FEATURED NEW INVESTIGATOR

Stem cell therapy in acute myocardial infarction: a review of clinical trials

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Stem cells (SCs) possess the ability to differentiate into cells of various tissues. Although the differentiation of SCs into functional cardiomyocytes has been difficult to demonstrate in humans, clinical trials using SCs in the setting of acute myocardial infarction (AMI) have demonstrated variable results. Interpretation of these trials has been difficult because of multiple variables, which include differences in trial design, cell type, timing of cell delivery, and outcome measurements. Herein, a summary of all clinical trials in subgroups of direct injection, indirect mobilization, and combination approaches of SC therapy in AMI is provided with significant findings in each group. (Translational Research 2010;155:10–19)

Abbreviations: AMI = acute myocardial infarction; BM = bone marrow; G-CSF = granulocyte-colony stimulating factor; IC = intracoronary; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PB = peripheral blood; PCI = percutaneous coronary intervention; RNV = radionuclidventriculography; SC = stem cell; SPECT = single photon emission computed tomography; UCB = umbilical cord blood

Until recently, the myocardium had been viewed as a terminally differentiated organ without potential for regeneration.[1] Although early reperfusion strategies for occluded arteries in acute myocardial infarction (AMI) have greatly improved morbidity and mortality in these patients, advances in treatment are limited by the inability to repair concomitantly damaged cardiac tissue.[2] This limitation has led to increasing use of stem cell (SC) therapies with the assumption that replacement or repair of damaged vascular and cardiac tissue could lead to improvement in myocardial function after AMI.

Although multiple experimental animal models and clinical trials of cell-based cardiac therapy have delivered promising results, the mechanisms of their effect are unclear. SCs, depending on their lineage, possess the ability to differentiate into cells of various tissues. Although the differentiation of SCs into functional cardiomyocytes has been difficult to demonstrate and fraught with controversy,[3] differentiation into functioning endothelium with improved blood flow has been better illustrated and accepted.[4] Studies in animal models have demonstrated improvement in myocardial function after targeted repair of infarcted myocardium via implantation of endothelial progenitor cells by various delivery methods,[5,6] whether derived from peripheral blood (PB),[4] bone marrow (BM),[7,8] or umbilical cord blood (UCB).[9-11] This has led to a variety of human clinical trials using SC to determine safety, feasibility, and outcomes in the setting of AMI.

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Clinical trials in humans have primarily used autologous BM-derived SCs because of the feasibility without concerns of yield as with PB-derived cells and rejection as with UCB-derived cells. Clinical trials of SC therapy in AMI can be classified into 3 major approaches of delivery: direct injection (Table I) using an intracoronary (IC) route,[12-24] indirect cytokine-induced mobilization (Table II) using granulocyte-colony stimulating factor (G-CSF),[25-33] or a combination approach (Table III) using initial mobilization followed by direct injection.[34-36] However, interpretation of these trials has been difficult because of multiple variables, which include differences in trial design, cell type, timing of cell delivery, and outcome measurements.

DIRECT INJECTION OF SCS

Direct delivery of BM-derived SCs has been investigated by various routes, including intracoronary, intravenous, intramyocardial, endomyocardial, retrograde coronary venous, and transvenous intramyocardial approaches; yet the optimal avenue is not known.[5,6] However, in the setting of AMI, when percutaneous coronary intervention (PCI) is routinely undertaken, the IC route seems to be the most feasible. A synopsis of the clinical trials to date in this category is summarized in Table I.

Strauer et al[12] first reported IC delivery of BM-derived SCs in a nonrandomized fashion to 10 patients 7 days post PCI and observed a decrease in infarct zone and an improvement in perfusion despite no significant change in left ventricular ejection fraction (LVEF) compared with controls at 3 months.[12] The 1st randomized clinical trial, TOPCARE-AMI, was conducted by IC delivery of PB-derived SCs to 30 patients and BM-derived SCs to 29 patients 5 days post PCI.[13] Although an improvement in LVEF was observed at 4 months and a decrease in infarct size at 12 months in both groups, there was no control group without cell therapy in the study for comparison. Meanwhile, Kuethe et al[14] published a small study in 5 patients with large anterior myocardial infarctions that received BM SCs 6 days post PCI that showed no significant increase in LVEF at 12 months. Chen et al[15] attempted to increase the yield of BM-derived SCs by *in vitro* culture of cells after BM harvest for 10 days and IC delivery 18 days post PCI to 35 patients, which demonstrated a larger increase in LVEF and a decrease in perfusion defect compared with controls at 3 and 6 months. The BOOST trial was the 1st randomized controlled clinical trial conducted in 60 patients in which half received BM-derived SC 5 days post PCI and confirmed improvement in LVEF by cardiac magnetic resonance imaging (MRI) at 6 months compared with the other half that served as control without cell therapy.[16] Bartunek et al,[17] in 19 of 35 patients who received IC injection of CD133-positive BM SCs 12 days post PCI, found significant improvement in LVEF by ventriculography at 4 months. However, Janssens et al[18] disputed these findings in their randomized controlled trial of 67 patients where 33 of them received IC BM-derived SCs within 24 h post PCI and displayed no significant change in LVEF by cardiac MRI compared with controls at 4 months.[18] The TCT-STAMI trial included 10 patients who received IC delivery of BM SCs within 24 h of PCI compared with 10 controls that showed a significant increase in LVEF by echocardiogram and a decrease in perfusion defect scores by single photon emission computed tomography (SPECT) at 6 months.[19] This finding spurned the 2 largest randomized clinical trials using BM-derived SC therapy in the setting of AMI. The ASTAMI trial, which recruited 100 patients, of whom 50 received IC delivery of BM-derived SCs 6 days post PCI, showed that there was no significant change in LVEF by echocardiography, SPECT, or MRI at 6 months.[20] In contrast, the larger REPAIR-AMI trial, which recruited 204 patients, 101 of whom received IC delivery of BM-derived SCs 4 days post PCI, demonstrated significant improvement in LVEF compared with controls by quantitative ventriculography at 4 months.[21] Meluzin et al[22] randomized 66 patients into equal groups of control, low-dose, and high-dose IC delivery of BM-derived SCs 7 days post PCI, and the authors also found incremental improvement in LVEF in a dose-dependent manner by SPECT at 3 months. Penicka et al[23] enrolled 27 patients, of which 17 received IC delivery of BM SCs 7 days after PCI and had no significant improvement in LVEF by echocardiography or decrease in infarct size by SPECT at 4 months. Tatsumi et al,[24] in a nonrandomized study of 54 patients, demonstrated no benefit of IC delivery of PB-derived SCs 3 days post PCI in 18 of those patients by ventriculography at 6 months.

INDIRECT MOBILIZATION OF SCS

Cytokine-induced mobilization of BM-derived SCs has been shown to induce angiogenesis and restore damaged myocardium, which resulted in improved left ventricular function and survival after myocardial infarction in experimental animal models.[7] AMI is followed by increased spontaneous mobilization of BM-derived SCs, and the extent and duration of this mobilization has been correlated with improvement of left ventricular function.[37] G-CSF is a known stimulator of SC and effectively mobilizes BM-derived SCs into the peripheral circulation, which thereby contributes to the improvement of myocardial function after AMI.[38] A