain cell preparations that are more effective, but also efficient to produce. Important ongoing clinical investigations such as the TIME and BAMI trials will add additional essential information and help define the possibility of using BMCs to treat disorders of cardiac injury, and numerous ongoing trials are testing other cell sources.

Although the results of this well-conducted trial may be disappointing or viewed by some as a setback, it should be remembered that definitive negative trials in a new area help to focus the design of future investigations, thereby ultimately advancing the field.

Acknowledgments

Funding/Support: This work is supported by grants RO1s-HL084275, HL094849, HL107110, HL110737, P20 HL101443, and U54 HL081028 from the National Institutes of Health and a sponsored research agreement with Biocardia.

Role of the Sponsors: The National Institutes of Health or Biocardia had no role in the preparation, review, or approval of the manuscript.

References

1. Traverse JH, Henry TD, Ellis SG, et al. Effect of intracoronary delivery of autologous bone marrow mononuclear cells 2 to 3 weeks following acute myocardial infarction on left ventricular function: the LateTIME randomized trial [published online November 14, 2011]. *JAMA*. 2011; 306(19): 2110–2119. [PubMed: 22084195]
2. Orlic D, Kajstura J, Chimenti S, et al. Bone marrow cells regenerate infarcted myocardium. *Nature*. 2001; 410(6829):701–705. [PubMed: 11287958]
3. Williams AR, Hare JM. Mesenchymal stem cells: biology, pathophysiology, translational findings, and therapeutic implications for cardiac disease. *Circ Res*. 2011; 109(8):923–940. [PubMed: 21960725]
4. Schächinger V, Erbs S, Elsässer A, et al. REPAIR-AMI Investigators. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med*. 2006; 355(12):1210–1221. [PubMed: 16990384]
5. Abdel-Latif A, Bolli R, Tleyjeh IM, et al. Adult bone marrow-derived cells for cardiac repair: a systematic review and meta-analysis. *Arch Intern Med*. 2007; 167(10):989–997. [PubMed: 17533201]
6. Assmus B, Rolf A, Erbs S, et al. REPAIR-AMI Investigators. Clinical outcome 2 years after intracoronary administration of bone marrow-derived progenitor cells in acute myocardial infarction. *Circ Heart Fail*. 2010; 3(1):89–96. [PubMed: 19996415]
7. Traverse JH, Henry TD, Vaughan DE, et al. Cardiovascular Cell Therapy Research Network (CCTRN). Rationale and design for TIME: a phase II, randomized, double-blind, placebo-controlled pilot trial evaluating the safety and effect of timing of administration of bone marrow

- mononuclear cells after acute myocardial infarction. *Am Heart J.* 2009; 158(3):356–363. [PubMed: 19699857]
8. Williams AR, Trachtenberg B, Velazquez DL, et al. Intramyocardial stem cell injection in patients with ischemic cardiomyopathy: functional recovery and reverse remodeling. *Circ Res.* 2011; 108(7):792–796. [PubMed: 21415390]
9. Rolf A, Assmus B, Schächinger V, et al. Maladaptive hypertrophy after acute myocardial infarction positive effect of bone marrow-derived stem cell therapy on regional remodeling measured by cardiac MRI. *Clin Res Cardiol.* 10.1007/s00392-011-0330-3
10. Trachtenberg B, Velazquez DL, Williams AR, et al. Rationale and design of the Transendocardial Injection of Autologous Human Cells (bone marrow or mesenchymal) in Chronic Ischemic Left Ventricular Dysfunction and Heart Failure Secondary to Myocardial Infarction (TAC-HFT) trial: a randomized, double-blind, placebo-controlled study of safety and efficacy. *Am Heart J.* 2011; 161(3):487–493. [PubMed: 21392602]
11. Hare JM, Traverse JH, Henry TD, et al. A randomized, double-blind, placebo-controlled, dose-escalation study of intravenous adult human mesenchymal stem cells (prochymal) after acute myocardial infarction. *J Am Coll Cardiol.* 2009; 54(24):2277–2286. [PubMed: 19958962]
12. Leri A, Kajstura J, Anversa P. Role of cardiac stem cells in cardiac pathophysiology: a paradigm shift in human myocardial biology. *Circ Res.* 2011; 109(8):941–961. [PubMed: 21960726]
13. Ieda M, Fu JD, Delgado-Olguin P, et al. Direct reprogramming of fibroblasts into functional cardiomyocytes by defined factors. *Cell.* 2010; 142(3):375–386. [PubMed: 20691899]
14. Hatzistergos KE, Quevedo H, Oskouei BN, et al. Bone marrow mesenchymal stem cells stimulate cardiac stem cell proliferation and differentiation. *Circ Res.* 2010; 107(7):913–922. [PubMed: 20671238]
15. Suzuki G, Iyer V, Lee TC, Canty JM Jr. Autologous mesenchymal stem cells mobilize cKit+ and CD133+ bone marrow progenitor cells and improve regional function in hibernating myocardium. *Circ Res.* 2011; 109(9):1044–1054. [PubMed: 21885831]