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Cell-Based Therapy for Ischemic Heart Disease

Guilherme V. Silva, MD

John F. Canales, MD

Emerson C. Perin MD, PhD

Executive Summary

New insights into the mechanisms of cardiac repair have provided evidence that the adult heart can at least partially repair injury and that vasculogenesis may not occur solely during embryonic development. These insights, in turn, have sparked strong interest in the field of stem cell therapy. Prompted by evidence that adult bone marrow harbors a reservoir of plastic cells, animal experiments have generated evidence supporting the use of stem cells for repairing cardiac tissue in diverse clinical settings. A prolific response from researchers has generated several phase I/II trials with fast growing evidence of safety and preliminary efficacy of stem cell therapy in both acute and chronic ischemic heart disease. This chapter is directed at the clinical cardiologist who will ultimately deliver this investigational therapy to patients.

Introduction

Stem cells are self-replicating cells capable of generating, sustaining, and replacing terminally differentiated cells. Stem cells can be subdivided into 2 large groups: embryonic and adult. Embryonic stem cells (ESC) are pluripotent cells, derived from the cell mass of the blastocyst, that maintain the ability to generate any terminally differentiated cell derived from any one of the three embryonic germ layers. Adult stem cells, on the other hand, are intrinsic to specific tissues of the postnatal organism and are committed to differentiate into those tissues.

Each *adult stem cell subtype* can be identified by cell surface receptors that selectively bind to particular signaling molecules. Each type of adult stem cell has a certain receptor or combination of receptors (ie, marker) that distinguishes it from other types of stem cells. A cell presenting the stem cell antigen-1 receptor is identified as Sca-1⁺. Cells exhibiting Sca-1 but not CD34 antigen or lineage-specific antigen (Lin) are identified as CD34⁻Sca-1⁺Lin⁻. This particular combination of surface receptors identifies mesenchymal stem cells (MSCs).

Adult bone marrow-derived stem cells are presently the cell types most widely utilized in cardiac stem cell therapy. A heterogeneous subset, termed *autologous bone marrow-derived mononuclear cells* (ABMMNCs), is composed of small amounts of stromal or mesenchymal stem cells (MSCs), hematopoietic progenitor cells (HPCs), endothelial progenitor cells (EPCs), and more committed cell lineages, such as natural killer lymphocytes, T lymphocytes, B lymphocytes, and others. *Adult MSCs* are cells from any adult tissue that can be expanded in culture and renew themselves and differentiate into several specific mesenchymal cell lineages. MSCs are present in different niches throughout the body, such as bone marrow and adipose tissue. MSCs are CD45⁻CD34⁺ bone marrow cells that can be readily grown in culture. They are rare in the bone marrow (<0.01% of nucleated cells, by some estimates) and thus 10 times less abundant than HPCs. *HSCs* are mostly found in the bone marrow and give rise to all the blood cell types, including both the myeloid (monocytes and macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets, and some dendritic cells) and lymphoid lineages (T-cells, B-cells, NK-cells, some dendritic cells). *Endothelial progenitor cells* can be isolated from the mononuclear fraction of the bone marrow or peripheral blood, as well as from fetal liver or umbilical cord blood. Lastly, although not “true” stem cells, *skeletal myoblasts* are worth mentioning because they too can be harvested and expanded to allow cardiovascular therapeutic utilization. Skeletal myoblasts are tissue-specific stem cells located between

the basal lamina and the sarcolemma on the periphery of the mature skeletal-muscle fiber that have the availability and capability to form myotubules which could possibly enable cellular replenishment in the failing heart.

Stem cells have been delivered indirectly through peripheral and coronary veins and coronary arteries, as well as directly by intramyocardial injections. Alternatively, another potential delivery strategy is the mobilization of stem cells from the bone marrow by means of cytokine therapy with or without peripheral harvesting. *Intracoronary infusion* is relatively safe. The technique is similar to that for coronary angioplasty, and involves positioning an over-the-wire angioplasty balloon in a coronary artery. Coronary blood flow is transiently stopped for 2 to 4 minutes while stem cells are infused under pressure. *Intramyocardial injection* can be performed via *transepical, transendocardial, or transc coronary venous routes*. *Transendocardial injection* is performed via a percutaneous femoral approach. An injection-needle catheter is advanced in a retrograde fashion across the aortic valve and positioned against the endocardial surface. Stem cells are then injected directly into targeted areas of the left ventricular wall. The main advantage of the transendocardial delivery route is the possibility of utilization of electromechanical mapping which will allow for injections exclusively in areas with preserved voltage (myocardial viability).

Clinical Trials in Ischemic Heart Disease

Refractory Angina

One of the very first studies evaluating the use of ABMMNC injection in patients with refractory angina was done by Tse and colleagues⁽¹⁾. In this study, ABMMNCs were transendocardially injected into 8 patients with severe ischemic heart disease and preserved left ventricular function, as indicated by the left ventricular ejection fraction (LVEF). After 3 months of follow-up, these researchers observed an improvement in symptomatology and myocardial perfusion. Cardiac magnetic resonance imaging showed improved perfusion and contractility in the ischemic region. Around the same time, Fuchs and colleagues⁽²⁾ conducted a clinical feasibility study of transendocardial delivery of filtered, unfractionated autologous bone marrow-derived (not mononuclear) cells in 10 patients with severe chronic, symptomatic myocardial ischemia not amenable to conventional revascularization. Twelve targeted injections (0.2 mL each) were administered into ischemic,

noninfarcted myocardium that was pre-identified with single-photon emission computed tomography (SPECT) perfusion imaging. The patients had no serious adverse effects (ie, arrhythmia, infection, myocardial inflammation, or increased scar formation). The treadmill exercise duration (available for 9 patients) did not change significantly (391 ± 155 seconds vs. 485 ± 198 seconds, $p=0.1$), but there was improvement in Canadian Cardiovascular Society angina scores (3.1 ± 0.3 vs. 2.0 ± 0.94 , $p=0.001$) and in stress scores involving segments within the injected regions (2.1 ± 0.8 vs. 1.6 ± 0.8 , $p < 0.001$).

Heart Failure

The first clinical trial in which transendocardially injected ABMMNCs were used to treat end-stage ischemic heart failure patients with severe systolic dysfunction included 21 patients⁽³⁾. The first 14 patients comprised the treatment group while the last 7 formed the control group. Baseline laboratory tests, exercise stress (ramp treadmill) studies, 2-dimensional Doppler echocardiography, SPECT perfusion scanning, and 24-hour Holter monitoring was done on all patients at baseline. Bone marrow-derived mononuclear cells were then harvested from each patient and processed for injection by a NOGA catheter. A total of 15 injections (0.2 cc each, totaling 30×10^6 cells per patient) were injected into areas of viable myocardium as identified by an electromechanical mapping (unipolar voltage of greater than 6.9 mV) (Figure 1). The treatment area was further correlated with baseline SPECT findings and only points with preserved viability were injected. All patients underwent noninvasive follow-up tests at 2

months, with the treatment group undergoing additional noninvasive testing and repeat invasive electro-mechanical mapping at 4 months. In the two groups, the demographics and exercise test variables did not differ significantly. No procedural complications occurred, and no periprocedural arrhythmias were identified. At 2 months, quantitative SPECT analysis showed a significant reduction in the total reversible defect in the treatment group compared to the controls ($p=0.02$). At 4 months, the LVEF in the treated patients had improved from a baseline of 20% to 29% ($p=0.003$), and the end-systolic volume was significantly reduced ($p=0.03$). Lastly, electromechanical mapping revealed significant mechanical improvement of the injected segments ($P < 0.0005$) (Fig 2). More importantly, at 6 and 12 months, total reversible defect, as measured by SPECT perfusion scanning, was significantly reduced in the treatment group as compared with the control group⁽⁴⁾. The treatment group also had significantly improved exercise capacity at 12 months (Table 1). Overall, transendocardial injection of ABMMNCs was safe and preliminarily effective. This was the first time objective evidence of perfusional and functional improvement had been seen in patients with severe ischemic heart failure treated solely with cell therapy. Table 2 summarizes the stem cell experience in chronic ischemic heart disease.

Skeletal Myoblasts

Clinical trials of skeletal myoblasts have focused on the treatment of patients with ischemic cardiomyopathy and systolic dysfunction. Overall, these trials have resulted in improved segmental contractility and global

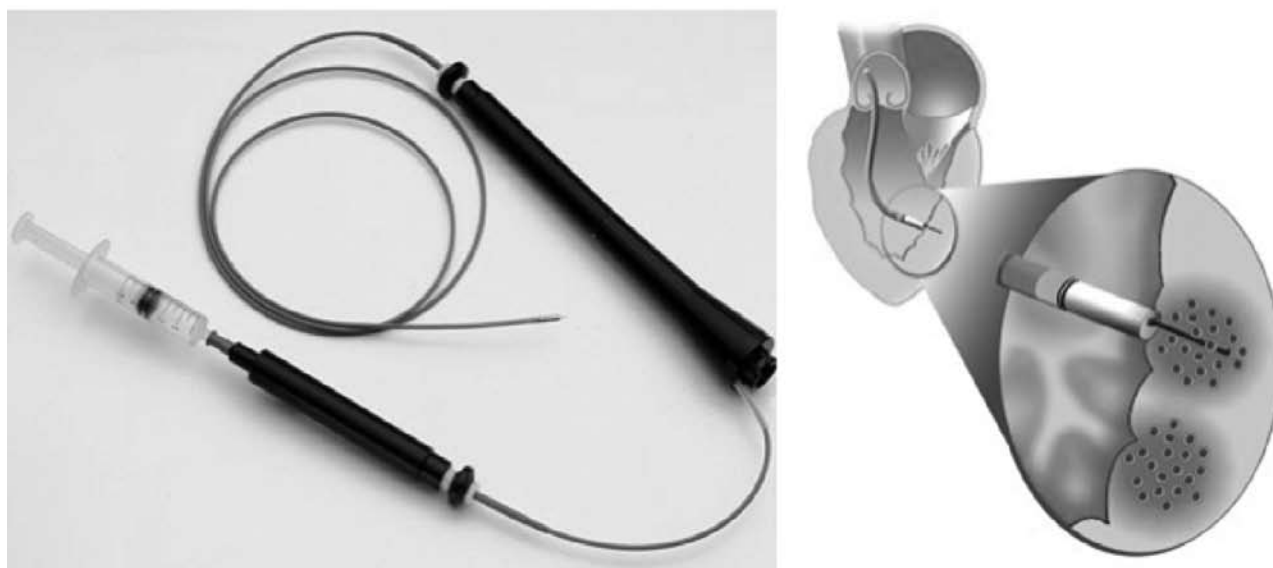


Figure 1

(Left) Myostar catheter with attached syringe. (Right) Illustration showing the catheter traversing the aortic valve and transendocardial extension of the needle with cell delivery (inset). Reprinted from *Circulation*. 2003;107:2294-2302

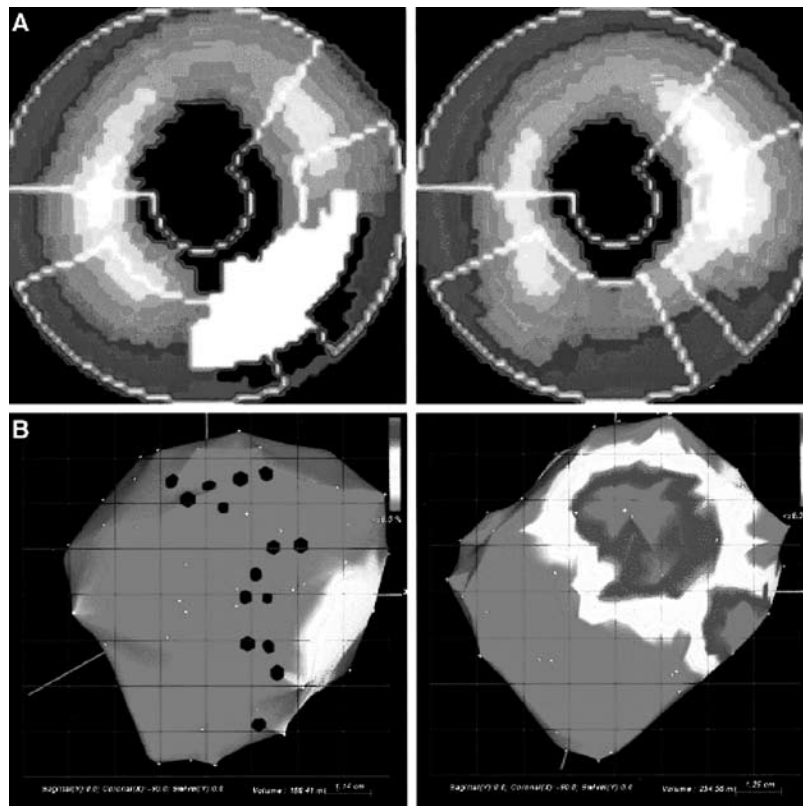


Figure 2

(A) SPECT polar map at baseline, showing an area of inferolateral, reversible ischemia in white and nonreversible stress defect in black (left). Follow-up SPECT at 2 months, showing complete resolution of ischemic defect and basilar nonreversible defect with a decrease in nonreversible apical defect (right). (B) Electromechanical maps from the same patient viewed from the inferior position. Mechanical map at the time of the injection procedure (left) shows the 15 injection sites in black distributed along the inferior wall. The follow-up mechanical map at 4 months (right) shows marked improvement in contractile function in the injected area.

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LVEF. The preferred delivery route has been surgical intramyocardial injection, and one feasibility trial of transendocardial injection has been reported in the literature so far (Table 3).

Acute Myocardial Infarction

Most of the clinical experience gained with stem cells has involved therapy for acute myocardial infarction (AMI), particularly intracoronary infusion of bone marrow cells. Table 4 summarizes the experience to date. In all of these trials, revascularization was performed promptly after the index myocardial infarction, and left ventricular systolic compromise was minor (in the BOOST trial, the baseline LVEF was 50%).

In one of the earliest trials, the Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI) trial, patients were randomly assigned to receive either bone marrow–derived mononuclear cells or EPCs via intracoronary infusion⁽⁸⁾. Compared with nonran-

domized matched reference patients, treated patients had a significantly improved global LVEF, as assessed by left ventricular angiography, regardless of cell type used. In a subgroup of this study population, LVEF was significantly increased, as assessed by cardiac magnetic resonance imaging (MRI), and infarct size was reduced, as assessed by late-enhancement MRI. Interestingly, the infused cells' ability to migrate was the most important predictor of infarct remodeling. Coronary flow reserve also increased, which was suggestive of neovascularization. The 1-year results of TOPCARE-AMI⁽¹⁵⁾ reinforced the notion that stem cells protect against ventricular remodeling. Despite the limited number of patients, contrast-enhanced MRI revealed a significantly increased LVEF ($p < 0.001$), significantly reduced infarct size ($p < 0.001$), and the absence of reactive hypertrophy, suggesting that the infarcted ventricles had been functionally regenerated. Scientific criticism of this trial has focused on the cell delivery method, which included transient coronary occlusion and flow

Table 1 Comparison of Clinical Values for the Treatment and Control Groups at Baseline, 2 Months, and 6 Months

	Baseline		2 Months		6 Months		P*
	Treatment	Control	Treatment	Control	Treatment	Control	
SPECT							
Total reversible defect, %	15.15±15	10.71±16.6	4.53±16.6	32.23±37.5	8.8±9	32.7±37	0.04
Total fixed defect (50%), %	41±11	36±10	39±8.8	36.4±12	38±6.7	36.4±12	0.3
Ramp Treadmill							
VO ₂ max, mL/kg/min	18±9	17.75±6.8	23.3±7	18±6.2	24.15±7	17.3±6	0.02
METS	5.09±2.5	5.07±1.96	6.68±2.35	5.16±2.45	7.19±2.4	4.92±1.7	0.01
PVC, n	2507±6243	672±1085	901±1236	2034±4528	3902±8267	1041±1971	0.4
dQRS, ms	136±15	145±61	145.9±25	130±27	144.8±25	140±61	0.62
LAS 40, ms	50±24	70±76	54±33	48±20	25±25	66±79	0.47
RMS 40, µV	22.2±22	23.3±23	23.3±19	24.6±28	25±25	30±27	0.70

SPECT, single-photon emission computed tomography; METS, metabolic equivalents; PVC, premature ventricular contraction; LAS 40, duration of terminal low-amplitude signal less than 40 mV; RMS 40, root mean square voltage in the terminal 40 ms of the QRS complex; dQRS, filtered QRS duration.

*P for comparisons between treatment and control groups by ANOVA.

Table 2 Selected clinical studies of bone marrow–derived cells transplantation in Chronic Ischemic Heart Disease

Study	Design (n)	Cell type	Delivery method	Results	Adverse events
Tse et al (1)	Series (8)	BMMC	Transendocardial	Improved symptoms and regional function	None reported
Fuchs et al (2)	Series (10)	BMMC	Transendocardial	Improved symptoms and regional perfusion	None reported
Perin et al (3,4)	Series (14) + control (7)	BMMC	Transendocardial	Improved EF and regional perfusion and symptoms	None reported
Stamm et al (5)	Series (12)	AC133+	Epicardial + CABG	Improved EF and regional perfusion	None reported
Erbs et al (6)	RCT, double blind (26)	CPC	Intracoronary post CTO recanalization	Decreased infarct size, increased EF, viability and coronary flow reserve	None reported
Hendrikx et al (7)	RCT (20)	BMMC	Epicardial + CABG	Improved regional function	None reported
TOPCARE-CHD (8)	3 phases randomized controlled crossover (75)	BMMC vs CPC	Intracoronary	Improved EF and regional contractility in patients treated with BMMC	3 Coronary dissections after infusion procedure 1 VF during infusion
FOCUS	RCT, single blind (30)	BMMC	Transendocardial	Ongoing	–

CTO, Chronic total occlusion; CPC, circulating progenitor cell.

Table 3 Selected clinical studies of skeletal myoblasts transplantation in cardiomyopathy

Study	Design (n)	Cell type	Delivery method	Results	Adverse events
Hagege et al (9)	Series (9)	SKM	Epicardial + CABG	Improved NYHA, EF, regional contractility	4 cases sustained VT
Herrerros et al (10)	Series (12) + historical control	SKM	Epicardial + CABG	Improved EF, regional contractility, viability	None reported
Siminiak et al (11)	Series (10)	SKM	Epicardial + CABG	Improved NYHA	4 cases sustained TV 1 early death (nonrelated)
POZNAN (12)	Series (10)	SKM	Transcoronary sinus	Improved NYHA, EF	Injection impossible in 1 patient
Dib et al (13)	Series (30)	SKM	Epicardial + CABG/LVAD	Improved EF, viability Long-term survival of SKM	3 episodes of NSVT
MAGIC	RCT, double blind (97) Dose testing	SKM	Epicardial + CABG	No effect on EF, positive remodeling in high-dose group	No increase in ventricular arrhythmia

EF, Left ventricular ejection fraction; LVAD, left ventricular assist device; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association functional class; RCT, randomized clinical trial; SKM, skeletal myoblast; VT, ventricular tachycardia.

cessation, and its potential for ischemic preconditioning. Such preconditioning has been shown to improve outcomes during AMI and may have contributed to the functional improvement noted in this trial. Moreover, the occurrence of in-stent thrombosis in one patient 3 days after undergoing cell therapy raised safety concerns.

To evaluate further this concern of restenosis after intracoronary infusion, Bartunek and colleagues investigated 35 patients with AMI after treatment with intracoronary infusion of AC133⁺ bone marrow cells⁽¹⁶⁾. The mean dose was 12.6 million cells and the mean infusion was 11.4 days after the index event. At 4-month follow-up, treated patients had an improved mean LVEF but higher rates of stent restenosis, stent reocclusion, and de novo coronary artery lesions than did the controls. Thus, this study further confirmed the concerns of increasing the disequilibrium between pro-atherogenic and anti-atherogenic factors with intracoronary infusion of enriched bone marrow stem cells.

On the other hand, the intracoronary route has also been used to deliver autologous MSCs. Chen and colleagues⁽¹⁷⁾ reported the first randomized clinical trial of these cells in 69 patients who underwent a primary percutaneous coronary intervention within 12 hours after an AMI. Either MSCs or saline was injected into the target coronary artery. At 3-month follow-up, left ventricular perfusion and the LVEF had significantly improved in the treatment group. Thus, now that intracoronary infusion of either ABMMNCs or MSCs (in this study) had been safely used with some improvement in LVEF, this set the stage for large randomized trials to examine the safety and efficacy of intracoronary infusion.

In the first randomized trial, BOOST (Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration)⁽¹⁸⁾, 60 patients received either bone marrow-derived ABMMNCs or optimal medical treatment after PCI. Stem cell therapy resulted in an increased LVEF and a reduced end-systolic volume, as assessed

Table 4 Selected clinical studies of cell therapy in acute myocardial infarction

Study	Design(n)	Cell type	Delivery method	Results	Adverse events
Strauer et al (14)	Series (10)	BMMC	Intracoronary	Feasible	None reported
TOPCARE (8,15)	Non-randomized (59)	BMMC versus circulating EPC	Intracoronary	Improved EF and perfusion Reduced infarct size	None reported at 1 yr
Chen et al (17)	RCT, open label (69)	MSC	Intracoronary	Improved EF and viability	None reported
BOOST (18, 19)	RCT, open label (60)	BMMC	Intracoronary	Transient EF improvement Improved diastolic dysfunction	None reported at 18 mo
Fernandez-Aviles et al (20)	Series (20)	BMMC	Intracoronary	Improved EF	None reported
REVIVAL-2 (21)	RCT, double blind (114)	G-CSF– mobilized PBSC	–	No effect on EF or infarction size	Muscle discomfort (G-CSF)
MAGIC Cell-3-DES (22)	RCT (96)	G-CSF– mobilized PBSC	Intracoronary	Improved EF	DES prevented restenosis
Janssens et al (23)	RCT, double blind (67)	BMMC	Intracoronary	Reduced infarct size and improvement in regional recovery	None reported
ASTAMI (24)	RCT, double blind (100)	BMMC	Intracoronary	No benefit of BMMC	None reported
REPAIR-AMI (25)	RCT, double blind (204)	BMMC	Intracoronary	Improved EF	None reported

BMMC, Bone marrow mononuclear cell; DES, drug eluting stent; EPC, endothelial progenitor cell; MSC, mesenchymal stem cell; PBSC, peripheral bone marrow stem cell.

by MRI. This improvement was attributed principally to increased contractility of the peri-infarct zones. Unlike earlier nonrandomized trials, the BOOST trial did not show a significant reduction in infarct size. The 18-month follow-up of patients in the BOOST trial was recently published⁽¹⁹⁾. The initial improvement in LVEF in the cell-treated group was not sustained when compared to the control group. However, the speed in which there was LVEF recovery over the 18 months was significantly higher in the cell-treated group.

A study by Janssens and colleagues⁽²³⁾ provides further insight into prevention of LV remodeling with intracoronary delivery of ABMMNCs after AMI. In a series of 67 patients, ABMMNCs were infused 24 hours after mechanical reperfusion. Following infusion,

patients were monitored for adverse events for 7 days, and then were discharged with follow-up acetate PET scanning, echocardiography with tissue Doppler and CineMRI at 4 months. The primary end point of mean global LVEF at 4-month follow-up was similar between the cell treated and placebo groups ($p=0.36$). Moreover, myocardial perfusion and metabolism (as measured by acetate PET scanning) were similarly increased in both groups. However, compared with the placebo infusion group, ABMMNC infusion was associated with a significant reduction in myocardial infarct size (ABMMNC treatment effect of 28%, $p=0.036$) and a better recovery of systolic function. Although the primary endpoint was not met, this additional reduction in infarct size in those receiving prompt revascularization

and ABMMNC suggests a potentially beneficial effect on LV remodeling.

Due to the discrepant LVEF results in the two previously mentioned trials, Lunde et al⁽²⁴⁾ investigated the effects of intracoronary injection of ABMMNCs in 100 patients with AMI. Patients were randomized to placebo or ABMMNC injection 4-8 days after AMI. LVEF, infarct size, and LV volumes were assessed by echocardiography, SPECT, and MRI at 2-3 weeks after AMI, and then again at 6 months after injection. In total, 47 patients underwent ABMMNC infusion at a median of 6 days after AMI with a mean of 87 million cells using the stop-flow technique. Compared to the control group, infusion of ABMMNC did not show any difference in LV function, infarct size, or left ventricular end diastolic volumes as measured by the three modalities. Adverse events in this very acute study were also not different between the two groups. Although the number of injected cells were not as many as those injected in the BOOST and Janssens trials, this study did add to the growing evidence of ABMMNC injection in AMI.

The most recent and methodologically sound study performed in AMI cell therapy, the REPAIR-MI trial, was recently published⁽²⁵⁾. In this study, 204 patients with AMI were randomly assigned to receive either an intracoronary infusion of progenitor cells derived from bone marrow (BMC) or placebo medium into the infarct artery 3 to 7 days after successful reperfusion therapy. There was a significantly greater absolute improvement in the global LVEF in the BMC group than in the placebo group (mean±SD increase, 5.5±7.3% vs. 3.0±6.5%; P=0.01). Patients with a baseline LVEF at or below the median value of 48.9% derived the most benefit. Most importantly, at 1 year, cell therapy resulted in reduction in the prespecified combined clinical end point of death, recurrent MI, and revascularization (p=0.01).

Taken together, the phase I intracoronary delivery trials have taught us that the magnitude of improvement after intracoronary infusion of stem cells is possibly mediated through prevention of remodeling. In Janssens' study⁽²³⁾, the importance of cell-delivery timing is once more evident. Early infusion of stem cells may result in even lower engraftment rates or higher rates of cell death given the adverse environment into which the cells are delivered. The modest therapeutic benefit seen in some of the trials could be due to patient selection. Most of the intracoronary studies were performed in patients with small areas of infarction and a preserved LVEF. The REPAIR-MI data corroborates that concept and sets the stage for future clinical trials possibly in patients with lower post-MI LVEF.

Conclusion

Despite many unresolved issues related to treatment dose, timing, and delivery, the clinical potential of stem cell therapy for cardiovascular disease is enormous. The potential to prevent post-MI left ventricular remodeling makes the future of cardiac stem cell therapy look very bright. There is the potential of setting a new standard in the treatment of AMI. The expectations of both patients and clinicians for this new therapeutic modality, however, are high and to achieve the full potential stem cell therapy has to offer will require continued cooperation and future close collaboration between basic and clinical scientists.

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